HIGHLIGHTS OF PRESCRIBING INFORMATION

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

BIVALIRUDIN in 0.9% Sodium Chloride Injection, for intravenous use
Initial U.S. Approval: 2000

INDICATIONS AND USAGE

Bivalirudin Injection is a direct thrombin inhibitor indicated for use as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI) including patients with heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis syndrome (HITTS). (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage is a 0.75 mg/kg intravenous bolus dose followed immediately by a 1.75 mg/kg/h intravenous infusion for the duration of the procedure. Five minutes 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. (2.1)
- Consider extending duration of infusion post-procedure up to 4 hours in patients with ST segment elevation MI (STEMI). (2.1)

DOSAGE FORMS AND STRENGTHS

Injection, clear and colorless solution in single dose containers. Ready to use:

250 mg of bivalirudin per 50 mL (5 mg/mL) (3)

500 mg of bivalirudin per 100 mL (5 mg/mL) (3)

CONTRAINDICATIONS

- Significant active bleeding (4)
- Hypersensitivity to bivalirudin or its components (4)

WARNINGS AND PRECAUTIONS

- Bleeding events: Bivalirudin increases the risk of bleeding. Its anticoagulant effect subsides approximately one hour after discontinuation. (5.1, 6.1, 12.2)
- Thrombotic risk with coronary artery brachytherapy: An increased risk of thrombus formation, including fatal outcomes, in gamma brachytherapy. (5.3)

ADVERSE REACTIONS

Most common adverse reaction was bleeding (3.7%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare at 1-866-888-2472 or the 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: 01/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Bivalirudin Injection is an anticoagulant for use in patients undergoing percutaneous coronary intervention (PCI) including patients with heparin-induced thrombocytopenia and heparin-induced thrombocytopenia and thrombosis syndrome.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of Bivalirudin Injection is an intravenous bolus dose of 0.75 mg/kg, followed immediately by a maintenance infusion of 1.75 mg/kg/h for the duration of the procedure. Five minutes 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.

Consider extending duration of infusion following PCI at 1.75 mg/kg/h for up to 4 hours post-procedure in patients with ST segment elevation MI (STEMI).

2.2 Dose Adjustment in Renal Impairment

Bolus Dose

No reduction in the bolus dose is needed for any degree of renal impairment.

Maintenance Infusion

In patients with creatinine clearance less than 30 mL/min (by Cockcroft Gault equation), reduce the infusion rate to 1 mg/kg/h. Monitor anticoagulant status in patients with renal impairment.

In patients on hemodialysis, reduce the infusion rate to 0.25 mg/kg/h *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

2.3 Instructions for Administration

Thawing and Inspection of Plastic Container

- Thaw frozen container at room temperature (25°C/ 77°F) or under refrigeration (5°C/41°F). Do not thaw by immersion in water baths or by microwave irradiation.
- Do not add supplemental medication.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Check for minute leaks by squeezing container firmly. If the outlet port protector is damaged, detached, or not present, discard container as solution path sterility may be impaired. Components of the solution may precipitate in the frozen state and will dissolve upon reaching room temperature with little or no agitation. Potency is not affected. Agitate after solution has reached room temperature. If after visual inspection the solution remains cloudy or if an insoluble precipitate is noted, if there are any leaks, or if any seals or outlet ports are not intact, the container should be discarded.
- Do not refreeze thawed Bivalirudin Injection. Thawed solution is stable for 14 days under refrigeration (5°C/41°F) or 24 hours at room temperature (25°C/77°F). Discard any unused portion.

Drug Compatibilities

No incompatibilities have been observed with administration sets.

Do not administer the drugs listed in Table 1 in the same intravenous line with Bivalirudin Injection.

Table 1. Drugs Not for Administration in the Same Intravenous Line with Bivalirudin Injection

Alteplase
Amiodarone HCl
Amphotericin B
Chlorpromazine HCl
Diazepam
Dobutamine
Prochlorperazine Edisylate
Reteplase
Streptokinase
Vancomycin HCl

3 DOSAGE FORMS AND STRENGTHS

Injection, clear and colorless solution:

- 250 mg of bivalirudin per 50 mL (5 mg/mL) in a single-dose GALAXY container supplied as a frozen, premixed, iso-osmotic, sterile, nonpyrogenic solution. Ready to use. Each container contains 250 mg of bivalirudin equivalent to an average of 275 mg bivalirudin trifluoroacetate*.

**The range of bivalirudin trifluoroacetate is 270 to 280 mg based on a range of trifluoroacetic acid composition of 1.7 to 2.6 equivalents.*

- 500 mg of bivalirudin per 100 mL (5 mg/mL) in a single-dose GALAXY container supplied as a frozen, premixed, iso-osmotic, sterile, nonpyrogenic solution. Ready to use. Each container contains 500 mg of bivalirudin equivalent to an average of 550 mg bivalirudin trifluoroacetate†.

†The range of bivalirudin trifluoroacetate is 540 to 560 mg based on a range of trifluoroacetic acid composition of 1.7 to 2.6 equivalents.

4 CONTRAINDICATIONS

Bivalirudin Injection is contraindicated in patients with:

- Significant active bleeding
- Hypersensitivity to Bivalirudin Injection or its components *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Bleeding Events

Bivalirudin increases the risk of bleeding *[see Adverse Reactions (6.1)]*. Bivalirudin's anticoagulant effect subsides approximately one hour after discontinuation *[see Clinical Pharmacology (12.2)]*.

5.3 Thrombotic Risk with Coronary Artery Brachytherapy

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

In the BAT trials, 79 of the 2161 (3.7%) of subjects undergoing PCI for treatment of unstable angina and randomized to bivalirudin experienced major bleeding events which consisted of: intracranial bleeding, retroperitoneal bleeding, and clinically overt bleeding with a decrease in hemoglobin >3 g/dL or leading to a transfusion of >2 units of blood.

6.2 Immunogenicity

As with all peptides, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to bivalirudin in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

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 post-approval 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, 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on use of bivalirudin in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Reproduction studies in rats and rabbits administered subcutaneously (SC) doses up to 1.6 times and 3.2 times the maximum recommended human dose (MRHD) of 15 mg/kg/day based on body surface area (BSA) during organogenesis, respectively, revealed no evidence of fetal harm.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

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 harm to the fetus attributable to bivalirudin.

At 500 mg/kg/day (equivalent to 5.4 times the maximum recommended human dose based on body surface area) subcutaneously, litter sizes and live fetuses in rats were reduced. Fetal skeletal variations were also noted. Some of these changes could be attributed to maternal toxicity observed at high doses.

There is no study covering the peri-natal period because of the potential complications of drug-induced hemorrhage during delivery.

8.2 Lactation

Risk Summary

It is not known whether bivalirudin is present in human milk. No data are available on the effects of bivalirudin on the breastfed child or on milk production.

Bivalirudin was administered to lactating rats in reproduction studies (*see Data*).

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Bivalirudin Injection and any potential adverse effects on the breastfed infant from Bivalirudin Injection or from the underlying maternal condition.

Data

Animal Data

Reproduction studies conducted in lactating female rats dosed subcutaneously daily with bivalirudin at doses up to 150 mg/kg/day (1.6 times the maximum recommended human dose, based on body surface area) from day 2 through day 20 of lactation revealed no adverse developmental outcomes to the pups.

8.4 Pediatric Use

Safety and effectiveness 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.

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 21% in patients with moderate and severe renal impairment and was reduced approximately 70% in dialysis-dependent patients *[see Clinical Pharmacology (12.3)]*. Reduce the infusion dose of Bivalirudin Injection and monitor the anticoagulant status more frequently in patients with renal impairment creatine clearance less than 30mL/min (by Cockcroft Gault equation) *[see Dosage and Administration (2.2)]*.

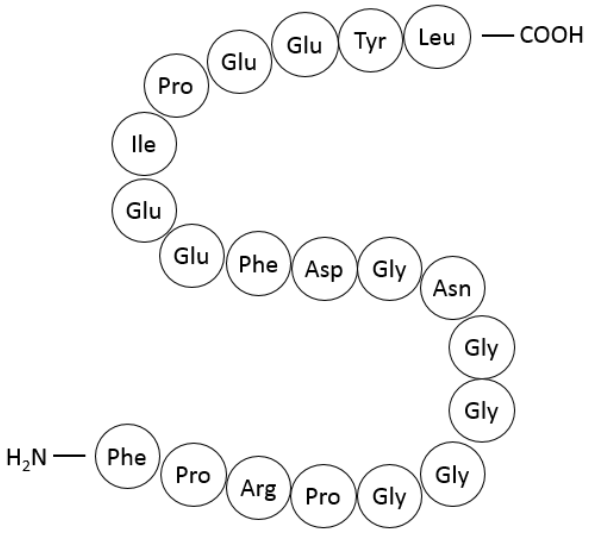
10 OVERDOSAGE

Cases of overdose of up to 10 times the recommended bolus or continuous infusion dose of Bivalirudin Injection 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 Injection 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 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 (Figure 1). The molecular weight of bivalirudin is 2180 daltons (anhydrous free base peptide). The active pharmaceutical ingredient is in the form of bivalirudin trifluoroacetate as a white to off-white powder.

Figure 1: Structural Formula of Bivalirudin



Bivalirudin Injection is supplied as a frozen, premixed, iso-osmotic, sterile, nonpyrogenic 50 mL or 100 mL solution containing 250 mg or 500 mg respectively as bivalirudin (equivalent to an average of 275 or 550 mg bivalirudin trifluoroacetate*) in the GALAXY single-dose container (PL 2040 Plastic). Sodium Chloride, USP has been added to adjust osmolality (0.9 g/100 mL).

The approximate osmolality for Bivalirudin Injection is 300 mOsmol/kg.

The pH of Bivalirudin Injection may have been adjusted with sodium hydroxide and/or hydrochloric acid to 5.2 to 6.0. The solution is intended for intravenous use at room temperature.

**The range of bivalirudin trifluoroacetate is 270 to 280 mg (250 mg strength) or 540 to 560 mg (500 mg strength) based on a range of trifluoroacetic acid composition of 1.7 to 2.6 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.

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. Bivalirudin also increases INR. Therefore

INR measurements made in Bivalirudin Injection treated patients may not be useful for determining the appropriate dose of warfarin.

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 intravenous bolus plus 2.5 mg/kg/h intravenous infusion (1.4 times higher than the approved dose of 1.75 mg/kg/h) 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 intravenous 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 intravenous bolus of 1 mg/kg and a 4-hour 2.5 mg/kg/h intravenous infusion.

Distribution

Bivalirudin does not bind to plasma proteins (except thrombin) or to red blood cells.

Elimination

Bivalirudin has a half- life of 25 minutes in PTCA patients with normal renal function. The total body clearance of bivalirudin in PTCA patients with normal renal function is 3.4 mL/min/kg.

Metabolism

Bivalirudin is metabolized by proteolytic cleavage.

Excretion

Bivalirudin undergoes glomerular filtration. Tubular secretion and tubular reabsorption are also implicated in the excretion of bivalirudin, although the extent is unknown.

Specific Populations

Patients with Renal Impairment

Total body clearance was similar for PTCA patients with normal renal function and with mild renal impairment. Clearance was reduced by 21% in patients with moderate and severe renal impairment with a half-life of 34 and 57 minutes, respectively. In dialysis patients, clearance was reduced by 70%, with a half- life of 3.5 hours. Approximately 25% bivalirudin is cleared by hemodialysis.

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

Bivalirudin Angioplasty Trial (BAT)

In the BAT studies, patients with unstable angina undergoing PCI were randomized 1:1 to a 1 mg/kg bolus of bivalirudin and then 2.5 mg/kg/h for four hours and then 0.2 mg/kg/h for 14 - 20 hours or to 175 IU/kg bolus of heparin followed by an 18-24 hour infusion of 15 IU/kg/h infusion. Additional heparin but not bivalirudin could be administered for ACT < 350 seconds. The studies were designed to demonstrate the superiority of bivalirudin to heparin on the occurrence of any of the following during hospitalization up to seven days of death, MI, abrupt closure of the dilated vessel, or clinical deterioration requiring revascularization or placement of an aortic balloon pump.

The 4312 subjects ranged in age from 29-90 (median 63) years. 68% were male, and 91% were Caucasian. Median weight was 80 kg (39-120 kg). 741 (17%) subjects had post-MI angina. Twenty-three percent of patients were treated with heparin within one hour prior to randomization.

The studies did not demonstrate that bivalirudin was statistically superior to heparin for reducing the risk of death, MI, abrupt closure of the dilated vessel, or clinical deterioration requiring revascularization or placement of an aortic balloon pump, but the occurrence of these events was similar in both treatment groups. Study outcomes are shown in Table 2.

Table 2: Incidences of In-hospital Endpoints in BAT Trial

Endpoint	Bivalirudin (n=2161)	HEPARIN (n=2151)
Primary endpoint[1]	7.9%	9.3%
Death, MI, revascularization	6.2%	7.9%
Death	0.2%	0.2%
MI	3.3%	4.2%

[1] 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

AT-BAT Trial (NCT# 00043940)

This was a single-arm open-label study in which 51 subjects with heparin-induced thrombocytopenia (HIT) or heparin induced thrombocytopenia and thrombosis syndrome (HITTS) undergoing PCI. The majority of patients achieved adequate ACT at the time of device activation and no major bleeding was reported. Two patients developed thrombocytopenia.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Bivalirudin Injection is supplied as a frozen, premixed, iso-osmotic, sterile, nonpyrogenic single-dose solution packaged in the GALAXY container. When thawed, a clear and colorless solution is obtained. The single-dose GALAXY plastic containers are available as follows:

Code	NDC	Container	Size	Number of Containers/Carton
2G3567	NDC 0338-9572-24	GALAXY single-dose	50 mL	24 count carton of 250 mg/50 mL (5 mg/mL) GALAXY containers
2G3566	NDC 0338-9576-12	GALAXY single-dose	100 mL	12 count carton of 500 mg/100 mL (5 mg/mL) GALAXY containers

The 250 mg and 500 mg strength drug products contain 250 mg or 500 mg respectively as bivalirudin (equivalent to an average of 275 or 550 mg bivalirudin trifluoroacetate*).

**The range of bivalirudin trifluoroacetate is 270 to 280 mg (250 mg strength) or 540 to 560 mg (500 mg strength) based on a range of trifluoroacetic acid composition of 1.7 to 2.6 equivalents.*

16.2 Storage

GALAXY containers should be stored frozen at or below -20°C/-4°F.

Product containers may be fragile in the frozen state.

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.

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