

DIGIFAB[®] DIGOXIN IMMUNE FAB (OVINE)

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

DigiFab[®], Digoxin Immune Fab (Ovine)

For Intravenous Injection Only – Lyophilized Powder for Solution
Initial U.S. Approval: 2001

INDICATIONS AND USAGE

DIGIFAB is a digoxin immune fab (ovine) and is indicated for treatment of life-threatening or potentially life-threatening digoxin toxicity or overdose. (1)

DOSAGE AND ADMINISTRATION

For intravenous use only

Clinical Conditions	Dosage
Acute ingestion of unknown amounts of digoxin and toxicity in the absence of a serum digitalis concentration or estimated ingestion amount	Administer 20 vials of DIGIFAB. Monitor for volume overload in small (< 20 Kg) children. Start with 10 vials followed by an additional 10 vials, if needed, to avoid a febrile reaction.
Chronic digoxin toxicity in the absence of a serum digitalis concentration	Administer 6 vials of DIGIFAB in Adults and Children ≥ 20 Kg. Administer 1 vial of DIGIFAB in Infants and Children < 20 Kg.
Acute ingestion of known amounts of digoxin	Dose (in vials) = $\frac{\text{Amount of digoxin ingested (in mg)}}{0.5 \text{ mg/vial}}$
Chronic digoxin toxicity and known serum digitalis concentration	Dose (in vials) = $\frac{(\text{Serum digoxin ng/mL})(\text{weight in kg})}{100}$

DOSAGE FORMS AND STRENGTHS

DIGIFAB is supplied as a sterile, lyophilized preparation. Each vial contains 40 mg of digoxin immune fab protein. (3)

CONTRAINDICATIONS

WARNINGS AND PRECAUTIONS

- Rapid drop in serum potassium concentration after treatment with DIGIFAB. Monitor frequently, especially after the first several hours of DigiFab administration. (5.1)
- Anaphylaxis and hypersensitivity reactions are possible. Patients with allergies to papain, chymopapain, other papaya extracts, or the pineapple enzyme bromelain may be at risk for an allergic reaction to DIGIFAB. (5.2)
- Clinically misleading reading of standard serum digoxin concentration may occur after administration of DIGIFAB due to interference with digitalis immunoassay measurements. (5.4)

ADVERSE REACTIONS

The most common adverse reactions (>7%) are worsening congestive heart failure (13%), hypokalemia (13%) and worsening atrial fibrillation (7%). (6)

To report SUSPECTED ADVERSE REACTIONS, contact BTG 1-877-377-3784, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2017

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DIGIFAB[®] DIGOXIN IMMUNE FAB (OVINE)

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DIGIFAB is indicated for the treatment of patients with life-threatening or potentially life-threatening digoxin toxicity or overdose, including:

- Known suicidal or accidental consumption of fatal doses of digoxin: 10 mg or more of digoxin in healthy adults, or 4 mg (or more than 0.1 mg/kg) in healthy children, or ingestion of an amount that can cause steady state serum concentrations of ≥ 10 ng/mL;
- Chronic ingestions causing steady-state serum digoxin concentrations > 6 ng/mL in adults or 4 ng/mL in children;
- Manifestations of life-threatening toxicity of digoxin overdose such as severe ventricular arrhythmias, progressive bradycardia, and second or third degree heart block not responsive to atropine, serum potassium levels exceeding 5.5 mEq/L in adults or 6 mEq/L in children with rapidly progressive signs and symptoms of digoxin toxicity.

2 DOSAGE AND ADMINISTRATION

For Intravenous Use Only

2.1 Dosage

General Guidelines:

Adjust the dosage of DIGIFAB according to the amount of digoxin to be neutralized.

Summary of Dosing Guidelines

Clinical Conditions	Dosage
Acute ingestion of unknown amounts of digoxin and toxicity in the absence of a serum digitalis concentration or estimated ingestion amount	Administer 20 vials of DIGIFAB. Monitor for volume overload in small (< 20 Kg) children. Start with 10 vials followed by an additional 10 vials, if needed, to avoid a febrile reaction.
Chronic digoxin toxicity in the absence of a serum digitalis concentration	Administer 6 vials of DIGIFAB in Adults and Children ≥ 20 Kg. Administer 1 vial of DIGIFAB in Infants and Children < 20 Kg.
Acute ingestion of known amounts of digoxin	Dose (in vials) = $\frac{\text{Amount of digoxin ingested (in mg)}}{0.5 \text{ mg/vial}}$
Chronic digoxin toxicity and known serum digitalis concentration	Dose (in vials) = $\frac{(\text{Serum digoxin ng/mL})(\text{weight in kg})}{100}$

Failure of the patient to respond to DIGIFAB should alert the physician to the possibility that the clinical problem may not be caused by digitalis toxicity.

DOSAGE CALCULATION

General

Methods for calculating a neutralizing dose of DIGIFAB, based on a known or estimated amount of digoxin or digitoxin in the body, are provided below. When using the dose calculation methods provided, the following guidelines should be considered:

- Inaccurate estimates of the amount of digitalis ingested or absorbed may occur due to non-steady state serum concentrations or due to digitalis assay limitations. Most serum digoxin assay kits are designed to measure concentrations less than 5 ng/mL; therefore, sample dilution is required to accurately measure serum concentrations > 5 ng/mL.
- Dosage calculations are based on a steady state volume of distribution of approximately 5 L/kg for digoxin, which is used to convert serum

digoxin concentrations to total body burden of digoxin in milligrams. The volume of distribution is a population average and may vary among individuals. Many patients may require higher doses for complete neutralization and doses should usually be rounded up to the nearest whole vial.

- If toxicity has not adequately reversed after several hours, or appears to recur, re-administration of DIGIFAB, at a dose guided by clinical judgment, may be necessary. If a patient is in need of re-administration of DIGIFAB due to recurrent toxicity, or to a new toxic episode that occurs soon after the first episode, measurement of free (unbound) serum digitalis concentrations should be considered since Fab may still be present in the body.
- Failure of a patient to respond to DIGIFAB treatment may indicate that the clinical problem is not caused by digitalis intoxication. If there is no response to an adequate dose of DIGIFAB, the diagnosis of digitalis toxicity should be questioned.

Calculation for Ingestion of Known Amount:

- Each vial of DIGIFAB (40 mg of purified digoxin-specific Fab) binds approximately 0.5 mg of digoxin.
- The total number of vials required can be calculated by dividing the total body load of digoxin in milligrams (mg) by 0.5 mg per vial (see Formula 1).
- Following an acute ingestion, total body load will be approximately equal to the amount ingested in milligrams for either digoxin capsules or digitoxin.
- In case of digoxin tablet ingestion, the total body load will be approximately equal to the amount ingested (in mg) multiplied by the bioavailability of the tablet preparation, which is 0.8.

Table 1 gives dosage estimates in number of vials for adults and children who have ingested a single large dose of digoxin and for whom the approximate number of tablets or capsules is known. The dose of DIGIFAB (in number of vials) represented in Table 1 can be approximated using the following formula:

Formula 1

$$\text{Dose (in \# of vials)} = \frac{\text{total digitalis body load in mg}}{0.5 \text{ mg of digitalis bound/vial}}$$

Table 1 Approximate Dose of DIGIFAB for Reversal of a Single Large Digoxin Overdose

Number of Digoxin Tablets or Capsules Ingested*	Dose of DIGIFAB # of vials
25	10
50	20
75	30
100	40
150	60
200	80

* 0.25 mg tablets with 80% bioavailability or 0.2 mg capsules with 100% bioavailability

If, after several hours, toxicity is not adequately reversed, or appears to recur, additional administration of DIGIFAB at a dose guided by clinical judgment may be required.

Calculations Based on Steady-State Serum Digoxin Concentrations:

Adults

Table 2 gives dosage estimates in number of vials for adult patients for whom a steady-state serum digoxin concentration is known. The dose of DIGIFAB (in number of vials) represented in Table 2 can be approximated using the following formula:

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Formula 2 (see Table 2)

$$\text{Dose (in \# of vials)} = \frac{(\text{Serum digoxin concentration in ng/mL})(\text{weight in kg})}{100}$$

Table 2 Adult Dose Estimate of DIGIFAB (in # of vials) from Steady-State Serum Digoxin Concentration

Patient Weight (kg)	Serum Digoxin Concentration (ng/mL)						
	1	2	4	8	12	16	20
40	0.5v	1v	2v	3v	5v	7v	8v
60	0.5v	1v	3v	5v	7v	10v	12v
70	1v	2v	3v	6v	9v	11v	14v
80	1v	2v	3v	7v	10v	13v	16v
100	1v	2v	4v	8v	12v	16v	20v

v = vials

Children:

- Table 3 gives dosage estimates in milligrams for infants and small (< 20 Kg) children based on the steady-state serum digoxin concentration.
- The dose of DIGIFAB represented in Table 3 can be estimated by multiplying the dose (in number of vials) calculated from Formula 2 by the amount of DIGIFAB contained in a vial (40 mg/vial) (see Formula 3).
- Administer smaller doses in children < 20 Kg requiring doses < 1mL with a tuberculin syringe after reconstituting 40 mg.
- For very small doses, a reconstituted vial can be diluted with 36 mL of sterile isotonic saline to achieve a concentration of 1 mg/mL.

Formula 3 (see Table 3)

$$\text{Dose (in mg)} = (\text{Dose in \# of vials}) (40 \text{ mg/vial})$$

Table 3 Infants and Small (< 20 Kg) Children Dose Estimates of DIGIFAB (in mg) from Steady State Serum Digoxin Concentration

Patient Weight (kg)	Serum Digoxin Concentration (ng/mL)						
	1	2	4	8	12	16	20
1	0.4 mg*	1 mg*	1.5 mg*	3 mg*	5 mg	6.5 mg	8 mg
3	1 mg*	2.5 mg*	5 mg	10 mg	14 mg	19 mg	24 mg
5	2 mg*	4 mg	8 mg	16 mg	24 mg	32 mg	40 mg
10	4 mg	8 mg	16 mg	32 mg	48 mg	64 mg	80 mg
20	8 mg	16 mg	32 mg	64 mg	96 mg	128 mg	160 mg

* dilution of reconstituted vial to 1 mg/mL may be desirable

Calculation Based on Steady-State Digitoxin Concentrations:

The dose of DIGIFAB for digitoxin toxicity can be approximated by using the following formula (which differs from Formula 2 in the denominator due to a 10-fold decrease in the volume of distribution of digitoxin as compared to digoxin).

Formula 4

$$\text{Dose (in \# of vials)} = \frac{(\text{Serum digitoxin concentration in ng/mL})(\text{weight in kg})}{1000}$$

If in any case, the dose estimated based on ingested amount (Formula 1) differs substantially from that calculated based on the serum digoxin or digitoxin concentration (Formulas 2 and 4), it may be preferable to use the higher dose estimate.

2.2 Preparation and Administration

- Each vial contains 40 mg of digoxin immune Fab protein and is intended for one time use only as it contains no preservatives
- Reconstitute each vial of DIGIFAB with 4 mL of Sterile Water for Injection USP and gently mix to provide a solution containing approximately 10 mg/mL of digoxin immune Fab protein.

- Use the reconstituted product promptly. If not used immediately, store under refrigeration at 2° to 8°C (36° to 46°F) for up to 4 hours. Add the reconstituted product to an appropriate volume of 0.9% sodium chloride for injection.

- Visually inspect reconstituted vials for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution is cloudy, turbid or if it contains particulates.

- Administer DIGIFAB slowly as an intravenous infusion over at least 30 minutes. Stop the infusion if infusion rate-related anaphylactoid-type reactions occur, such as hypotension, wheezing, or urticaria. The infusion can be re-started at a slower rate. Give DIGIFAB by bolus injection, if cardiac arrest is imminent. An increased incidence of infusion-related reactions may be expected with bolus injection.

- For infants and small children who may require very small doses, reconstitute the 40 mg vial as directed and administer undiluted using a tuberculin syringe. For very small doses, a reconstituted vial can be diluted with an additional 36 mL of isotonic saline to achieve a concentration of 1 mg/mL.

3 DOSAGE FORMS AND STRENGTHS

DIGIFAB is supplied as a sterile, purified, lyophilized preparation containing 40 mg of digoxin immune Fab protein per vial.

4 CONTRAINDICATIONS

There are no known contraindications to the use of DIGIFAB.

5 WARNINGS AND

PRECAUTIONS 5.1 General

Suicidal ingestion may result from more than one drug. Toxic effects of other drugs or poisons should not be overlooked, especially in cases where signs and symptoms of digitalis toxicity are not relieved by administration of DIGIFAB.

Rapid drop in serum potassium concentration may occur after treatment with DIGIFAB. Monitor frequently, especially after the first several hours of DIGIFAB administration (see 5.4 Laboratory Tests).

Patients with poor cardiac function may deteriorate secondary to the withdrawal of the inotropic action of digoxin by DIGIFAB. If needed, provide additional support by using other intravenous inotropes such as dopamine, dobutamine or vasodilators. However, take additional care not to aggravate the digitalis induced rhythm disturbances. Postpone re-digitalization, if possible, until the Fab fragments have been eliminated from the body, which may require several days, and patients with impaired renal function may require a week or longer.

5.2 Hypersensitivity Reactions

Anaphylaxis and hypersensitivity reactions are possible. Carefully monitor all patients treated with DIGIFAB for signs and symptoms of an acute allergic reaction (e.g., urticaria, pruritus, erythema, angioedema, bronchospasm with wheezing or cough, stridor, laryngeal edema, hypotension, tachycardia) and treat immediately with appropriate emergency medical care (e.g., oxygen, diphenhydramine, corticosteroids, volume expansion and airway management), if one occurs.

If an anaphylactic reaction occurs during the infusion, terminate DIGIFAB administration at once and administer appropriate treatment. Balance the need for epinephrine against its potential risk in the setting of digitalis toxicity. Patients with known allergies to sheep protein are particularly at risk for an anaphylactic reaction, as are individuals who have previously received intact ovine antibodies or ovine Fab.

Do not administer DIGIFAB to patients with a known history of hypersensitivity to papaya or papain unless the benefits outweigh the risks and appropriate management for anaphylactic reactions is readily available.

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Prior treatment with digoxin-specific ovine immune Fab carries a theoretical risk of sensitization to ovine serum protein and possible diminution of the efficacy of the drug due to the presence of human antibodies against ovine Fab. To date, there have been no clinical reports of human anti-ovine immunoglobulin antibodies causing a reduction in binding of ovine digoxin immune Fab or neutralization response to ovine digoxin immune Fab.

5.3 Use of DIGIFAB in Renal Failure

The elimination half-life of DIGIFAB in renal failure has not been clearly defined. Monitor patients with severe renal failure who receive DIGIFAB for digitalis toxicity for a prolonged period for possible recurrence of toxicity.

Monitoring of free (unbound) digoxin concentrations after the administration may be appropriate in order to establish recrudescence toxicity in renal failure patients.⁵

5.4 Laboratory Tests

DIGIFAB may interfere with digitalis immunoassay measurements. Thus, standard serum digoxin concentration measurements may be clinically misleading until the Fab fragments are eliminated from the body. This may take several days or a week or more in patients with markedly impaired renal function. Therefore, serum samples for digoxin concentration should be obtained before DIGIFAB administration, if at all possible. Such measurements would establish the level of serum digoxin at the time of diagnosis of digitalis intoxication.

At least 6 to 8 hours are required for equilibration of digoxin between serum and tissue, so absorption of the last dose may continue from the intestine. Therefore, serum measurements may be difficult to interpret if samples are drawn soon after the last digitalis dose.

The total serum digoxin concentration may rise precipitously following administration of DIGIFAB, but this will be almost entirely bound to the Fab fragment and therefore not able to react with receptors in the body.

Patients should be closely monitored, including temperature, blood pressure, electrocardiogram, and potassium concentration, during and after administration of DIGIFAB. Digoxin causes a shift of potassium from inside to outside the cell, such that severe intoxication can cause a life-threatening elevation of serum potassium. This may lead to increased urinary excretion of potassium so that a patient may have hyperkalemia but a whole body deficit of potassium. When the toxic effects of digoxin are reversed by DIGIFAB, potassium shifts back into the cell with a resulting decline in serum potassium concentration. This hypokalemia may develop rapidly. For these reasons, serum potassium concentration should be followed closely, especially during the first several hours after DIGIFAB administration. Cautious potassium supplementation should then be given when necessary.

ADVERSE REACTIONS

The most common adverse reactions (> 7%) related to DIGIFAB administration are worsening congestive heart failure (13%), hypokalemia (13%) and worsening atrial fibrillation (7%).

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the clinical trials of DIGIFAB, 6 of 15 patients in the digoxin overdose study had a total of 17 adverse events. Three events occurred in one patient and consisted of the following: pulmonary edema, bilateral pleural effusion and renal failure. The events were determined to be likely due to the loss of digoxin inotropic support in combination with the patient's underlying medical condition. Of 8 healthy volunteers who received DIGIFAB, two experienced an adverse reaction that was considered to be related to DIGIFAB. The reactions were; one episode of phlebitis of the infusion-site vein and one episode of transient postural hypotension.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Animal reproduction studies have not been conducted with DIGIFAB. It is also not known whether DIGIFAB can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. DIGIFAB should be given to a pregnant woman only if clinically needed.

8.2 Lactation

Risk Summary

It is not known whether DIGIFAB is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when DIGIFAB is administered to a nursing woman. DIGIFAB should be given to nursing mothers only if clinically needed.

8.4 Pediatric Use

Safety data in pediatric population is limited. The pediatric dosing estimation is based on calculations for adult dosing.

8.5 Geriatric Use

Specific studies in elderly patients have not been conducted. Of the 15 patients given DIGIFAB for digoxin toxicity in one clinical trial, the average age of all patients was 64 years and over half of the patients (8 of the 15) were 65 years of age or older. The oldest patient studied was 86 years old. There is no evidence that the efficacy of DIGIFAB would be altered due to advanced age alone; however, elderly patients have a higher chance of having impaired renal function and therefore should be monitored more closely for recurrent toxicity (See 5.3 Use of DIGIFAB in renal failure).

11 DESCRIPTION

DIGIFAB [Digoxin Immune Fab (Ovine)] is a sterile, lyophilized preparation of digoxin-immune ovine Fab (monovalent) immunoglobulin fragments. These fragments are obtained from the blood of healthy sheep immunized with a digoxin derivative, digoxin-dicarboxymethoxylamine (DDMA), a digoxin analogue which contains the functionally essential cyclopentaperhydrophenanthrene: lactone ring moiety coupled to keyhole limpet hemocyanin (KLH).

The final product is prepared by isolating the immunoglobulin fraction of the ovine serum, digesting it with papain and isolating the digoxin-specific Fab fragments by affinity chromatography. These antibody fragments have a molecular weight of approximately 46,000 Da.

Each vial of DIGIFAB, which will bind approximately 0.5 mg digoxin, contains 40 mg of digoxin immune Fab, 75 mg (approx) of mannitol USP, and 2 mg (approx) sodium acetate USP as a buffering agent.

The product contains no preservatives and is intended for intravenous administration after reconstitution with 4 mL of Sterile Water for Injection USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

DIGIFAB has an affinity for digoxin in the range of 10^9 to $10^{10} M^{-1}$, which is greater than the affinity of digoxin for its sodium pump receptor, the presumed receptor for its therapeutic and toxic effects. When administered to the intoxicated patient, DIGIFAB binds to molecules of digoxin reducing free digoxin levels, which results in a shift in the equilibrium away from binding to the receptors, thereby reducing cardio-toxic effects. Fab-digoxin complexes are then cleared by the kidney and reticuloendothelial system.

12.3 Pharmacokinetics

The pharmacokinetics and pharmacodynamics of DIGIFAB were assessed in a randomized and controlled study of DIGIFAB and Digibind[®] (comparator Fab product for treatment of digoxin toxicity). Sixteen healthy subjects were given 1 mg of intravenous digoxin followed by an approximately equimolar neutralizing dose of either DIGIFAB (n=8) or Digibind[®] (n=8). The objective of the pharmacokinetic and pharmacodynamic study was to compare

DIGIFAB[®] DIGOXIN IMMUNE FAB (OVINE)

parameters for DIGIFAB to those for Digibind[®].⁷ The pharmacokinetics of both digoxin and Fab were determined and found to be similar for both products. The similar volumes of distribution (0.3 L/kg and 0.4 L/kg for DIGIFAB and Digibind[®], respectively) indicate considerable penetration from the circulation into the extracellular space and are consistent with previous reports of ovine Fab distribution, as are the elimination half-life values (15 hours and 23 hours for DIGIFAB and Digibind[®], respectively).⁸⁻

¹² The elimination half-life of 15-20 hours in patients with normal renal function appears to be increased up to 10 fold in patients with renal impairment, although volume of distribution remains unaffected.¹²

The primary outcome measure for this study was the serum level of free (unbound) digoxin. The results demonstrated that both products reduced the level of free digoxin in the serum to below the limit of assay quantitation for several hours after Fab administration. Cumulative urinary excretion of digoxin was comparable for both products and exceeded 40% of the administered dose by 24 hours. These results demonstrate that DIGIFAB and Digibind[®] have equivalent pharmacodynamic effects on the digoxin parameters that are relevant to the treatment of digoxin toxicity.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal carcinogenicity and reproduction studies have not been conducted with DigiFab.

13.2 Animal Toxicology and/or Pharmacology

No toxic effects were observed when DIGIFAB was administered to healthy male Sprague Dawley rats in equimolar doses sufficient to neutralize a 1 mg/kg dose of digoxin. In these studies, the physiologic changes produced by toxic serum concentrations of digoxin were ameliorated rapidly by the administration of DIGIFAB or comparator product Digibind[®]. Statistically equivalent responses were observed with both DIGIFAB and Digibind[®] to the following variables: PTQ index, heart rate, mean arterial pressure, ventilation, arterial blood gases, and serum potassium concentrations.

14 CLINICAL STUDIES

One prospective multi-center safety, efficacy and pharmacokinetic study in patients presenting with life-threatening digoxin toxicity was conducted in U.S. and Finland.

The objective of the study was to demonstrate safety, pharmacokinetics, and clinical response of DIGIFAB in patients. Results were compared to historical data on Digibind[®]. Fifteen patients received doses of DIGIFAB based on its theoretical binding capacity for digoxin, and based on the known amount of digoxin ingested or on blood concentrations of digoxin at the time of admission.

Serum free digoxin concentrations fell to undetectable concentrations in all patients following DIGIFAB administration. Ten of the 15 patients studied who had baseline ECG abnormalities improved within 4 hours after the DIGIFAB infusion. The remaining 5 patients who had baseline ECG abnormalities remained unchanged throughout the 24-hour assessment period, and in one case through the 30-day follow up period. Seven out of the 15 patients (47%) studied had complete resolution of digoxin toxicity within 4 hours of DIGIFAB administration, and 14 patients (93%) were classified as having resolved their digoxin toxicity by 20 hours. In this study, where 2/15 patients had serum available for human anti-ovine antibody determination, there was no measurable immune response.

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

DigiFab is supplied as a carton that contains 1 vial of product (diluent not included).

- NDC 50633-120-11
- Store at 2° to 8°C (36° to 46°F).
- Do not freeze.
- Use within 4 hours after reconstitution.

17 PATIENT COUNSELING INFORMATION

Advise patients to contact their physician immediately if they experience any signs and symptoms of delayed allergic reactions or serum sickness (e.g., rash, pruritus, urticaria) after hospital discharge.

Manufactured for
and distributed by:

BTG International Inc.
West Conshohocken, PA 19428

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