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.

---DOSAGE AND ADMINISTRATION---
For intravenous use only

<table>
<thead>
<tr>
<th>Clinical Conditions:</th>
<th>Dosage:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute ingestion of unknown amounts of digoxin and toxicity in the absence of a serum digitalis concentration or estimated ingestion amount</td>
<td>Administer 20 vials of DIGIFAB. Monitor for volume overload in small (&lt; 20 Kg) children. Start with 10 vials followed by an additional 10 vials, if needed, to avoid a febrile reaction.</td>
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<td>Administer 6 vials of DIGIFAB in Adults and Children ≥ 20 Kg. Administer 1 vial of DIGIFAB in Infants and Children &lt; 20 Kg.</td>
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<td>Chronic digoxin toxicity and known serum digitalis concentration</td>
<td>Dose (in vials) = (Serum digoxin ng/mL)(weight in kg) / 100</td>
</tr>
</tbody>
</table>

---CONTRAINDICATIONS---
Rapid drop in serum potassium concentration after treatment with DIGIFAB. Monitor frequently, especially after the first several hours of DigiFab administration. (5.1)

---WARNINGS AND PRECAUTIONS---
- 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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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DIGIFAB® (DIGOXIN IMMUNE FAB (OVINE)) is indicated for the treatment of patients with life-threatening or potentially life-threatening digitalis 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 digitalis 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

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<tr>
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</tr>
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</table>

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.

DOSEAGE 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 toxicity. 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

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

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

<table>
<thead>
<tr>
<th>Number of Digoxin Tablets or Capsules Ingested*</th>
<th>Dose of DIGIFAB # of vials</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>75</td>
<td>30</td>
</tr>
<tr>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>150</td>
<td>60</td>
</tr>
<tr>
<td>200</td>
<td>80</td>
</tr>
</tbody>
</table>

* 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:
**DIGIFAB® DIGOXIN IMMUNE FAB (OVINE)**

**Formula 2 (see Table 2)**

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

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Adult Dose Estimate of DIGIFAB (in # of vials) from Steady-State Serum Digoxin Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Weight (kg)</td>
<td>Serum Digoxin Concentration (ng/mL)</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>40</td>
<td>0.5v</td>
</tr>
<tr>
<td>60</td>
<td>0.5v</td>
</tr>
<tr>
<td>70</td>
<td>1v</td>
</tr>
<tr>
<td>80</td>
<td>1v</td>
</tr>
<tr>
<td>100</td>
<td>1v</td>
</tr>
</tbody>
</table>

\(v = \text{vials}\)

**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 < 1 mL 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)**

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

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Infants and Small (&lt; 20 Kg) Children Dose Estimates of DIGIFAB (in mg) from Steady State Serum Digoxin Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Weight (kg)</td>
<td>Serum Digoxin Concentration (ng/mL)</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>0.4 mg*</td>
<td>1 mg*</td>
</tr>
<tr>
<td>1 mg*</td>
<td>2.5 mg*</td>
</tr>
<tr>
<td>2 mg*</td>
<td>4 mg</td>
</tr>
<tr>
<td>4 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>8 mg</td>
<td>16 mg</td>
</tr>
</tbody>
</table>

\(* \text{dilution of reconstituted vial to 1 mg/mL may be desirable}\)

Calculation Based on Steady-State Digoxitin Concentrations:
The dose of DIGIFAB for digoxitin 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 digoxitin as compared to digoxitin).

**Formula 4**

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

If in any case, the dose estimated based on ingested amount (Formula 1) differs substantially from that calculated based on the serum digoxitin or digoxitin 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 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.
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 digoxin 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 recrudescent toxicity in renal failure patients.

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 whole body deficit of potassium. Therefore, serum samples for digoxin concentration should be obtained after DIGIFAB administration, if at all possible. Such measurements would establish the level of serum digoxin at the time of diagnosis of digitalis intoxication.

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parameters for DIGIFAB to those for Digibind®. 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). 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.

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 of 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

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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