

**DigiFab**<sup>™</sup>  
Digoxin Immune  
Fab (Ovine)

**Clinical Product Monograph**

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**EXECUTIVE SUMMARY**

For patients with serious digoxin toxicity, immunotherapy with digoxin-specific Fab fragments is the treatment of choice. DigiFab™ [Digoxin Immune Fab (Ovine)] is a new, digoxin-specific, antibody fragment preparation for the treatment of digoxin toxicity. Throughout its clinical development, DigiFab has been shown to be clinically interchangeable with another marketed product, Digibind®, which is indicated for the same conditions. The clinical claims, indications, and usage of DigiFab are outlined below.

Pharmacodynamic evidence supporting the efficacy of DigiFab in patients with digoxin toxicity includes a clinical response rate of 93%, in which the response was assessed by a constellation of factors including electrocardiogram (ECG) normalization. The response rate of DigiFab is similar to the response rate of Digibind.

Key concepts presented in this monograph include the following:

- Digoxin remains a widely prescribed drug for the treatment of cardiac conditions, especially in the elderly.
- Because it has a narrow therapeutic range, under certain circumstances, digoxin therapy may result in life-threatening toxicity.
- DigiFab and Digibind similarly bind and inactivate digoxin in healthy volunteers.
- DigiFab binds and inactivates digoxin and is effective in reversing signs and symptoms of digoxin toxicity in patients.
- DigiFab is indicated for the same conditions as Digibind (digoxin toxicity).
- The clinical claims and usage of DigiFab are identical to Digibind.
- No unexpected safety concerns were identified in DigiFab clinical studies.
- No clinically significant abnormal laboratory values have been attributed to DigiFab, and Human Anti-Sheep Antibody (HASA) was negative in all treated subjects who were tested.
- Dosing recommendations and administration of DigiFab are identical to Digibind.

**INTRODUCTION**

Digoxin remains a widely prescribed drug for the treatment of cardiac conditions, especially in the elderly. Because of its narrow therapeutic range, digoxin therapy may result in life-threatening toxicity either through overdose or via a chronic accumulation in the body during usual treatment. The latter occurs mainly in the elderly and those who have a reduced ability to excrete the drug from the body due to poor kidney function.<sup>1,2</sup>

The introduction of digoxin-specific Fab fragments has revolutionized the treatment of severe digoxin intoxication and has been welcomed as a safe method for prompt correction of a potentially life-threatening condition.<sup>3,4</sup> Numerous clinical studies have demonstrated that even refractory arrhythmias associated with dramatically elevated digoxin levels can be reversed within minutes after administration of digoxin immune ovine Fab fragments (ie, Digibind).<sup>5</sup>

DigiFab™ [Digoxin Immune Fab (Ovine)] is a new, digoxin-specific, antibody fragment preparation for the treatment of digoxin toxicity. The indications for DigiFab are the same as those for Digibind, as are the clinical claims and usage.

DigiFab has a well-defined mechanism of action in binding and thus reversing toxic symptoms of digoxin. Therefore, the Food and Drug Administration (FDA) concurred that clinical equivalence between DigiFab and Digibind would not need to be evaluated as long as the biochemical product characterization and pharmacokinetic/pharmacodynamic parameters were similar. Thus, the DigiFab clinical program was designed to demonstrate the clinical interchangeability of DigiFab and Digibind as evidenced by equally effective binding of serum free digoxin, and pharmacodynamic equivalence as evidenced by concomitant digoxin loss.<sup>6,7</sup>

This clinical monograph will review the factors contributing to digoxin toxicity and provide an overview of DigiFab clinical pharmacology, pharmacokinetics, safety, indications, usage, and dosing calculations.

## DIGOXIN AND DIGOXIN TOXICITY

### Digoxin Indications and Uses

Digoxin remains a widely prescribed drug for the treatment of cardiac conditions, especially in the elderly. The primary indications for digoxin are atrial fibrillation and heart failure. The cardiovascular effects of digoxin are quite complex and are due to a combination of mechanisms, including inactivation of the sodium-potassium pump, increase in peripheral vascular tone, and sensitization of baroreceptors. The net effect of digoxin on the heart is increased ectopic impulse formation with reduced conduction velocity.<sup>8</sup>

### Digoxin Toxicity

Because of its narrow therapeutic range, digoxin therapy may result in life-threatening toxicity either through acute overdose or via a chronic accumulation in the body during usual treatment. The latter occurs mainly in the elderly and those who have a reduced ability to excrete the drug from the body due to poor kidney function.<sup>1,2</sup> The elderly use approximately 80% of digitalis products; 25% of the population older than 85 years use digoxin. Importantly, the risk of an adverse event caused by digoxin toxicity increases significantly with advancing age—a person 85 years old or older is twice as likely to experience a digoxin-associated adverse event compared with patients aged 65 through 74 years.<sup>9</sup> Other risk factors for digoxin toxicity (**Table 1**)<sup>1,3,9</sup> include hypothyroidism, amyloidosis, and use of interacting drugs. Concomitant drug interactions can either be by direct alterations of digoxin pharmacokinetics or by interfering with digoxin pharmacodynamics.

The signs and symptoms of acute digoxin toxicity may differ from the signs and symptoms of chronic intoxication (**Table 2**).<sup>8,9,10</sup> Acute intoxication is characterized by nausea and vomiting, along with evidence of cardiotoxicity. Chronic toxicity may

Factor	Effect
Advanced age, coexistent disease	Decreased renal digoxin clearance Decreased volume of distribution Decreased lean body mass Decreased serum albumin Increased adipose tissue
Renal insufficiency	Decreased digoxin clearance
Hypoxia Chronic pulmonary disease Hypokalemia Hypomagnesemia Hypercalcemia Ischemic heart disease	Myocardium sensitized to effects, increased digoxin receptor binding
Hypothyroidism	Altered metabolism or elimination
Amyloidosis	Unknown
Drug Interactions	
β-adrenergic blockers	Increased atrioventricular node depression
Diuretics*	Hypokalemia, hypomagnesemia, hypercalcemia
Amphotericin B	Hypokalemia
β-agonists	Additive sympathetic stimulation
Quinidine Amiodarone HCl Verapamil HCl Propafenone HCl Spironolactone Propranolol Diphenoxylate HCl	Increased digoxin serum level

\*Thiazide diuretics

present with nonspecific symptoms, such as malaise and weakness and, rarely, visual disturbances. In many patients, the sole evidence may be the appearance of a new cardiac dysrhythmia (eg, premature ventricular contractions [PVCs], conduction block, paroxysmal atrial tachycardia [PAT] with block, junctional tachycardia, ventricular tachycardia).<sup>8</sup> It is beyond the scope of this monograph to describe in detail the cardiovascular manifestations of digoxin toxicity. For a recent review, see Ma et al, 2000.<sup>8</sup>

Parameter	Acute Digoxin Intoxication	Chronic Digoxin Intoxication
Symptoms	Nausea and vomiting most consistent findings; diarrhea occasionally observed	Anorexia, nausea, vomiting, headache, malaise, fatigue, weakness, drowsiness common; paresthesias, confusion, disorientation, aphasia, delirium, hallucinations, visual disturbances sometimes reported; convulsions rarely
ECG findings	ECG may indicate supraventricular arrhythmias, in general, with heart block and bradycardia most common; generally, ventricular arrhythmias rare	All types of arrhythmias have been reported; most common are: nonparoxysmal nodal tachycardia, atrial tachycardia with AV dissociation, bidirectional ventricular tachycardia
Potassium	Normal or increased, depending on magnitude of overdose and time course	Normal to decreased, depending on use of diuretics, nutritional status, and presence of other actors known to affect potassium levels
Serum digoxin	High levels always expected	Levels may be in therapeutic range but are usually elevated; borderline normal values may represent toxicity

### Management of Digoxin Toxicity

The key to successful treatment of digoxin toxicity is early recognition.<sup>3,8</sup> Patients who experience digoxin toxicity may require a range of supportive and adjunctive therapies. Patients with evidence of clinical deterioration and hemodynamic instability require aggressive treatment. As with any drug overdose, initial management includes airway protection and ventilatory support, and cardiovascular support with crystalloids, sympathomimetics (cautiously), and antiarrhythmic agents. Prevention of continued intestinal absorption of digoxin may be achieved with gastrointestinal decontamination and activated charcoal therapy. Frequent monitoring of the patient's ECG, vital signs, and serum electrolytes should also be performed.<sup>8,10,11</sup>

The introduction of digoxin-specific Fab fragments has revolutionized the treatment of severely toxic patients and has been welcomed as a safe method for prompt correction of a potentially lethal condition.<sup>3,4</sup> Numerous clinical studies have shown that even refractory arrhythmias associated with dramatically elevated glycoside levels can be reversed within minutes after administration of digoxin immune ovine Fab fragments (ie, DigiBind).<sup>5</sup>

**DIGIFAB™ CLINICAL PHARMACOLOGY**

DigiFab™ [Digoxin Immune Fab (Ovine)] is a sterile, purified, 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.<sup>7,12</sup>

**Mechanism of Action**

DigiFab has a greater affinity for digoxin (range,  $10^9$  to  $10^{10}$  M<sup>-1</sup>) than does digoxin for its sodium pump receptor, the presumed receptor responsible for its therapeutic and toxic effects. When administered intravenously to a patient with digoxin toxicity, DigiFab binds free digoxin and removes digoxin from within tissue. The digoxin-DigiFab complexes are sequestered in the extracellular fluid, thereby reducing cardiotoxicity. The complexes are then cleared by the kidney and reticuloendothelial system.<sup>7,12</sup>

**Clinical Pharmacokinetics**

The biodistribution and half-life of ovine Fab fragments have been studied previously in humans treated with a digoxin-specific ovine Fab fragment product (ie, Digibind).<sup>5,13-16</sup> In patients without renal insufficiency, digoxin-specific Fab fragments have a volume of distribution of approximately 0.4 L/kg, and are eliminated rapidly by renal and non-renal routes with a half-life of approximately 14-20 h and a

systemic clearance of 0.3 mL/min•kg.<sup>14-16</sup> The elimination half-life appears to be increased up to 10-fold in patients with renal impairment, although volume of distribution remains unaffected.<sup>16</sup> In a pharmacodynamic and pharmacokinetic comparative trial<sup>17</sup> (see **Review of DigiFab™ Clinical Studies**), the profiles of DigiFab and Digibind were similar, including similar volumes of distribution and elimination half life (**Table 3**).<sup>17</sup>

	Mean Value (± SD)	
	DigiFab (N=8)	Digibind (N=8)
Cl <sub>total</sub> (mL/min•kg)	0.4 (0.06)*	0.3 (0.06)
T <sub>1/2</sub> (h)	15.4 (3.8)†	23.2 (6.1)
C <sub>max</sub> (µg/mL)	12.5 (2.8)	13.0 (1.8)
V <sub>c</sub> (L/kg)	0.08 (0.02)	0.07 (0.01)
V <sub>d</sub> (L/kg)	0.3 (0.1)	0.4 (0.1)

\*P=0.0004  
 †P=0.008  
 Cl<sub>total</sub> = clearance; T<sub>1/2</sub> = half life; C<sub>max</sub> = maximum concentration;  
 V<sub>c</sub> = central compartment volume of distribution; V<sub>d</sub> = volume of distribution

**DIGIFAB™ CLINICAL STUDIES**

There have been two clinical trials conducted with DigiFab™ [Digoxin Immune Fab (Ovine)]: a pharmacokinetic and pharmacodynamic study of DigiFab as compared to Digibind in healthy volunteers, and a prospective multicenter study of the efficacy of DigiFab in patients presenting with life-threatening digoxin toxicity. Because of the unique pharmacology of DigiFab, both trials included clinical and pharmacokinetic assessments. In addition to Fab fragment concentrations, free and total digoxin concentrations were measured in the two trials and pharmacokinetic parameter estimates were performed using both non-compartmental and compartmental methods.<sup>7,12,18</sup>

**Pharmacokinetic and Pharmacodynamic Study**

In this randomized, controlled, parallel study,<sup>17</sup> 16 healthy subjects were given 1 mg of intravenous digoxin as a 5-minute bolus infusion, followed 2 hours later by an approximately equimolar intravenous neutralizing dose (76 mg) of either DigiFab (n=8) or Digibind (n=8). The primary objective of this study was to demonstrate that both Fab fragment products (DigiFab and Digibind) had comparable bioaffinity (*in vivo* binding) for digoxin. Prior to and following administration of digoxin, blood samples were collected at predetermined time intervals for 48 hours and urine samples were collected for 24 hours. The primary outcome measure was the serum level of free (unbound) digoxin as measured by area under the curve (AUC) from 2 hours to 48 hours. Secondary endpoints included pharmacokinetic parameters for total digoxin and ovine Fab fragments, and serial ECGs.

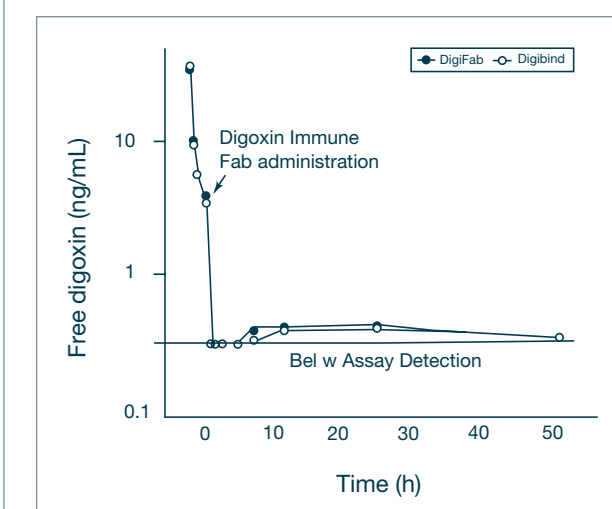
**Results**

In this study, all subjects were relatively young, Caucasian, and ranged from age 22 to 33. Both groups contained 4 women and 4 men and were well matched.

**Serum Free Digoxin**

Mean pre-Fab serum free digoxin levels were  $4.5 \pm 3.1$  ng/mL and  $4.0 \pm 0.35$  ng/mL for DigiFab and Digibind, respectively. Following Fab fragment administration, these values declined to below the limit of assay quantitation (0.3 ng/mL) for several hours in both groups. The AUCs were not statistically different between the DigiFab and Digibind groups ( $0.25 \pm 0.07$  ng/mL•h/kg and  $0.25 \pm 0.06$  ng/mL•h/kg, respectively). As shown in (**Figure 1**),<sup>17</sup> post-Fab portion of the curve clearly reflects similar behavior of free digoxin in response to both DigiFab and Digibind.

**Figure 1. Serum Free Digoxin Concentrations Versus Time in Healthy Volunteers.<sup>17</sup>**

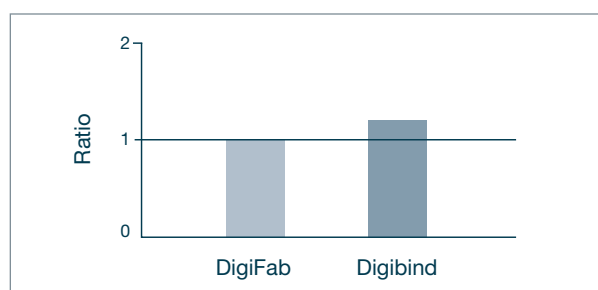


### Total Digoxin

Total serum digoxin  $C_{max}$  values immediately after digoxin infusion and after DigiFab/Digibind infusion were similar (DigiFab:  $45 \pm 14$  vs  $44 \pm 11$  ng/mL; Digibind:  $50 \pm 17$  vs  $41 \pm 9$  ng/mL), providing indirect evidence of equal bioaffinity for digoxin between the two products. This is because, immediately after digoxin is administered, digoxin is still contained within the central compartment and has not distributed into the tissues. Therefore, the total digoxin concentration after a 5-minute digoxin bolus theoretically represents the total body burden of digoxin within the central compartment. Following equimolar neutralizing doses of either DigiFab or Digibind, the equilibrium of digoxin concentrations is altered such that the concentration of digoxin in the central compartment increased. Hence, the total digoxin  $C_{max}$  values after a digoxin infusion, and before redistribution, should be very similar to the  $C_{max}$  values after Fab fragment infusion if complete digoxin neutralization has taken place. As shown in **Figure 2**,<sup>17</sup> mean pre/post DigiFab and Digibind ratios are approximately 1.0, reflecting complete digoxin neutralization.

Pharmacokinetic profiles also were similar for both products (see **Table 3**).<sup>17</sup> 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

**Figure 2. Ratio of Mean  $C_{max}$  Values of Total Digoxin Prior to and After Fab Fragment Administration in Healthy Volunteers Treated with DigiFab (N=8) and Digibind (N=8).**<sup>17</sup>



space.<sup>5,13-16</sup> Cumulative urinary excretion of digoxin was comparable for both products and exceeded 40% of the administered dose by 24 hours.

### DigiFab™ Efficacy Study

The DigiFab efficacy study<sup>18</sup> was a prospective, multicenter study designed to determine the pharmacokinetics, pharmacodynamics, and safety of DigiFab in patients with life-threatening digoxin toxicity.

### Methods

Patients were enrolled on the basis of digoxin ingestion plus one or more of the following: (1) serum potassium  $> 5.5$  mEq/L, (2) ECG changes consistent with hyperkalemia in the face of digoxin toxicity, (3) hemodynamic compromise associated with arrhythmias such as bradycardia, high-grade atrioventricular blockade, or extrasystole, (4) cardiovascular compromise requiring the use of catecholamines, atropine, or intravenous antiarrhythmics, (5) serum digoxin  $> 4.5$  ng/mL in a non-cardiac patient, (6) bradycardia  $< 40$  beats/min that is unresponsive to 1 mg of atropine sulfate or  $< 60$  beats/min in a patient with poor prognostic factors, (7) signs and symptoms of profound neurological abnormalities, or (8) known ingestion in a child of  $> 0.1$  mg/kg digoxin or a steady state serum level  $> 5$  ng/mL with clinical symptoms.

After initial evaluation (history, physical examination, ECG and the determination of baseline laboratory measurements) and informed consent, each enrolled patient received DigiFab in an amount calculated to be approximately equimolar to the total body burden of digoxin. If the amount ingested was unknown and digoxin concentrations unavailable, the initial dose in adults was 20 vials (the recommended empiric dose for Digibind). The protocol dosing for children was 10 vials initially, followed by an additional 10 vials at the physician's discretion; however, no children were enrolled in the study. Patients were closely monitored

in the hospital for at least 24 hours, and longer as required to evaluate safety and develop a reliable pharmacokinetic profile. Serum and urine were collected to assess free and total digoxin and total Fab fragment levels for the purposes of determining pharmacokinetic parameters of DigiFab and digoxin immediately prior to DigiFab administration and upon completion of DigiFab infusion at a series of time points. Serial ECGs, rhythm strips, vital signs, and electrolyte measurements were collected to determine the pharmacodynamic effects of DigiFab. Patients were monitored for adverse events throughout the study.

### Efficacy Measures

Because of the known mechanism of action for digoxin-specific Fab fragments in binding free digoxin in serum and extracellular fluid, the emphasis in the clinical evaluation of this investigational Fab fragment product was on assessment of digoxin binding. The primary efficacy parameter was reduction of free serum digoxin to less than 0.5 ng/mL at the end of DigiFab infusion. Results were compared to historical data for Digibind.

One secondary efficacy parameter was clinical therapeutic response, as measured by the percent of patients with resolution of digoxin-induced toxicity at 4 hours following DigiFab administration. Response to DigiFab was evaluated by the investigator and recorded at a number of assessment time points. Each evaluation included ECG and rhythm strip, vital signs, and electrolytes. Toxicity was judged to be *resolved* if the patient showed complete resolution of all signs and symptoms of digoxin toxicity within 4 hours of DigiFab treatment. Toxicity was judged to be *not resolved* if symptoms or signs of digoxin toxicity were still present.

Another secondary parameter was to characterize the pharmacokinetic disposition of DigiFab and free and total digoxin.

## Results

### Demographics

DigiFab patients (N=15) were primarily elderly Caucasian adults with digoxin toxicity caused mostly by chronic therapeutic dosing. Six (40%) patients were male and 9 (60%) were female. Mean age overall was 64 years. Digoxin ingestion was reported as chronic for 10 (67%) patients, suicidal for 5 (33%), acute on chronic for 3 (20%), acute for 1 (7%), and accidental for 1 (7%). Baseline digoxin levels ranged from 1.1 ng/mL to 13 ng/mL (median = 2.8 ng/mL). Nine of the 15 patients had abnormal renal function (baseline serum creatinine  $> 1.5$  mg/dL; range 1.8 to 6.3 mg/dL). Thirteen patients were under treatment with digoxin for underlying heart dysfunction: 5 for atrial fibrillation, 3 for congestive heart failure, 2 for a combination of both, 1 for a tachycardia, 1 for a combination of tachycardia and coronary artery disease, and 1 for an unclear reason.

### Efficacy Results

The primary outcome of the study was met in that serum free digoxin concentrations fell to undetectable levels following DigiFab administration in all 15 patients (**Table 4**). Maximum rebound free digoxin concentrations averaged  $1.4 (\pm 0.8)$  ng/mL, range 0.3 to 2.8 ng/mL. The average time to maximum free serum digoxin rebound was 15.1 hours (range, 6.5 to 36.5). All patients, as expected, had total serum digoxin increase 10- to 21-fold from baseline (see **Table 4**).

Complete resolution of the symptoms of digoxin toxicity was experienced by seven patients (47%) at 4 hours, nine (60%) at 6 hours, eleven (73%) at 8 hours, and fourteen (93%) at 20 hours (**Figure 3**).<sup>18</sup> Ten of the patients (67%) showed ECG improvement within 24 hours. The data for the proportion of patients who responded to treatment with DigiFab are similar to, and consistent with, historical data

**Table 4. Median Free and Total Digoxin Serum Levels in Patients with Digoxin Toxicity (N=15)**

Time (h)	Median Serum Digoxin Level (ng/mL)	
	Free	Total
Baseline	2.8	4.0
0	BLQ	48
0.5	BLQ	47.5
1.0	BLQ	46
2.0	BLQ	49
4.0	BLQ	47
6.0	0.3	38.5
8.0	0.5	32
12.0	0.8	20.5
16.0	0.75	14
20.0	0.85	11
24.0	0.95	14

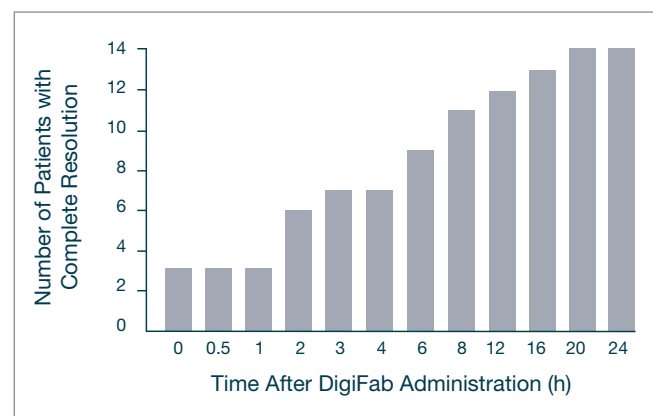
BLQ = below level of quantification

available for Digibind (Table 5).<sup>5,13,18</sup> Without any prospective expectation for statistical comparison of clinical responses, these results with DigiFab are consistent with the historical data for Digibind.

#### Pharmacokinetic Results

DigiFab clearance averaged  $0.4 \pm 0.2$  mL/min•kg and half-life averaged  $16.9 \pm 6.6$  hours—values that are similar to those obtained in the study of healthy volunteers, in which clearance and half-life were  $0.4 \pm 0.06$  mL/min•kg and  $15.4 \pm 3.8$  hours, respectively.  $C_{max}$  values varied greatly (range 8.2 to 118 µg/mL), reflecting the wide range of doses administered (see Table 6).<sup>18</sup>

**Figure 3. Cumulative Resolution of Digoxin Toxicity in Patients Treated with DigiFab (N=15)<sup>18</sup>**



**Table 5. Response to Digoxin Immune Ovine Fab Fragments for Digoxin Toxicity: DigiFab Versus Digibind<sup>5,13,18</sup>**

Measure	DigiFab (N=15)	Digibind* (N=717)†	Digibind* (N=148)‡
Resolved all signs and symptoms	14 (93%)	357 (50%)	119 (80%)
Partial improvement of signs and symptoms	NA	172 (24%)	14 (10%)
Complete OR partial response	14 (93%)	529 (74%)	133 (90%)
No response	1 (7%)	89 (12%)	15 (10%)
Response uncertain/not reported	NA	99 (14%)	NA

NA=not applicable

\*Historical data

†Hickey et al, 1991<sup>19</sup>

‡Antman et al, 1990<sup>7</sup>

**Table 6. Mean Pharmacokinetic Parameters for Patients Taking DigiFab for Digoxin Toxicity (N=15)<sup>18</sup>**

Parameter	Mean Value (± SD)
Cl (mL/min•kg)	0.4 (0.2)
$T_{1/2}$ (h)	16.9 (6.6)
$C_{max}$ (µg/mL)	30.2 (27.8)
$T_{max}$ (h)	1.2 (1.2)

Cl = clearance;  $T_{1/2}$  = elimination half-life;  $C_{max}$  = maximum concentration;  $T_{max}$  = time to maximum concentration

#### DigiFab™ Clinical Studies Summary and Conclusions

Data from clinical trials of DigiFab support its efficacy for the treatment of digoxin toxicity or overdose. Pharmacokinetic and pharmacodynamic evidence support the following observations:

- Equimolar doses of DigiFab and Digibind similarly bind and inactivate digoxin in healthy volunteers.
- DigiFab and Digibind have similar pharmacodynamic effects on the digoxin parameters that are relevant to the treatment of digoxin toxicity.
- DigiFab binds and inactivates digoxin in patients experiencing toxicity and is effective in reversing signs and symptoms of digoxin toxicity.

#### DIGIFAB™ SAFETY

The possible risks and adverse effects that follow the administration of heterologous animal proteins in humans include anaphylactic or anaphylactoid responses, or a delayed immune response or serum sickness. Because the Fab fragment of the antibody lacks the antigenic determinants of the Fc fragment, it should pose less of an immunogenic threat to patients than intact immunoglobulin molecules. Being monovalent, Fab fragments are also unlikely to form extended immune complexes with the antigen. Patients with known allergies to ovine Fab fragments would be at risk, as would individuals who have previously received intact ovine antibodies. As with Digibind, papain is used to cleave the whole antibody into Fab and Fc fragments, so traces of papain or inactivated papain residues may be present in DigiFab™ [Digoxin Immune Fab (Ovine)]. Patients with allergies to papain, chymopapain, other papaya extracts, or the pineapple enzyme bromelain, may, therefore, also be at risk of an allergic reaction to Fab fragments (ie, DigiFab, Digibind).<sup>7,12</sup>

#### Clinical Product Monograph

Patients receiving large doses of digoxin immune Fab fragments may experience infusion-related reactions (acute anaphylactoid). These may occur later than the acute anaphylactic type reaction, are dose- and rate-related and are due to non-specific degranulation of histamine from mast cells. Anaphylactoid reactions have been reported during the rapid infusion of heterologous proteins including immunoglobulins and monoclonal antibodies. In addition, acute or delayed hypersensitivity reactions may occur as the result of sensitization to ovine Fab fragments. Delayed reactions, such as serum sickness, are rarely associated with Fab fragment administration. Lacking the Fc component, cross-linking of proteins is unlikely to occur, thus serum sickness is mechanistically improbable.

#### Safety Parameters Measured

All patients and volunteers treated with DigiFab were evaluated for safety during hospitalization and at follow-up. Safety assessments were based on physical examination, vital signs (heart rate, blood pressure, respiration rate, temperature), ECG, clinical laboratory measures, and interviews for subjective complaints.

#### Vital Signs and Physical Examination

Vital sign changes noted in all trials were consistent with expected course of events. In general, blood pressure was reduced over time, heart rate increased over time and, in clinically unstable patients, respirations decreased with resolution of digoxin effects. No changes in temperature were noted.

For all trials, there were no abnormal physical findings other than those consistent with digoxin toxicity (eg, nausea, visual disturbances, somnolence). Healthy volunteers reported findings such as digoxin infusion-related phlebitis or redness.

### Adverse Events

No unexpected safety concerns have been identified in DigiFab clinical studies. The adverse event profile of DigiFab is consistent with historical experience for Digibind. HASA was negative in all subjects tested. Across all trials, no DigiFab infusion was terminated due to an adverse event, and no clinically or statistically significant abnormal laboratory values were attributed to DigiFab.

Six of 15 patients in the digoxin overdose study<sup>18</sup> had a total of 17 adverse experiences deemed “remotely associated” with DigiFab. Three of these events were deemed “severe”, all occurred in one patient and consisted of the following: pulmonary edema, bilateral pleural effusion and renal failure. After reviewing the case, it was determined that these events were likely due to the loss of digoxin inotropic support in combination with the patient’s underlying medical condition. The other remotely related events included constipation, nausea, vomiting, headache, and disorientation. Of 8 healthy volunteers who received DigiFab, only 2 experienced an adverse reaction that was considered to be associated with DigiFab.<sup>7,12</sup> The reactions were 1 episode of phlebitis of the infusion vein and 1 episode of moderate postural hypotension, which became mild prior to resolution.

### Safety Summary and Conclusions

The following safety conclusions were drawn from the DigiFab development program:

- No unexpected safety concerns were identified in DigiFab clinical studies.
- The majority of adverse reactions to DigiFab were mild or moderate in severity.
- The adverse event profile of DigiFab was similar to that of Digibind.
- No clinically or statistically significant abnormal laboratory values have been attributed to DigiFab.
- Post-treatment HASA was negative in all subjects tested.

## DIGIFAB™ INDICATIONS AND USAGE

### Indications

DigiFab™ [Digoxin Immune Fab (Ovine)] is indicated for the same conditions as Digibind—treatment of patients with life-threatening or potentially life-threatening digoxin toxicity or overdose (Table 7).<sup>12</sup> The clinical claims, indications, and usage are identical to Digibind. Since human experience is limited, and the consequences of repeated exposure are unknown, DigiFab is not indicated for milder cases of digoxin toxicity.

**Table 7. DigiFab Indications<sup>12</sup>**

- Known suicidal or accidental consumption of fatal doses of digoxin, including ingestion of 10 mg or more of digoxin in previously healthy adults, 4 mg (or more than 0.1 mg/kg) in previously healthy children, or ingestion causing steady state serum concentrations greater than 10 ng/mL
- Chronic ingestions causing steady-state serum digoxin concentrations exceeding 6 ng/mL in adults or 4 ng/mL in children
- Manifestations of life-threatening toxicity due to digoxin overdose, including severe ventricular arrhythmias (such as ventricular tachycardia or fibrillation), 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

### Contraindications

There are no known contraindications to the use of DigiFab.<sup>12</sup>

### Warnings

- Suicidal ingestion may involve more than one drug. Toxic effects of other drugs or poisons should not be overlooked, especially in cases where signs and symptoms of digoxin toxicity are not relieved by administration of DigiFab.
- The possible risks and side-effects that attend the administration of heterologous animal proteins in humans include anaphylactic and anaphylactoid

reactions, delayed allergic reactions and a possible febrile response to immune complexes formed by animal antibodies.<sup>20</sup> Because the Fab fragment of the antibody lacks the antigenic determinants of the Fc fragment, it should pose a reduced immunogenic threat to patients compared with intact immunoglobulin molecules. Being monovalent, DigiFab is also unlikely to form extended immune complexes with the antigen. Although no patient in the clinical studies of DigiFab has experienced a severe anaphylactic reaction, the possibility of an anaphylactic reaction should be considered. All patients should be informed of the possibility of an anaphylactic reaction and when receiving DigiFab should be carefully monitored for signs and symptoms of an acute allergic reaction (eg, urticaria, pruritus, erythema, angioedema, bronchospasm with wheezing or cough, stridor, laryngeal edema, hypotension, tachycardia) and treated immediately with appropriate emergency medical care (eg, oxygen, diphenhydramine, corticosteroids, volume expansion and airway management). If an anaphylactic reaction occurs during the infusion, DigiFab administration should be terminated at once and appropriate treatment administered. The need for epinephrine should be balanced against its potential risk in the setting of digoxin toxicity. Patients with known allergies to sheep protein would be particularly at risk for an anaphylactic reaction, as would individuals who have previously received intact ovine antibodies or ovine Fab fragments.

- Papain is used to cleave the whole antibody into Fab and Fc fragments, and trace amounts of papain or inactivated papain residues may be present in DigiFab. Patients with allergies to papain, chymopapain, other papaya extracts, or the pineapple enzyme bromelain may also be at risk for an allergic reaction to DigiFab. In addition,

## Clinical Product Monograph

it has been noted in the literature that some dust mite allergens and some latex allergens share antigenic structures with papain and patients with these allergies may be allergic to papain.<sup>21,22</sup> DigiFab should not be administered 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. Skin testing has not proved useful in predicting allergic response to Digibind.<sup>23</sup> Because of this, and because it may delay urgently needed therapy, skin testing was not performed during the clinical studies of DigiFab and is not suggested prior to dosing with this product.<sup>12</sup>

### Precautions

#### General

Standard management of digoxin intoxication includes withdrawal of the intoxicating agent, correction of electrolyte disturbances (especially hyperkalemia), acid-base imbalances, hypoxia and treatment of cardiac arrhythmias.

Massive digoxin intoxication can cause hyperkalemia; administration of potassium supplements in the setting of digoxin intoxication may be hazardous. After treatment with DigiFab, the serum potassium concentration may drop rapidly and must be monitored frequently, especially after the first several hours after DigiFab is given (see **Laboratory Tests**).<sup>12</sup>

Patients with poor cardiac function may deteriorate secondarily to the withdrawal of the inotropic action of digoxin by DigiFab. If needed, other intravenous inotropes such as dopamine, dobutamine or vasodilators can provide additional support. However, care must be taken not to aggravate the digoxin-induced rhythm disturbances. Re-digitalization should be postponed, 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.<sup>12</sup>

#### **Use of DigiFab™ in Renal Failure**

The elimination half-life of DigiFab in renal failure has not been clearly defined, although patients with renal dysfunction have been successfully treated with Digibind.<sup>13,24</sup> There is no evidence to suggest that the time-course of therapeutic effect is any different in these patients than in patients with normal renal function, but excretion of the Fab fragment-digoxin complex from the body is probably delayed. There is one case report of recurrence of atrioventricular block due to digoxin in a functionally anephric patient 10 days after its initial reversal by ovine Fab fragment therapy.<sup>24</sup> This clinical event persisted for more than a week. In patients that are functionally anephric, failure to clear the Fab fragment-digoxin complex from the blood by glomerular filtration and renal excretion may be anticipated. It is uncertain whether the failure to eliminate the Fab fragment-digoxin complex in severe renal impairment may lead to re-intoxication with digoxin following the release of previously bound digoxin into the blood. However, patients with severe renal failure who receive DigiFab for digoxin toxicity should be monitored 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.<sup>12,25</sup>

#### **Formation of Antibodies to DigiFab™**

Prior treatment with digoxin-specific ovine immune Fab fragments carries a theoretical risk of sensitization to ovine serum protein (see **Warnings**) and possible diminution of the efficacy of the drug due to the presence of human antibodies against ovine Fab fragments. Human antibodies to ovine Fab fragments have been reported in some patients receiving Digibind, however, to date, there have been no clinical reports of human anti-ovine immunoglobulin antibodies causing a reduction in binding of ovine

digoxin immune Fab fragments or neutralization response to ovine digoxin immune Fab fragments.<sup>12</sup>

#### **Laboratory Tests**

**DigiFab will interfere with digoxin immunoassay measurements in the same way that has been reported for Digibind.<sup>26,27</sup> 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 digoxin 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 digoxin dose. Patients should be closely monitored, including temperature, blood pressure, electrocardiogram, and potassium concentration, during and after administration of DigiFab. The total serum digoxin concentration may rise precipitously following administration of DigiFab, but the digoxin will be almost entirely bound to the Fab fragments and therefore not able to react with receptors in the body.<sup>12</sup>

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 DigiFab reverses the toxic effects of digoxin, 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. Potassium supplementation should then be given cautiously, when necessary.<sup>12</sup>

#### **Information for Patients**

Patients should be advised to contact their physician immediately if they experience any signs and symptoms of delayed allergic reactions or serum sickness (eg, rash, pruritus, urticaria) after hospital discharge.

#### **Drug Interactions**

Studies of drug interactions have not been conducted with DigiFab or Digibind.

#### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

#### **Pregnancy**

Both DigiFab and Digibind have been designated Pregnancy Category C. Animal reproduction studies have not been conducted with DigiFab or Digibind. It is also not known whether digoxin Fab fragments 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 clearly needed.

#### **Nursing Mothers**

It is not known whether Fab fragments are 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.

#### **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 **Precautions**).

#### **Pediatric Use**

Specific studies in pediatric patients have not been conducted and no pediatric patients were enrolled in the clinical studies of DigiFab. A similar digoxin ovine Fab fragment product (Digibind) has been used successfully to treat infants.<sup>5</sup> As with all drugs, the use of DigiFab in infants and children should be based on careful consideration of the benefits compared with the potential risks.

### Adverse Reactions

Based on experience with Digibind, the following adverse reactions could occur with the use of DigiFab:

- Exacerbation of low cardiac output states and congestive heart failure due to the withdrawal of inotropic effect of digoxin.
- Hypokalemia due to reactivation of the sodium-potassium ATPase (see **Laboratory Tests**).
- Rapid ventricular response in patients with atrial fibrillation due to withdrawal of the effects of digoxin on the atrioventricular node.
- Rare allergic reactions (see **Warnings**). Patients with a history of allergy, especially to antibiotics, appear to be at particular risk.<sup>23</sup>

### Overdosage

The maximum amount of DigiFab that can safely be administered in single or multiple doses has not been determined. Doses ranging from 1 to 40 vials (40 to 1600 mg) have been safely administered in controlled clinical trials of DigiFab. In addition, much higher doses (up to 13 g) of a similar immune Fab fragment product (CroFab™) have been safely administered to patients for crocotalid envenomations.<sup>28</sup>

## DIGIFAB™ DOSAGE AND ADMINISTRATION

### General Guidelines

Dosing and administration for DigiFab [Digoxin Immune Fab (Ovine)] are the same as that of Digibind. Doses will vary according to the amount of digoxin or digitoxin to be neutralized.

### DigiFab Dosing

Appropriate dosing of DigiFab is based on the total body burden of digoxin, which can be estimated using the patient's weight if the amount of drug ingested is known (as in an acute intoxication) or if the steady-state concentration is known.<sup>12</sup>

### Acute Ingestion of Unknown Amounts

If a patient presents with life-threatening digoxin toxicity caused by an acute ingestion and neither a serum digoxin concentration nor an estimated ingestion amount is available, 20 vials of DigiFab may be administered (NOTE: this is the same dosage recommended for empiric dosing of Digibind for acute digoxin toxicity). This amount should be adequate to treat most life-threatening overdoses in adults and children. However, in small children it is important to monitor for volume overload. In general, a larger dose of DigiFab has a faster onset of effect but may enhance the possibility of a febrile reaction. In such cases, 10 vials may be administered first with careful monitoring of the patient's response followed at the physician's discretion by 10 additional vials and continued monitoring. Failure of the patient to respond to DigiFab should alert the physician to the possibility that the clinical problem may not be caused by digoxin toxicity.<sup>12</sup>

### Toxicity During Chronic Therapy

In adult patients who are in acute distress or for whom a serum digoxin concentration is not available, 6 vials (240 mg) should be adequate to reverse

most cases of chronic toxicity. For infants and small children ( $\leq 20$  kg) on chronic therapy with digoxin and showing signs of toxicity, a single vial should be sufficient (NOTE: this is the same empiric dose recommended by Digibind for dosing of chronic digoxin toxicity).

### Dosage Calculation Based on Known or Estimated Dose of Digoxin

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<sup>12</sup>:

- Dosage calculation is the same method utilized when calculating Digibind doses.
- Inaccurate estimates of the amount of digoxin ingested or absorbed may occur due to non-steady state serum concentrations or due to digoxin assay limitations. Most serum digoxin assay kits are designed to measure concentrations  $< 5$  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 digoxin concentrations should be considered since Fab fragments 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 digoxin intoxication. If there is no response to an adequate dose of DigiFab, the diagnosis of digoxin toxicity should be questioned.

### For Ingestion of Known Amount

Each vial of DigiFab contains 40 mg of purified digoxin-specific Fab fragments, which will bind approximately 0.5 mg of digoxin (NOTE: each vial of Digibind contains 38 mg of purified digoxin-specific Fab fragments, which will also bind 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**).<sup>12</sup> Following an acute ingestion, total body load will be approximately equal to the amount ingested in milligrams for either digoxin capsules or digitoxin. If digoxin tablets were ingested, 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.

**Dosing Table 1**<sup>12</sup> 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 digoxin tablets or capsules is known. The dose of DigiFab (in number of vials) represented in **Dosing Table 1** can be approximated using the following formula:

Formula 1	
Dose =	$\frac{\text{total digitalis body load in mg}}{0.5 \text{ mg of digitalis bound/vial}}$
(in # of vials)	

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.

Number of Digoxin Tablets or Capsules Ingested*	Dose of DigiFab (Number of Vials) <sup>†</sup>
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

#### Calculations Based on Steady-State Serum Digoxin Concentrations

**Dosing Table 2<sup>12</sup>** 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 **Dosing Table 2** can be approximated using the following formula (**Formula 2**):

**Dosing Table 3<sup>12</sup>** gives dosage estimates in milligrams for **infants and small children** based on the steady-state serum digoxin concentration. The

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

\*Steady state levels do not occur until 6 hours post-digoxin dose  
v = vials

#### Formula 2

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

(in # of vials)

\*Steady state levels do not occur until 6 hours post-digoxin dose

dose of DigiFab represented in **Dosing 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**).<sup>12</sup> Since infants and small children can have much smaller dosage requirements, it is recommended that the 40 mg vial be reconstituted as directed and administered with a tuberculin syringe. 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 Dosing Table 3)

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

**Dosing Table 3. Infants and Small Children Dose Estimates of DigiFab (in mg) from Steady-State\* Serum Digoxin Concentration<sup>12</sup>**

Patient Weight (kg)	Serum Digoxin Concentration (ng/mL)						
	1	2	4	8	12	16	20
1	0.4 mg <sup>†</sup>	1 mg <sup>†</sup>	1.5 mg <sup>†</sup>	3 mg <sup>†</sup>	5 mg	6.5 mg	8 mg
3	1 mg <sup>†</sup>	2.5 mg <sup>†</sup>	5 mg	10 mg	14 mg	19 mg	24 mg
5	2 mg <sup>†</sup>	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

\*Steady state levels do not occur until 6 hours post-digoxin dose

<sup>†</sup>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 (**Formula 4**; 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).<sup>12</sup>

#### Formula 4

$$\text{Dose} = \frac{(\text{Serum digoxin concentration in ng/mL}) (\text{weight in kg})}{1000}$$

(in # of vials)

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.

#### Administration

Each vial of DigiFab should be reconstituted with 4 mL of Sterile Water for Injection USP and gently mixed to provide a solution containing approximately 10 mg/mL of digoxin immune Fab protein. The reconstituted product should be used promptly. If not used promptly, it may be stored under refrigeration (2 - 8°C) for up to 4 hours. The reconstituted product may be added to an appropriate volume of 0.9% sodium chloride for injection.<sup>12</sup>

DigiFab should be administered slowly as an intravenous infusion over at least 30 minutes. If infusion rate-related reactions occur, the infusion should be stopped and restarted at a slower rate. If cardiac arrest is imminent, DigiFab can be given by bolus injection. With bolus injection, an increased incidence of infusion-related reactions may be expected.<sup>12</sup>

For infants and small children who may require very small doses, it is recommended that the 40-mg vial be reconstituted as directed and administered 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.<sup>12</sup>

#### How supplied

DigiFab is supplied as a sterile, purified, lyophilized preparation. Each vial contains 40 mg of digoxin immune Fab protein, but contains no preservatives and is intended for one-time use.

Each box contains 1 vial of DigiFab.

The product should be stored at 2 - 8°C. Do not freeze. The product must be used within 4 hours after reconstitution.

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## PRESCRIBING INFORMATION

### DIGIFAB™ DIGOXIN IMMUNE FAB (OVINE)

#### DESCRIPTION

DigiFab™ (Digoxin Immune Fab (Ovine)) is a sterile, purified, 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-dicarbonylmethoxyamine (DDMA), a digoxin analogue which contains the functionally essential cyclopentapyrrophenanthrene 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 pepsin 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 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.

#### CLINICAL PHARMACOLOGY

##### Mechanism of Action

DigiFab has an affinity for digoxin in the range of  $10^6$  to  $10^{10}$  M<sup>-1</sup>, 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.

##### Animal Studies

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 another ovine digoxin-specific immune Fab, Digibind™ (manufactured by GlaxoSmithKline). Statistically equivalent responses were observed with both DigiFab and Digibind to the following variables: PTO index, heart rate, mean arterial pressure, ventilation, arterial blood gases, and serum potassium concentrations.

##### Clinical Pharmacokinetics

The pharmacokinetics 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 pharmacokinetic profiles of Fab were similar for both products.<sup>1</sup> 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).<sup>4</sup> 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.<sup>1</sup>

##### Clinical Studies

There have been two clinical trials conducted with DigiFab: a pharmacokinetic and pharmacodynamic study of DigiFab as compared to Digibind in healthy volunteers, and a prospective multi-center study of the efficacy of DigiFab in patients presenting with life-threatening digoxin toxicity.

The objective of the pharmacokinetic and pharmacodynamic study was to compare these parameters for DigiFab to those for Digibind.<sup>1</sup> This trial was conducted in healthy volunteers who were administered a 1 mg intravenous dose of digoxin, followed 2 hours later by an equimolar neutralizing dose of either DigiFab or Digibind. The pharmacokinetics of both digoxin and Fab were determined (see Clinical Pharmacokinetics for Fab pharmacokinetic parameters). The primary outcome measure 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. In this study, no patients developed a measurable immune response (human anti-ovine antibodies) to DigiFab.

The objective of the efficacy study was to demonstrate safety and also to determine the pharmacokinetics of, and clinical response to, DigiFab in patients. Results were compared to historical data on another U.S. marketed ovine digoxin immune Fab product, 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. This study was conducted in both the U.S. and in Finland.

The primary outcome of the study was met in that serum free digoxin concentrations in all patients fell to undetectable levels following DigiFab administration. This was an expected outcome that is consistent with data in the literature showing that free digoxin concentrations fall rapidly following administration of Digibind.<sup>2</sup> In the DigiFab trial, an independent blinded review of each patient's ECG showed that 10 of the 15 patients studied had ECG abnormalities that improved within 4 hours after the DigiFab infusion. The remaining 5 patients had ECG abnormalities that were unchanged from baseline throughout the 24-hour assessment period, and in one case through the 30-day follow up period. Although the reason for the lack of ECG resolution could not be clearly determined in all cases, it is possible that the ECG abnormalities

## Clinical Product Monograph

observed in these patients were not entirely due to digoxin toxicity, but rather to another underlying cardiac problem. Assessing all manifestations of toxicity, investigators classified 7 out of the 15 patients (47%) studied as having 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. The data for the proportion of patients who responded to treatment with DigiFab was similar to, and consistent with, historical data available for Digibind.<sup>2,3</sup> In this study, where 2/10 patients had serum available for human anti-ovine antibody determination, there was no measurable immune response.

#### INDICATIONS AND USAGE

DigiFab is indicated for the treatment of patients with life-threatening or potentially life-threatening digoxin toxicity or overdose. Although designed specifically to treat digoxin overdose, a product very similar to DigiFab (Digibind) has been used successfully to treat life-threatening digoxin overdose.<sup>2</sup> Since human experience is limited, and the consequences of repeated exposure are unknown, DigiFab is not indicated for milder cases of digitalis toxicity.

Clinical conditions requiring administration of DigiFab include:

- Known suicidal or accidental consumption of fatal doses of digoxin, including ingestion of 10 mg or more of digoxin in previously healthy adults, 4 mg (or more than 0.1 mg/kg) in previously healthy children, or ingestion causing steady state serum concentrations greater than 10 ng/mL.
- Chronic ingestions causing steady-state serum digoxin concentrations exceeding 6 ng/mL in adults or 4 ng/mL in children; and
- Manifestations of life-threatening toxicity due to digoxin overdose, including severe ventricular arrhythmias (such as ventricular tachycardia or fibrillation), 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.

#### CONTRAINDICATIONS

There are no known contraindications to the use of DigiFab.

#### WARNINGS

- Suicidal ingestion may involve 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.
- The possible risks and side-effects that attend the administration of heterologous animal proteins in humans include anaphylactic and anaphylactoid reactions, delayed allergic reactions and a possible febrile response to immune complexes formed by animal antibodies.<sup>5</sup> Since the Fab fragment of the antibody lacks the antigenic determinants of the Fc fragment, it should pose a reduced immunogenic threat to patients compared with intact immunoglobulin molecules. Being monovalent, the product is also unlikely to form extended immune complexes with the antigen. Although no patient in the clinical studies of DigiFab has experienced a severe anaphylactic reaction, the possibility of an anaphylactic reaction should be considered. All patients should be informed of the possibility of an anaphylactic reaction and when receiving DigiFab should be carefully monitored 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 treated immediately with appropriate emergency medical care (e.g., oxygen, diphenhydramine, corticosteroids, volume expansion and airway management). If an anaphylactic reaction occurs during the infusion, DigiFab administration should be terminated at once and appropriate treatment administered. The need for epinephrine should be balanced against its potential risk in the setting of digitalis toxicity. Patients with known allergies to sheep protein would be particularly at risk for an anaphylactic reaction, as would individuals who have previously received intact ovine antibodies or ovine Fab.
- Papain is used to cleave the whole antibody into Fab and Fc fragments, and trace amounts of papain or inactivated papain residues may be present in DigiFab. Patients with allergies to papain, chymopapain, other papaya extracts, or the pineapple enzyme bromelain may also be at risk for an allergic reaction to DigiFab. In addition, it has been noted in the literature that some dust mite allergens and some latex allergens share antigenic structures with papain and patients with these allergies may be allergic to papain.<sup>10</sup> DigiFab should not be administered 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. Skin testing has not proved useful in predicting allergic response to Digibind.<sup>11</sup> Because of this, and because it may delay urgently needed therapy, skin testing was not performed during the clinical studies of DigiFab and is not suggested prior to dosing with this product.

#### PRECAUTIONS

##### General

Standard management of digitalis intoxication includes withdrawal of the intoxicating agent, correction of electrolyte disturbances (especially hyperkalemia), acid-base imbalances, hypoxia and treatment of cardiac arrhythmias.

Massive digitalis intoxication can cause hyperkalemia; administration of potassium supplements in the setting of digitalis intoxication may be hazardous. After treatment with DigiFab, the serum potassium concentration may drop rapidly and must be monitored frequently, especially after the first several hours after DigiFab is given (see Laboratory Tests).

Patients with poor cardiac function may deteriorate secondary to the withdrawal of the inotropic action of digoxin by DigiFab. If needed, additional support can be provided by using other inotropic inotropes such as dopamine, dobutamine or vasodilators. However, care must be taken not to aggravate the digitalis induced rhythm disturbances. Re-digitalization should be postponed, 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.

**Use of DigiFab in Renal Failure**

The elimination half-life of DigiFab in renal failure has not been clearly defined, although patients with renal dysfunction have been successfully treated with DigiFab<sup>14,15</sup>. There is no evidence to suggest that the time-course of therapeutic effect is any different in these patients than in patients with normal renal function, but excretion of the Fab fragment-digoxin complex from the body is probably delayed. There is one case report of recurrence of atrioventricular block due to digoxin in a functionally anephric patient 10 days after its initial reversal by ovine Fab therapy<sup>16</sup>. This clinical event persisted for more than a week. In patients that are functionally anephric, failure to clear the Fab-digoxin complex from the blood by glomerular filtration and renal excretion may be anticipated. It is uncertain whether the failure to eliminate the Fab-digoxin complex in severe renal impairment may lead to re-intoxication with digoxin following the release of previously bound digoxin into the blood. However, patients with severe renal failure who receive DigiFab for digitalis toxicity should be monitored 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<sup>17</sup>.

**Formation of Antibodies to DigiFab**

Prior treatment with digoxin-specific ovine immune Fab carries a theoretical risk of sensitization to ovine serum protein (see WARNINGS) and possible diminution of the efficacy of the drug due to the presence of human antibodies against ovine Fab. Human antibodies to ovine Fab have been reported in some patients receiving DigiFab, however, 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.

**Laboratory Tests**

**DigiFab will interfere with digitalis immunoassay measurements in the same way that has been reported for Digibind<sup>14,15</sup>. 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. Patients should be closely monitored, including temperature, blood pressure, electrocardiogram, and potassium concentration, during and after administration of DigiFab. 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.

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.

**Information for Patients:**

Patients should be advised 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.

**Drug Interactions:**

Studies of drug interactions have not been conducted with DigiFab.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:**

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

**Pregnancy:**

Pregnancy Category C. 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 clearly needed.

**Nursing Mothers:**

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.

**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 PRECAUTIONS).

**Pediatric Use:**

Specific studies in pediatric patients have not been conducted and no pediatric patients were enrolled in the clinical studies of DigiFab. A similar digoxin ovine Fab product, Digibind, has been used successfully to treat infants<sup>18</sup>. As with all drugs, the use of DigiFab in infants and children should be based on careful consideration of the benefits compared with the potential risks.

**ADVERSE REACTIONS**

Based on experience with Digibind, the following adverse reactions could occur with the use of DigiFab:

- Exacerbation of low cardiac output states and congestive heart failure due to the withdrawal of inotropic effect of digitalis.
- Hypokalemia due to reactivation of the sodium-potassium ATPase (see Laboratory Tests).
- Rapid ventricular response in patients with atrial fibrillation due to withdrawal of the effects of digitalis on the atrioventricular node.
- Rare allergic reactions (see WARNINGS). Patients with a history of allergy, especially to antibiotics, appear to be at particular risk.<sup>11</sup>

In the clinical trials of DigiFab, 6 of 15 patients in the digoxin overdose study had a total of 17 adverse experiences, most were mild to moderate in nature and all were deemed "remotely associated" with DigiFab. Three events were deemed "severe", all occurred in one patient and consisted of the following: pulmonary edema, bilateral pleural effusion and renal failure. After reviewing the case, it was determined that these events were 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, only 2 experienced an adverse reaction that was considered to be associated with DigiFab. The reactions were 1 episode of plebitis of the infusion vein and 1 episode of moderate postural hypotension, which became mild prior to resolving.

**OVERDOSAGE**

The maximum amount of DigiFab that can safely be administered in single or multiple doses has not been determined.

**DOSAGE AND ADMINISTRATION**

**General Guidelines**

The dosage of DigiFab will vary according to the amount of digoxin or digitoxin to be neutralized.

**Dosage for Acute Ingestion of Unknown Amounts of Digoxin or Digitoxin**

If a patient presents with life-threatening digitalis toxicity caused by an acute ingestion and neither a serum digitalis concentration nor an estimated ingestion amount is available, 20 vials of DigiFab may be administered. This amount should be adequate to treat most life-threatening overdoses in adults and children. However, in small children it is important to monitor for volume overload. In general, a larger dose of DigiFab has a faster onset of effect but may enhance the possibility of a febrile reaction. In such cases, 10 vials may be administered first with careful monitoring of the patient's response followed at the physician's discretion by 10 additional vials and continued monitoring. 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 for Toxicity During Chronic Therapy**

For adult patients who are in acute distress or for whom a serum digoxin concentration is not available, 6 vials (240 mg) should be adequate to reverse most cases of toxicity. For infants and small children ( $\leq 20$  kg) on chronic therapy with digoxin and showing signs of toxicity a single vial should be sufficient.

**DOSAGE CALCULATION**

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.

**For Ingestion of Known Amount:**

Each vial of DigiFab contains 40 mg of purified digoxin-specific Fab, which will bind 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. If digoxin tablets were ingested, 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 =  $\frac{\text{total digitalis body in mg}}{0.5 \text{ mg of digitalis bound/vial}}$   
(in # of vials)

**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:**

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:

**Formula 2 (see Table 2)**

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

Table 3 gives dosage estimates in milligrams for infants and small 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). Since infants and small children can have much smaller dosage requirements, it is recommended that the 40 mg vial be reconstituted as directed and administered with a tuberculin syringe. 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)**

Dose (in mg) = Dose (in # of vials) (40 mg/vial)

**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**

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

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.

**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

**Table 3. Infants and Small 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

**Administration**

Each vial of DigiFab should be reconstituted with 4 mL of Sterile Water for Injection USP and gently mixed to provide a solution containing approximately 10 mg/mL of digoxin immune Fab protein. The reconstituted product should be used promptly. If not used immediately, it may be stored under refrigeration (2 - 8°C) for up to 4 hours. The reconstituted product may be added to an appropriate volume of 0.9% sodium chloride for injection.

DigiFab should be administered slowly as an intravenous infusion over at least 30 minutes. If infusion rate-related reactions occur, the infusion should be stopped and re-started at a slower rate. If cardiac arrest is imminent, DigiFab can be given by bolus injection. With bolus injection, an increased incidence of infusion-related reactions may be expected.

For infants and small children who may require very small doses, it is recommended that the 40-mg vial be reconstituted as directed and administered 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.

**HOW SUPPLIED**

DigiFab is supplied as a sterile, purified, lyophilized preparation. Each vial contains 40 mg of digoxin immune Fab protein, contains no preservatives and is intended for one time use.

Each box contains 1 vial of DigiFab.

**STORAGE CONDITIONS**

The product should be stored at 2 - 8°C (36° to 46° F). Do not freeze. The product must be used within 4 hours from reconstitution.

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