DigiFab™
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.1,2

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.3,4 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 (i.e., Digibind).5

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.6,7

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.
Clinical Product Monograph

Management of Digoxin Toxicity

The key to successful treatment of digoxin toxicity is early recognition.3,8 Patients who experience digoxin toxicity may require a range of supportive and adjunctive therapies. Patients with evidence of clinical deterioration and 

Table 1. Factors That Increase the Risk for Digoxin Toxicity

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age, congestive disease</td>
<td>Decreased renal digoxin clearance</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Decreased digoxin clearance</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Myocardium sensitized to effects, increased digoxin receptor binding</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Unknown</td>
</tr>
<tr>
<td>Drug interactions</td>
<td></td>
</tr>
<tr>
<td>B-adrenergic blockers</td>
<td>Increased atrioventricular node depression</td>
</tr>
<tr>
<td>Diuretics*</td>
<td>Hypokalemia, hypomagnesemia, hypocalcemia</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Hypokalemia</td>
</tr>
<tr>
<td>S-agonists</td>
<td>Additive sympathetic stimulation</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Increased digoxin serum level</td>
</tr>
</tbody>
</table>

*Phasic 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 rhythm (eg, premature ventricular contractions [PVCs], conduction block, paroxysmal atrial tachycardia, paroxysmal atrial tachycardia, PACs). 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, 2000.4

Table 2. Signs and Symptoms of Acute and Chronic Digoxin Toxicity

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

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.3,4 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).5
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-dicarboxymethylamine (DDMA), a digoxin analogue which contains the functionality essential cyclopentapeptidehydroxyphenylalanine/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.7,12

Mechanism of Action

DigiFab has a greater affinity for digoxin (range, 10^9 to 10^10 M^-1) 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.7,12

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).7,13-16 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.13,15 The elimination half-life appears to be increased up to 10-fold in patients with renal impairment, although volume of distribution remains unaffected.14 In a pharmacodynamic and pharmacokinetic comparative trial (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).17

Table 3. Pharmacokinetic Parameters for Digibind and DigiFab in Healthy Volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Digibind (N=8)</th>
<th>DigiFab (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl (mL/min/kg)</td>
<td>0.4 (0.06)*</td>
<td>0.3 (0.06)</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>23.2 (6.1)</td>
<td>15.4 (3.8)†</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>12.5 (3.6)</td>
<td>13.0 (1.8)</td>
</tr>
<tr>
<td>V1 (L/kg)</td>
<td>0.07 (0.02)</td>
<td>0.08 (0.02)</td>
</tr>
<tr>
<td>V2 (L/kg)</td>
<td>0.3 (0.1)</td>
<td>0.4 (0.1)</td>
</tr>
<tr>
<td>Vc (L/kg)</td>
<td>0.08 (0.02)</td>
<td>0.07 (0.02)</td>
</tr>
<tr>
<td>Vd (L/kg)</td>
<td>0.3 (0.1)</td>
<td>0.4 (0.1)</td>
</tr>
</tbody>
</table>

* P = 0.0004   † P = 0.008

Cltotal = clearance; T1/2 = half life; Cmax = maximum concentration; Vc = central compartment volume of distribution; Vd = 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.7,12

Pharmacokinetic and Pharmacodynamic Study

In this randomized, controlled, parallel study,17 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 of DigiFab or Digibind. 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) for several hours in both groups. The AUCs were not statistically different between the DigiFab and Digibind groups (0.25 ± 0.07 ng/mL•h/kg and 0.25 ± 0.06 ng/mL•h/kg, respectively). As shown in (Figure 1),17 post-Fab portion of the curve clearly reflects similar behavior of free digoxin in response to both DigiFab and Digibind.

Table 3. Pharmacokinetic Parameters for Digibind and DigiFab in Healthy Volunteers

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<tr>
<td>V1 (L/kg)</td>
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</tr>
<tr>
<td>V2 (L/kg)</td>
<td>0.3 (0.1)</td>
<td>0.4 (0.1)</td>
</tr>
<tr>
<td>Vc (L/kg)</td>
<td>0.08 (0.02)</td>
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<td>0.4 (0.1)</td>
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* P = 0.0004   † P = 0.008

Cltotal = clearance; T1/2 = half life; Cmax = maximum concentration; Vc = central compartment volume of distribution; Vd = volume of distribution.

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 ± 3.1 ng/mL and 4.0 ± 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 ± 0.07 ng/mL•h/kg and 0.25 ± 0.06 ng/mL•h/kg, respectively). As shown in (Figure 1),17 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.
Total Digoxin
Total serum digoxin Cmax values immediately after digoxin infusion and after DigiFab/Digibind infusion were similar (DigiFab: 45 ± 14 vs 44 ± 11 ng/mL; Digibind: 50 ± 17 vs 41 ± 9 ng/mL), providing indirect evidence of equal bioavailability 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 equiparal 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 Cmax values after a digoxin infusion, and before redistribution, should be very similar to the Cmax values after Fab fragment infusion if complete digoxin neutralization has taken place. As shown in Figure 2,17 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).18 The similar volumes of distribution (0.3 L/kg and 0.4 L/kg for DigiFab and Digibind, respectively) indicate considerable penetration of the circulation into the extravascular space.18,19 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 study18 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 bradyarrhythmias, high-grade atioventricular blockade, or tachyarrhythmias, (4) cardiovascular compromise requiring the use of catecholamines, atropine, or intravenous antidyrrhythmics, (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 strips, 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 (± 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).

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.
available for Digibind (Table 5). 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 ± 0.2 mL/min·kg and half-life averaged 16.9 ± 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 ± 0.06 mL/min·kg and 15.4 ± 3.8 hours, respectively. Cmax values varied greatly (range 8.2 to 118 µg/mL), reflecting the wide range of doses administered (see Table 6).

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

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Median Serum Digoxin Level (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Free</td>
</tr>
<tr>
<td>Baseline</td>
<td>2.8</td>
</tr>
<tr>
<td>0</td>
<td>BLQ</td>
</tr>
<tr>
<td>0.5</td>
<td>BLQ</td>
</tr>
<tr>
<td>1.0</td>
<td>BLQ</td>
</tr>
<tr>
<td>2.0</td>
<td>BLQ</td>
</tr>
<tr>
<td>4.0</td>
<td>BLQ</td>
</tr>
<tr>
<td>6.0</td>
<td>0.3</td>
</tr>
<tr>
<td>8.0</td>
<td>0.5</td>
</tr>
<tr>
<td>12.0</td>
<td>0.8</td>
</tr>
<tr>
<td>16.0</td>
<td>0.75</td>
</tr>
<tr>
<td>20.0</td>
<td>0.85</td>
</tr>
<tr>
<td>24.0</td>
<td>0.95</td>
</tr>
</tbody>
</table>

BLQ = below level of quantification

### Table 5. Response to Digoxin Immune Ovine Fab Fragments for Digoxin Toxicity: DigiFab Versus Digibind

<table>
<thead>
<tr>
<th>Measure</th>
<th>DigiFab (N=15)</th>
<th>Digibind* (N=717)</th>
<th>Digibind* (N=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolved all signs and symptoms</td>
<td>14 (93%)</td>
<td>357 (50%)</td>
<td>119 (80%)</td>
</tr>
<tr>
<td>Partial improvement of signs and symptoms</td>
<td>NA</td>
<td>172 (24%)</td>
<td>14 (10%)</td>
</tr>
<tr>
<td>Complete OR partial response</td>
<td>14 (83%)</td>
<td>529 (74%)</td>
<td>133 (90%)</td>
</tr>
<tr>
<td>No response</td>
<td>1 (7%)</td>
<td>89 (12%)</td>
<td>15 (10%)</td>
</tr>
<tr>
<td>Response uncertain/NA</td>
<td>NA</td>
<td>99 (14%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA=not applicable

### Table 6. Mean Pharmacokinetic Parameters for Patients Taking DigiFab for Digoxin Toxicity (N=15)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Value (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl (mL/min·kg)</td>
<td>0.4 (0.2)</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>16.9 (5.6)</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>30.2 (7.6)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.2 (0.3)</td>
</tr>
</tbody>
</table>

Cl = clearance; T1/2 = elimination half-life; Cmax = maximum concentration; Tmax = time to maximum concentration

### Table 5. Pharmacokinetic Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Value (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl (mL/min·kg)</td>
<td>0.4 (0.2)</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>16.9 (5.6)</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>30.2 (7.6)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.2 (0.3)</td>
</tr>
</tbody>
</table>
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 had a total of 17 adverse experiences 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 unrelated events included constipation, nausea, vomiting, headache, and disorientation. Of the 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 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).

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**

- 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 0.5 mg/kg) in previously healthy children, or ingestion causing steady state serum concentrations greater than 10 ng/mL.

- Chronic ingestion 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.

**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. 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 (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 digoxin toxicity. Patients with known allergies to sheep protein should receive DigiFab only if appropriate treatment is readily available. Skin testing has not proved useful in predicting allergic response to Digibind.

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**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.

**Indications**
DigiFab is indicated for the same conditions as Digibind—treatment of patients with life-threatening or potentially life-threatening digoxin toxicity or overdose (Table 7).

**Adverse Events**
No unexpected safety concerns have been identified in DigiFab clinical studies. 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.

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 unrelated events included constipation, nausea, vomiting, headache, and disorientation. Of the 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 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.

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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.14,20 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.21 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 administration of DigiFab may be appropriate in order to establish recrudescence of toxicity in renal failure patients.21-23

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.12

Laboratory Tests

DigiFab will interfere with digoxin immunonephelometry measurements in the same way that has been reported for Digibind.11,21-23 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.22

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 hypokalemia 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.12

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 or Digibind.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal carcinogenicity and reproduction studies have not been conducted with DigiFab or Digibind. It is also not known whether Fab fragments would affect fertility or cause abortion in 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. Therefore, the use of DigiFab in breastfeeding women should be based on careful consideration of the benefits compared with the potential risks.

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.12 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.  

**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 crotalid envenomations. 

**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.  

**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 feasible 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. 

**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 ≤ 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). 

**Dose 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:

- 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 does 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 digitoxin). 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.

**Dosing 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 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:

<table>
<thead>
<tr>
<th>Formula 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose =</td>
</tr>
<tr>
<td>(in # of vials)</td>
</tr>
</tbody>
</table>

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.
Dosing Table 1. Approximate Dose of DigiFab for Reversal of Single-Large Digitalis Overdose

<table>
<thead>
<tr>
<th>Number of Digitalis Tablets or Capsules Ingested</th>
<th>Dose of DigiFab (in # 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

Calculations Based on Steady-State Serum Digoxin Concentrations

Dosing 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 Dosing Table 2 can be approximated using the following formula (Formula 2):

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

Dosing 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 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). 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)

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

Dosing Table 4. Adults Dose Estimate of DigiFab (in mg) from Steady-State Serum Digoxin Concentration

<table>
<thead>
<tr>
<th>Patient Weight (kg)</th>
<th>Patient Serum Digoxin Concentration (ng/mL)</th>
<th>Dose of DigiFab (in mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.4 mg</td>
<td>1 mg</td>
</tr>
<tr>
<td>2</td>
<td>1 mg</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>3</td>
<td>2 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>4</td>
<td>4 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>5</td>
<td>8 mg</td>
<td>16 mg</td>
</tr>
</tbody>
</table>

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

Calculation based on Steady-State Digoxin Concentrations

The dose of Digibax for digoxin 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 digoxin as compared to digoxin.

Formula 4

\[
\text{Dose (in mg)} = \frac{\text{Serum digoxin concentration in ng/mL} \times \text{weight in kg}}{1000}
\]

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

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.

Digibax 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, Digibax 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

Digibax 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 Digibax.

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

REFERENCES

review of each patient's ECG showed that 10 of the 15 patients studied had ECG abnormalities that improved within 4 hours ...

2In the DigiFab trial, an independent blinded action of digoxin by DigiFab. If needed, additional support can be provided by using other intravenous inotropes such as ...

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.6

• Papain is used to cleave the whole antibody into Fab and Fc fragments, and trace amounts of 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...

• Suicidal ingestion may involve more than one drug. Toxic effects of other drugs or poisons ...

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There have been two clinical trials conducted with DigiFab: a pharmacokinetic and pharmaco-dynamic study of DigiFab as compared to Digibind in healthy volunteers, and a prospective clinical studies of digitalis intoxication includes withdrawal of the intoxicating agent, correction of electrolyte disturbances (especially hyperkalemia), acid-base imbalances, hypoxia and treatment of cardiac arrhythmias.

General management of digoxin intoxication includes withdrawal of the intoxicating agent, restoration of electrolytes, correction of acid-base disturbances, hypoxia and treatment of cardiac arrhythmias. In this study, none of the patients had severe hyperkalemia (adults: more than 6.0 mg/dL, children: more than 4.9 mg/dL).

The CRAR model is an algorithm that allows assessment of digoxin dose requirements for the treatment of digoxin intoxication. The CRAR model is based on the pharmacokinetics of digoxin and the individual patient's digoxin concentration-time profile. The CRAR model takes into account the patient's body weight, renal function, age, sex, and other factors that may affect the clearance of digoxin.

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Digoxin can cause a life-threatening elevation of serum potassium. This may lead to increased urinary excretion of potassium so that serum potassium may fall within 1-2 hours after DigiFab administration. Cautious potassium supplementation should then be provided when necessary.

**Dosage for Toxicity During Chronic Therapy**

If a patient presents with life-threatening digitalis toxicity caused by an acute ingestion and neither a serum digitalis nor DigiFab level is available, 6 vials (240 mg) should be adequate to reverse most cases of toxicity. For infants and small children who may require very small doses, it is recommended that the single vial should be reconstituted as directed and administered undiluted using a tuberculin syringe. For very small children, 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 contains three vials of 80 mg each (total of 240 mg) of digoxin-specific F(ab)2 fragments. Each DigiFab vial contains 8 mg of digoxin. After reconstitution, each vial contains 1 mg/mL of digoxin. DigiFab is supplied as a white powder, lyophilized preparation. Each unit contains 20 mg of digoxin in three vials: paptient, control, and chemotherapy for the time and dose for each patient. Each dose contains 1 mg of DigiFab.

**STORAGE CONDITIONS**

This product should be stored at 2°C to 8°C (36° to 46°F). Do not freeze. The product must be protected from light. It should be used as soon as possible.

**REFERENCES**