SUMMARY BASIS FOR APPROVAL
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-dicarboxymethoxylamine (DDMA), a digoxin analogue which contains the functionally essential cyclopentaperhydrophenanthrene:lactone ring moiety coupled to keyhole limpet hemocyanin (KLH). The sheep are pathogen free and are from prion-free herds in Australia. The final product is prepared by isolating the immunoglobulin fraction of the ovine serum, digesting it with papain and isolating the digoxin-specific Fab fragments by affinity chromatography. These antibody fragments have a molecular weight of approximately 46,000 Da.

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

The dating period or shelf-life of DigiFab is 36 months from the date of manufacture when stored at 2 - 8 "C. Two viral clearance process steps of dissimilar mode of action are employed in the manufacturing process. The product meets the following final container specifications:

Parameter	Specification
Potency (binding capacity)	≥10.5 µg digoxin/mg protein
Potency (binding avidity)	≥1x10^{9} M^{-1}
pH	4.5 – 5.5
Total protein	36 – 44 mg/vial
Molecular weight distribution	≥90% Fab
Residual moisture	<3.0% w/w
Mannitol	67 – 84 mg/vial
Papain	<0.8% w/w
Ovine albumin	<1.0% w/w
Ovine Fc	<1.0% w/w
acetonitrile	<41 µg/vial *
Mercury	None **

* meets ICH guideline Q3C for residual solvents
** at a limit of detection of 1.4 ppm (1.4 µg/ g)

Acetonitrile is a processing residual, while mercury in the form of thimerosal is used in the manufacture of the similar product Crotalidae Polyvalent Immune Fab (Ovine); it is assayed for only as a precautionary check.

CLINICAL PHARMACOLOGY

Mechanism of Action

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

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: PTQ 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.' 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).[2-6] The elimination half-life of 15-20 hours in patients with normal renal function appears to be increased up to IO fold in patients with renal impairment, although volume of distribution remains unaffected.[6]

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.' 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.[2] In the DigiFab trial, an independent blinded review of each patients 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 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 is similar to, and consistent with, historical data available for Digibind.[2,3] 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 digitoxin overdose[7]. 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'. 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[9,10] 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." 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 intravenous 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 Digibind[3,12]. 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'*. 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 recrudescent toxicity in renal failure patients[13].

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 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 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[14,15]. 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.[2] 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."

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 patients 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 phlebitis 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 Digitoxln

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 patients 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 (≤ 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

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

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

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

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

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

Calculations Based on Steadv-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)

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

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)

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

Calculation based on Steadv-State Diqitoxin 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 IO-fold decrease in the volume of distribution of digitoxin as compared to digoxin).

Formula 4

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

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

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*	2.5mg*	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.

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

REFERENCES

1. Ward, SB, Sjostrom L, and Ujhelyi MR. Comparison of the pharmacokinetics and *in vivo* binding affinity of DigiTAb versus Digibind. Therapeutic Drug Monitoring 2000; 22:599-607.

2. Antman EM, Wenger TL, Butler VP, Haber E, and Smith TW. Treatment of 150 cases of life threatening digitalis intoxication with digoxin-specific fab antibody fragments. *Circulation. 1990;* 81:1744-1 *752.*

3. Hickey AR, Wenger TL, Carpenter VP, et *a/.* Digoxin immune fab therapy in the management of digitalis intoxication: safety and efficacy results of an observational surveillance study. *J Am Coll Cardiol. 1991;* 17:590-98.

4. Wenger TL, Butler VP Jr, Haber E, Smith TW. Treatment of 63 severely digitalis-toxic patients with digoxin-specific antibody fragments. *J Am Coll Cardiol. 1985; 5* (supp.):118A-123A.

5. Schaumann W, Kaufmann B, Neubert P, Smolarz A. Kinetics of the fab fragments of digoxin antibodies and of bound digoxin in patients with severe digoxin intoxication. *Eur J C/in Pharmacol. 1986;* 30:527-33.

6. Ujhelyi MR, Robert S. Pharmacokinetic aspects of digoxin-specific fab therapy in the management of digitalis toxicity. *Clin Pharmacokinet. 1995;* 28(6):483-93.

7. Smith TW, Butler VP Jr, Haber E, Fozzard H, Marcus FI, Bremner WF, Schulman IC, Phillips A. Treatment of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments: Experience in 26 cases. N Engl J Med 1982; 307:1357-1362.

8. Kojis FG. Serum sickness and anaphylaxis: analysis of cases of 6,211 patients treated with horse serum for various infections. *Am J Dis Children. 1942;* 64:93-143, *313-350.*

9. Quarre JP, Lecomte J, Lauwers D, Gilbert P, Thiriaux J. Allergy to latex and papain. J Allergy Clin Immunol 1995; 95(4):922.

10. Baur X, Chen Z, Rozynek P, Düser D, Raulf-Heimsoth M. Cross-reacting IgE antibodies recognizing latex allergens, including Hev b 1, as well as papain. Allergy 1995; 50(7):604-609.

11. Kirkpatrick CHG, Digibind® Study Advisory Panel. Allergic histories and reactions of patients treated with digoxin immune fab (ovine) antibody. *Am J of Emer Med. 1991;* 9(supp.1):7-10.

12. Wenger TL. Experience with digoxin immune fab (ovine) in patients with renal impairment. *Am J of Emer* Med. 1991; 9(supp. 1):21-23.

13. Valdes R, Jortani SA. Monitoring of unbound digoxin in patients with antidigoxin antigen-binding fragments: a model for the future? *Clin Chem. 1998; 44(9):1883-l 885.*

14. Gibb I, Adams PC, Parnham AJ, Jennings K. Plasma digoxin: assay anomolies in fab-treated patients. *Br J Clin Pharmacol. 1983;* 16:445-447.

15. Rainey PM. Effects of digoxin immune fab (ovine) on digoxin immunoassay. *Am J Clin Pathol. 1989;* 92(6):779-786.

Rx only

Manufactured by: Protherics Inc.
Nashville, TN 37212

U.S. License No. 1575

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STN: 1039 10 (formerly PLA: 99-0947)

Title: DigiFab™ - Digoxin Immune Fab (Ovine)

Submit date: July 3 1, 1999

Sponsor: Protherics, Inc.

CLINICAL REVIEW

INTRODUCTION

This product is intended by its manufacturer to be very similar to Digibind, the licensed digoxin immune Fab (ovine). FDA concurred, early in clinical development, that this product has a well defined mechanism of action in binding and thus reversing toxic symptoms of digoxin, and thus that the development program would emphasize pharmacokinetic/pharmacodynamic aspects of treatment. Specifically, FDA concurred that clinical equivalence between the investigational Fab and Digibind would not need to be evaluated as long as the biochemical product characterization and pharmacokinetic/pharmacodynamic parameters were similar. Thus the original Phase 3 trial consisted of a single cohort with a primary endpoint of binding all free digoxin in the serum, compared to historical data for Digibind. Dosing was either calculated on the amount of digoxin ingested or on a serum measurement, or was up to 20 vials if that information was not available. When enrollment into the study turned out to be slow, the manufacturer proposed a normal volunteer study in which subjects would be dosed with 1 mg digoxin, followed 2 hours later with an exact stoichiometric neutralizing dose of either the investigational Fab or Digibind. FDA agreed that such a well-controlled study would provide comparative data, including reversal of ECG changes, between the two Fab products that could not practicably be obtained in the clinical setting of digoxin overdose, and thus further agreed to consider a marketing application with results of the normal volunteer study and data from a reduced number of overdose patients.

Pharmacokinetics/Pharmacodynamics

Normal Volunteer Studv

The normal volunteer study was single center, open label, randomized, and parallel rather than crossover design to avoid any possible interference by development of human anti-sheep antibodies (HASA). Intracutaneous and conjunctival testing was conducted to assess potential allergic reactions in this subject population, although not considered necessary in clinical situations of potentially life-threatening overdose. Sixteen subjects initially received an intravenous injection of 1 mg digoxin, followed 2 hours later by 76 mg of either investigational Fab,or Digibind. The primary endpoint was area under the curve (AUC) for free digoxin from 2 hours to the last measurement at 48 hours. Secondary endpoints included PK parameters for total digoxin and ovine Fab, and serial ECGs for interval analysis. All subjects were Caucasian, relatively young (22 - 33 years old), and were exactly balanced by gender. Following digoxin

infusion, serum digoxin concentration decreased approximately ten-fold in 2 hours. Over the same interval, all the subjects showed a decrease in T wave amplitude and most had a decrease in the corrected QT interval (QTc), but there were no consistent changes in the PR interval. Using a calculated index, PTQ = PR x T / QTc, values increased for all subjects in a rather uniform manner.

Following the 30-minute intravenous infusion of investigational Fab or Digibind, levels of free digoxin in serum were reduced to less than 0.3 ng/ml, the assay's limit of detection. In some of the subjects, there was a rebound in free digoxin in serum between 8 and 24 hours. The rebound occurred slightly earlier in the test cohort, with 4 subjects showing free digoxin at 8 hours compared to one subject in the Digibind control cohort. The areas under the rebound curves were not statistically different between the test and Digibind control cohorts.

Initially after infusion, Fab levels in serum decreased rapidly and similarly in the two cohorts, approximately ten-fold between 2 and 8 hours. Subsequently, the second phase of clearance was slightly faster in the test cohort, so that at 48 hours about 1% of the investigational Fab was present in serum compared to slightly more than 2% of Digibind. The AUCs from 2 hours to 4 (extrapolated) were significantly different, 41 :g/ml*hr for investigational Fab versus 60.5 :g/ml*hr for Digibind.

Total serum digoxin levels showed even greater divergence between cohorts than Fab levels, particularly in the 8- 12 hour time range, with 2 hour to 4 AUCs of 406 ng/ml*hr in the test cohort and 769 ng/ml*hr in the Digibind control cohort ($p < 0.0001$). However, excretion of digoxin into the urine was nearly the same 42% for both cohorts between 0 and 24 hours and thus the calculated renal clearance for digoxin is higher for the test cohort than for the Digibind control cohort, 20.8 ml/min versus 11.6 ml/min respectively.

PTQ indices were similar between cohorts between 0 and 2 hours (from digoxin injection to Fab injection) and between 2 and 4 hours. Thereafter, however, the PTQ indices fell more rapidly in the Digibind control cohort than in the test cohort, with the difference being statistically significant at 8 hours (but not statistically different at subsequent time points). These clinical differences could be due to the highly statistically significant differences in pharmacokinetics mentioned above. Renal clearance for digoxin is inversely related to the AUC for total digoxin, which in turn is inversely proportional to the volume of distribution for digoxin. Thus the higher AUC for total digoxin in the Digibind control cohort must mean that there is a lower volume of distribution for total digoxin in the Digibind control cohort. This is simply on the basis of mass balance -- since urine digoxin is the same between cohorts and total digoxin in the serum is higher in the Digibind control cohort, by inference there must be lower tissue digoxin in the Digibind control cohort. Lower tissue digoxin in the Digibind control cohort could explain the difference seen in PTQ indices between cohorts.

The sponsor did not measure the binding affinity for the Digibind control lot used in the normal volunteer study, so its precise value is not available. The package insert for Digibind indicates a lot release range for binding affinity to digoxin of 10^9/M to 10^{11}/M. The literature supports the concept that antibodies with affinity for digoxin > 10^9/M would be effective in reducing digoxin levels in cardiac tissue, where the binding affinity would be at least ten-fold lower. However,

the greater the discrepancy between antibody and cardiac tissue binding to digoxin, the more rapid would be the expected shift in equilibrium between the two compartments. Thus if the Digibind lot used in this clinical study had greater affinity for digoxin than the investigational Fab, the result could be a more rapid appearance in the serum in the Digibind control cohort. Although this result was actually observed in the trial, it should be noted that either Fab could be released at an affinity just over 10^9/M, so that the observed trial differences could have been reversed if the binding affinity of the investigational Fab lot had been greater than that of the Digibind lot. However, the manufacturing history of the investigational Fab indicates maximum binding affinities in the 10^{10}/M range, in contrast to maximum binding affinities for Digibind in the 10^{11}/M range. It is unclear whether a difference in PTQ indices at 8 hours post-treatment, such as observed in this carefully controlled, stoichiometrically balanced study, would ever be apparent in clinical practice

Digoxin Overdose Study

Dosing for the investigational Fab in the clinical study was based on known ingestion or measured serum levels of free digoxin, and was calculated to be stoichiometrically equivalent to ingested digoxin. Following infusion of investigational Fab, free digoxin in serum was at or below the assay's limit of detection (0.3 ng/ml) for all 15 patients. As is well described in the literature from clinical experience with Digibind, initial dosing by stoichiometric equivalence results in the clearance of substantial Fab that is not bound to digoxin, and thus there is a rebound of free digoxin into the serum. In this study, the mean free digoxin level in serum at baseline was 3.7 ng/ml; the mean time for reappearance of free digoxin in serum was 9.6 hours, the mean C_{max} was 1.4 ng/ml, and the mean T_{max} was 15.1 hours.

Efficacy

Digoxin Overdose Studv

Patients were enrolled on the basis of digoxin ingestion plus one or more of the following: (i) serum $K^+ > 5.5$ mEq/L, (ii) ECG changes consistent with hyperkalemia in the face of digoxin toxicity, (iii) hemodynamic compromise associated with arrhythmias such as bradycardia, high-grade atrio-ventricular blockade, or extrasystoles, (iv) cardiovascular compromise requiring the use of catecholamines, atropine, or intravenous antiarrhythmics, (v) serum digoxin > 4.5 ng/ml in a non-cardiac patient, (vi) bradycardia < 40 that is unresponsive to 1 mg of atropine sulfate or < 60 in a patient with poor prognostic factors, (vii) signs and symptoms of profound neurological abnormalities, or (viii) known ingestion in a child of > 0.1 mg/kg digoxin or a steady state serum level > 5 ng/ml with clinical symptoms.

Because of the known mechanism of action for digoxin-specific Fab in binding free digoxin in serum and extracellular fluid, the emphasis in the clinical evaluation of this investigational Fab was on assessment of digoxin binding. The primary endpoint was reduction of free digoxin in serum to less than 0.5 ng/ml at the end of Fab infusion. It was recognized during review of the

Phase 3 trial that secondary endpoints would be more informative; but since a comparative trial was not considered necessary by FDA, the trial could not practicably be designed with clinical responses as the primary endpoint, even on the basis of historical controls.

One secondary objective of the digoxin overdose study was to assess the clinical responses of patients at 4 hours post-dosing. FDA requested evaluation of the percentage ofpatients whose symptoms were completely resolved at 4 hours, since the licensing study for Digibind assessed complete resolution of digoxin toxicity at 4 hours. Enrollment was slower than anticipated, with the final report including data on 15 instead of 25 patients. Of these 15 patients, complete resolution of digoxin toxicity was experienced by seven (47%) at 4 hours, nine (60%) at 6 hours, 11 (73%) at 8 hours, and 14 (93%) at 20 hours, although only ten of the patients (67%) showed ECG improvement within 24 hours. By way of comparison, the published report of a multicenter trial for Digibind in 148 evaluable patients indicates that 80% resolved all signs and symptoms of digoxin toxicity with an additional 10% showing improvement, although the time to improvement was not provided. Since the published report does not provide details of ECG analysis, no comparison of ECG improvement can be made to the investigational Fab. In 80 patients in the Digibind trial for whom data were available on time to complete response, the time ranged from 0.5 to 6 hours, with "most" having a complete response by 4 hours. The median level of free digoxin in serum was higher in the Digibind trial at entry (8.0 ng/ml) than in the 15 patients under consideration here (4.1 ng/ml).

Most patients did not show complete resolution of their symptoms by 4 hours after treatment with the investigational Fab, although most had a complete response within 6 to 8 hours and the percentage who experienced complete resolution within 24 hours was high. The single patient who did not respond continued to exhibit ECG abnormalities out to the 30-day follow-up visit, which suggests that the ECG abnormalities were unrelated to digoxin overdose. Without any prospective expectation for statistical comparison of clinical responses, these data appear to be consistent with the historical data for Digibind. The subtle differences observed in the normal volunteer study, which may have been due to different affinities for the particular lots of investigational versus control Fab, would likely be obscured in any practicable equivalence trial by variability among overdose patients in the amount and distribution of digoxin overdose.

Safety

Normal Volunteer Study

Six (of 8) volunteers in the test cohort reported a total of 15 adverse events, and five (of 8) volunteers in the Digibind control cohort reported a total of 9 adverse events. Apparently by chance alone, there were 6 injection site adverse events (in 3 subjects) temporarily related to the digoxin infusion in the test cohort, but only 1 headache temporarily related to the digoxin infusion in the control cohort, leaving a total of 9 and 8 adverse events respectively in the test and control cohorts. Two subjects in each cohort reported influenza-like symptoms, starting at 1 and 3 days in the test cohort and 6 and 20 days in the control cohort. Of the remaining 7 events in the test cohort, those which occurred in the first study day were postural hypotension (2 events in the same subject, drug-related), mild phlebitis of the infusion vein (drug-related), and mild bloating. Of the remaining 6 events in the control cohort, those which occurred in the first study

day were mild nausea during the Digibind infusion (drug-related) and mild pain at the infusion site (at 21 hours).

Testing of serum collected at week 4 revealed no human anti-sheep antibody (HASA) response.

Digoxin Overdose Study

A total of 58 adverse events were reported in 15 patients, 30 of them in a single patient. Events that occurred in more than one patient were abdominal pain, constipation, nausea, worsening of congestive heart failure, hypokalemia, shortness of breath, and urinary tract infection. Exacerbation of congestive heart failure, due to withdrawal of the inotropic effects of digoxin, is a known risk mentioned in the package insert for Digibind. Hypokalemia is also a known risk of reactivation of the sodium/potassium ATPase (Digibind package insert). Of the 17 adverse events judged by the investigators to be remotely related to the study drug, ten occurred in the single patient mentioned above and included the only three severe adverse events judged to be remotely related (pulmonary edema on day 2 and 16, bilateral pleural effusion on day 7, and renal failure on day 14). This patient's digoxin toxicity resolved at 12 hours and she was later transferred out of intensive care, only to be readmitted on day 16. There was one death in the trial, attributed to lung cancer in the follow-up period.

Although 11 of 15 patients returned for the 4-week follow-up visit, in only two cases were HASA data obtained; both were below quantifiable limits.

The adverse events observed in this study appear to be consistent with adverse events that are associated with use of the licensed Digibind Fab.

Summary Basis of Approval Signature Page

8-30-01
Basil Golding, M.D. Date

Laurie Norwood 8/31/01
Laurie Norwood Date

8/30/01
Douglas Frazier Date

8/31/01
Pankaj Amin Date

8/31/01
Paul Aebersold Date

8/31/01
Jose Tavarez Date

8/30/01
Sheila Rawls Date

8/30/01
Mark Weinstein Date

8/30/01
Joan May Date