

PRODUCT MONOGRAPH

Pr **DigiFab**[®]

Digoxin Immune Fab (Ovine) for injection

Sterile lyophilized powder 40 mg/vial

Specific Antibody for Digoxin

BTG International Inc.
300 Four Falls Corporate Center
300 Conshohocken State Road, Suite 300
West Conshohocken, PA 19428

Date of Approval:
July 16, 2018

www.btgplc.com

Submission Control no.: 212414

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION	3
SUMMARY PRODUCT INFORMATION.....	3
DESCRIPTION.....	3
INDICATIONS AND CLINICAL USE	3
CONTRAINDICATIONS	4
WARNINGS AND PRECAUTIONS	4
ADVERSE REACTIONS	8
DRUG INTERACTIONS	9
DOSAGE AND ADMINISTRATION	10
OVERDOSAGE	15
ACTION AND CLINICAL PHARMACOLOGY	15
STORAGE AND STABILITY	15
SPECIAL HANDLING INSTRUCTIONS.....	15
DOSAGE FORMS, COMPOSITION AND PACKAGING	15
PART II: SCIENTIFIC INFORMATION	16
PHARMACEUTICAL INFORMATION.....	16
CLINICAL TRIALS	16
DETAILED PHARMACOLOGY	19
MICROBIOLOGY	19
TOXICOLOGY	20
REFERENCES	20
PART III: CONSUMER INFORMATION	22

DIGIFAB[®]
Digoxin Immune Fab (Ovine)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Sterile lyophilized powder/40 mg of digoxin-specific Fab fragments	Mannitol and sodium acetate

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

Each vial of DigiFab[®], which will bind approximately 0.5 mg digoxin, contains 40 mg of digoxin immune Fab, 75 mg (approx) of mannitol USP, and 2 mg (approx) sodium acetate USP as a buffering agent. The product contains no preservatives and is intended for intravenous administration after reconstitution with 4 mL of Sterile Water for Injection USP.

INDICATIONS AND CLINICAL USE

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[®], manufactured by GlaxoSmithKline) has been used successfully to treat life-threatening digitoxin overdose(1). Since human experience is limited, and the consequences of repeated exposure are unknown, DigiFab[®] is not indicated for milder cases of digoxin toxicity.

Clinical conditions in which DigiFab[®] may be used 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 AND PRECAUTIONS

General

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 adverse reactions produced by the administration of heterologous animal proteins to humans include anaphylactic and anaphylactoid reactions, delayed allergic reactions and a possible febrile response to immune complexes formed by animal antibodies(2). 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 digoxin toxicity. Patients with known allergies

to sheep protein would be particularly at risk for an anaphylactic reaction, as would individuals who have previously received intact ovine antibodies or ovine Fab.

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(3;4). 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[®](5). 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.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

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

Cardiovascular

Patients with intrinsically poor cardiac function may deteriorate from withdrawal of the inotropic action of digoxin. When needed, additional support can be provided by use of intravenous inotropes, such as dopamine or dobutamine, or vasodilators. One must be careful in using catecholamines not to aggravate digoxin-induced toxic rhythm disturbances. Clearly, other types of digitalis glycosides should not be used in this setting. Redigitalization should be postponed, if possible, until the Fab fragments have been eliminated from the body, which may require several days. Patients with impaired renal function may require a week or longer (see WARNINGS AND PRECAUTIONS; Renal section).

Dependence/Tolerance

As DigiFab[®] is administered acutely in a health care facility, and is not expected to be given more than one time, physical or psychological dependence or tolerance is not expected to occur.

Endocrine and Metabolism

Massive digoxin intoxication can cause hyperkalemia; administration of potassium supplements in the setting of massive intoxication may be hazardous (see WARNINGS AND PRECAUTIONS; Monitoring and Laboratory Tests section). After treatment with DigiFab[®], the serum potassium concentration may drop rapidly and must be monitored frequently, especially during the first several hours after DigiFab[®] is given (see WARNINGS AND PRECAUTIONS; Monitoring and Laboratory Tests section).

Immune/Sensitivity/Resistance

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

Renal

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[®] (6;7). 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 Digibind[®] (7). 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 digoxin toxicity should be monitored for a prolonged period for possible recurrence of toxicity. Monitoring of free (unbound) digoxin concentrations after the administration may be appropriate in order to establish recrudescence toxicity in renal failure patients (8).

Skin

Acute or delayed allergic reactions can occur with the use of DigiFab[®] and may manifest as pruritic or urticarial rash (see WARNINGS AND PRECAUTIONS; General section). In addition, phlebitis during infusion can occur and was reported in one subject during clinical studies (see ADVERSE REACTIONS).

Special Populations

Pregnant Women

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. There is very limited information on the use of another ovine Fab product, the pit viper antivenom, CroFab, in pregnant women. In two cases reported in the literature, pregnant women were given CroFab with no deleterious effects to the mother or developing fetus (9;10)

Nursing Women

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.

Pediatrics

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(11). 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.

Geriatrics

Specific studies in elderly patients have not been conducted. The average age of 15 patients given DigiFab[®] for digoxin toxicity in one clinical study 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 to suggest that the efficacy of DigiFab[®] would be altered due to advanced age alone, however elderly patients are more likely to have impaired renal function and therefore should be monitored more closely for recurrent toxicity (see WARNINGS AND PRECAUTIONS; Renal section).

Monitoring and Laboratory Tests

DigiFab[®] will interfere with digoxin immunoassay measurements in the same way that has been reported for Digibind[®](12;13). 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 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.

Ability to perform tasks that require judgment, motor or cognitive skills

Visual or cognitive impairment has not been reported with the use of DigiFab®.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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 WARNINGS AND PRECAUTIONS; Monitoring and Laboratory Tests section).
- 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 AND PRECAUTIONS; General section). Patients with a history of allergy, especially to antibiotics, appear to be at particular risk(5).

Clinical Trial Adverse Drug Reactions

Because clinical studies are conducted under very specific conditions, the adverse drug reaction rates observed in clinical studies may not reflect the rates observed in practice and should not be compared to the rates in clinical studies of other similar drugs. Adverse drug reaction information from clinical studies is useful for identifying the types of adverse drug reactions that might occur in practice and for approximating how likely they are to occur.

There have been two clinical studies conducted with DigiFab®. A total of 23 subjects received DigiFab® with doses ranging from 1 vial (40 mg) to 20 vials (800 mg). In one study, of patients with digoxin toxicity, 6 of 15 patients had a total of 17 adverse events; most of these adverse events were mild to moderate in nature and all were deemed "remotely associated" with DigiFab®. Three events were deemed "severe", all occurred in one patient and consisted of the following: pulmonary edema, bilateral pleural effusion and renal failure. After reviewing the case, it was determined that these events were likely due to the loss of digoxin inotropic support in combination with the patient's underlying medical condition. In a second study where 8 healthy subjects received 76 mg of DigiFab® 2 hours following a 1 mg dose of digoxin, only 2 subjects experienced an adverse event that was considered to be associated with DigiFab®. The adverse events were 1 episode of phlebitis of the infusion vein and 1 episode of moderate postural hypotension, which became mild prior to resolving.

A summary of the adverse events reported in clinical trials TAb007-01 (n=15) and TAb007-02 (n=8) is provided in Table 1.

Table 1 Adverse Events In Clinical Trials

System Organ Class	Frequency^a	Percentage	Undesirable Effect
Metabolism and Nutrition Disorders	Common	8.7% 4.3%	Hypokalaemia Hyperkalaemia
Nervous System Disorders	Common	4.3%	Headache Confusional state
Gastrointestinal Disorders	Common	4.3%	Nausea Vomiting Diarrhoea Constipation Abdominal distension Abdominal Pain
Cardiac Disorders	Common	8.7% 4.3%	Cardiac failure Atrial Fibrillation Chest pain
Vascular Disorders	Common	8.7% 4.3%	Orthostatic Hypotension Hypotension
Musculoskeletal and connective tissue disorders	Common	8.7 %	Influenza-like illness
Renal and urinary disorders	Common	4.3%	Renal Failure
General disorders and administration site conditions	Common	4.3%	Fatigue Infusion site phlebitis

^a Adverse reactions are presented by system organ class in order of decreasing frequency. Frequencies of patients experiencing an adverse event are defined as follows:

Very Common = >10%.

Common = 1 to 10%

Uncommon = 0.1 to 1%

Rare = 0.01 to 0.1%

Very Rare = 0.001 to 0.01%

Post-market Adverse Drug Reactions

Since 2001, there has been one report each of arrhythmia, bradycardia and palpitations and one report each of hyperkalemia, creatinine increased, bone density decreased, and blood urea increased.

DRUG INTERACTIONS

Drug-Drug, Drug-Food, and Drug-Herb Interactions

Interactions with other drugs, food or herbs have not been established with DigiFab[®].

Drug-Laboratory Test Interactions

DigiFab[®] will interfere with digoxin immunoassay measurements in the same way that has been reported for Digibind[®](12;13). Thus, standard serum digoxin concentration measurements may be clinically misleading until the Fab fragments are eliminated from the body (see WARNINGS AND PRECAUTIONS; Monitoring and Laboratory Tests section).

DOSAGE AND ADMINISTRATION

Dosing Considerations

The dosage of DigiFab[®] will vary according to the amount of digoxin or digitoxin to be neutralized. The average dose used during clinical testing was 4 vials.

Recommended Dose and Dosage Adjustments

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

If a patient presents with life-threatening digoxin toxicity caused by an acute ingestion and neither a serum digoxin concentration nor an estimate of the amount ingestion is available, 20 vials of DigiFab[®] may be administered. This amount should be adequate to treat most life threatening overdoses in adults and children. However, in small children it is important to monitor for volume overload. In general, a larger dose of DigiFab[®] has a faster onset of effect but may enhance the possibility of a febrile reaction. In such cases, 10 vials may be administered first with careful monitoring of the patient's response followed, at the physician's discretion, by 10 additional vials and continued monitoring. Failure of the patient to respond to DigiFab[®] should alert the physician to the possibility that the clinical problem may not be caused by digoxin 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. The following guidelines should be considered when using the dose calculation methods provided:

- 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 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 digoxin 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 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, 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 2 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, and their strength, is known. The dose of DigiFab[®] (in number of vials) represented in Table 2 can be approximated using the following formula:

Formula 1:

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

Table 2. Approximate Dose of DigiFab® for Reversal of a Single Large Digoxin Overdose

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

^a 0.25 mg tablets with 80% bioavailability or 0.2 mg capsules with 100% bioavailability

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

Calculations Based on Steady-State Serum Digoxin Concentrations:

Table 3 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 3 can be approximated using the following formula:

Formula 2 (see Table 3):

Calculation with digoxin in ng/mL:

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

Calculation with digoxin in nmol/L (S.I. units):

$$\text{Dose (in \# of vials)} = \frac{(\text{Serum digoxin concentration in nmol/L} \times 0.781) (\text{weight in kg})}{100}$$

Table 4 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.

Table 3. 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

Formula 3 (see Table 4):

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

Table 4. 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 ^a	1 mg ^a	1.5 mg ^a	3 mg ^a	5 mg	6.5 mg	8 mg
3	1 mg ^a	2.5mg ^a	5 mg	10 mg	14 mg	19 mg	24 mg
5	2 mg ^a	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

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

Calculation Based on Steady-State Digitoxin Concentrations:

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

Formula 4:

Calculation with digitoxin in ng/mL:

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

Calculation with digitoxin in nmol/L (S.I. units):

$$\text{Dose (in \# of vials)} = \frac{(\text{Serum digitoxin concentration in nmol/L} \times 0.765) (\text{weight in kg})}{1000}$$

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

Administration

Reconstitution:

Parenteral Products:

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
40 mg	4 mL	4 mL	10 mg/mL

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.

OVERDOSAGE

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

ACTION AND 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.

Pharmacokinetics

The pharmacokinetics of DigiFab[®] have been assessed in a randomized and controlled study of DigiFab[®] and Digibind[®] (comparator Fab product for the treatment of digoxin toxicity). Sixteen healthy subjects were given 1 mg of digoxin intravenously, followed by an approximately equimolar neutralizing dose of either DigiFab[®] (n=8) or Digibind[®] (n=8). The pharmacokinetic profiles of the two Fab products were similar(14). The volumes of distribution, which were similar (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)(6;11;15-17). The elimination half-life of 15-20 hours in patients with normal renal function appears to be increased by up to 10-fold in patients with renal impairment, although the volume of distribution remains unaffected(17).

STORAGE AND STABILITY

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

SPECIAL HANDLING INSTRUCTIONS

Not applicable

DOSAGE FORMS, COMPOSITION AND PACKAGING

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[®].

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Digoxin Immune Fab (Ovine)

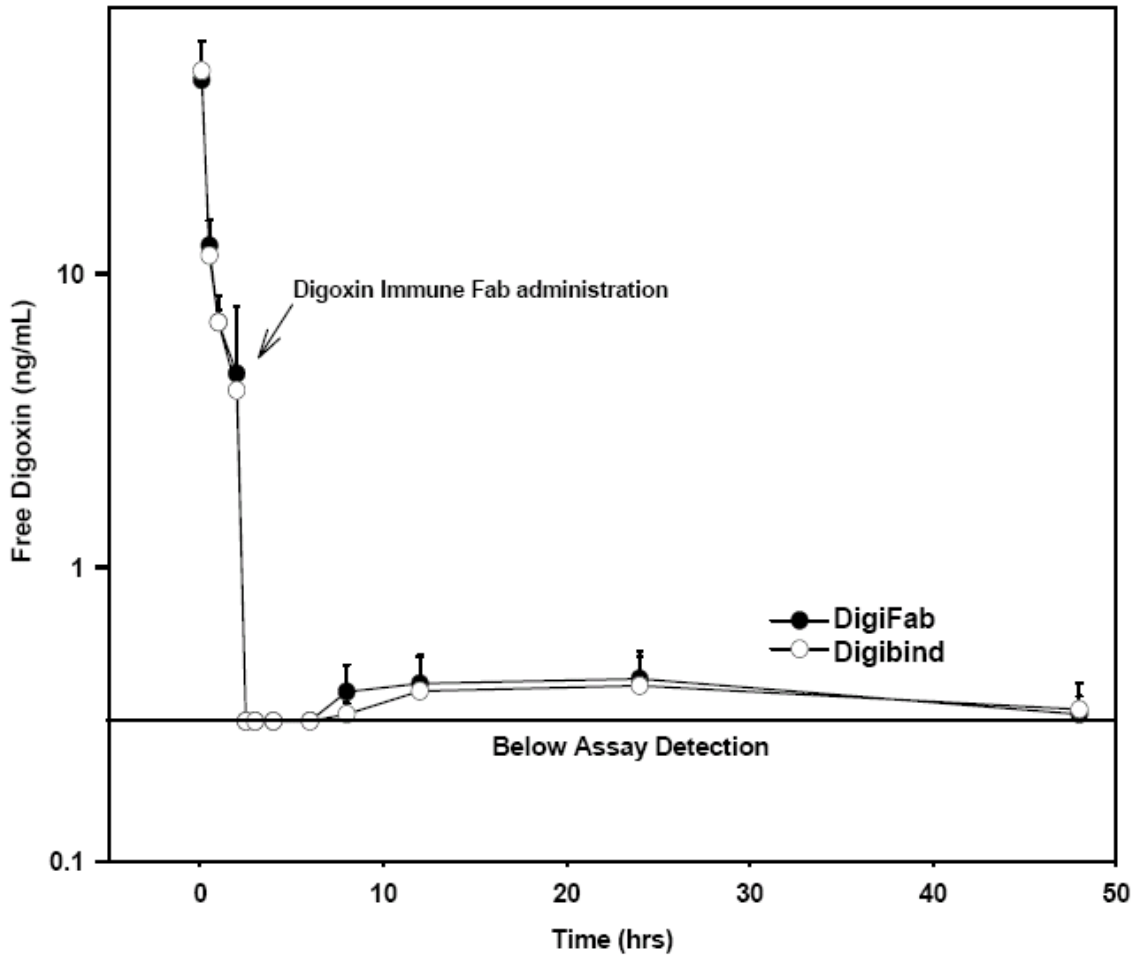
Molecular weight: approximately 46,000 Da

CLINICAL TRIALS

There have been two clinical studies conducted with DigiFab[®], Digoxin Immune Fab (Ovine): a pharmacokinetic and pharmacodynamic study of DigiFab[®] compared to Digibind[®] in healthy subjects, 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 DigiFab[®] to Digibind[®]. The study was conducted in healthy subjects (see Table 1 for subject demographics) 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 DETAILED PHARMACOLOGY). 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 (0.3 ng/mL) for several hours after Fab administration (Figure 1). 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.

Figure 1. Serum Concentration Versus Time for Free Digoxin



The objective of the patient study was to demonstrate reduction of serum free digoxin concentrations, safety, pharmacokinetics, and clinical response to DigiFab[®] in patients with digoxin toxicity (see Table 1 for patient demographics). Results were compared to historical data on another 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 serum concentrations of digoxin at the time of admission. This study was conducted in the U.S. and 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[®](11). In the DigiFab[®] study, an independent blinded review of each patient's ECG showed that 10 of the 15 patients studied had ECG abnormalities that improved within 4 hours after the DigiFab[®] infusion, although 4 of these 10

patients had ECG abnormalities that worsened within 24 hours of their initial improvement, and in one case through the 30-day follow up period. Although the reason for the lack of resolution of ECG abnormalities 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. Based on an assessment of 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 their digoxin toxicity resolved 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[®] (Table 2).(6;11)

Table 1. Summary of Subject Demographics for Clinical Studies of DigiFab[®]

Study number	Study design	Dosage, route of administration and duration	Study subjects	Mean age (Range)	Gender
TA007-01	Open-label, multicenter, historical control	Dosage of DigiFab [®] calculated based on estimated body load of digoxin, intravenous, one time dose	n= 15	64 (40 – 85)	Male: 6 (40%) Female: 9 (60%)
TA007-02	Open-label, single center, randomized, parallel active control	1 mg dose of digoxin, followed 2 hours later by 76 mg of either DigiFab [®] or Digibind [®] , intravenous, one time dose	N = 16 (8 subjects per group)	27 (22 – 33)	Male: 8 (50%) Female: 8 (50%) (4 of each per group)

Table 2. Patient Response to Digoxin Fab Treatment for Digoxin Toxicity

	DigiFab (n=15)	Hickey Study (n=717)	Antman Study (n=148)
Resolved All Signs & Symptoms	14 (93%)	357 (50%)	119 (80%)
Partial Improvement of Signs & Symptoms	Not Applicable	172 (24%)	14 (10%)
Complete or Partial Response	14 (93%)	529 (74%)	133 (90%)
No Response	1 (7%)	89 (12%)	15 (10%)
Response Uncertain/Not Reported	Not Applicable	99 (14%)	Not Applicable

DETAILED PHARMACOLOGY**Animal Studies**

A 4-arm comparison study was conducted in healthy male Sprague Dawley rats (n=40, 10 per group). Animals were randomly assigned to receive DigiFab[®], Digibind[®], nonspecific Fab (protein control), or a saline/sorbitol solution (excipient control). DigiFab[®] and Digibind[®] were administered in equimolar doses sufficient to neutralize a 1 mg/kg dose of digoxin. In this study the physiologic changes produced by toxic serum concentrations of digoxin were ameliorated rapidly by the administration of both DigiFab[®] and Digibind[®]. Statistically equivalent responses were observed with both DigiFab[®] and Digibind[®] to the following variables: PTQ index, heart rate, mean arterial pressure, ventilation, arterial blood gases, and serum potassium concentrations. No toxic effect of any of the experimental agents was observed.

Clinical Pharmacokinetics

The pharmacokinetics of DigiFab[®] have been assessed in a randomized and controlled study of DigiFab[®] and Digibind[®] (comparator Fab product for treatment of digoxin toxicity) as described in the CLINICAL TRIALS Section above. The volume of distribution (0.3 L/kg) indicates considerable penetration from the circulation into the extracellular space and the volume of distribution and the elimination half-life (15 hours) is consistent with previous reports of ovine Fab distribution and elimination (reported to be between 15 and 23 hours).(6;11;14-17) The elimination half-life 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(17).

MICROBIOLOGY

Not available

TOXICOLOGY

Not available

REFERENCES

- (1) Smith TW, Butler VP, Jr., Haber E, Fozzard H, Marcus FI, Bremner WF et al. Treatment of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments: experience in 26 cases. *N Engl J Med* 1982; 307(22):1357-1362.
- (2) Kojis FG. Serum sickness and anaphylaxis; analysis of cases of 6211 patients treated with horse serum for various infections. *Am J Dis Children* 1942; 64:93-143.
- (3) Quarre JP, Lecomte J, Lauwers D, Gilbert P, Thiriaux J. Allergy to latex and papain. *J Allergy Clin Immunol* 1995; 95(4):922.
- (4) Baur X, Chen Z, Rozynek P, Duser M, Raulf-Heimsoth M. Cross-reacting IgE antibodies recognizing latex allergens, including Hev b 1, as well as papain. *Allergy* 1995; 50(7):604-609.
- (5) Kirkpatrick CH. Allergic histories and reactions of patients treated with digoxin immune Fab (ovine) antibody. The Digibind Study Advisory Panel. *Am J Emerg Med* 1991; 9(2 Suppl 1):7-10.
- (6) Hickey AR, Wenger TL, Carpenter VP, Tilson HH, Hlatky MA, Furberg CD et al. 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(3):590-598.
- (7) Wenger TL. Experience with digoxin immune Fab (ovine) in patients with renal impairment. *Am J Emerg Med* 1991; 9(2 Suppl 1):21-23.
- (8) Valdes R, Jr., Jortani SA. Monitoring of unbound digoxin in patients treated with anti-digoxin antigen-binding fragments: a model for the future? *Clin Chem* 1998; 44(9):1883-1885.
- (9) Mullen WM, Dart RC, Olson KR. Use of CroFab in an Eight Month Pregnant Woman. *J Toxicol.Clin Toxicol.* 40[5], 675. 2002.
- (10) Kravitz J., Gerardo CJ. Copperhead snakebite treated with Crotalide Polyvent Immune Fab (Ovine) antivenom in third trimester pregnancy. *Clinical Toxicology* 44, 353-354. 2006.
- (11) Antman EM, Wenger TL, Butler VP, Jr., Haber E, Smith TW. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. Final report of a multicenter study. *Circulation* 1990; 81(6):1744-1752.
- (12) Gibb I, Adams PC, Parnham AJ, Jennings K. Plasma digoxin: assay anomalies in Fab-treated patients. *Br J Clin Pharmacol* 1983; 16(4):445-447.

- (13) Rainey PM. Effects of digoxin immune Fab (ovine) on digoxin immunoassays. *Am J Clin Pathol* 1989; 92(6):779-786.
- (14) Ward SB, Sjostrom L, Ujhelyi MR. Comparison of the pharmacokinetics and in vivo bioaffinity of DigiTAb versus Digibind. *Ther Drug Monit* 2000; 22(5):599-607.
- (15) 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(5 Suppl A):118A-123A.
- (16) 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 Clin Pharmacol* 1986; 30(5):527-533.
- (17) Ujhelyi MR, Robert S. Pharmacokinetic aspects of digoxin-specific Fab therapy in the management of digitalis toxicity. *Clin Pharmacokinet* 1995; 28(6):483-493.

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

DigiFab® Digoxin Immune Fab (Ovine)

This leaflet is part III of a three-part “Product Monograph” published when DigiFab® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DigiFab®. Contact your doctor or pharmacist if you have any questions about DigiFab®.

ABOUT THIS MEDICATION

What the medication is used for:

DigiFab®, Digoxin Immune Fab (Ovine) is used in the treatment of life-threatening toxicity caused by digoxin.

What it does:

DigiFab® is made up of antibody fragments that will bind specifically to the digoxin in your body. By binding to the digoxin, DigiFab® will counteract the effect of the digoxin and assist in its removal from your body.

When it should not be used:

DigiFab® should not be used if:

1. You have had a serious allergic reaction to DigiFab® or to a similar product, Digibind®, in the past.
2. You have a serious allergy to any ingredient in DigiFab® (See below, medicinal and nonmedicinal ingredients) including to papain, which is used in its manufacture.

In some cases of life-threatening digoxin toxicity, regardless of allergic history, your doctor may choose to use DigiFab® because the benefit of using it outweighs the risk of an allergic reaction.

What the medicinal ingredient is:

The active medicinal ingredient in DigiFab® is digoxin-specific antibody fragments (Fab).

What the important nonmedicinal ingredients are:

DigiFab® contains the following inactive ingredients: mannitol and sodium acetate.

What dosage forms it comes in:

DigiFab® is available as a sterile, freeze-dried powder. Each vial contains 40 mg of purified digoxin-specific Fab. One box contains one vial of DigiFab®.

WARNINGS AND PRECAUTIONS

BEFORE you use DigiFab®, talk to your doctor or pharmacist if:

1. You have any allergies to this drug or its ingredients.
2. You have allergies to antibiotics.
3. You have a history of asthma.
4. You have an allergy to papain, chymopapain, or other papaya extracts or to pineapples (an enzyme called bromelain).
5. You have an allergy to latex.
6. You have kidney disease.
7. You are taking digoxin for heart problems.
8. You are pregnant or breastfeeding.

INTERACTIONS WITH THIS MEDICATION

There are no known interactions between DigiFab® and food or herbal products.

PROPER USE OF THIS MEDICATION

Usual dose:

The dosage of DigiFab® varies according to the amount of digoxin in your body. The average dose used during clinical testing was 4 vials, but the dose can vary between 1 and 20 vials, depending on how much digoxin is in your body.

Your doctor or pharmacist will calculate the dose of DigiFab® you need. Sterile water will be added to the vials to dissolve the powder, and then the contents of the vials will be added to a bag of saline. The contents of the bag will be given to you by an infusion (through a needle in a vein). In some cases, if necessary, the total dose will be directly injected into a vein using a syringe.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, DigiFab® can cause side effects, although not everyone gets them. The following side effects may occur and you should tell your doctor or nurse immediately if you experience them:

1. Allergic reactions including rash with or without itching
2. Shaking, chills, or fever
3. Swelling of the throat, tongue or face
4. Difficulty breathing

IMPORTANT: PLEASE READ

5. Pain or redness at the infusion site
6. Worsening congestive heart failure (shortness of breath or swelling in arms or legs)

This is not a complete list of side effects. For any unexpected effects while taking DigiFab[®], contact your doctor or nurse.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

A serious allergic reaction occurs very rarely. No serious allergic reactions have occurred in the clinical studies with DigiFab[®].

If a severe allergic reaction occurs during infusion of DigiFab[®], your doctor or nurse should stop the infusion. You will then be given medication to treat the allergic reaction.

HOW TO STORE IT

You will be given DigiFab[®] in the hospital. The hospital will store the medication correctly, in the refrigerator at a temperature between 2 and 8 °C.

Once the vials of DigiFab[®] have been reconstituted (water added to make a solution), it should be used immediately, and at least within 4 hours.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/healthcanada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax, or
- Calling toll-free at 1-866-234-2345

Note: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.btgplc.com>

Or by contacting;

BTG International Canada Inc.,
1-844-233-7167

This leaflet was prepared by BTG International Inc.

BTG International Inc.
300 Four Falls Corporate Center
300 Conshohocken State Road, Suite 300
West Conshohocken, PA 19428
USA



June 2018

Digibind[®] is a registered trademark of Glaxo Group Limited.

DigiFab[®] is a registered trademark of BTG International Inc.

BTG and the BTG roundel logo are registered trademarks of BTG International Ltd in the US, EU and certain other territories, and are trademarks of BTG International Ltd elsewhere.