DigiFab®, Digoxin-specific antibody fragment F(Ab) (Ovine) Powder for Injection

DigiFab® Injection

NAME OF THE MEDICINE

Digoxin-specific antibody fragment F(Ab) (Ovine)

DESCRIPTION

DigiFab®, digoxin-specific antibody fragment F(Ab) (Ovine) Powder for Injection, is a sterile, purified, lyophilized off-white powder of digoxin-specific antibody ovine Fab (monovalent) immunoglobulin fragments. These fragments are obtained from blood of healthy sheep immunized with a digoxin derivative, digoxin-dicarboxymethoxylamine (DDMA), a digoxin analogue which contains the functionally essential cyclopentaperhydrophenanthrene:lactone ring moiety coupled to keyhole limpet hemocyanin (KLH).

The final product is prepared by isolating the immunoglobulin fraction of the ovine serum, digesting it with papain and isolating the digoxin-specific Fab fragments by affinity chromatography. These antibody fragments have a molecular weight of approximately 46,000 Da.

Each vial of DIGIFAB, will bind approximately 0.5 mg digoxin, contains 40 mg of digoxin-specific antibody fragment F(Ab), 75 mg of mannitol USP, and 1.7 mg sodium acetate USP as a buffering agent.

The pH of the reconstituted solution is in between 4.5 – 5.5.

The product contains no preservatives and is intended for intravenous administration after reconstitution with 4 mL of Sterile Water for Injection.

PHARMACOLOGY

Pharmacodynamics

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 receptor [sodium, potassium adenosine triphosphatase (ATPase)], 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 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). The elimination half-life of 15-20 hours in patients with normal renal function appears to be increased up to 10-fold in patients with renal impairment, although volume of distribution remains unaffected.

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CLINICAL TRIALS

The total number of people treated with this medication in trials is small and the data regarding dosing and outcomes are limited.

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 16 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 Pharmacokinetics Section 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 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.

In the DIGIFAB trial (TAb007-01), an independent blinded review of each patient's ECG showed that 10 of the 15 patients studied had ECG abnormalities that improved within 4 hours after the DIGIFAB infusion. The remaining 5 patients had ECG abnormalities that were unchanged from baseline throughout the 24-hour assessment period, and in one case through the 30-day follow up period. Although the reason for the lack of ECG resolution could not be clearly determined in all cases, it is possible that the ECG abnormalities 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. In this study, where 2/15 patients had serum available for human anti-ovine antibody determination, there was no measurable immune response.

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INDICATIONS

Digoxin-specific antibody fragment F(Ab) (Ovine) DIGIFAB is indicated for the treatment of known (or strongly suspected) life-threatening digoxin toxicity associated with ventricular arrhythmias, progressive bradycardia, or second or third degree heart block not responsive to atropine, and where additional measures besides withdrawal of digoxin and correction of serum electrolyte abnormalities are considered necessary. Consequences of multiple dosing with DIGIFAB have not been evaluated.

CONTRAINDICATIONS

Hypersensitivity to the active substance or any of the excipients.

PRECAUTIONS

General

Digoxin specific antibody fragments F(Ab) (Ovine) has been used on only a limited scale in man and its safety has therefore not yet been completely defined.

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.

Standard management of digitalis intoxication includes withdrawal of the intoxicating agent, correction of electrolyte disturbances (especially hypokalaemia and hypomagnesemia), 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 for the first few hours following DIGIFAB administration (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.

Hypersensitivity Reactions

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 experienced a severe anaphylactic reaction, the number of patients exposed was small, therefore 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 discontinued at once and appropriate treatment administered. The need for adrenaline 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. Some dust mite allergens and some latex allergens share antigenic structures with papain and patients with these allergies may be allergic to papain. 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.

Prior treatment with digoxin-specific ovine immune Fab carries a theoretical risk of sensitization to ovine serum protein and possible diminution of the efficacy of the drug due to the presence of human antibodies against ovine Fab. 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.

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.

Effects on Fertility
There have been no studies performed in animals to evaluate effects on fertility.

Use in Pregnancy
Pregnancy Category B2.
There is no data on the use of DIGIFAB in pregnant women. The use of DIGIFAB should be considered only if the expected clinical benefit of treatment to the mother outweighs any possible risk to the developing fetus.
Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Use in Lactation
It is not known whether DIGIFAB is excreted in human breast milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with DIGIFAB.

Paediatric 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. 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.

Use in the Elderly
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 Use of DIGIFAB in Renal Failure).

Carcinogenicity
Animal carcinogenicity and reproduction studies have not been conducted with DIGIFAB.

Genotoxicity
Genotoxicity studies have not been conducted with DIGIFAB.

Formation of Antibodies to DIGIFAB
Prior treatment with digoxin-specific ovine antibody fragment carries a theoretical risk of sensitization to ovine serum protein (see **PRECAUTIONS**) and possible diminution of 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.

Effect on Laboratory Tests
DIGIFAB will interfere with digitalis immunoassay measurements in the same way that has been reported for Digibind. Thus, standard serum digoxin concentration measurements may be clinically misleading until the Fab fragments are eliminated from the body. This may take several days or a week or more in patients with markedly impaired renal function. Therefore, serum samples for digoxin concentration should be obtained before DIGIFAB administration, if at all possible. Such measurements would establish the level of serum digoxin at the time of diagnosis of digitalis intoxication.

At least 6 to 8 hours are required for equilibration of digoxin between serum and tissue, so absorption of the last dose may continue from the intestine. Therefore, serum measurements may be difficult to interpret if samples are drawn soon after the last digitalis dose.

The total serum digoxin concentration may rise precipitously following administration of DIGIFAB, but this will be almost entirely bound to the Fab fragment and therefore not able to react with receptors in the body.

Patients should be closely monitored, including temperature, blood pressure, electrocardiogram, and potassium concentration, during and after administration of DIGIFAB. Digoxin causes a shift of potassium from inside to outside the cell, such that severe acute intoxication can cause an 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.

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. 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.

INTERACTIONS WITH OTHER MEDICINES

Studies of drug interactions have not been conducted with DIGIFAB.

ADVERSE EFFECTS

As a limited number of patients were exposed in clinical studies, reporting of any concerns or adverse events to the sponsor or the Therapeutic Goods Administration (TGA) is encouraged.

Adverse reactions reported from 23 subjects in clinical studies are listed in Table 1 according to system organ class. Adverse reactions are ranked by frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000) very rare (<1/10,000), including isolated reports.

Exacerbation of low cardiac output states and congestive heart failure or a rapid ventricular response in patients with atrial fibrillation may occur owing to withdrawal of effect of digoxin.

Adverse reactions may occur up to 14 days after the infusion has been administered.

Table 1. Adverse Reactions According to System Organ Class

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System organ class	Frequency	Undesirable effect
Metabolism and nutrition disorders	Common	Hypokalaemia, hyperkalaemia
Nervous system disorders	Common	Headache, confusional state
Gastrointestinal disorders	Common	Nausea, vomiting, diarrhoea, constipation, abdominal distension
Cardiac disorders	Common	Worsening of cardiac failure Chest pain Hypotension Orthostatic hypotension
Musculoskeletal and connective tissue disorders	Common	Influenza-like illness
Renal and urinary disorders	Common	Renal failure
General disorders and administration site conditions	Common	Fatigue Infusion site phlebitis

DOSAGE AND ADMINISTRATION

General Guidelines

Digoxin-specific antibody fragment F(Ab) (Ovine), DIGIFAB, is administered by the intravenous route over 30 minutes. If cardiac arrest is imminent, it can be given as a bolus injection. The dosage of DIGIFAB will vary according to the amount of digoxin to be neutralized. Consequences of multiple dosing with DIGIFAB have not been evaluated.

Dosage Calculation

For calculation of the appropriate dosage, please utilise either the tables, the dosing calculation example, or the dose determination flowchart that follow.

The management of patients with digoxin toxicity follows a step-wise decision process, as shown in Table 2.

Table 2. Stepwise Management of Patients with Digoxin Toxicity

Step 1	Decide if digoxin poisoning is (i) acute or (ii) chronic.
Step 2	Is the patient (i) an adult or a child >20 kg or (ii) a child ≤20 kg?
Step 3	Is (i) the amount of digoxin ingested known or is (ii) the serum concentration of digoxin known or (iii) are either of these unknown

Step 1 (i) Acute digoxin poisoning

Half the estimated dose required for full neutralisation can be given initially followed by monitoring for 6-12 hours if there is a full response. The remainder may be given if there is no clinical response within 2 hours.

Rationale: in acute digoxin poisoning, the serum digoxin concentration does not reflect total body load and complete neutralisation is not necessary in digoxin-naïve patients.

Step 1 (ii) Chronic digoxin poisoning
Half the estimated dose required for full neutralisation can be given initially followed by monitoring for 6-12 hours. The remainder may be given if there is recurrence of toxicity.

Rationale: in chronic digoxin poisoning, the dose of antibody required for full neutralisation depends on the total body load of cardiac glycoside which has to be counteracted. However, as these patients are receiving digoxin therapeutically, full neutralisation is not necessary.

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Table 3. Dose Calculation for Full Neutralisation in Digoxin Poisoning in Adults and Children > 20kg

Step 2 (i) Adults and children > 20 kg	
Step 3 (i)	Dose of digoxin ingested known Full neutralisation dose of DIGIFAB is: Number of vials = $\frac{\text{Amount of digoxin ingested (mg) x bioavailability of digoxin preparation*}}{\text{0.5 mg/vial}}$ Round up to the nearest vial (see Table 4, providing DIGIFAB dose by amount of digoxin ingested and bioavailability of the digoxin preparation). * bioavailability = 0.7 for digoxin tablets or 0.8 for digoxin elixir To calculate the number of milligrams to be prescribed: multiply the number of vials by 40 (as there are 40 mg/vial).
OR *Step 3 (ii)*	Serum digoxin concentration known Full neutralisation dose of DIGIFAB is: Number of vials = [serum digoxin concentration (ng/mL) X weight (kg)] / 100 Round up to the nearest vial (see dosing calculation example below Table 5 for known serum digoxin concentration) To calculate the number of milligrams to be prescribed: multiply the number of vials by 40 (as there are 40 mg/vial). Converting units of digoxin ng/mL to / from nmol/L ng/mL (or µg/L) x 1.28 = nmol/L nmol/L x 0.781 = ng/mL (or µg/L)
OR *Step 3 (iii)*	Dose of digoxin unknown and serum digoxin concentration unknown **For acute digoxin poisoning:** Dose initially with five (5) vials of DIGIFAB if the patient is hemodynamically stable, or 10 – 20 vials if the patient is not stable. A larger dose of DIGIFAB may have a faster onset of effect but may enhance the possibility of a febrile reaction. In such cases, 5 or 10 vials may be administered first with careful monitoring of the patient's response followed by additional vials and continued monitoring. **For chronic digoxin poisoning:** Dose initially with two (2) vials of DIGIFAB, followed by an additional two vials 30 minutes later if symptoms persist or recur.

Refer to the Dose Determination Flowchart provided in Figure 1 for adults and children > 20 kg.

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Table 4. DIGIFAB Dose by Vial Based on Milligrams Digoxin Ingested and Bioavailability of Digoxin Preparation

Digoxin Dose Ingested (mg)	Number of DIGIFAB Vials* (0.7 bioavailability – tablets)	Number of DIGIFAB Vials* (0.8 bioavailability – elixir)
1	2	2
2	3	4
3	5	5
4	6	7
5	7	8
6	9	10
7	10	12
8	12	13
9	13	15
10	14	16
15	21	24
20	28	32

* Calculations are rounded up to the nearest vial

Table 5. Dose Calculation for Full Neutralisation in Digoxin Poisoning in Children ≤20 kg

Step 2 (ii) Children ≤20 kg	
Step 3 (ii)	Serum digoxin concentration known Full neutralisation dose of DIGIFAB is: Number of vials = [serum digoxin concentration (ng/mL) X weight (kg)] / 100 Round up to the nearest vial (see dosing calculation example below for known serum digoxin concentration) To calculate the number of milligrams to be prescribed: multiply the number of vials by 40 (as there are 40 mg/vial).
OR *Step 3 (iii)* Alternate for children <20kg when serum digoxin not known	Serum digoxin concentration not known Dose initially with one vial of DIGIFAB and repeat if symptoms persist or recur.

Dosing Calculation Example for Known Serum Digoxin Concentration: Adult patient weighing 60 kg with chronic overdose and a known serum digoxin concentration of 3 ng/mL.

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- Calculate DIGIFAB dose by multiplying the serum concentration by the patient's weight and dividing by 100. Dose = (60 kg x 3 ng/mL)/100 = 1.8 vials (round up to 2 vials)
- Administer ½ the calculated dose (1 vial of DIGIFAB) and monitor the patient closely for persistent or recurrent signs and symptoms of toxicity. Administer second vial if symptoms persist or recur.

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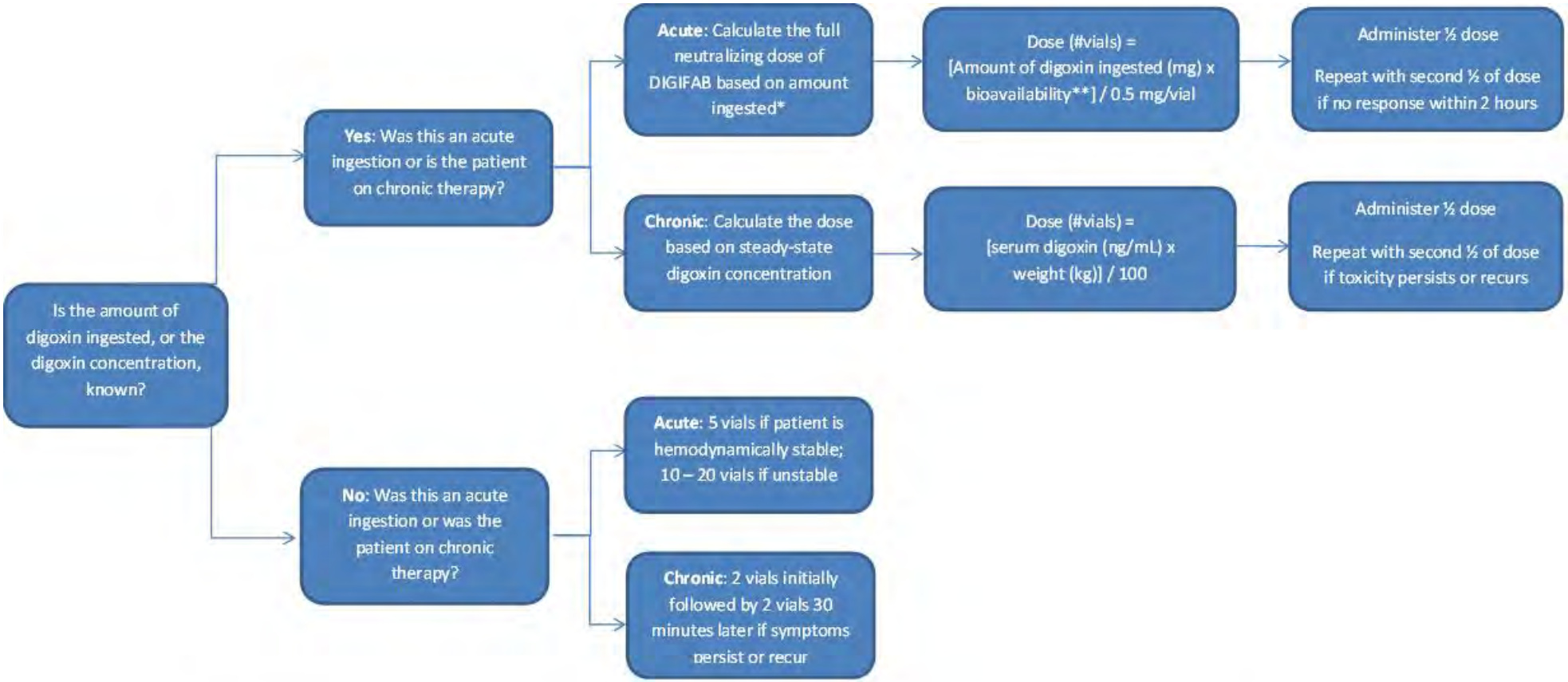
Figure 1. Determining the dose of DIGIFAB for Adults and Children > 20 kg



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Method of Preparation for Administration
Each vial should be reconstituted with 4 mL of Sterile Water for Injection by gentle mixing. This produces an approximately isosmotic solution with a protein concentration of 10 mg/mL that may be diluted further to any convenient volume with sterile saline suitable for infusion.

For infants and small children who may require very small doses, reconstitute the 40 mg vial as directed and administer undiluted using a tuberculin syringe. For very small doses, a reconstituted vial can be diluted with an additional 36 mL of isotonic saline to achieve a concentration of 1 mg/mL.

Use immediately after reconstitution. The reconstituted solution should be a clear to slightly opalescent, colourless to pale yellow solution.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

DIGIFAB Injection should be used in one patient on one occasion only. It contains no anti-microbial preservative. Unused solution should be discarded.

Method of Administration
The final solution of DIGIFAB should be infused intravenously over a 30-minute period.

OVERDOSAGE

The maximum amount of DIGIFAB that can safely be administered in single or multiple doses has not been determined. Please refer to **PRECAUTIONS** section regarding withdrawal of the inotropic action of digoxin by DIGIFAB, which may be of concern in overdosage of DIGIFAB. For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

DIGIFAB, Digoxin-specific antibody fragment F(Ab) (Ovine) Powder for Injection contains 40 mg of purified lyophilized digoxin-specific Fab fragments, 75 mg mannitol and 1.7 mg sodium acetate. DIGIFAB is supplied in a single, clear, neutral glass vial closed with a butyl rubber stopper and fitted with aluminium flip top seal. One 10mL glass vial of DIGIFAB per pack.

Store at 2°C to 8°C. (Refrigerate. Do not freeze). Use immediately after opening.

AUST R 203623
Phebra product code-INJ172

NAME AND ADDRESS OF THE SPONSOR

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Telephone: 1800 720 020

Manufactured by: BTG International Inc.
West Conshohocken, PA 19428
USA

POISONS SCHEDULE OF THE MEDICINE

DigiFab®, Digoxin-specific antibody fragment F(Ab) (Ovine) Powder for Injection

Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods: 14 February 2014

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