

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DigiFab® (referred to as DIGIFAB) 40 mg/vial digoxin immune Fab, Powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each glass vial of DIGIFAB contains 40 mg of digoxin immune Fab (ovine) protein as a sterile, lyophilized, off white powder.

For a full list of excipients see Section 6.1

3. PHARMACEUTICAL FORM

Powder for Solution for Infusion

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DIGIFAB is indicated for the treatment of known (or strongly suspected) life-threatening digoxin toxicity associated with ventricular arrhythmias or bradyarrhythmias unresponsive to atropine where measures beyond withdrawal of digoxin and correction of serum electrolyte abnormalities are considered necessary.

4.2. Posology and method of administration

Posology

It is advised to discuss management of patients with digoxin toxicity with the UK National Poisons Information Service at the following contact phone number: 0844 892 0111

Management follows a step-wise decision process, as shown:

Step 1	Decide if digoxin poisoning is (i) acute, (ii) acute-on-chronic or (iii) 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?

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) Acute-on-chronic digoxin poisoning

A full neutralisation dose of DIGIFAB can be given if the amount of digoxin ingested is known. If the amount of digoxin ingested is not known then a half-neutralising dose of DIGIFAB based on serum digoxin concentration should be used 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.

The usual dose for adults and children over 20 kg may vary between one half of a vial (20 mg DIGIFAB) to 20 vials (800 mg DIGIFAB). More vials may be needed dependent upon the amount of digoxin consumed.

Step 1 (iii) 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.

Dose calculation for full neutralisation in digoxin poisoning:

Step 2 (i) Adults and children > 20 kg	
Step 3 (i)	<p>Dose of digoxin ingested known</p> <p>Full neutralisation dose of DIGIFAB is:</p> <p>Number of vials = Amount of digoxin ingested (mg) x 1.6</p> <p>Round up to the nearest vial</p> <p>To calculate the number of milligrams to be prescribed: multiply the number of vials by 40 (as there are 40 mg/vial).</p>
Step 3 (ii)	<p>Serum digoxin concentration known</p> <p>Full neutralisation dose of DIGIFAB is:</p> <p>Number of vials =</p> <p>[serum digoxin concentration (ng/mL) X weight (kg)] / 100</p> <p>Round up to the nearest vial</p> <p>To calculate the number of milligrams to be prescribed: multiply the number of vials by 40 (as there are 40 mg/vial).</p>
Step 2 (ii) Children <20 kg	
Step 3 (i)	<p>Serum digoxin concentration known</p> <p>Full neutralisation dose of DIGIFAB is:</p> <p>Number of vials =</p> <p>[serum digoxin concentration (ng/mL) X weight (kg)] / 100</p> <p>Round up to the nearest vial</p> <p>To calculate the number of milligrams to be prescribed: multiply the number of vials by 40 (as there are 40 mg/vial).</p>
Step 3	<p>Serum digoxin concentration not known</p> <p>One vial of DIGIFAB will usually be sufficient for full neutralisation.</p>
Alternate for children <20kg when serum digoxin not known	

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)

Paediatric population

The safety and efficacy of DIGIFAB in children has not yet been established.

Method of administration

DIGIFAB should be reconstituted prior to administration according to the instructions provided in section 6.6.

The final solution of reconstituted and diluted DIGIFAB should be infused intravenously over a 30 minute period.

Record the name of the patient and batch number of the product in order to maintain a link between the patient and the batch of the product.

4.3. Contraindications

Hypersensitivity to the active substance or any of the excipients.

4.4. Special warnings and precautions for use

UK National Poisons Information Service

It is advised to discuss management of patients with digoxin toxicity with the UK National Poisons Information Service at the following contact phone number: 0844 892 0111.

Risk of infusion-related reactions or hypersensitivity

As with any intravenous protein product, infusion-related reactions or hypersensitivity reactions are possible. It is recommended that patients are monitored for signs and symptoms of anaphylaxis and an acute allergic reaction. Medical support must be readily available when DIGIFAB is administered.

If an anaphylactic reaction occurs during an infusion then administration of DIGIFAB must be stopped immediately. Repeat dosing with DIGIFAB may give rise to an anaphylactic reaction. Repeat dosing must only be done when it is considered that clinical benefit outweighs the risk.

The likelihood of an allergic reaction may be higher in subjects who:

- are allergic to sheep-derived proteins (as may be found in cheeses and meats). Digoxin immune Fab is produced from sheep protein.
- are allergic to papain, an extract of the papaya fruit. Papain is used to cleave the whole antibody into Fab and Fc fragments: traces of papain or inactivated papain residues may be present in DIGIFAB. Papain shares allergenic

structures with (i) chymopapain and other papaya extracts, (ii) bromelain found in pineapple, (iii) dust mite allergens and (iv) latex allergens.

Immunoassay interference/Laboratory tests

Digoxin assay kits may not be able to measure accurately digoxin concentrations greater than 5 ng/mL (6.4 mmol/L). Exercise caution when using digoxin concentrations above these figures to calculate the dose of DIGIFAB is required.

DIGIFAB may interfere with digoxin immunoassay measurements. Therefore, standard serum digoxin measurements may be clinically misleading until the Fab fragments are eliminated from the body. This may take several days or more than a week in patients with impaired renal function. The total serum digoxin concentration as measured by immunoassay may rise rapidly following administration of DIGIFAB. Serum digoxin will be almost entirely bound by DIGIFAB and therefore not able to react with receptors in the body.

General management of patients

Dosage estimates are based on a steady-state volume of distribution of 5 L/kg for digoxin in order to convert serum digitalis concentration to the amount of digitalis in the body. These volumes are population averages and vary widely among individuals.

Ordinarily, improvements in signs and symptoms of digoxin toxicity begin within 30 minutes following completion of administration of DIGIFAB.

Patients should have continuous electrocardiographic monitoring during and for at least 24 hours after administration of DIGIFAB. Temperature, blood pressure and potassium concentration should be monitored during and after DIGIFAB administration.

Patients previously dependent on the inotropism of digoxin may develop signs of heart failure when treated with DIGIFAB. After successful management of poisoning, digoxin has had to be reinstated in some cases.

If, after several hours, toxicity has not adequately reversed or appears to recur, re-administration of DIGIFAB at a dose guided by clinical judgement may be required.

Failure of the patient to respond to DIGIFAB should alert the physician to the possibility that the clinical problem may not be due to digoxin toxicity.

Suicidal ingestion may involve more than one drug. Toxic effects of other drugs or poisons should not be overlooked, particularly where failure to respond to DIGIFAB raises the possibility 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.

There is no information on re-administration of DIGIFAB to patients for a second (or more) episode of digoxin toxicity.

Impaired renal function

It may be expected that excretion of the Fab-digoxin complexes from the body is slowed in the presence of renal impairment and that digoxin may be released after some days from retained Fab-digoxin complexes.

Impaired hepatic function

There is no information on the use of DIGIFAB in subjects with hepatic impairment.

General handling

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

Repeated use

There are no data on repeated dosing of DIGIFAB.

Paediatric population

There is limited information on the use of DIGIFAB in the paediatric population.

4.5. Interactions with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6. Fertility, Pregnancy and lactation

Pregnancy

There are 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 foetus.

Breastfeeding

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

Fertility

There are no fertility data.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed

4.8. Undesirable effects

Adverse reactions are ranked by frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$) very rare ($< 1/10,000$), including isolated reports.

Summary of the safety profile

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

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.

Tabulated list of adverse reactions

Adverse reactions reported from 23 subjects in clinical studies are listed below according to system organ class.

System organ class	Frequency	Adverse reactions
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

Paediatric population

No paediatric patients were included in the clinical studies in support of the indication.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9. Overdose

No case of overdose has been reported in adults or paediatrics.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC Code: VO3A B24 Digitalis antitoxin

Mechanism of action

Digoxin immune Fab has a high affinity for digoxin.

Pharmacodynamic effect

Digoxin immune Fab binds digoxin and so reduces the concentration of free digoxin.

Clinical efficacy and safety

When DIGIFAB is administered to a patient with digoxin toxicity, there is a reduction in the serum concentration of free digoxin leading to a reduction in toxicity.

Paediatric population

There is limited information on use in the paediatric population.

5.2. Pharmacokinetic properties

In a study of healthy volunteers who were administered 76 mg of DIGIFAB[®] iv 2 hours after 1 mg digoxin iv, the serum elimination half-life of DIGIFAB was (about) 15 hours.

Renal impairment

It may be expected that excretion of the Fab-digoxin complexes from the body is slowed in the presence of renal impairment and that digoxin may be released after some days from retained Fab-digoxin complexes.

Hepatic impairment

There is no information on the use of DIGIFAB in subjects with hepatic impairment.

Paediatric population

No data are available.

5.3. Preclinical safety data

There are no preclinical safety data of relevance to the prescriber that are additional to safety data already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium acetate
Acetic acid
Mannitol

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3. Shelf life

3 years
From a microbiological point of view, the product should be used immediately after reconstitution.

6.4. Special precautions for storage

Store between 2 and 8°C. Do not freeze.
Keep vial in outer carton in order to protect from light.
For storage conditions of the reconstituted medicinal product see section 6.3

6.5. Nature and contents of container

Single clear, neutral glass vial closed with a butyl rubber stopper and fitted with an aluminum flip top seal. One glass vial container in an outer pack.

6.6. Special precautions for disposal

Instructions for Disposal

Any unused product should be disposed of in accordance with local requirements.

General Instructions

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

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 (0.9% NaCl) suitable for infusion.

7. MARKETING AUTHORISATION HOLDER

Protherics UK Limited
Blaenwaun, Ffostrasol,
Llandysul, Ceredigion, SA44 5JT

8. MARKETING AUTHORISATION NUMBER(S)

PL 21744/0001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorization: 01/07/2011

Renewal: 15/03/2016

10. DATE OF REVISION OF THE TEXT

December 2017