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 or cardiac glycoside poisoning associated with ventricular arrhythmias or bradyarrhythmias unresponsive to atropine where measures beyond withdrawal of digoxin or cardiac glycosides 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 or cardiac glycoside poisoning with TOXBASE (UK National Poisons Information Service) at the following contact phone number: 0344 892 0111 (in Ireland NPIC (01) 809 2566) and/or refer to the most up to date TOXBASE guidance at https://www.toxbase.org/

The dose of DIGIFAB depends on the clinical situation and on whether plasma digoxin concentration is available.

Summary of Dosing Guidelines

For poisoning from pharmaceutical digoxin:

A. Cardiac arrest due to digoxin toxicity:

Urgently administer digoxin-specific FAB fragments as an IV bolus, further doses may be required if an adequate clinical response is not seen after 30 minutes:

Weight (adult and children)	**DigiFab dose** (each vial should be reconstituted with 4 mL of sterile water by gentle mixing)
>40 kg	5 vials (200 mg)

20-40 kg	2 vials (80 mg)
≤20 kg	1 vial (40 mg)

B. Severe bradyarrhythmia or life-threatening ventricular arrhythmia.

OR

C. Severe hyperkalaemia (e.g. K^+ greater than 6.5 mmol/L) resistant to adequate rehydration and conventional treatments.

NOTE: this applies to acute digoxin overdose on top of usual therapy, acute overdose in digoxin-naive patient and digoxin toxicity from chronic therapy.

1. When digoxin concentration is available (measured 6 hours after overdose, unless urgently indicated in patient with arrhythmia).

   Number of vials = (serum digoxin concentration (ng/mL) X weight (kg)) ÷ 200

   Round up to the nearest vial. Each vial should be reconstituted with 4 mL of sterile water by gentle mixing.

2. When only ingested dose is available:

   Number of vials = Amount of digoxin ingested (mg) X 0.8

   Round up to the nearest vial. Each vial should be reconstituted with 4 mL of sterile water by gentle mixing.

Digoxin concentrations in mmol/L should be converted to ng/mL (same as µg/L) for the estimations above by using the formula:

[Digoxin] nmol/L x 0.781 = [Digoxin] ng/mL

For poisoning from cardiac glycosides other than pharmaceutical digoxin:

A. Cardiac arrest due to cardiac glycosides other than digoxin:

Urgently administer digoxin-specific FAB fragments as an IV bolus; further doses may be required if an adequate clinical response is not seen after 30 minutes:

Weight (adult and children)	**DigiFab dose** (each vial should be reconstituted with 4 mL of sterile water by gentle mixing)
>40 kg	5 vials (200 mg)
20-40 kg	2 vials (80 mg)
≤20 kg	1 vial (40 mg)

B. Severe bradyarrhythmia or life-threatening ventricular arrhythmia

OR

C. Severe hyperkalaemia (e.g. K^+ greater than 6.5 mmol/L) resistant to adequate rehydration and conventional treatments:

Urgently administer digoxin-specific antibody FAB fragments as an IV bolus; repeat doses

after 15 – 30 minutes if response is inadequate:

Weight (adult and children)	**DigiFab dose** (each vial should be reconstituted with 4 mL of sterile water by gentle mixing)
>40 kg	2 vials (80 mg)
≤40 kg	1 vial (40 mg)

Paediatric population

Data on the safety and efficacy of DIGIFAB in children are limited.

Method of administration

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

Depending upon clinical circumstances, the final solution of reconstituted and diluted DIGIFAB may be infused intravenously over a 30 minute period.

4.3. Contraindications

Hypersensitivity to the active substance or any of the excipients.

4.4. Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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: 0344 892 0111 (in Ireland NPIC (01) 809 2566).

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.

- are allergic to alpha-gal or have been diagnosed with alpha-gal syndrome. Alpha-gal is a sugar molecule found in most mammals. Alpha-gal syndrome is a type of food allergy to red meat and other products made from mammals.

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 required. Digoxin assays react unpredictably with non-digoxin cardiac glycosides. Digoxin assay kit levels must not be used to dose DIGIFAB in these situations.

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 for digoxin toxicity 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.

In cardiac glycoside poisoning, the duration of effect may depend on the specific toxin ingested and time lapse since intake.

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 reinstituted 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 or cardiac glycoside poisoning.

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 or cardiac glycoside poisoning alone. If there is no response to an adequate dose of DIGIFAB, the diagnosis of digoxin toxicity or cardiac glycoside poisoning should be questioned.

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

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 aftersome 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. Small children < 20 kg should be monitored for volume overload.

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 (≥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.

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 clinical studies in 23 subjects with digoxin toxicity and 57 subjects with yellow oleander (*Thevetia peruviana*) toxicity and are listed below according to system organ class.

System organ class	**Frequency**	**Adverse reactions**
Immune system disorders	Common	Hypersensitivity reactions
Metabolism and nutrition disorders	Common	Hypokalaemia, hyperkalaemia
Nervous system disorders	Common	Headache, confusional state
Cardiac disorders	Common	Worsening of cardiac failure, chest pain, hypotension, orthostatic hypotension
Gastrointestinal disorders	Common	Nausea, vomiting, diarrhoea, constipation, abdominal distension
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 for the treatment digoxin toxicity. Eleven adolescent patients aged 13-17 received treatment with DIGIFAB in the clinical study in the treatment of yellow oleander toxicity. The frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

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 theYellow 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. *In vitro* binding studies show that digoxin immune Fab has similar binding affinities for digoxin and plant cardiac glycoside analogues.

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.

Similarly, DIGIFAB binds to other cardiac glycosides reducing serum concentrations.

Paediatric population

There is limited information on use in the paediatric population. The pharmacological effects of DIGIFAB are the same in adults and 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

June 2024