Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for digoxin-specific antibody fragment F(Ab) (Ovine)

Proprietary Product Name: DigiFab

Sponsor: Phebra Pty Ltd

May 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of commonly used abbreviations

Abbreviation	Meaning
AE	Adverse Event
AUC	Area under curve
AUMC	Area under the first-moment versus time curve
Az	Smallest disposition rate constant
BP	Blood pressure
Bpm	Beats per minute
BUN	Blood urea nitrogen
CK	Creatine kinase
CRF	Case report form
CV	Coefficient of variation
Clast	Last measured concentration
Cltotal	Systemic clearance
Clrenal	Renal clearance
Clnon-renal	Non renal clearance
Cmax	Maximum concentration
CFR	Code of Federal Regulations
CRF	Case Report Form
D	Dose in mg
DBP	Diastolic blood pressure
ECG	Electrocardiogram
Fab	Fragment antigen binding
GCP	Good Clinical Practice
GOT	Aspartarte aminotransferase
GPT	Alanine aminotransferase
GT	Glutamyl transpeptidase
HASA	Human Anti-Sheep Antibody

Abbreviation	Meaning
Hr	Hour(s)
IC	Informed Consent
IgG	Immunoglobulin G
IRB	Institutional Review Board
Ke	Elimination rate constant
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
LOQ	Limit of quantification
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean cell volume of erythrocytes
Min	minute(s)
MHRA	Medical and Healthcare products Regulatory Agency
MRT	Mean residence time
N	Number
NA	Not applicable
NS	Not significant
P	Probability
PD	Pharmacodynamic
PK	Pharmacokinetic
PTQ	PR interval x T score/QT c
PTT	Partial thromboplastin time
RIA	Radioimmunoassay
SBP	Systolic blood pressure
SD	Standard deviation
SEM	Standard error of the mean

Abbreviation	Meaning
SD	Standard Deviation
T	Time of infusion
t l/2p	Terminal slope elimination half-life
t 1/2a	Distribution (a) half-life
Tmax	Time to maximum concentration
Vdss	Steady state volume of distribution
Vc	Volume of central compartment
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	12 February 2014
Active ingredient:	Digoxin-specific antibody fragment F(Ab) (Ovine)
Product name:	DigiFab
Sponsor's name and address:	Phebra Pty Ltd 19 Orion Road Lane Cove West NSW 2066
Dose form:	Powder for injection (after reconstitution with 4 mL of Sterile Water for Injection).
Strength:	40 mg
Container:	Glass vial
Pack size:	One 10 mL glass vial of DigiFab per pack
Approved therapeutic use:	*Digoxin-specific antibody fragment F(ab) (Ovine) DigiFab is indicated for the treatment of known for 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 ore considered necessary. Consequences of multiple dosing with DigiFab have not been evaluated.*
Route of administration:	Intravenous (IV)
Dosage:	See Product Information (PI) Attachment 1
ARTG number:	203623

Product background

This AusPAR describes the application by Phebra Pty Ltd to register a new biological entity, digoxin-specific antibody fragment, f(ab), (DigiFab). DigiFab is a digoxin antidote for the treatment of known (or strongly suspected) life-threatening digoxin toxicity.

Digoxin is a cardiac glycoside used for the treatment of heart diseases such as certain types of arrhythmias and congestive heart failure. Digoxin has a narrow therapeutic range and digoxin toxicity can occur due to impaired renal function, drug interactions, alterations in plasma electrolytes (especially potassium and magnesium) and metabolic disturbances. Digoxin toxicity is uncommon but patient mortality is high in cases of severe digoxin poisoning. The dosage of DigiFab is not dependent on patient weigh but on the

amount of digoxin present and will vary according to the amount of digoxin to be neutralised.

DigiFab is obtained from blood of healthy sheep immunised with a digoxin derivative, digoxin-dicarboxymethoxylamine (DDMA), a digoxin analogue. Antibodies produced to DDMA have a greater affinity for digoxin than does digoxin for its sodium pump receptor. When injected into the intoxicated patient, DigiFab binds free digoxin resulting in a shift in the equilibrium away from the tissues, thereby reducing cardiotoxicity. Fab glycoside immune complexes are then cleared by the kidney and reticuloendothelial system. Antibodies specific for this structure are needed for antidote potency.

DigiFab is an orphan drug and was designated as such in Australia on 19 May 2011.

DigiFab has not been considered by the TGA's Advisory Committee on Prescription Medicines (ACPM) previously. At present, the standard of care applied in the treatment of life-threatening digoxin, or digitalis poisoning in Australia is Digibind. This product is currently registered on the Australian Register of Therapeutic Goods (ARTG) and marketed by GlaxoSmithKline (GSK). DigiFab and Digibind are manufactured by similar but not identical methods. Though technically constituting different protein products, both antibody fragments bind to free digoxin.

There are also other measures available to manage patients with digoxin poisoning (such as liquid charcoal, cholestyramine or magnesium sulphate), these all have limitations, such as requiring administration within 30 minutes of overdose, having a long administration time and/or only providing short term management of cardiac symptoms. DigiFab would provide an alternative treatment option for this condition and would safeguard supply of a potentially life-saving product for the treatment of digoxin and digitoxin poisoning for the Australian population.

There are 2 specific TGA adopted European guidelines which may be relevant to this submission, besides the general guidelines:

- CPMP/ICH/2711/99. Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population. Effective: 19 April 2001
- CHMP/EWP/83561/2005. Guideline on Clinical Trials in Small Populations. Effective: December 2006

Regulatory status

This product is considered as a new biological entity for Australian regulatory purposes.

The following table summarises the international regulatory status of this product.

Table 1. International regulatory status

Country	Approval date	Approved Indication
United States	31 August 2001	For the treatment of life-threatening or potentially life-threatening digoxin toxicity.
Switzerland	8 January 2010	For the treatment of life-threatening or potentially life-threatening digoxin toxicity.
Canada	23 December 2010	For the treatment of life-threatening or potentially life-threatening digoxin

Country	Approval date	Approved Indication
		toxicity.
United Kingdom (national application)	1 July 2011	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.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Structure

DigiFab is a biologically derived product comprising sheep immunoglobulin Fab fragments. The exact molecular formula of the active ingredient is unknown but its general structure is that of an ovine Fab with specificity for digoxin.

The company states that DigiFab has been developed as a clinically interchangeable alternative to Digibind (GlaxoSmithKline).

Manufacture

The drug substance is affinity purified digoxin specific Fab fragments of sheep antibodies. The immunogen (conjugate) is shipped to Australia from the United Kingdom (UK) for immunisation and bleeding of the sheep and separation of the serum, then shipped back frozen to the UK for the majority of the processing through to a formulated bulk product. The immunogen is a digoxin-dicarboxymethoxylamine (DDMA): keyhole limpet haemocyanin conjugate.

DDMA is a digoxin analogue that contains the functionally essential cyclopentaperhydrophenanthrene:lactone ring moiety.

All viral/prion safety issues have been addressed.

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use. Appropriate validation data have been submitted in support of the test procedures.

Stability of the drug substance has been demonstrated at the proposed commercial-scale stored in disposable plastic bags identical in composition to those used for storage of bulk drug substance. Since the manufacture of the conformance lots, a minimum of one lot per annum has been placed on real time stability.

Three batches of commercial scale DigiFab drug substance batches were placed on real time stability studies following the introduction of the requirement for a sterile drug substance and following the introduction of polarization fluorescence immunoassay (PFIA) as the potency method. All of these studies at the intended commercial scale, using the intended commercial process and stored in scaled down versions of the bulk storage bag at the bulk storage temperature of 2 to 8°C.

Drug product

The product consists of lyophilised affinity purified specific anti-digoxin ovine Fab in a clear, colourless, neutral glass vial closed with a butyl rubber stopper and fitted with an aluminium flip top seal.

The Drug Product is to be reconstituted with 4 mL Sterile Water for Injection, which is not included in the packaging, by gentle mixing.

The Drug Product is produced by sterile filtering and lyophilising the drug substance. Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Justification for not providing photostability data is provided.

The proposed shelf life is 3 years when stored at 2 to 8°C. This is acceptable.

Biopharmaceutics

Biopharmaceutic data are not required for this product because it is administered intravenously.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological and container data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

There are no Quality Objections to the registration of this product.

The PI and Consumer Medicines Information (CMI) documents have been appropriately updated and are acceptable from a Quality perspective.

The sponsor has submitted updated Good Manufacturing Practice (GMP) evidence for the two sites where the original certification has expired. This is currently being processed by TGA.

Condition of registration

An electronic draft of the Certified Product Details (CPD) should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

III. Nonclinical findings

Introduction

Due to the well documented safety and pharmacokinetics of affinity purified fab antibodies including Digibind, classical nonclinical toxicology as well as absorption, distribution, metabolism and excretion studies were not required for this product.[1, 2, 3, 4] The nonclinical data package comprised 3 studies investigating the efficacy of DigiFab compared with Digibind.

Ochs and Smith (1977)[3] reported that the toxic effects of digoxin may manifest at free plasma concentrations of 10 nM or less. The authors estimated that antibody affinity constants must therefore be at least 10^9, or more, if free glycoside concentrations are to be lowered to negligible levels without the use of excessive amounts of antibody. The sponsor states that affinity constants calculated for DigiFab are in the range of 10^9-10^{10} M^{-1} theoretically supporting the *in vivo* efficacy of the fab fragment.

In support of efficacy, a single injection of DigiFab in equimolar doses sufficient to neutralise a 1 mg/kg dose of digoxin was well tolerated in rats and was shown to be similarly efficacious as Digibind in reversing digoxin induced cardiac toxicity and hyperkalemia. Furthermore, no statistically significant differences were observed between DigiFab and Digibind when measuring heart rate, mean arterial pressure, ventilation and arterial blood gases. DigiFab and Digibind showed comparable in vitro binding to digoxin and several other cardiac glycosides including digitoxin, digoxigenin, digitoxigenin, lantanoside C, thevetin, bufalin and proscillaridin A.

In summary the nonclinical package supports efficacy of DigiFab as an antidote for life threatening digoxin poisoning.

Pharmacology

No new data submitted.

Pharmacokinetics

No new data submitted.

Toxicology

Paediatric use

According to the draft Product Information document, no specific studies have been conducted in paediatric patients and no paediatric patients were enrolled in the clinical studies. However, the proposed dosage includes instructions for children, including

[1]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.
[2]Kearns GL, Moss MM, Clayton BD, Hewett DD. Pharmacokinetics and efficacy of digoxin specific fab fragments in a child following massive digoxin overdose. J Clin Pharmacol 1989; 29(10):901-908.
[3]Ochs HR, Smith TW. Reversal of advanced digitoxin toxicity and modification of pharmacokinetics by specific antibodies and fab fragments. Journal of Clinical Investigation 1977;60: 1303-1313
[4]Smith TW, Lloyd BL, Spicer N, Haber E. Immunogenicity and kinetics of distribution and elimination of sheep digoxin-specific IgG and fab fragments in the rabbit and baboon. Clin Exp Immunol 1979; 36(3):384-396.

children < 20 kg. A similar digoxin ovine fab product, Digibind, has been successfully used in infants. Nonclinical studies in support of paediatric DigiFab use were not submitted.

Nonclinical summary and conclusions

- The nonclinical data package comprised 3 studies which investigated the efficacy of DigiFab compared with the current product Digibind. Due to the well documented safety and pharmacokinetics of affinity purified fab antibodies including Digibind, and considering the proposed single dose application for treatment of a potentially life threatening condition, the lack of nonclinical toxicology, as well as absorption, distribution, metabolism and excretion studies was acceptable.
- No nonclinical studies investigating safety or efficacy in juvenile animals were submitted.
- The sponsor reported DigiFab affinity constants for digoxin in the range of 10^9 to 10^{10} M-1. DigiFab and Digibind showed comparable in vitro binding to digoxin and several other cardiac glycosides including digitoxin, digoxigenin, digitoxigenin, lantanoside C, thevetin, bufalin and proscillaridin A.
- DigiFab was well tolerated in rats when administered as a single injection in equimolar doses sufficient to neutralise a 1 mg/kg dose of digoxin and was shown to be similarly efficacious as Digibind in reversing digoxin induced cardiac toxicity and hyperkalemia. The nonclinical data supports the efficacy of DigiFab for the proposed indication.
- There are no nonclinical objections to registration. Due to the ovine protein nature of the product, animal toxicity studies are of limited value; the safety assessment of DigiFab in humans will rely on the clinical data. The nonclinical evaluator also recommended changes to the draft Product Information. The details of these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

At present, the standard of care applied in the treatment of life-threatening digoxin or digitalis poisoning in Australia is Digibind. This is a product, which is clinically interchangeable with DigiFab, is currently registered on the Australian Register of Therapeutic Goods and marketed by GlaxoSmithKline (GSK). Although it is possible to adopt other measures to manage patients suffering from digoxin poisoning, such as administration of liquid charcoal, cholestyramine or magnesium sulphate, these all have limitations, either requiring administration within 30 minutes of overdose, a long administration time, or are purely for short term management of the cardiac symptoms. The introduction of DigiFab would be a valuable addition to the treatment options for this condition and would safeguard supply of a potentially life-saving product for the treatment of digoxin and digitoxin poisoning for the Australian population.

Many clinical studies have shown that binding of digoxin by Fab fragments promptly reduces the toxic activity of the drug[5,6,7]. Therefore, the clinical studies were designed to demonstrate primarily that DigiFab, when administered to patients who were experiencing digoxin toxicity, would reduce serum free digoxin levels to below a clinically meaningful concentration (<0.5 ng/ml). The studies also evaluated the ability of DigiFab to neutralise the toxic effects of digoxin and reverse potentially life-threatening toxic manifestations of digoxin overdose and toxicity. Due to the well understood safety and mechanism of action of Digibind and similarity of DigiFab, it was considered relevant to conduct a clinical program to show that DigiFab binds and inactivates digoxin in healthy subjects in an equivalent manner to Digibind and produces the same clinical benefit in intoxicated patients.

> Comments: It is important to note that authorisation of DigiFab is not being sought on the basis of being a biosimilar. However, it is acknowledged that this comparison of DigiFab with the already approved Digibind would still be relevant to the demonstration of efficacy for DigiFab. Furthermore, evidence for efficacy of DigiFab is provided from the clinical studies in terms of binding of DigiFab to digoxin (measured as free and total digoxin concentrations) and clinical evidence of concomitant loss of toxic effects of digoxin (ECG changes, clinical sequelae).

Scope of the clinical dossier

The submission contained the following clinical information:

Three clinical studies, TAb007-01, TAb007-02 and PR007-CLN-rpt-003, are the only studies to have been specifically performed on DigiFab worldwide.

1. One clinical pharmacology study:
   - TAb007-02: a Phase III, open-label, parallel, pharmacokinetic and pharmacodynamic comparison between DigiTAb* and Digibind in 16 healthy subjects given 1 mg of intravenous digoxin.

     *DigiFab was initially called DigiTAb, throughout the remainder of this overview only the term DigiFab will be used.
2. Two clinical studies:
   - TAb007-01: an ongoing historically controlled, open-label, multicentre trial to determine the safety, pharmacokinetics, and pharmacodynamics of DigiFab administered to patients with potentially life-threatening digoxin toxicity.
   - PR007-CLN-rpt003: a multicentre retrospective review of the clinical efficacy and safety of DigiFab in digoxin poisoned patients.

Studies TAb007-01 and TAb007-02 were designed to compare DigiFab (known as DigiTAb at the time of these studies) to Digibind in a clinical development program. Study PR007-CLNrpt- 003, a retrospective study on the use of DigiFab in the US, was initiated at the request of the Medical and Healthcare products Regulatory Agency (MHRA) to provide additional evidence of efficacy.

[5]Smith, T. W., Butler, V. P., Jr., Haber, E., Fozzard, H., Marcus, F. I., Bremner, W. F., Schulman, I. C., Phillips, A. Treatment of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments: experience in 26 cases. New England Journal of Medicine 25 Nov 1982 307: 1357-1362

[6]Antman, E. M., Wenger, T. L., Butler, V. P., Jr., Haber, E., Smith, T. W. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. Final report of a multicenter study. Circulation Jun 1990 81: 1744-1752

[7]Wenger, T. L., Butler, V. P., Jr., Haber, E., Smith, T. W. Treatment of 63 severely digitalis-toxic patients with digoxin-specific antibody fragments. Journal of the American College of Cardiology May 1985 5: 118A-123A

DigiFab was originally developed in the US; therefore, some documents in the enclosed dossier refer to the active ingredient by its US approved name of "Digoxin Immune Fab (Ovine)" instead of the Australia Approved name "Digoxin-specific antibody fragment f(Ab) (Ovine)". The sponsors have assured the TGA that both these names refer to the same active ingredient. It is important to note that DigiFab was initially called DigiTAb and both these terms have been used interchangeably in the CSRs in the submitted dossier and throughout this evaluation report.

> Comments: Life-threatening digoxin toxicity is not common and, as such, DigiFab has been designated an orphan medicinal product in Australia which requires the prevalence of the condition to be less than 2000 patients. The rarity of the condition, coupled with the indicated use in a hospital emergency setting, means that a conventionally designed clinical trial program was not appropriate or even possible for DigiFab. The nature of the condition severely restricted the ability to recruit adequate numbers of subjects in order to pursue formal randomised, controlled trials. It is acknowledged that the clinical data set is limited compared with the current expectations for a standalone marketing authorisation application but this is a result of the emergency nature and the prevalence of the condition for which the product will be used. The sponsor does not intend to conduct further clinical studies of DigiFab.

Paediatric data

The submission did not include paediatric data. Specific studies in paediatric patients have not been conducted and no paediatric 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.

Good clinical practice

All studies were conducted in accordance with the protocol and Good Clinical Practices (GCP) including the archiving of patient records and informed consent documents.

Pharmacokinetics

Studies providing pharmacokinetic data

There were 2 clinical pharmacology studies (TAb007-02 and TAb007-001), both provided PK and PD data.

Table 2 shows the studies relating to each PK topic.

Table 2. Submitted pharmacokinetic studies.

PK topic	Subtopic		Study ID
PK in healthy adults	General PK -	Single dose	TAb007-02
	-	Multi-dose	NA
	Bioequivalence† -	Single dose	NA
	-	Multi-dose	NA

PK topic	Subtopic	Study ID
	Food effect	NA
PK in special populations	Target population § - Single dose	TAb007-01
	- Multi-dose	NA
	Hepatic impairment	NA
	Renal impairment	Literature only
	Neonates/infants/children/adolescents	NA
	Elderly	NA
Genetic/gender -related PK	Males versus females	Not evaluated
	Other genetic variables	NA
PK interactions		Not evaluated
Population PK analyses	Healthy subjects	NA
	Target population	NA
	Other	NA

NA- Not applicable.

Evaluator's overall conclusions on pharmacokinetics

A parallel comparison Study TAb007-02 evaluated bioequivalence of proposed DigiFab (DigiTAb) to the currently marketed Digibind in 16 healthy subjects. Both DigiTAb and Digibind are ovine affinity purified Fab antibody fragments raised against digoxin which have similar in vitro binding affinities for digoxin. Since it would be difficult to show bioequivalence in patients, this study was undertaken in volunteers who were given a 1 mg digoxin dose intravenously, followed by observation for two hours and then given an equimolar dose of either DigiTAb or Digibind.

Generally, bioequivalence between a currently marketed product and a generic competitor is demonstrated by showing that both have similar distribution and elimination characteristics by serially measuring blood concentrations. However, this may be misleading for antibody products since efficacy depends on binding capacity and affinity. Therefore the aim of Study TAb007-02 was to demonstrate that DigiTAb and Digibind were equally effective in binding and neutralizing serum free digoxin as this is the best parameter that is indicative of the biological activity and its antidote efficacy. Secondary outcome parameters were pharmacokinetic dispositions of total digoxin and ovine Fab, which were used to support the bioaffinity data.

The primary study endpoint was a reduction in free digoxin serum concentrations to below 0.3 ng/mL represented by serum free digoxin area under the plasma concentration time curve (AUC). Results showed that both Digibind and DigiTAb reduced serum free digoxin concentration to zero in all subjects. The very nature of this endpoint precludes a statistical comparison[8] between groups. These data demonstrate that both Digibind and DigiTAb bind and neutralise digoxin in a similar manner.

The fact that the maximum total digoxin concentrations immediately after the DigiTAb and Digibind infusions were similar to the maximum concentrations immediately after the digoxin infusion is indirect evidence supporting equal bioaffinity of the two products for digoxin. Both DigiTAb and Digibind caused most of the administered digoxin to re-distribute back into the central compartment. These data indicate that DigiTAb binds and neutralises digoxin in a manner equivalent to Digibind and that DigiTAb leads to effective reversal of digoxin toxicity.

It was also observed in this study that systemic Fab and total digoxin clearance were significantly greater in subjects who received DigiTAb compared with those who received Digibind. Much of the difference in systemic clearance of total digoxin appears to be due to an increased renal clearance of total digoxin in subjects receiving DigiTAb. Thus, it appears that DigiTAb is handled by the systemic circulation differently than Digibind. As DigiTAb is eliminated from the circulation faster than Digibind, it eliminates digoxin from the circulation faster as well. However, differences in Fab pharmacokinetic parameters can exist between DigiTAb and Digibind independently of similar measures of digoxin neutralisation.

The elimination half-life of DigiFab in renal failure has not been clearly defined. It is noted that 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 patients with renal dysfunction than in patients with normal renal function. However, as it is probable that excretion of the Fab fragment-digoxin complex from the body is delayed patients with severe renal failure who receive DigiFab for digitalis toxicity should be monitored for a prolonged period for possible recurrence of toxicity and this fact has been adequately addressed in the proposed PI.

Studies of drug interactions have not been conducted with DigiFab.

Pharmacodynamics

Table 3 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 3. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on digoxin levels and PD effects of digoxin	Study TAb007-02
Secondary Pharmacology		NA

[8]This is because free digoxin concentrations below the assay limit of quantitation, if they could be determined, are substantially below clinically meaningful concentrations and the clinical significance of a statistical difference (if it could be measured) would be inconsequential.

PD Topic	Subtopic	Study ID
Gender other genetic and Age-Related Differences in PD Response	Effect of gender	NA
	Effect of genetic characteristics	NA
	Effect of age	NA
PD Interactions	Not evaluated	NA
Population PD and PK-PD analyses	Healthy subjects	NA
	Target population	NA

§ Subjects who would be eligible to receive the drug if approved for the proposed indication. ‡ And adolescents if applicable.

Evaluator's overall conclusions on 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 patients with digoxin toxicity, 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.

Both DigiFab and Digibind were equally effective in binding and neutralising digoxin despite differences in pharmacokinetics of DigiFab and Digibind (ovine Fab). DigiFab reduced free digoxin levels to below the lower limit of quantification (LOQ) for up to 8 h after which there was some rebound of free serum digoxin levels (but these were still close to the LOQ).

In Study TAb007-02 after the digoxin infusion there were no consistent changes in the PR interval but the corrected QT (QTc) interval shortened and all patients had T-wave depression. Combining these parameters, the PTQ index increased about 250% after administering digoxin and had not returned to baseline values even after seven days. After Fab administration, the PTQ index decreased in both the Digibind and DigiTAb groups, although there was a statistically significant difference at eight hours after digoxin dosing between the Digibind and DigiTAb group, with a lower PTQ in the Digibind group. This was partly due to a diminished response in two of the male volunteers in the DigiTAb group, whereas the two females groups showed a comparable decrease. The diminished response for the male volunteers could not entirely be explained by a greater plasma clearance of Fab or re-occurrence of free digoxin, however, they had relatively low urine Fab concentrations, suggesting greater renal catabolism of the Fab.

Dosage selection for the pivotal studies

Not applicable.

Efficacy

Of the 3 studies included in the dossier submitted by the sponsor, only 2 Studies (PR007-CLN-rpt003 and TAb007-001) involved patients (Study TAb007-2 was conducted in

healthy subjects). There were no randomised, controlled studies due to the nature of the proposed indication and both the studies in patients only involved historical control (TAb007-001) or a retrospective review of clinical cases (PR007-CLN-rpt003). Hence, these studies may not meet the criteria of being 'pivotal' studies under regulatory guidelines, but they are pivotal to the evaluation of this submission and have been discussed in this section of the evaluation report due to the following reasons:

1. the rare and emergency nature of the proposed indication of digoxin toxicity,
2. these two clinical studies (and Study TAb007-02 in healthy subjects) are the only studies specifically conducted with DigiFab worldwide, and
3. the sponsor does not intend to conduct further clinical studies of DigiFab.

Evaluator's conclusions on clinical efficacy

The three studies submitted in this dossier (TAb007-01, TAb007-02 and PR007-CLN-rpt 003) were adequate considering the rare and emergency nature of the proposed indication of digoxin toxicity. It is acknowledged that these three clinical studies are the only ones to have been specifically performed on DigiFab worldwide. Life-threatening digoxin toxicity is a rare condition and DigiFab has been designated an orphan medicinal product in Australia. A total of 37 subjects or patients received DigiFab in the clinical program.

The most important clinical endpoint in examining the efficacy of DigiFab is the assessment of serum free digoxin concentrations. Standard pharmacologic texts such as Goodman and Gilman describe the therapeutic effects of digoxin as being related to its serum concentrations. There is a well-established relationship between neutralisation of digoxin and clinical symptom resolution. Therefore, digoxin neutralisation determined by assessment of serum digoxin levels is an appropriate primary endpoint for assessment of Fab efficacy in the prospective Study TAb007-01.

The efficacy of DigiFab in terms of clinical resolution of symptoms associated with digoxin toxicity was also evaluated in these studies. The ability to determine whether clinical symptoms have resolved will depend on whether the symptoms are due only to digoxin toxicity or are confounded by an underlying renal or cardiac condition. Such underlying conditions are more likely to be present in patients with chronic digoxin toxicity who have been taking digoxin to treat underlying disease than in those with acute toxicity following an attempted suicide or an overdose. The resolution of clinical symptoms will be more clearly and rapidly seen in patients who have acute toxicity and no underlying condition than in those who have chronic toxicity.

The study designs had certain limitations and it is acknowledged that comparison with historical data presents some difficulties, as does a retrospective review, and patient numbers were limited due to the nature of the condition.

In Study TAb007-01 involving 15 patients with digoxin toxicity, serum free digoxin concentrations (the primary efficacy endpoint for this study) fell to or below the level of detection (0.3 ng/mL) following DigiTAb administration in all patients. Seven of 15 (47%) patients treated had complete resolution of digoxin toxicity by 4 h after DigiTAb administration and 14 (93%) patients had complete resolution by 20 h. Ten patients (67%) showed improvement in their electrocardiogram (ECG) within 4 h of DigiTAb administration.

The results from the retrospective Study PR007-CLN-rpt 003 involving 14 patients corroborate efficacy and safety findings from the prospective DigiFab study of 15 patients (TAb007-02). For all efficacy endpoints, there was a progressively increasing rate of improvement over time across all patients with evaluable data. By the end of the 72 h post-treatment time interval, 100% (11/11) of evaluable patients demonstrated cardiac

improvement , 100% (6/6) demonstrated improvement in gastrointestinal abnormalities, 88% (7/8) showed improvement in neurological abnormalities general clinical disposition improved in 100% (9/9) of evaluable, and the rate of normalisation of serum potassium levels was 86% (6/7). No patients demonstrated worsening of any efficacy endpoint during any time interval for which data were available after treatment.

These two independent studies were able to demonstrate that administration of DigiFab resulted in effective improvement in life-threatening digoxin toxicity in a majority of the patients treated. As the half-life of digoxin in patients with normal renal function is around 2 days, and even longer in patients with renal impairment, rapid reduction of digoxin concentrations, and resolution of digoxin toxicity, as demonstrated in the studies of DigiFab would not have been expected to occur spontaneously within 24 hours, without the intervention of DigiFab. It is not possible to rule out that resolution of toxic effects was related to time (for example, metabolism and elimination of digoxin via biological processes) but this is a limitation inherent to uncontrolled, retrospective studies.

Despite a small number of patients and the limitations associated with the use of a historical control and with the conduct of a retrospective review, there were pharmacodynamic effects (reduction in serum free digoxin levels) and clinical responses that provided evidence of the efficacy of DigiFab in the treatment of digoxin toxicity. However, efficacy of repeated dose of DigiFab was not evaluated adequately (only 1 patient in retrospective study PR007-CLN-rpt003 received 2 doses of DigiFab).

Safety

Studies providing evaluable safety data

The following 3 studies provided evaluable safety data with DigiFab:

1. TAb007-01: a prospective, historically controlled, multicentre study of the safety, pharmacokinetics and pharmacodynamics of DigiFab in patients presenting with life-threatening digoxin toxicity. Patients in the historical control group were treated with Digibind.
2. PR007-CLN-rpt003: Multicenter Retrospective Review of the Clinical Efficacy and Safety of DigiFab in Digoxin Poisoned Patients.
3. TAb007-02: an open-label, parallel, randomised, pharmacokinetic and pharmacodynamic comparison between DigiFab and Digibind in healthy volunteers.

All patients and healthy subjects treated with DigiFab were evaluated for safety during hospitalisation and at follow-up. Safety assessments were based on physical examination, vital signs (heart rate, blood pressure, respiration rate and temperature), ECG, clinical laboratory measures and interviews for subjective complaints. All patients and healthy subjects in the clinical trials of DigiFab were assessed for adverse events (AEs) while institutionalised or hospitalised. Follow-up visits were scheduled to assess any delayed or late adverse reactions to the study medication which may have presented after hospital discharge (except in the retrospective review study, PR007-CLN-rpt003). In the healthy subject Study TAb007-02, subjects were hospitalised for one day and follow-up visits were at 48 h, 7 days and 26 to 30 days after digoxin was administered. Digoxin toxic patients treated with DigiFab were assessed for AEs by direct observation during hospitalisation; patients in Study TAb007-01 were instructed to inform the study coordinator or the investigator of any AE that occurred after hospital discharge. During the 26 to 30 day follow-up visit, patients were asked about AEs in general. Safety was measured in the retrospective Study PR007-CLN-rpt003 as the total number of serious and non-serious drug-related AEs, the total number of drug-related AEs per patient and the rates of occurrence of specific drug-related AEs according to the patient records.

Integrated statistical analysis was not performed because the populations in the 3 studies were not similar. Descriptive statistics (number, percentage, mean, median, standard deviation and range) were calculated for all trials as applicable.

Patient exposure

A total of 37 subjects have received DigiFab in clinical trials (8 healthy subjects and 29 patients with digitalis toxicity); 8 subjects received active comparator. All healthy subjects and all but one patient in the digoxin toxicity trials were treated with a single dose of DigiFab. One patient received a second dose of DigiFab in Study PR007-CLN-rpt003 (Table 4). The mean age of patients in the clinical studies was 64 to 71 years with majority (50-60%) being female; however, the study in healthy subjects had a younger population with mean age of 29 years (Table 5).

Table 4. Extent of exposure to DigiFab

Protocol	DigiFab Dose	No. Treated
TAb007-02 (Healthy subjects)	76 mg	8
TAb007-01 (Digoxin toxicity)	1-20 vials, 40-45 mg/vial	15
PR007-CLN-rpt001 (Retrospective review)	1-10* vials, 40mg/vial	14
Total number patients/subjects treated		37

* One patient received 7 vials as an initial dose with 3 further vials as a second dose.

Table 5. Demographic data

Demographic Parameters	TAb007-01	PR007-CLN-rpt003	TAb007-02	
	DigiFab n=15	DigiFab n=14	DigiFab n=8	Digibind n=8
Mean age, years (±SD)	64 (15)	71(14)	29 (4)	26 (2)
Age range, years	40-85	47-90	22-33	24-30
Mean body weight kg (±SD)	72 (20)	79.5 (20.1)	74 (9)	72 (7)
Mean height cm (±SD)	165 (9)	164.3 (14.6)	180 (7)	174 (6)
Gender:				
Male	6 (40%)	7(50%)	4 (50%)	4 (50%)
Female	9 (60%)	7(50%)	4 (50%)	4 (50%)

Postmarketing experience

DigiFab has been marketed and used in patients in the USA since February 2002. Recently, DigiFab was also approved in the United Kingdom (UK), Canada and Switzerland. It is not possible to determine the number of patients treated or the doses received but an estimate based on the average dose (4 vials) used in the DigiFab study (TAb007-01) would indicate 74,830 patients received DigiFab during that time. There have been five (5) spontaneous cases up to the 31 August 2011 and all of the events involved cases of digoxin toxicity and elevated digoxin levels. The reporters' assessments of these cases were based solely on the fact that serum digoxin concentrations did not respond as expected. Additional clinical information related to these patients was unavailable despite attempts to obtain it. It was not possible to confirm potency of the DigiFab preparations with the exception of once case (this batch of DigiFab was found to pass specification). No further action was taken regarding these events and these events were not considered to be indicative of an adverse trend in relation to DigiFab product quality.

This additional postmarketing evidence supports the relative safety of DigiFab, although the applicant acknowledges that adverse drug reactions (ADRs) are underreported and the acute nature of treatment with DigiFab makes it difficult to identify ADRs, particularly if hypersensitivity is delayed.

In 2013, there was a spontaneous serious adverse event was received from a nurse concerning death of a male due to digoxin toxicity. Based on review of the limited information provided by the sponsor for this case, it is very difficult to rule out any relationship between lack of efficacy of DigiFab and death due to digoxin toxicity in this patient. However, interpretation is limited by lack of information on the actual digoxin-specific Fab used in this patient, dose and time of administration.

Also in 2013, there was a report of death from toxic digoxin levels/Digoxin level was higher (8.1 µg/L) [Drug effect decreased]. This spontaneous adverse event was received from a pharmacist concerning a patient, age and gender not reported. The patient's medical history included atrial fibrillation from an unspecified date, for which digoxin was given. According to the lab results, there was slight reduction in digoxin levels following administration of DigiFab, but these were again raised to toxic levels (8.1 µg/ml) before death of the patient. It is very difficult to rule out any relationship between lack of efficacy of DigiFab and death due to digoxin toxicity in this patient. However, there is very limited data available case including confirmed digoxin levels and dose and timing of digoxin immune Fab administration with relation to digoxin toxicity.

During the course of this evaluation, there was a report of a serious adverse event (SAE) (death of an elderly patient.). Review of the report suggested that the death which occurred 5 days following administration of DigiFab was due to fatal acute kidney injury, dehydration, chronic heart failure, ischaemic heart disease (IHD) and anaemia to be unrelated to DigiFab. Following review of limited data available, it appears that this case report does not modify the risk benefit balance of DigiFab.

> Comments: Overall, review of the above 3 spontaneous reports of deaths suggest that cause of death may have been related to lack of efficacy of DigiFab. However, interpretation is limited by lack of adequate data especially regarding temporal relationships and inadequate information on serum digoxin levels.

Safety issues with the potential for major regulatory impact

Cardiovascular safety

The incidence of CV AEs was high but this would be expected considering the nature of the disease being treated.

Unwanted immunological events

There were no reports of anaphylactic or anaphylactoid reactions in the 3 clinical studies provided in this submission.

However, 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 (such as urticaria, pruritus, erythema, angioedema, bronchospasm with wheezing or cough, stridor, laryngeal oedema, hypotension, tachycardia) and treated immediately with appropriate emergency medical care (such as 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 adrenaline 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. Following discharge from the hospital, patients should be advised to contact their physician immediately if they experience any signs and symptoms of delayed allergic reactions or serum sickness (such as rash, pruritus and urticaria) after hospital discharge. 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.

All the above facts have been adequately covered in the proposed PI for DigiFab.

Evaluator's overall conclusions on clinical safety

All patients and healthy subjects treated with DigiFab were evaluated for safety during hospitalisation and at follow-up. Safety assessments were based on physical examination, vital signs (heart rate, blood pressure, respiration rate, and temperature), ECG, clinical laboratory measures and interviews for subjective complaints. A total of 37 subjects or patients have received DigiFab in clinical studies (TAb007-01, TAb007-02 and PR007-CLN-rpt003. Doses of DigiFab ranged from 76 mg in the healthy subject study (N = 8) up to 800 mg (20 vials; average dose 160 mg or 4 vials) in the patient studies (N = 29). All healthy subjects, and all except one patient in the digoxin toxicity studies, were treated with a single dose of DigiFab. One patient in study PR007-CLN-rpt003 received two doses of DigiFab.

In the clinical studies of DigiFab, 6 of 15 patients in the digoxin overdose study (TAb007-01) had a total of 17 AEs , most were mild to moderate in nature and all were deemed only "remotely associated" with DigiFab. Three events were deemed "severe", all occurred in one patient and consisted of the following: pulmonary oedema, 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. The remaining 41 AEs that occurred during the study were deemed "not associated" with DigiFab. In Study PR007-CLN-rpt003 a total of 14 AEs were identified in 10 patients during and/or up to 72 h after the initiation of treatment. Two serious AEs (SAEs) were reported (cardiac arrest and respiratory failure), both of which were judged to be unrelated to DigiFab therapy. Only two (14%) events were deemed as related to the study drug; both were cardiovascular disorders (hypotension, severe; tachycardia, moderate).

Of 8 healthy subjects who received DigiFab in Study TAb007-02, only 2 experienced an AE that was considered to be associated with DigiFab. The reactions were 1 episode of phlebitis of the infusion vein and 1 episode of moderate postural hypotension, which became mild prior to resolving. In all 3 clinical studies, the patients (or healthy subjects in Study TAb007-01) experienced no anaphylactic or anaphylactoid reactions.

Rebound of serum free digoxin levels is unlikely to be of significant clinical consequence in patients with normal renal function, however 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 DigiFab therapy. This clinical event persisted for more than a week. Failure to clear the Fab-digoxin complex from the blood by glomerular filtration and renal excretion may be anticipated in anephric patients. 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 recrudescent toxicity in renal failure patients. The above facts have been adequately addressed in the proposed PI for DigiFab.

Based on experience with the highly similar product 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;
- Hypokalaemia due to reactivation of the sodium-potassium ATPase;

- Rapid ventricular response in patients with atrial fibrillation due to withdrawal of the effects of digitalis on the atrioventricular node;
- Rare allergic reactions.

These have been adequately mentioned in proposed PI and Consumer Medicines Information (CMI) for DigiFab.

Clinical laboratory data support the safety of DigiFab. No clinically or statistically significant abnormal laboratory values were attributed to DigiFab in the clinical studies undertaken (although only creatinine and potassium levels were recorded from the retrospective review study). No Human Anti-Sheep Antibody (HASA) response was observed in any of the patients or subjects tested.

Across studies, no DigiFab infusion was terminated due to an AE, nor were there any DigiFab related deaths. There was one unrelated death and three other patients who experienced 4 serious AEs in the study TAb007-01. None of these serious adverse events (SAEs) were considered related to DigiFab but were considered to be related to the underlying cardiac condition of the patient and due to withdrawal of inotropic support of digoxin.

Although it is recognised that there are difficulties deriving meaningful and definitive conclusions on safety based on the size and nature of the studies conducted, it is apparent that DigiFab was generally well tolerated in the two populations studied (healthy subjects and patients with digoxin toxicity). No unexpected safety concerns were identified and no patient treated in the digoxin-toxicity study had an AE that was considered possibly, probably or definitely related to DigiFab. In comparison, historical data on Digibind in the studies reported by Antman (1990)[9] and Hickey (1991)[10] showed that 7 to 9% of patients experienced an AE considered possibly or probably related to Digibind. The AE profile was similar to that of Digibind in the study of healthy subjects.

DigiFab has been marketed and used in patients in the USA since February 2002. More recently DigiFab was also approved in the UK, Canada and Switzerland and it is estimated that 74,830 patients received DigiFab during that time. The postmarketing evidence supports the relative safety of DigiFab, although the applicant acknowledges that adverse drug reactions (ADRs) are underreported and the acute nature of treatment with DigiFab makes it difficult to identify ADRs, particularly if hypersensitivity is delayed. Finally, a patient registry is currently underway in the UK to collect additional information on safety and immunogenicity associated with the use of DigiFab. As no subjects under 18 years of age, pregnant or lactating women, patients with hepatic impairment, patients with previous pacemaker insertion or who have been treated with a previous dose of digoxin immune Fab were included in the DigiFab studies, the safety of these populations will be followed closely through routine post-approval pharmacovigilance.

Safety of repeated dose of DigiFab was not evaluated adequately (only 1 patient in retrospective study PR007-CLN-rpt003 received 2 doses of DigiFab).

[9]Antman, E. M., Wenger, T. L., Butler, V. P., Jr., Haber, E., Smith, T. W. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. Final report of a multicenter study. Circulation Jun 1990 81: 1744-1752

[10]Hickey, A. R., Wenger, T. L., Carpenter, V. P., Tilson, H. H., Hlatky, M. A., Furberg, C. D., Kirkpatrick, C. H., Strauss, H. C., Smith, T. W. Digoxin Immune Fab therapy in the management of digitalis intoxication: safety and efficacy results of an observational surveillance study. J Am Coll.Cardiol. 1 Mar 1991 17: 590-598

First round benefit-risk assessment

First round assessment of benefits

The benefits of DigiFab in the proposed usage are:

- Despite a small number of patients and the limitations associated with the use of a historical control and with the conduct of a retrospective review in the 2 clinical studies (TAb007-02 and PR007-CLN-rpt 003), there were pharmacodynamic effects (reduction in serum free digoxin levels) and clinical responses that provided evidence of the efficacy of DigiFab in the treatment of digoxin toxicity.
- DigiTAb (DigiFab) was shown to bind digoxin in a manner equivalent to Digibind, reducing serum free digoxin levels to below 0.3 ng/ml (lower limit of quantification (LOQ)) in all treated healthy subjects (TAb007-02).
- DigiFab was generally well tolerated in the two populations studied (healthy subjects and patients with digoxin toxicity). No unexpected safety concerns were identified and no patient treated in the digoxin-toxicity study had an AE that was considered possibly, probably or definitely related to DigiFab.
- DigiFab would help to provide supply of a potentially life-saving product for the treatment of digoxin poisoning for the Australian population.

First round assessment of risks

The risks of DigiFab in the proposed usage are:

- Comparison with historical data (Study TAb007-01) presents some difficulties in interpretation of efficacy and safety of DigiFab, as does a retrospective review (PR007-CLN-rpt003).
- Of the 29 patients evaluated in the 2 clinical DigiFab studies, majority had chronic digitalis poisoning. Efficacy/ safety of DigiFab were not evaluated adequately in patients with acute digoxin toxicity.
- Efficacy and safety was only evaluated following a single dose of DigiFab (only 1 patient in retrospective Study PR007-CLN-rpt003 received 2 doses of DigiFab).
- The number of patients evaluated is much below recommended guidelines for a new chemical entity (NCE) although it is acknowledged that digoxin toxicity is rare and the emergency nature of the proposed indication makes recruiting patients into trials difficult.
- 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. Although no patient in the clinical studies of DigiFab has experienced a severe anaphylactic reaction, the possibility of an anaphylactic reaction cannot be ruled out and should be considered.

First round assessment of benefit-risk balance

Life-threatening digoxin toxicity is not common and, as such, DigiFab has been designated an orphan medicinal product in Australia whereby the prevalence of the condition must be less than 2000 patients. It is acknowledged that the clinical data set is limited compared with the current expectations for a stand-alone marketing authorisation application but this is a result of the emergency nature and the rare prevalence of the condition. The

nature of the condition severely restricted the ability to recruit adequate numbers of subjects in order to pursue formal randomised, controlled trials.

Antibody preparations in the treatment of digoxin toxicity have been available for over twenty years. The majority of literature reports on the efficacy and safety of digoxin toxicity antibody therapy relate to Digibind, as this was the first digoxin-specific Fab product approved in the UK (1985), USA (1986) and Australia (1991). Although authorisation of DigiFab is not being sought on a biosimilar basis, demonstration of equivalent digoxin binding capacity of DigiFab with already approved Digibind would still be relevant to the demonstration of efficacy for DigiFab. Furthermore, evidence for efficacy of DigiFab is provided from the clinical studies in terms of binding of DigiFab to digoxin (measured as free and total digoxin concentrations), together with clinical evidence (ECG changes, clinical sequelae) of concomitant loss of glycoside effects.

Although it is acknowledged that comparison with historical data presents some difficulties, as does a retrospective review and patient numbers were limited due to the nature of the condition, these two independent studies were able to demonstrate that administration of DigiFab resulted in effective improvement in life-threatening digoxin toxicity in a majority of the patients treated.

DigiFab has very recently been granted approval under Section 19A of the Therapeutic Goods Act 1989, for the importation and supply of this unregistered therapeutic good.

Although it is recognised that there are difficulties deriving meaningful and definitive conclusions on safety based on the size and nature of the studies conducted, it is apparent that DigiFab was generally well tolerated in the two populations studied (healthy subjects and patients with digoxin toxicity). No unexpected safety concerns were identified and no patient treated in the digoxin-toxicity study had an adverse event that was considered possibly, probably or definitely related to DigiFab.

In conclusion, for patients with serious digoxin toxicity, immunotherapy with digoxin specific Fab remains the treatment of choice. DigiFab successfully reduces free digoxin concentrations, which is the primary efficacy endpoint for demonstration of efficacy. Although the clinical studies were small due to the rarity and nature of the condition and there were limitations associated with a comparison against a historical control and with a retrospective review, free digoxin concentrations were shown to be reduced by DigiFab, where it was possible to measure this parameter. In addition, DigiFab was effective in reversing the signs and symptoms of digoxin toxicity in patients. DigiFab was also well tolerated in both study populations and no unexpected safety concerns were identified. No clinically significant abnormal laboratory values have been attributed to DigiFab, and Human Anti-Sheep Antibody (HASA) was negative in all subjects tested. Additionally postmarketing evidence provides support to the relative safety of DigiFab. The benefit-risk balance for DigiFab as a treatment for life threatening digoxin toxicity is favourable and considering the anticipated withdrawal of Digibind from the marketplace will safeguard supply of a potentially life-saving product.

First round recommendation regarding authorisation

It is recommended that DigiFab be approved for proposed indication of

> *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 or bradyarrhythmias not responsive to atropine and where additional measures besides withdrawal of digoxin and correction of serum electrolyte abnormalities are considered necessary.*

The approval is subject to incorporation of changes to the proposed PI.

Clinical questions

Pharmacokinetics

None.

Pharmacodynamics

With regard to secondary pharmacodynamic effects, it is noted that after Fab dosing in Study TAb007-02, the PTQ index decreased in both groups. However, the fall was greater in the Digibind group and the difference from the result seen in the DigiFab group was statistically significant at 8 h. This difference would suggest a continued effect of digoxin in the DigiFab (DigiTAb) group which is contrary to what one would expect from the actual results for free and total digoxin. The sponsor is to provide critical comment on this difference and whether it may or may not be of clinical significance.

Efficacy

None.

Safety

It is noted that a patient registry is currently underway in the UK to collect additional information on safety and immunogenicity associated with the use of DigiFab. Has the sponsor any intention to set up a similar registry in Australia should the drug be approved and if not, why not? Does the sponsor see any impediment in its being able to gain access to any reports which may be issued from the UK registry? Will reports from the UK registry be actively sought by the sponsor as part of its overall programme of pharmacovigilance monitoring?

Second round evaluation of clinical data submitted in response to questions

The following section describes the sponsor's response to the *Clinical questions* posed above and the evaluator's comment on the sponsor's response.

Pharmacodynamics

Sponsor's response

In Study TAb007-02 the DigiFab and Digibind dosing groups produced similar reductions in PTQ index values. They fell in tandem for up to 4 h post digoxin until they temporarily separated. The observed PTQ index difference between the groups is also exaggerated by the focus of attention on the graph in the study report on the time period from 0 to 12 h. The only statistically significant difference was observed at the 8 h time-point. Subsequently, the PTQ index values for the two groups converged at 48 to 168 h post-digoxin, when no further differences were observed.

The changes in the PTQ index were due to a decrease in T-wave amplitude and similar differences between the groups were observed when T-wave depression was analysed. The T-wave represents the repolarisation of the ventricles and is the most difficult of the electrocardiographic deflections to interpret with certainty. It may also change under physiological conditions such as anxiety or fear. As the serum concentrations of total digoxin decreased faster in the DigiFab group and there were no measurable concentrations of free digoxin up to 8 h, the sponsors claim that it is difficult to explain the differences observed in T-wave depression between the two groups.

This study had a small sample size (n=8 per group; 4 male and 4 female) and the transient difference seen at 8 h may be attributable to two male subjects in the DigiFab group who had higher PTQ index values compared to other subjects. The two female subgroups (4 in each group) showed a comparable decrease in PTQ index values for DigiFab and Digibind. The published literature describing the relationship between PTQ index, a derived value, and digoxin concentration shows that there is considerable inter-patient variability in response and that the PTQ index responds slowly to changes in digoxin concentrations.[11] The single transient difference in PTQ index seen between DigiFab and Digibind at 8 h is considered spurious and probably resulted from the small sample size and known inter-patient variability in ECG responses with digoxin, particularly in patients without digoxin toxicity (that is, healthy volunteers). Hence, the sponsors state that they would not expect the changes in PTQ index to be a reliable surrogate marker of digoxin pharmacologic activity in such a small study and they believe that the observed difference in this study of healthy volunteers is not likely to be clinically meaningful.

Evaluator's comments on sponsor's response

The explanation provided by the sponsors is acceptable.

Safety

Sponsor's response

The sponsors have highlighted the orphan drug status of the proposed product for registration, with less than 2000 cases per year requiring administration of the proposed product. Such a patient registry collects information that is voluntarily provided by physicians and patients, which only forms a small portion of the total patients exposed to the product. Based on this, the sponsor (Phebra) sees only a limited value in setting up a separate patient registry for Australia, on top of the current pharmacovigilance programme. The UK has a much larger patient population compared to Australia with similar demographics; it is believed to be a relevant and greater source of information on safety and immunogenicity associated with the use of DigiFab. Information from the UK patient registry will be readily available to Phebra as per the current safety data exchange and contractual agreements and reports from UK registry will be actively sought as part of the overall pharmacovigilance monitoring programme of Phebra. Updates and safety issues identified from the UK patient registry will be discussed in Periodic Safety Update Reports (PSURs) and the Risk management Plan (RMP) will be updated as required.

Evaluator's comments on sponsor's response

Although the sponsors do not plan to set up a patient registry in Australia, they have confirmed that the information from the UK patient registry will be readily available to them and will be included in the updated PSURs and RMP.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of responses to clinical questions, the benefits of DigiFab in the proposed usage are unchanged from those identified in the First Round Evaluation.

[11] Joubert, P., Kroening, B., Weintraub, M., Fleckenstein, L. Correlation between electrocardiographic changes, serum digoxin, and total body digoxin content. *Clinical Pharmacology and Therapeutics* Dec 1976 20: 676-681

Second round assessment of risks

After consideration of responses to clinical questions, the risks of DigiFab in the proposed usage are unchanged from those identified in the First Round Evaluation.

Second round assessment of benefit-risk balance

After consideration of responses to clinical questions, the benefit-risk balance of DigiFab in the sponsor's proposed usage are unchanged from those identified in the First Round Evaluation.

Second round recommendation regarding authorisation

It was recommended that DigiFab be approved for a revised indication of:

> *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 or bradyarrhythmias not responsive to atropine and where additional measures besides withdrawal of digoxin and correction of serum electrolyte abnormalities are considered necessary. However, the consequences of multiple dosing with DigiFab have not been evaluated.*

The approval was subject to incorporation of changes to the proposed PI.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan RMP version 1 (dated 21 June 2012) which was reviewed by the TGA's Office of Product Review (OPR). A summary of the RMP has been provided below.

Table 6. Summary of Risk Management Plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risks: By blocking the toxic and therapeutic effect of digoxin, DigiFab may exacerbate the underlying cardiac disease for which the patient is being given digoxin	Routine pharmacovigilance	Routine risk minimization Activities. This risk is specifically mentioned in the PI
Important potential risks: Allergic reactions	Routine pharmacovigilance	Routine risk minimization Activities. This risk is specifically mentioned in the PI

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important missing information: Usage in patients under 18 years of age, pregnant or lactating women, patients with hepatic impairment or patients of ethnic origin other than Caucasian, and patients with previous pacemaker insertion or who have been treated with a previous dose of digoxin immune Fab Effects of DigiFab medication errors and overdoses.	Routine pharmacovigilance	Routine risk minimization activities via post-marketing pharmacovigilance The fact that these populations were not studied is included in the PI.

Reconciliation of issues outlined in the RMP report

The following table summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 7. Table 17. RMP Round 1 evaluation, sponsor's response and RMP Round 2 evaluation.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Could the sponsor please provide a glossary of important terms–abbreviations used in the RMP.	*The RMP Glossary was provided as requested.*	The sponsor's response is satisfactory
It is recommended to the Delegate that Digoxin assay measurement be added to the ongoing safety concerns as an important potential risk.	*The RMP will be updated to include the digoxin assay meaurement as an important potential risk. The proposed text to be included is the following:* *Safety Concern* *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*	The sponsor's response is satisfactory

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	several days or more than a week in patients with impaired renal function. *Proposed risk minimization activities* *The risk is specifically mentioned in the Product Information.*	
The evaluation of the RMP for DigiFab submitted in the United Kingdom (approval in 2011) recommended the need to establish a patient registry in order to improve knowledge of effectiveness and safety and the development of immunogenicity for patients who receive DigiFab for digoxin overdose. Could the sponsor inform the TGA whether the UK patient registry has been established? Findings from the patient registry should be discussed in PSUR's and the RMP updated as required.	*The UK patient registry has been established and will be discussed in the PSUR. Updates to the RMP will also be made as required.*	The sponsor's response is satisfactory. It is recommended that findings through analysis of the registry data are communicated to the TGA at the same time as they are communicated to other regulatory agencies.
It is recommended to the sponsor that they adapt the posology recommended by the Australian Poisons Information Centres as this service offers trained staff-led advice on management of subjects with digoxin toxicity.	Refer to sponsor's response to Recommendation 5. Below.	Refer to evaluator's comment below.
In regard to the proposed routine risk minimisation activities, the draft product information document - dosage and administration section lacks clarity. The sponsor is recommended to provide 'real world' examples of DigiFab dose calculation for an adult and a child for the following toxicity scenarios: -acute, acute on chronic and chronic. Furthermore the addition of flow charts to aid providers in calculating the dose is recommended.	*'A revised dosage and administration section is proposed below; however, in accordance with the instruction in the RMP evaluation report, the product information (PI) has not been updated to include this revised section yet. The revised dosing section refers to a flow chart, which Phebra proposes would be an addendum to the PI, to aid providers in calculating the recommended dose. A copy of the dose determination*	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	flowchart is enclosed with this response'	
In regard to the proposed routine risk minimisation activities, the draft consumer medicine information document is considered satisfactory although it is recommended that the consumer medicine information sheet be updated to include the contact details for the Australian Poisons Information Centres.	*'Please note that the contact details of Australian Poisons Information Centre (13 11 26) is already included in the proposed consumer medicine information sheet provided with the initial submission to the TGA, on page 2, under "if you are given too much (overdose)".*	The sponsor's response is satisfactory.

Summary of recommendations

It was considered that the sponsor's response to the TGA's request for information has adequately addressed most of the issues identified in the RMP evaluation report. Outstanding issues are described below.

Outstanding issues

Issues in relation to the RMP

Details on the following outstanding issues are also discussed in the table '*Reconciliation of issues outlined in the RMP report*':

> *Recommendation 3:* The OPR evaluator noted that a patient registry has been established in the UK. The evaluator recommends that findings through analysis of the registry data are communicated to the TGA at the same time as they are communicated to other regulatory agencies.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

The OPR evaluator supports the Committee's view that the proposed Australian PI does not adequately address the consequences of overdosing, dosing in bradycardia and the problem of rapid reversal. It was recommended to the Delegate that the PI be updated to include advice on the consequences of overdosing, dosing in bradycardia and the problem of rapid reversal.

Suggested wording for conditions of registration

RMP

Implement RMP version 1 dated 21 June 2012 and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator has no objections to the registration of DigiFab with regards to formulation, manufacture, specifications, stability, viral and prion safety grounds, microbiology, quality, container safety and labelling.

Nonclinical

The nonclinical evaluator has no objections to the registration of DigiFab for the proposed indication. The data package comprised 3 studies comparing the efficacy of DigiFab with Digibind. The lack of nonclinical toxicology and PK studies was considered acceptable because of the well documented safety and PK of other affinity purified fab antibodies, including Digibind. No nonclinical studies investigating safety or efficacy in juvenile animals were submitted.

Clinical

The clinical evaluator has reviewed the submitted data, which included:

1. One clinical pharmacology study:
   - TAb007-02: a Phase III, open-label, parallel, pharmacokinetic and pharmacodynamic comparison between DigiTAb* and Digibind in 16 healthy subjects given 1 mg of intravenous digoxin.

     *DigiFab was initially called DigiTAb, throughout the remainder of this overview only the term DigiFab will be used.
2. Two clinical studies:
   - TAb007-01: an ongoing historically controlled, open-label, multicentre trial to determine the safety, pharmacokinetics, and pharmacodynamics of DigiFab administered to patients with potentially life-threatening digoxin toxicity.
   - PR007-CLN-rpt003: a multicentre retrospective review of the clinical efficacy and safety of DigiFab in digoxin poisoned patients.

The clinical evaluator recommended approval in the evaluation report. The concerns noted by the evaluator included:

- The small number of patients providing data, and the limitations associated with the use of an historical control and a retrospective review in the 2 DigiFab clinical studies.
- Lack of safety and efficacy data for repeated doses of DigiFab and in patients with acute digoxin toxicity.
- Potential for anaphylactic reactions.

Pharmacology

The pharmacology findings include:

- DigiFab has an affinity for digoxin in the range of 10^9 to 10^{10} M^{-1}
- DigiFab and Digibind were comparable in their ability to reduce serum free digoxin to levels below the assay limit of quantitation (LOQ), demonstrating equivalent bioaffinity. The majority of serum free digoxin concentrations remained below the assay LOQ for up to 8 hours in both groups.
- DigiFab and Digibind administration resulted in similar immediate increases in total digoxin concentrations, followed by a slow biexponential decline. Total digoxin AUC

values in the DigiFab group (406 ± 102 ng/mL*hr) were significantly lower than the values for the Digibind group (769 ± 162 ng/mL*hr).

- Cumulative urinary excretion of digoxin was comparable for DigiFab and Digibind and exceeded 40% of the administered dose by 24 hours.
- Total digoxin systemic and renal clearance was significantly greater in the DigiFab group (43.8 ± 13.3 mL/minute, and 20.8 ± 6.6 mL/min, respectively) compared to the Digibind group (22.5 ± 4.2 mL/minute and 11.6 ± 2.8 mL/min, respectively).
- Other DigiFab PK parameters were similar to Digibind (peak plasma concentration (Cmax), distribution half-life, and volume of distribution).
- There are no studies of DigiFab in patients with renal impairment and little data with other similar digoxin-specific Fab products. However, it appears that renal clearance is reduced by approximately 50%, and the elimination half-life increased by up to 10 fold.
- Estimated potency of DigiFab is that 1 mg of Fab will bind approximately 13 µg of digoxin (that is, approximately 76 mg of Fab will bind 1 mg of digoxin). This is consistent with the potency of Digibind.
- While there was statistically significant greater decrease in the PTQ index (a combination function of the PR-interval, corrected QT-time and T-wave depression in the ECG) with Digibind compared with DigiFab (suggesting continued effect of digoxin in the DigiFab group), this was not reflected in the actual measurements of free and total digoxin. (As per the sponsor's response on this issue, the likely explanation for this difference is the small sample size, and the known inter-patient variability in ECG responses with digoxin. This is considered acceptable).

Efficacy

Study TAb007-01

This is an ongoing, historically controlled, open-label, multicentre trial of DigiFab administered to patients of any age with potentially life-threatening cardiac toxicity caused by an acute or chronic ingestion of digoxin. Results are presented based on the 15 patients enrolled to date. The primary efficacy outcome was the reduction of serum free digoxin concentrations to <0.5 ng/mL, a concentration that was determined to be below the clinically therapeutic range. Clinical efficacy was a secondary objective, measured by the percent of patients showing resolution in digoxin-induced arrhythmias, high-grade conduction block, and/or severe neurological signs and symptoms at 2 and 4 h after DigiFab treatment.

Patients were included if they demonstrated acute or chronic digoxin toxicity in the following manner: ECG changes consistent with hyperkalemia in the face of digoxin toxicity; hemodynamic compromise associated with arrhythmias or requiring the use of epinephrine, atropine or antiarrhythmic agents; serum digoxin concentration > 4.5 ng/mL with symptoms of digoxin toxicity; digoxin-induced bradycardia unresponsive to atropine or signs and symptoms of profound neurological abnormalities; or a known ingestion in a child of > 0.1 mg/kg of digoxin.

The historical Digibind control data included an open-label multicentre study in 150 patients (including 25 aged ≤ 16 years) with life-threatening digitalis intoxication recruited between 1974 and 1986(Antman et al. 1990)[9], and 717 adult patients from a post-marketing surveillance study (Hickey et al. 1991)[10].

The dose of DigiFab was based on the amount needed to perform approximately equimolar neutralisation of the total body burden of digoxin, based on either the serum

concentration or known amount of digoxin ingested (median 2 vials, range 1to 20 vials). If the amount ingested was unknown and digoxin concentration was not available, the initial dose in adults was 20 vials. Patients were administered a single dose of DigiFab (with repeat doses allowed at the investigator's discretion). In the historical Digibind studies, a similar dose was used in the Hickey study (median 3 vials, range <1 – 40 vials) but a higher dose in the Antman study (median 5 vials, range up to 40 vials).

Of the 15 patients enrolled, 60% were female, mean age was 64 years (range 40-85 years), and the main causes of digoxin toxicity were chronic ingestion (67%), or suicide attempt (33%). The principal presentation was hemodynamic compromise (60%), and/or digoxin level >4.5 ng/mL (47%). The median baseline free serum digoxin concentration was 2.8 ng/mL (range: 1.1 to 13.0 ng/mL).

Overall, patient characteristics were similar in the historical studies, although adult patients in the Hickey study had a higher median age. A significantly higher ratio of patients had acute digoxin toxicity in the Antman study than in the DigiFab study, but there were no differences in this parameter between the DigiFab and Hickey studies. In the Antman study[9], cardiovascular manifestations of digitalis toxicity were known in 148 cases and included second or third degree block (53%), ventricular tachycardia (46%), ventricular fibrillation (33%), ventricular asystole (11%) and hyperkalemia (37%). In the Hickey study[10], cardiovascular manifestations included ventricular fibrillation (10%), asystole (9%) ventricular tachycardia (20%), hyperkalemia (26%), third-degree atrioventricular (AV) block (27%), ventricular extrasystoles (29%), second-degree AV block (27%), supraventricular arrhythmia (27%), first-degree AV block (17%), and nausea and vomiting (48%). The median baseline free serum digoxin/digitoxin concentration was 8.0 and 156.0 ng/mL, respectively in the Antman study and not reported in the Hickey study.

Of the 13 patients with a sample collected at the end of DigiFab infusion (0 h), all had free serum digoxin concentrations at or less than the assay limit of quantitation (0.3 ng/mL). The remaining 2 patients had a sample collected at 0.5 h post DigiFab infusion and also had free serum digoxin concentrations < 0.3 ng/mL. All patients maintained these levels for an average of 9.6 h after Fab infusion (range: 4.5 to 24.5 h). The maximum rebound free digoxin concentration averaged 1.4 ± 0.8 ng/mL (range: 0.3 to 2.8 ng/mL). The time to maximum free serum digoxin rebound averaged 15.1 h (range: 6.5 to 36.5 h).

Of the Digibind studies, only Antman and colleagues reported serum digoxin concentrations and only in a subset of 11 patients. All reported a free serum digoxin level of near zero after the infusion.

Complete clinical resolution of digoxin toxicity was reported in 6 (40%) of patients within 2 hours of DigiFab administration, with one additional patient resolving by 3 hours. All 7 patients (47%) maintained this at 4 h. By 20 h post infusion 14 (93%) of patients were considered by investigators to have resolution of their digoxin toxicity. In the Antman study[9], resolution of all signs and symptoms of digoxin toxicity were reported in 119 (80%) of 148 evaluable patients, and improved in 14 (10%), generally by 4 h post Digibind infusion. In the Hickey study[10], 357 (50%) of 717 patients showed complete resolution, and 172 (24%) showed partial improvement.

Blinded review of patient ECGs by an independent panel of physicians determined that 10 (67%) of patients had ECG abnormalities that improved within 4 h after the DigiFab infusion, with 6 patients maintaining the improvement throughout 24 h of hospitalisation. The remaining 5 patients had ECG abnormalities that were unchanged from baseline throughout hospitalisation.

Study PR007-CLN-rpt003

This was a multicentre, retrospective review of the medical records of 14 patients treated with one or more doses of DigiFab (as required) for life-threatening digoxin toxicity. Response to treatment was evaluated as the rates of improvement in cardiac (judged by review of ECG and rhythm recordings by an expert consensus panel), gastrointestinal, and neurological manifestations during four post-treatment time intervals (0 to 4 h, >4 to 12 h, >12 to 24 h, and >24 to 72 h), relative to baseline. Rates of improvement in general clinical status as well as normalisation of serum potassium levels were also assessed.

Patients were included if they were treated with DigiFab between January 1, 2003 and July 31, 2006; had a serum digoxin level ≥ 2 ng/mL before the start of DigiFab therapy; had one or more of the following life-threatening cardiac abnormalities, evident on ECG or rhythm strip (when available), within 6 h before the start of DigiFab: (1) Ventricular rate <45 beats per minute (bpm), (2) second degree heart block, (3) third degree/complete heart block, (4) Asystole, (5) Ventricular tachycardia, (6) Ventricular fibrillation. Patients with a pacemaker at baseline were excluded.

Of the 14 patients that met the inclusion/exclusion criteria, the majority were Caucasian (79%), 50% were female, mean age was 71 years (range 47 to 90 years), and all were treated for toxicity related to accidental/unintentional, chronic exposure. The principal cardiac rhythm abnormality was slow ventricular rate (<45 bpm) in 12 (86%) patients.

Cardiac (ECG) improvement was demonstrated in 3/7 (43%) of evaluable patients[12] at 0 to 4 h, 4/6 (67%) at >4 to 12 h, 7/9 (78%) at >12 to 24 h, and 11/11 (100%) at >24 to 72 h. In 4 of the 11 patients who ultimately improved, lack of data may have obscured improvement in an earlier time interval. There was no worsening of cardiac abnormalities at any post-treatment time interval in any patient.

The other manifestations of digoxin toxicity (gastrointestinal, neurological, general clinical status, and abnormal potassium levels) all showed varying degrees of improvement with DigiFab treatment at each time interval.

Safety

All 3 studies reported safety data. A total of 37 subjects (8 healthy subjects and 29 patients with digitalis toxicity) received a single dose of DigiFab, with the exception of 1 patient in Study PR007-CLN-rpt003 who received a second dose. The median dose of DigiFab administered was 80 mg (range 40 to 900 mg) in Study TAb007-01, 76 mg in TAb007-02, and 2 vials in PR007-CLN-rpt003. In the historical Digibind control studies, the median dose of Digibind was 200 mg (120 to 480 mg) [Antman study[9]] and 120 mg (98 to 1600 mg) [Hickey study[10]].

In Study TAb007-01 there were no AEs deemed possibly, probably or definitely related to the use of DigiFab (17 AEs were judged "remotely related", with 3 deemed "severe" [pulmonary oedema, bilateral pleural effusion and renal failure]). In comparison, 14 (9%) of patients on Digibind in the Antman study had AEs that were judged possibly or probably drug-related (hypokalaemia, exacerbation of CCF, hypotension). In the Hickey study, 52 (7%) patients reported AEs that were judged possibly or probably caused by Digibind (allergic responses, recurrence of digitalis toxicity, complications with readministration of digitalis, cardiovascular events).

In the retrospective Study PR007-CLN-rpt003, 2 AEs were judged from the patient medical records to be related to DigiFab: both were cardiovascular disorders (hypotension [severe]; tachycardia [moderate]).

[12]Patients with no ECG at the end of the relevant interval, or who were paced were not included in the denominator.

In Study TAb007-02, AEs that may have been associated with the Fab infusions included brief nausea during a Digibind infusion and hypotension 5 h after a DigiFab infusion.

No anaphylactic or anaphylactoid reactions were reported in the DigiFab studies. There were 2 potential acute hypersensitivity reactions (bronchospasm, hypotension) although only the hypotension was considered possibly related to treatment. To date, there have been no clinical reports of human anti-ovine immunoglobulin antibodies to DigiFab. No acute allergic reactions or serum sickness-type illnesses to Digibind were reported in the Antman study, while the Hickey study reported that 6 patients developed allergic reactions (2 with pruritic rash; 1 with pruritic rash, facial swelling and flushing; 1 with urticaria; 1 with thrombocytopenia; and 1 with rigors but no fever). Two other patients experienced fever and dyspnoea but these were attributed to underlying conditions and not to Digibind. The temporal relationship to Digibind was not described.

A total of 3 deaths were recorded in the DigiFab studies. One patient died in study TAb007-01 (lung cancer, not considered related to treatment) and there were 2 deaths in Study PR007-CLN-rpt003 (both occurred > five days after the end of DigiFab therapy, and were considered the result of complications of underlying medical conditions). In the Antman study, 43 deaths were reported, although the majority of deaths were ascribed to underlying heart disease still present after resolution of digitalis toxicity. Hickey and colleagues reported 171 deaths, with none of the deaths attributed to Digibind. Eighty-six deaths occurred within 2 days and 142 occurred within 3 weeks after Digibind treatment.

Postmarketing data

There were 5 spontaneous case reports of digoxin toxicity and elevated digoxin levels up to the 31 August 2011. The reporters' assessments of these cases were based solely on the fact that serum digoxin concentrations did not respond as expected. There have been 3 reports of death in 2013 (2 due to digoxin toxicity and 1 due to fatal acute kidney injury, dehydration, chronic heart failure, IHD and anaemia). All had limited data for review making it difficult to determine whether these deaths were related to DigiFab.

Risk management plan

The Office of Product Review has accepted the Risk Management Plan (RMP) for DigiFab (version 1, 21 June 2012) including the sponsor's response to the Outcome of Second Round Evaluations dated 3 October 2013 and recommended further changes to the RMP as outlined below from their report:

OPR sought ACSOM advice on 3 issues:

1. Need for additional pharmacovigilance and risk minimisation strategies because of a lack of long-term DigiFab follow-up data.

   ACSOM noted that the proposed UK registry would be a useful source of data and that the UK RMP advised that the data would be provided by the sponsor in any RMP updates and the PSUR. The OPR evaluator recommended that analysis findings of the registry data are communicated to the TGA at the same time as they are communicated to other regulatory agencies. With the exception of serious adverse reaction reports and significant safety issues which should be reported as per the *Australian Requirements and Recommendations for Pharmacovigilance Responsibilities of Sponsors of Medicines*, provision of the registry data in the PSURs and RMP updates is considered acceptable.

2. Consequences of inaccurate digoxin measurement on the potential for DigiFab medication errors and overdose.

   ACSOM noted the importance of obtaining digoxin levels prior to treatment with DigiFab to avoid full neutralisation of the digoxin and an exacerbation of the condition

the digoxin was initially treating. They did not consider there to be any utility in attempting to assay digoxin levels after administration of DigiFab, unless obtaining a measure of free digoxin levels and advised that clinical monitoring for signs of digoxin toxicity would be the most pragmatic option to take. This is considered to be adequately addressed in the proposed PI.

3. Clarity of the dosage and administration instructions, and whether flow charts and "real world" dose calculation examples would improve the clarity.

   ACSOM advised that the dosage and administration section in the draft PI was in need of improvement, and considered the inclusion of "real world" dose calculation examples based on the established clinical guidelines would improve the clarity of this section. They also noted that the PI does not adequately address the consequences of overdosing, dosing in bradycardia and the problem of rapid reversal. The proposed dosing instructions in the Australian PI are essentially the same as those in the US label, EU Summary of Product Characteristics (SmPC)and eTG, once the bioavailability of the tablet is taken into consideration (see equations for full neutralisation dose below):

   eTG: Dose (# vials) = (Amount digoxin taken (mg) x 0.8) / 0.5 mg per vial = Amount digoxin taken (mg) x 1.6

   FDA label: Dose (# vials) = Amount digoxin taken (mg) / 0.5 mg per vial = Amount digoxin taken (mg) x 2.0 (for capsule with 100% bioavailability, x 1.6 for tablet with 80% bioavailability)

   EU SmPC: Dose (# vials) = Amount digoxin taken (mg) x 1.6

The sponsor has updated the *Dosage and Administration* section with one example, but inserting a table(s) as per the US label (see table 8 below) may be more useful. Regarding the consequences of overdosing, and the problem of rapid reversal, it is considered that they are adequately addressed in the *Precautions* section of the proposed PI. Dosing in bradycardia is not discussed in either the US label or EU SmPC. The only mention of (progressive) bradycardia in the US label refers to it as a clinical manifestation of life-threatening toxicity due to digoxin overdose in the *Indications and Usage* section.

Table 8. Approximate dose of DigiFab for reversal of single large digoxin overdose

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

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

Table 8 continued. 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

· Other RMP issues were satisfactorily resolved.

The sponsor should address these matters in the Pre-ACPM Response and follow up where appropriate with the Office of Product Review.

Risk-benefit analysis

Delegate considerations

Efficacy

DigiFab has demonstrated a similar binding affinity to Digibind in Study TAb007-02, reducing serum free digoxin levels to < 0.3 ng/ml (LOQ) in all treated healthy subjects. Additionally, despite the methodological limitations of the 2 clinical studies (use of historical controls, retrospective medical file review), there was comparable improvement in clinical manifestations of digoxin toxicity (cardiac/ECG, gastrointestinal, neurological, etc) with DigiFab and Digibind.

Safety

DigiFab has demonstrated an acceptable safety profile consistent with what is expected in patients with digoxin toxicity and/or the underlying disease requiring digoxin treatment. The safety profile was also consistent with that of Digibind, the currently approved digoxin immune Fab (Ovine).

Indication

The clinical evaluator proposed amending the indication to include:

> *However, the consequences of multiple dosing with DigiFab have not been evaluated.*

This was accepted by the sponsor. The proposed indication now reads:

> *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 or bradyarrhythmias 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.*

Dosage and administration

OPR sought ACSOM advice about the need for improved clarity in the DigiFab dosing and administration instructions, and whether further information was needed on the consequences of overdosing, dosing in bradycardia and the problem of rapid reversal. The proposed dosing instructions are consistent with those in the US label, the EU SmPC, and the eTG, but they could be further improved with the inclusion of tables of doses as per the US label. ACSOM also noted that there was a lack of information regarding the consequences of overdosing, dosing in bradycardia and the problem of rapid reversal. These issues are not specifically addressed in either the US label or the EU SmPC, but appear to be adequately addressed in the *Precautions* section of the PI. It is noted that digoxin tablets in Australia have a 70% bioavailability (paediatric elixir 80% bioavailability), whereas dose instructions take account of tablets having 80% bioavailability (effect on the required number of vials of DigiFab in Table 9 below). This may need to be reflected in the dose calculations.

The Delegate sought ACPM's advice on these matters.

Table 9. Number of DigiFab vials required

Digoxin Dose Ingested (mg)	# DigiFab Vials (0.8 bioavailability)	# DigiFab Vials (0.7 bioavailability)
1	1.6	1.4
2	3.2	2.8
3	4.8	4.2
4	6.4	5.6
5	8	7
6	9.6	8.4
7	11.2	9.8
8	12.8	11.2
9	14.4	12.6
10	16	14
20	32	28

Data deficiencies

Only 2 studies in patients (n=29) were submitted in support of DigiFab, and there were no randomised, controlled studies (TAb007-001 involved historical controls, and PR007-CLN-rpt003 a retrospective review of clinical cases). All but 1 patient received a single dose of DigiFab and only 5 patients had acute digoxin toxicity. No information on safety or efficacy in children was provided. However, given the rare and emergency nature of the proposed indication of digoxin toxicity and the similarity of DigiFab to the currently approved Digibind with respect to binding affinity, this should be acceptable.

ACPM advice sought

The committee is requested to provide advice on the following specific issues:

1. DigiFab has demonstrated a similar binding affinity to Digibind, but the clinical and safety evidence submitted are limited. Are these data sufficient to support DigiFab's use for digoxin toxicity?
2. Do the dose instructions require further clarification? Would a table of dose estimates (as per the US PI be useful)?
3. Digoxin tablets in Australia have a 70% bioavailability (elixir 80% bioavailability), whereas the proposed dose instructions assume tablets have 80% bioavailability. Given the approximation already implicit in the DigiFab dose calculations, should the dose equation incorporate this and how?
4. Is the "Dose Determination Flowchart" required? If so, is it acceptable to include it in Addendum 1 to the PI (as a last page), or should it appear in the *Dosage and Administration* section?

5. Would the consequences of multiple dosing referred to in the indication be better placed in the *Dosage and Administration* section of the PI?

The committee was also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application

Conditions of registration

The following are proposed as conditions of registration:

1. The implementation in Australia of the Risk Management Plan (RMP) for DigiFab (version 1 dated 21 June 2012) and any subsequent revisions, as agreed with the TGA.
2. An electronic draft of the Certified Product Details (CPD) should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

The Delegate had no reason to say, at this time, that the application for DigiFab should not be approved for registration.

Response from sponsor

Phebra was in agreement with the Delegate's assessment of the application.

The sponsor responded to the recommendations made on the proposed Product Information (PI) in the Delegate's Request for ACPM's Advice. The details of the sponsor's response are beyond the scope of this AusPAR.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered DigiFab powder for injection containing 40 mg of digoxin-specific antibody fragment F(Ab) (Ovine) to have an overall positive benefit–risk profile for the indication;

> *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.*

In making this recommendation the ACPM;

- noted the relative rarity of prescribing this type of product
- expressed concern over the lack of paediatric data supplied and the need for such data

Specific advice

The ACPM provided the following specifically requested advice:

1. DigiFab has demonstrated a similar binding affinity to Digibind, but the clinical and safety evidence submitted are limited. Are these data sufficient to support DigiFab's use for digoxin toxicity?

The ACPM was of the view that, in addition to the demonstration of similar binding affinity to Digibind, the limited clinical evidence was sufficient to support safe use of DigiFab in Australia with an appropriate caveat re lack of product experience and trial data.

The ACPM noted the clinical evaluator's comment *…number of patients treated in clinical trials do not allow for a meaningful calculation of the frequency of AEs.* The ACPM advised that a sponsor commitment to post marketing surveillance was required.

2. Do the dose instructions require further clarification? Would a table of dose estimates (as per the US PI be useful)?

The ACPM noted that the sponsor has provided this in the Pre-ACPM response following the Delegate's query.

3. Digoxin tablets in Australia have a 70% bioavailability (elixir 80% bioavailability), whereas the proposed dose instructions assume tablets have 80% bioavailability. Given the approximation already implicit in the DigiFab dose calculations, should the dose equation incorporate this and how?

The ACPM noted that the sponsor has provided both estimates within DigiFab dose calculations provided in the Pre-ACPM response.

4. Is the "Dose Determination Flowchart" required? If so, is it acceptable to include it in Addendum 1 to the PI (as a last page), or should it appear in the Dosage and Administration section?

The "Dose Determination Flowchart" should be included in *Dosage and Administration* section of PI for clarity. There also needs to be an added clear statement *...for appropriate dosage please utilise the table or flowchart*.

5. Would the consequences of multiple dosing referred to in the indication be better placed in the Dosage and Administration section of the PI?

The ACPM were of the view that this information may be usefully included in both sections of the PI.

Further advice

The ACPM expressed a strong expectation that, in lieu of an Australian specific registry, information from the UK Registry and local post marketing surveillance would provide a useful source of data and represent a reasonable % of sales data (unlike data available to date).

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

· Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

· A statement in the *relevant* section of the PI and of the CMI along the lines of *…the total number of people treated with this medication in trials is small and the data regarding dosing and outcomes are limited*.

- A statement in the *Clinical Trials* section of the PI adding the number of subjects recruited into the PK study (note numbers of other 2 studies included).
- More clarity in the statements in the PI and relevant sections of the CMI in reference to reporting any concerns and adverse events in particular.
- As the product is not for self-injection, the statement in the CMI describing the solution appearance should be removed.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of DigiFab Digoxin-specific antibody fragment f(Ab) (ovine), 40mg, powder for injection, vial glass type I, indicated for:

> *Digoxin-specific antibody fragment F(ab) (Ovine) DigiFab is indicated for the treatment of known for 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 ore considered necessary. Consequences of multiple dosing with DigiFob have not been evaluated.*

Specific conditions applying to these therapeutic goods

1. The DigiFab Risk Management Plan (RMP), version 1, dated 21 June 2012, included with submission PM-2012-03387-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia. An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance in dudes the submission of Periodic Safety Update Reports (PSURs).
2. The analysis findings of the UK Registry data for DigiFab are provided to the TGA at the same time as they are provided to other regulatory agencies or, as a minimum, at least annually for a period of 3 years following registration.
3. An electronic draft of the Certified Product Details (CPD) should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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