NAME OF THE MEDICINE

Digibind, Digoxin immune Fab (Ovine), is a sterile lyophilized powder of antigen binding fragments (Fab) derived from specific antidigoxin antibodies raised in sheep. Production of antibodies specific for digoxin involves conjugation of digoxin as a hapten to human albumin. Sheep are immunised with this material to produce antibodies specific for the antigenic determinants of the digoxin molecule. The antibody is then papain digested and digoxin-specific Fab fragments of the antibody are isolated and purified by affinity chromatography. These antibody fragments have a molecular weight of approximately 46,200.

DESCRIPTION

Each vial which will bind approximately 0.5 mg of digoxin (or digitoxin) contains 38 mg of digoxin-specific Fab fragments derived from sheep plus 75 mg of sorbitol as a stabiliser and 28 mg of sodium chloride. It contains no preservatives.

Digibind is administered by intravenous injection after reconstitution with Sterile Water for injection (4 mL per vial).

PHARMACOLOGY

After intravenous injection of Digoxin immune Fab (Ovine) in the baboon, digoxin specific Fab fragments are excreted in the urine with a biological half-life of about 9 to 13 hours. In humans with normal renal function the half-life appears to be 15 to 20 hours. Experimental studies in animals indicate that these antibody fragments have a large volume of distribution in the extracellular space, unlike whole antibody which distributes in a space only about twice the plasma volume. Ordinarily, following administration of Digibind, improvement in signs and symptoms of digitalis intoxication begins within one-half hour or less. The affinity of Digibind for digoxin is high and greater than that of digoxin for its receptor (sodium, potassium ATPase). The average affinity of Digibind for digitoxin is approximately $1.55 \times 10^{10} \text{M}^{-1}$.

Digibind binds molecules of digoxin, making them unavailable for binding at their site of action on cells in the body. The Fab fragment-digoxin complex accumulates in the blood, from which it is excreted by the kidney. The net effect is to shift the equilibrium away from binding of digoxin to its receptors in the body, thereby reversing its effects.

INDICATIONS

Digoxin immune Fab (Ovine) Digibind is indicated for treatment of potentially life-threatening digoxin intoxication. Although designed specifically to treat life-threatening digoxin overdose, it has also been used successfully to treat life-threatening digitoxin overdose. Since human experience is limited and the consequences of repeated exposures are unknown, Digibind is not indicated for milder cases of digitalis toxicity.

Manifestations of life-threatening toxicity include severe ventricular arrhythmias such as ventricular tachycardia or ventricular fibrillation, or progressive bradyarrhythmias such as severe sinus bradycardia or second or third degree heart block not responsive to atropine.
Ingestion of more than 10 mg of digoxin in previously healthy adults or 4 mg of digoxin in previously healthy children, or ingestion causing steady-state serum concentrations greater than 10 ng/mL often results in cardiac arrest. Digitalis-induced progressive elevation of the serum potassium concentration also suggests imminent cardiac arrest. If the potassium concentration exceeds 5 mEq/L in the setting of severe digitalis intoxication, Digibind therapy is indicated.

CONTRAINDICATIONS

There are no known contraindications to the use of Digibind.

PRECAUTIONS

Suicidal ingestion often involves more than one drug: thus toxicity from other drugs should not be overlooked.

Although no allergic responses have yet occurred in man, the sample size is small and one should therefore consider the possibility of anaphylactic, hypersensitivity or febrile reactions. As the experience of rechallenge with Digibind is not known at present, the use in previously exposed patient is not recommended. If an anaphylactoid reaction occurs, the drug infusion should be discontinued and appropriate therapy initiated using adrenaline, aminophylline, oxygen, volume expansion, diphenhydramine, corticosteroids and airway management as indicated. Since the Fab fragment of the antibody lacks the antigenic determinants of the Fc fragment, it should pose less of an immunogenic threat to patients than does an intact immunoglobulin molecule. Papain is used to cleave the whole antibody into Fab and Fc fragments, and traces of papain or inactivated papain residues may be present in Digibind. Patients with known allergies to papain, chymopapain, or other papaya extracts, and individuals who have previously received antibodies or Fab fragments raised in sheep may be particularly at risk.

Skin Testing

Skin testing for allergy was performed during the clinical investigation of Digibind. Only one patient developed erythema at the site of skin testing, with no accompanying wheal reaction; this individual had no adverse reaction to systemic treatment with Digibind. Since allergy testing can delay urgently needed therapy, it is not routinely required before treatment of life-threatening digitalis toxicity with Digibind.

Skin testing may be appropriate for high risk individuals, especially patients with known allergy to sheep proteins or those previously treated with Digoxin immune Fab (Ovine). The intradermal skin test can be performed by:

1. Diluting 0.1 mL of reconstituted Digibind (9.5 mg/mL) in 10 mL sterile isotonic saline (1:100 dilution, 95 µg/mL).
2. Inject 0.1 mL of the 1:100 dilution (9.5 µg) intradermally and observe for an urticarial wheal surrounded by a zone of erythema. The test should be read at 20 minutes.

The scratch test procedure is performed by placing one drop of a 1:100 dilution of Digibind on the skin and then making a ¼ inch scratch through the drop with a sterile needle. The scratch site is inspected at 20 minutes for an urticarial wheal surrounded by erythema.

If skin testing causes a systemic reaction, a tourniquet should be applied about the site of testing and measures to treat anaphylaxis should be instituted. Further administration of
Digibind should be avoided unless its use is absolutely essential, in which case the patients should be treated with corticosteroids and diphenhydramine, and preparations made for treating anaphylaxis.

**General**

Digoxin immune Fab (Ovine) has been used on only a limited scale in man and its safety has therefore not yet been completely defined.

Standard therapy for digitalis intoxication includes withdrawal of the drug and correction of factors that may contribute to toxicity, such as electrolyte disturbances, hypoxia, acid-base disturbances and agents such as catecholamines. Also, treatment of arrhythmias may include judicious potassium supplements, lidocaine, phenytoin, procanamide and/or propranolol; treatment of sinus bradycardia or atrioventricular block may involve atropine or pacemaker insertion. Massive digitalis intoxication can cause hyperkalaemia; administration of potassium supplements in the setting of massive intoxication may be hazardous (see **LABORATORY TESTS**). After treatment with Digibind, the serum potassium concentration may drop rapidly and must be monitored frequently, especially over the first several hours after Digibind is given (see **LABORATORY TESTS**).

The elimination half-life in the setting of renal failure has not been clearly defined. Several patients with mild to moderate renal dysfunction have been successfully treated with Digibind. There is no evidence to suggest the time course of therapeutic effect is any different in these patients than in patients with normal renal function, but excretion of the Fab fragment-digoxin complex from the body is probably delayed. In patients who are functionally anephric, one would anticipate failure to clear the Fab fragment-digoxin complex from the blood by glomerular filtration and renal excretion. In this setting the reticuloendothelial system might eliminate the complex. Whether this would lead to detoxification or to re-intoxication following release of newly unbound digoxin into the blood is not at present known.

Patients with intrinsically poor cardiac function may deteriorate from withdrawal of the inotropic action of digoxin. Studies in animals have shown that the reversal of inotropic effect is relatively gradual, occurring over hours. When needed, additional support can be provided by use of intravenous inotropes, such as dopamine or dobutamine, or vasodilators. One must be careful in using catecholamines not to aggravate digitalis toxic rhythm disturbances. Clearly, other types of digitalis glycosides should not be used in this setting.

Redigitalisation should not be initiated until the Fab fragments have been eliminated from the body, which may require several days. Patients with impaired renal function may require a week or longer. The possibility of re-emergence of digitalis toxicity following the breakdown of the digitalis-antibody fragment complex has not been studied in man.

**Effects on fertility**

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

**Use in Pregnancy (Category B2)**

There are no adequate and well-controlled studies using digoxin-specific antibody Fab fragments in pregnant women. Treatment of 5 pregnant baboons with digoxin-specific antibody Fab fragments by intravenous infusion daily (at up to 2-fold the maximum recommended human dose on a mg/kg basis) for 60 days during the third trimester resulted in no treatment-related adverse effects on tolerability, gestation, parturition or infant viability. Transient antibodies to digoxin-specific antibody Fab fragments were observed in 1 of 5 pregnant animals on Days 15 and 30 of the dosing period, but no later in gestation. No animal studies have evaluated the placental transfer of Digibind or its potential embryo-foetal effects when used in the first or second trimester.
In the absence of adequate experience of administration of digoxin-specific antibody Fab fragments to pregnant women, the potential benefit to the mother must be weighed against the unknown risks to the foetus.

**Use in lactation**
It is not known whether Digibind is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Digibind is administered to a nursing woman.

Intravenous administration of Digibind to female baboons during gestation and early postnatal period at doses of 18-27 mg/kg/day (up to approximately twice the clinical exposure at the MRHD, based on dose) was associated with infant serum Digibind levels up to 63% of maternal serum levels on post partum Day 7. It is not known whether the transfer of the Fab fragments occurred either *in utero* or during the lactation period.

No animal studies have been performed to determine the level of Digibind secreted in breast milk.

**Paediatric use**
Digibind has been successfully used in infants with no apparent adverse sequelae. As in all other circumstances, use of this drug in infants should be based on careful consideration of the benefits of the drug balanced against the potential risk involved.

**Carcinogenicity**
There have been no studies performed in animals to evaluate carcinogenic potential.

**Genotoxicity**
There have been no studies performed to evaluate genotoxic potential.

**Laboratory Tests**
Serum digoxin or digitoxin concentration should be obtained before Digibind administration if at all possible. These measurements may be difficult to interpret if drawn soon after the last digitalis dose, since at least 5 to 6 hours are required for equilibration of digoxin between serum and tissue. Patients should be closely monitored, including temperature, blood pressure, electrocardiogram and potassium concentration, during and after administration of Digibind. The total serum digoxin concentration may rise precipitously following administration of Digibind but this will be almost entirely bound to the Fab fragment and therefore not able to react with receptors in the body. Digibind will interfere with digitalis immunoassay measurements. Thus, the standard serum digoxin concentration measurement can be clinically misleading until the Fab fragment is eliminated from the body, which may require several days. Patients with impaired renal function may require a week or longer before the standard serum digoxin concentration assay will give reliable results.

Potassium concentrations should be followed carefully. Severe digitalis intoxication can cause life-threatening elevation in serum potassium concentration by shifting potassium from inside to outside the cell. The elevation in serum potassium concentration can lead to increased renal excretion of potassium. Thus, these patients may have hyperkalaemia with a total body deficit of potassium. When the effect of digitalis is reversed by Digibind, potassium shifts back inside the cell, with a resulting decline in serum potassium concentration. Hypokalaemia may thus develop rapidly. For these reasons, serum potassium concentration should be monitored repeatedly, especially over the first several hours after Digibind is given, and cautiously treated when necessary.

**ADVERSE EFFECTS**
Adverse reactions to digoxin immune Fab have been minimal. There have been 3 cases of sensitivity reactions: 1 case of erythema at the site of injection; 1 case of facial swelling and hives occurring halfway through the 30-minute infusion (which was stopped); and 1 case of rash and urticaria occurring 1 day after the digoxin immune Fab infusion was completed (the cause was not established). No incidents of anaphylaxis, serum sickness or febrile reactions have occurred. In a few instances, low cardiac output states and congestive heart failure could have been exacerbated by withdrawal of the inotropic effects of digitalis. Hypokalaemia may occur from re-activation of (sodium, potassium) ATPase (see LABORATORY TESTS). Patients with atrial fibrillation may develop a rapid ventricular response from withdrawal of the effects of digitalis on the atrioventricular node.

DOSEAGE AND ADMINISTRATION

Digoxin immune Fab (Ovine) Digibind is administered by the intravenous route over 30 minutes. It is recommended that it be infused through a 0.22 µm membrane filter. If cardiac arrest is imminent, it can be given as a bolus injection.

The dosage of Digibind varies according to the amount of digoxin to be neutralised. The average dose used during clinical testing was 10 vials. Dosing guidelines are given below. If after several hours toxicity has not adequately reversed or appears to recur, readministration of Digibind at a dose guided by clinical judgement may be required. If a patient presents with digitalis toxicity from an acute ingestion, and neither a serum digitalis concentration nor an estimated ingestion amount is available, 20 vials (760 mg) of Digibind can be administered. This amount will be adequate to treat most life-threatening ingestions in both adults and children. However, in small children it is important to monitor for volume overload. Failure to respond to Digibind raises the possibility that the clinical problem is not caused by digitalis intoxication. If there is no response to an adequate dose of Digibind, the diagnosis of digitalis toxicity should be questioned.

Dosage Estimates
The dose administered need not be exactly equimolar, especially since digoxin body load calculations are only approximate. In general, a large Digibind dose has a faster onset of effect but enhances the possibility of an allergic or febrile reaction. The following tables give approximate Digibind doses based on an estimate of the number of digoxin tablets (0.25 mg) ingested as a single dose and is applicable to adults or children. More accurate calculations to estimate Digibind requirements are given below.

| TABLE 1: Approximate DIGIBIND Dose for Reversal of a Single Ingestion Digoxin Overdose |
|-----------------------------------------------|--------|----------|
| Number of Digoxin Tablets Ingested*          | DIGIBIND Dose | No. of Vials |
| 25                                           | 380    | 10       |
| 50                                           | 760    | 20       |
| 75                                           | 1140   | 30       |
| 100                                          | 1520   | 40       |
| 150                                          | 2280   | 60       |
| 200                                          | 3040   | 80       |

* Based on a 0.25 mg tablet with 80% bioavailability

Table 2 gives dosage estimates of Digibind for adults, derived from the steady state serum digoxin concentration. The dose is expressed in number of vials.
TABLE 2: Adult Dose Estimate of DIGIBIND (in # of vials) from Steady-State Serum Digoxin Concentration

<table>
<thead>
<tr>
<th>Serum Digoxin Concentration (ng/mL)</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Weight (kg)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0.5 v</td>
<td>1 v</td>
<td>2 v</td>
<td>3 v</td>
<td>5 v</td>
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<td>0.5 v</td>
<td>1 v</td>
<td>3 v</td>
<td>5 v</td>
<td>7 v</td>
<td>10 v</td>
<td>12 v</td>
</tr>
<tr>
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<td>6 v</td>
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<td>2 v</td>
<td>3 v</td>
<td>7 v</td>
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<td>13 v</td>
<td>16 v</td>
</tr>
<tr>
<td>100</td>
<td>1 v</td>
<td>2 v</td>
<td>4 v</td>
<td>8 v</td>
<td>12 v</td>
<td>16 v</td>
<td>20 v</td>
</tr>
</tbody>
</table>

* v = vials

Table 3 gives dosage estimates of Digibind for infants and children, derived from the steady state serum digoxin concentration. Since infants can have much smaller dosage requirements, it is recommended that the 38 mg vial be reconstituted as directed and administered with tuberculin syringe. For very small doses, a reconstituted vial can be diluted with 34 mL of sterile isotonic saline to achieve a concentration of 1 mg/mL.

TABLE 3: Infants and Small Children Dose Estimates of DIGIBIND (in mg) from Steady-State Serum Digoxin Concentration

<table>
<thead>
<tr>
<th>Serum Digoxin Concentration (ng/mL)</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
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</thead>
<tbody>
<tr>
<td>Patient Weight (kg)</td>
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<td>3</td>
<td>1*</td>
<td>2*</td>
<td>5</td>
<td>9</td>
<td>14</td>
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</tr>
<tr>
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<tr>
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<td>15</td>
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<td>46</td>
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<td>15</td>
<td>30</td>
<td>61</td>
<td>91</td>
<td>122</td>
<td>152</td>
</tr>
</tbody>
</table>

* Dilution of reconstituted vial to 1 mg/mL may be desirable.

**Exact Dosage Calculation**

The equimolar dose of Digibind required is calculated from the total amount of digoxin (or digitoxin) in the patient's body. An estimate of total body load is based either on the known acutely ingested dose or is estimated by using a steady state serum concentration. For toxicity from an acute ingestion, the total body load of digoxin in mg will be approximately equal to the dose ingested in mg (× 0.80 to correct for incomplete absorption of tablets). The total body load of digitoxin in mg is equal to the dose ingested in mg. To estimate total load from the steady-state serum concentration, the patient's serum digoxin concentration (SDC) in ng/mL is multiplied by the assumed volume of distribution of digoxin in the body (5 L/kg) times patient weight (in kg) to give total body load in µg. This is divided by 1000 to obtain the estimated amount of digoxin in the body in mg.

**For digoxin**

\[
\text{Body load in mg} = \frac{(\text{SDC})(5) \times \text{weight in kg}}{1000}
\]

For patients toxic from digitoxin, total body load can be estimated by using the value 0.5L/kg volume of distribution in place of the 5 L/kg for digoxin.

**For digitoxin**

\[
\text{Body load in mg} = \frac{(\text{SDC})(0.5) \times \text{weight in kg}}{1000}
\]
Each vial of Digibind contains 38 mg of purified digoxin-specific Fab fragments which will bind approximately 0.5 mg of digoxin (or digitoxin). Thus, one can calculate the total number of vials required by dividing the total body load in mg by 0.5 mg/vial.

\[
\text{Dose (in # of vials)} = \frac{\text{Body Load (mg)}}{0.5 (mg / vial)}
\]

If the calculation based on ingested dose differs substantially from the calculation based on serum digoxin or digitoxin concentration, it may be preferable to administer an amount based on the higher calculation. Erroneous calculations may result from inaccurate estimates of the amount ingested or absorbed or from non-steady state serum digoxin or digitoxin concentrations. Inaccurate serum digoxin concentration measurements are a possible source of error; this is especially so for very high values, since most assay kits are not designed to measure values above 5 ng/mL.

The volume of distribution of both digoxin and digitoxin are variable. For the purposes of the calculations of dosage presented above these have been assumed to be 5 L/kg for digoxin and 0.5 L/kg for digitoxin. Individual patients may vary from this average value. Thus, further dosing may be required guided by clinical judgement.

Reconstitution
The contents in each vial to be used should be dissolved with 4 mL of Sterile Water for injection, by gentle mixing, to give an approximately isosmotic solution with a protein concentration of 9.5 mg/mL. Reconstituted product should be used promptly. If it is not used immediately, it may be stored at 2°C to 8°C for up to 4 hours. The reconstituted product may be diluted if desired with sterile isotonic saline to a convenient volume. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

OVERDOSAGE
Contact the Poisons Information Centre (telephone 131126) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS
Vials containing 38 mg of purified lyophilized digoxin-specific Fab fragments. Box of 1.

Store at 2°C to 8°C. (Refrigerate. Do not freeze). Protect from light. Reconstituted product may be stored at 2°C to 8°C for up to 4 hours (See Reconstitution in Dosage and Administration).

NAME AND ADDRESS OF THE SPONSOR:
GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia Victoria 3155
POISON SCHEDULE OF THE MEDICINE: S4

DATE OF APPROVAL: 13 October 2008

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