

# **NEW ZEALAND DATA SHEET**

## **1. LANOXIN**

Digoxin tablets 62.5mcg (0.0625mg) and 250mcg (0.250mg); Paediatric Elixir 50mcg/mL

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Tablets: Each tablet contains 62.5mcg (0.0625mg), 250mcg (0.250mg) Digoxin BP

Paediatric Elixir: 50mcg Digoxin BP in each 1mL

For full list of excipients, see section 6.1

## **3. PHARMACEUTICAL FORM**

### Tablets PG 62.5mcg

Blue, round, biconvex tablets debossed "DO6" and each containing 62.5mcg (0.0625mg) Digoxin BP.

### Tablets 250mcg

White, round, biconvex tablets, bisected and debossed "DO25" and each containing 250mcg (0.250mg) Digoxin BP.

### Paediatric Elixir 50mcg/mL

A clear, yellow, lime flavoured solution containing 50mcg (0.050mg) Digoxin BP in each 1mL of sweetened, aqueous-alcoholic vehicle.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Cardiac Failure

LANOXIN is indicated in the management of chronic cardiac failure where the dominant problem is systolic dysfunction. Its therapeutic benefit is greatest in those patients with ventricular dilatation.

LANOXIN is specifically indicated where cardiac failure is accompanied by atrial fibrillation.

Supraventricular Arrhythmias

LANOXIN is indicated in the management of certain supraventricular arrhythmias, particularly atrial flutter and fibrillation, where a major beneficial effect is reduction of the ventricular rate.

### **4.2 Dose and method of administration**

The dose of LANOXIN for each patient has to be tailored individually according to age, lean body weight and renal function. Suggested doses are intended only as an initial guide.

LANOXIN PG Oral Solution, 50mcg in 1mL, is supplied with a graduated pipette and this should be used for measurement of all doses.

### **Adults and children over 10 years**

#### Rapid Oral Loading

If medically appropriate, rapid digitalisation may be achieved in a number of ways, such as the following:

750 to 1500mcg (0.75 to 1.5mg) as a single dose.

Where there is less urgency, or greater risk of toxicity e.g. in the elderly, the oral loading dose should be given in divided doses 6 hours apart, with approximately half the total dose given as the first dose.

Clinical response should be assessed before giving each additional dose (see section 4.4 Special warnings and precautions for use).

#### Slow Oral Loading

In some patients, for example those with mild heart failure, digitalisation may be achieved more slowly with doses of 250 to 750mcg (0.25 to 0.75mg) daily for 1 week followed by an appropriate maintenance dose. A clinical response should be seen within one week.

NOTE: The choice between slow and rapid oral loading depends on the clinical state of the patient and the urgency of the condition.

#### Maintenance Dose

The maintenance dosage should be based upon the percentage of the peak body stores lost each day through elimination. The following formula has had wide clinical use:-

$$\text{Maintenance dose} = \frac{\text{Peak body stores} \times \text{daily loss in percent}}{100}$$

Where:- Peak body stores = loading dose

$$\text{Daily loss (in percent)} = 14 + \frac{\text{creatinine clearance (C}_{cr})}{5}$$

C<sub>cr</sub> is creatinine clearance corrected to 70kg bodyweight or 1.73m<sup>2</sup> body surface area. If only serum creatinine (S<sub>cr</sub>) concentrations are available, a C<sub>cr</sub> (corrected to 70 kg bodyweight) may be estimated in men as

$$C_{cr} = \frac{(140 - \text{age})}{S_{cr} \text{ (in mg/100mL)}}$$

NOTE: Where serum creatinine values are obtained in micromol/L, these may be converted to mg/100mL (mg %) as follows:-

$$S_{cr}(\text{mg/100mL}) = \frac{S_{cr} \text{ (micromol/L)} \times 113.12}{10,000}$$

$$= \frac{S_{cr} \text{ (micromol/L)}}{88.4}$$

Where 113.12 is the molecular weight of creatinine.

For women, this result should be multiplied by 0.85.

N.B.: These formulae cannot be used for creatinine clearance in children.

In practice, this will mean that most patients with heart failure will be maintained on 125 to 250 mcg (0.125 to 0.25 mg) digoxin daily; however in

those who show increased sensitivity to the adverse effects of digoxin, a dose of 62.5mcg (0.0625mg) daily or less may suffice. Conversely, some patients may require a higher dose.

Neonates, infants and children up to 10 years of age (if cardiac glycosides have not been given in the preceding two weeks):-

In the newborn, particularly in the premature infant, renal clearance of digoxin is diminished and suitable dose reductions must be observed, over and above general dosage instructions.

Beyond the immediate newborn period, children generally require proportionally larger doses than adults on the basis of body weight or body surface area, as indicated in the schedule below. Children over 10 years of age require adult dosages in proportion to their body weight.

#### Oral loading dose

This should be administered in accordance with the following schedule:-

- Preterm neonates < 1.5kg - 25mcg/kg per 24 hours.
- Preterm neonates 1.5kg to 2.5kg - 30mcg/kg per 24 hours.
- Term neonates to 2 years - 45mcg/kg per 24 hours.
- 2 to 5 years - 35mcg/kg per 24 hours.
- 5 to 10 years - 25mcg/kg per 24 hours.

The loading dose should be administered in divided doses with approximately half the total dose given as the first dose and further fractions of the total dose given at intervals of 4 to 8 hours, assessing clinical response before giving each additional dose.

#### Maintenance

The maintenance dose should be administered in accordance with the following schedule:-

Preterm neonates:- daily dose = 20% of 24-hour loading dose.

Term neonates and children up to 10 years:- daily dose = 25% of 24-hour loading dose.

These dosage schedules are meant as guidelines and careful clinical observation and monitoring of serum digoxin levels (see Monitoring) should be used as a basis for adjustment of dosage in these paediatric patient groups.

If cardiac glycosides have been given in the two weeks preceding commencement of LANOXIN therapy, it should be anticipated that optimum loading doses of LANOXIN will be less than those recommended above.

#### **The elderly**

The tendency to impaired renal function and low lean body mass in the elderly influences the pharmacokinetics of LANOXIN such that high serum digoxin levels and associated toxicity can occur quite readily, unless doses of LANOXIN lower than those in non-elderly patients are used. Serum digoxin levels should be checked regularly and hypokalaemia avoided.

#### **Dose Recommendations in Specific Patients Groups**

See section 4.4 Special warnings and precautions for use.

### Monitoring

Serum concentrations of digoxin may be expressed in Conventional Units of ng/mL or SI Units of nmol/L. To convert ng/mL to nmol/L, multiply ng/mL by 1.28.

The serum concentration of digoxin can be determined by radioimmunoassay.

Blood should be taken 6 hours or more after the last dose of LANOXIN.

There are no rigid guidelines as to the range of serum concentrations that are most efficacious. Several post hoc analyses of heart failure patients in the Digitalis Investigation Group trial demonstrates that at low serum concentrations (0.5 – 0.9 ng/mL), the use of digoxin was associated with reductions in mortality and hospitalisation. Patients with higher digoxin levels (>1ng/mL) had a higher incidence of morbidity and mortality, although at these concentrations digoxin reduces heart failure hospitalisation. Therefore, the optimal trough digoxin serum level may be 0.5 ng/mL (0.64 nanomol/L) to 1.0 ng/mL (1.28 nanomol/L).

Digoxin toxicity is more commonly associated with serum digoxin concentration greater than 2ng/mL. However, serum digoxin concentration should be interpreted in the clinical context. Toxicity may occur with lower digoxin serum concentrations. In deciding whether a patient's symptoms are due to digoxin, the clinical state together with the serum potassium level and thyroid function are important factors (see section 4.9 Overdose).

Other glycosides, including metabolites of digoxin, can interfere with the assays that are available and one should always be wary of values which do not seem commensurate with the clinical state of the patient.

### **4.3 Contraindications**

LANOXIN is contra-indicated in intermittent complete heart block or second degree atrioventricular block, especially if there is a history of Stokes-Adams attacks.

LANOXIN is contra-indicated in arrhythmias caused by cardiac glycoside intoxication.

LANOXIN is contra-indicated in supraventricular arrhythmias associated with an accessory atrioventricular pathway, as in the Wolff-Parkinson-White syndrome, unless the electrophysiological characteristics of the accessory pathway and any possible deleterious effect of digoxin on these characteristics have been evaluated. If an accessory pathway is known or suspected to be present and there is no history of previous supraventricular arrhythmias, LANOXIN is similarly contra-indicated.

LANOXIN is contra-indicated in ventricular tachycardia or ventricular fibrillation.

LANOXIN is contra-indicated in hypertrophic obstructive cardiomyopathy, unless there is concomitant atrial fibrillation and heart failure but even then caution should be exercised if LANOXIN is to be used.

LANOXIN is contra-indicated in patients known to be hypersensitive to digoxin or other digitalis glycosides or to any component of the preparation.

#### 4.4 Special warnings and precautions for use

##### Arrhythmias

Arrhythmias may be precipitated by digoxin toxicity, some of which can resemble arrhythmias for which the drug could be advised. For example, atrial tachycardia with varying atrioventricular block requires particular care as clinically the rhythm resembles atrial fibrillation.

Many beneficial effects of digoxin on arrhythmias result from a degree of atrioventricular conduction blockade. However, when incomplete atrioventricular block already exists the effects of a rapid progression in the block should be anticipated. In complete heart block the idioventricular escape rhythm may be suppressed.

In some cases of **sinoatrial disorder (i.e. Sick Sinus Syndrome)** digoxin may cause or exacerbate sinus bradycardia or cause sinoatrial block.

The administration of digoxin in the period immediately following myocardial infarction is not contra-indicated. However, the use of inotropic drugs in some patients in this setting may result in undesirable increases in myocardial oxygen demand and ischaemia, and some retrospective follow-up studies have suggested digoxin to be associated with an increased risk of death. The possibility of arrhythmias arising in patients who may be hypokalaemic after myocardial infarction and are likely to be haemodynamically unstable must be borne in mind. The limitations imposed thereafter on direct current cardioversion must also be remembered.

Patients with heart failure associated with cardiac amyloidosis  
Treatment with digoxin should generally be avoided in patients with heart failure associated with cardiac amyloidosis. However, if alternative treatments are not appropriate, digoxin can be used to control the ventricular rate in patients with cardiac amyloidosis and atrial fibrillation.

##### Myocarditis

Digoxin can rarely precipitate vasoconstriction and therefore should be avoided in patients with myocarditis.

##### Thiamine deficiency

Patients with beri beri heart disease may fail to respond adequately to digoxin if the underlying thiamine deficiency is not treated concomitantly.

##### Constrictive pericarditis

Digoxin should not be used in constrictive pericarditis unless it is used to control the ventricular rate in atrial fibrillation or to improve systolic dysfunction.

##### Improved exercise tolerance

Digoxin improves exercise tolerance in patients with impaired left ventricular systolic dysfunction and normal sinus rhythm. This may or may not be associated with an improved haemodynamic profile. In patients receiving diuretics and an ACE inhibitor, or diuretics alone, the withdrawal of digoxin has been shown to result in clinical deterioration.

The use of therapeutic doses of digoxin may cause prolongation of the PR interval and depression of the ST segment on the electrocardiogram. Digoxin may produce false positive ST-T changes on the electrocardiogram during

exercise testing. These electrophysiologic effects reflect an expected effect of the drug and are not indicative of toxicity.

#### Cardiac glycosides

In cases where cardiac glycosides have been taken in the preceding two weeks the recommendations for initial dosing of a patient should be reconsidered and a reduced dose is advised.

#### Renal function

The dosing recommendations should be reconsidered if patients are elderly or there are other reasons for the renal clearance of digoxin being reduced. A reduction in both initial and maintenance doses should be considered.

Patients receiving digoxin should have their serum electrolytes and renal function (serum creatinine concentration) assessed periodically; the frequency of assessments will depend on the clinical setting.

Determination of the serum digoxin concentration may be very helpful in making a decision to treat with further digoxin, but other glycosides and endogenous digoxin-like substances may cross-react in the assay giving false-positive results. **Observations while temporarily withholding digoxin might be more appropriate.**

#### Respiratory disease

Patients with severe respiratory disease may have an increased myocardial sensitivity to digitalis glycosides.

**Hypokalaemia** sensitises the myocardium to the actions of cardiac glycosides.

**Hypoxia, hypomagnesaemia and marked hypercalcaemia** increase myocardial sensitivity to cardiac glycosides.

#### Hypothyroidism, hyperthyroidism

Administering LANOXIN to a patient with thyroid disease requires care. Initial and maintenance doses of LANOXIN should be reduced when thyroid function is subnormal. In hyperthyroidism there is relative digoxin resistance and the dose may have to be increased. During the course of treatment of thyrotoxicosis, dosage should be reduced as the thyrotoxicosis comes under control.

Patients with **malabsorption syndrome or gastro-intestinal reconstructions** may require larger doses of digoxin.

#### Direct current cardioversion

The risk of provoking dangerous arrhythmias with direct current cardioversion is greatly increased in the presence of digitalis toxicity and is in proportion to the cardioversion energy used.

For elective direct current cardioversion of a patient who is taking digoxin, the drug should be withheld for 24 hours before cardioversion is performed. In emergencies, such as cardiac arrest, when attempting cardioversion the lowest effective energy should be applied.

Direct current cardioversion is inappropriate in the treatment of arrhythmias thought to be caused by cardiac glycosides.

Many beneficial effects of digoxin on arrhythmias result from a degree of atrioventricular conduction blockade. However, when incomplete atrioventricular block already exists the effects of a rapid progression in the block should be anticipated. In complete heart block, the idioventricular escape rhythm may be suppressed.

The administration of digoxin in the period immediately following myocardial infarction is not contra-indicated. However, the use of inotropic drugs in some patients in this setting may result in undesirable increases in myocardial oxygen demand and ischaemia, and some retrospective follow-up studies have suggested digoxin to be associated with an increase risk of death. The possibility of arrhythmias arising in patients who may be hypokalaemic after myocardial infarction and are likely to be cardiologically unstable must be borne in mind. The limitations imposed thereafter on direct current cardioversion must also be remembered.

#### Laboratory Test Interference

Falsely elevated serum levels of digoxin may occur when samples from patients receiving enzalutamide are analysed using the chemiluminescent microparticle immunoassay (CMIA), independently of being treated with digoxin. In case of doubtful results, it is recommended to confirm digoxin serum levels with an alternative assay without known interference, in order to avoid any unnecessary discontinuation or decrease in the dose of digoxin (see section 4.5).

### **4.5 Interaction with other medicines and other forms of interaction**

These may arise from effects on the renal excretion, tissue binding, plasma protein binding, distribution within the body, gut absorptive capacity, P-glycoprotein activity and sensitivity to digoxin. Consideration of the possibility of an interaction whenever concomitant therapy is contemplated is the best precaution and a check on serum digoxin concentration is recommended when any doubt exists.

Digoxin is a substrate of P-glycoprotein. Thus, inhibitors of P-glycoprotein may increase blood concentrations of digoxin by enhancing its absorption and/or by reducing its renal clearance (See section 5.2). Induction of P-glycoprotein can result in a decrease in the concentration of digoxin in the blood.

#### Combinations that should be avoided

*Combinations which can increase effects of digoxin when co-administered:*  
Digoxin, in association with beta-adrenoceptor blocking drugs, may increase atrio-ventricular conduction time.

Agents causing hypokalaemia or intracellular potassium deficiency may cause increased sensitivity to digoxin; they include lithium salts, corticosteroids, carbenoxolone and some diuretics. Co-administration with diuretics such as loop or hydrochlorothiazide should be under close monitoring of serum electrolytes and renal function.

Calcium, particularly if administered rapidly by the I.V. route, may produce serious arrhythmias in digitalized patients.

Sympathomimetic drugs have direct positive chronotropic effects that can promote cardiac arrhythmias and may also lead to hypokalaemia, which can lead to or worsen cardiac arrhythmias. Concomitant use of digoxin and sympathomimetics may increase the risk of cardiac arrhythmias.

#### Combinations requiring caution

*Combinations which can increase the effects of digoxin when co-administered:* amiodarone, flecainide, prazosin, propafenone, quinidine, spironolactone, macrolide antibiotics e.g. erythromycin and clarythromycin, tetracycline (and possibly other antibiotics), gentamicin, itraconazole, isavuconazole, posaconazole, quinine, trimethoprim, alprazolam, indomethacin, propantheline, nefazodone, atorvastatin, cyclosporine, epoprostenol (transient), vasopressin receptor antagonists (tolvaptan and conivaptan), carvedilol, ritonavir/ritonavir containing regimens, taleprevir, dronedarone, ranolazine, telmisartan, venetoclax, ticagrelor, daclatasvir, flibanserin, mirabegron, simeprevir, velpatasvir, canagliflozin, ivacaftor, vandetanib, lapatinib vemurafenib and osimertinib.

The concomitant use of digoxin and sennosides may be associated with a moderate increase in the risk of digoxin toxicity in heart failure patients.

Patients receiving digoxin are more susceptible to the effects of suxamethonium-exacerbated hyperkalaemia.

Co-administration of lapatinib with orally administered digoxin resulted in an increase in the AUC of digoxin. Caution should be exercised when dosing digoxin concurrently with lapatinib.

Drugs that modify afferent and efferent arteriole vascular tone may alter glomerular filtration. Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) decrease angiotensin II-mediated efferent arteriole vasoconstriction, while non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 enzyme (COX-2) inhibitors decrease prostaglandin-mediated afferent arteriole vasodilation. ARBs, ACEIs, NSAIDs, and COX-2 inhibitors did not significantly alter digoxin pharmacokinetics or did not alter PK parameters in a consistent manner. However, these drugs may modify renal function in some patients, resulting in a secondary increase in digoxin.

Calcium channel blocking agents may either increase or cause no change in serum digoxin levels. Verapamil, felodipine and tiapamil increase serum digoxin levels. Nifedipine and diltiazem may increase or have no effect on serum digoxin levels while isradipine causes no change. Calcium channel blockers are also known to have depressant effects on sinoatrial and atrioventricular nodal conduction, particularly diltiazem and verapamil.

Proton pump inhibitors (PPI) are able to increase plasma levels of digoxin by inhibiting its efflux, resulting in increased plasma levels of digoxin. Metabolism of digoxin in the gastrointestinal tract is inhibited by omeprazole, resulting in increased plasma levels of digoxin. Similar effects have been reported with pantoprazole and rabeprazole to a lesser extent.

*Combinations which can decrease the effects of digoxin when co-administered:* antacids, some bulk laxatives, kaolin-pectin, acarbose, neomycin, penicillamine, rifampicin, some cytostatics, metoclopramide, sulphasalazine, adrenaline, salbutamol, cholestyramine, phenytoin, St John's wort (*Hypericum perforatum*), bupropion and supplemental enteral nutrition.

Bupropion and its major circulating metabolite, with and without digoxin, stimulated OATP4C1-mediated digoxin transport. Digoxin has been identified as a substrate for OATP4C1 in the basolateral side of the proximal renal tubules. Binding of bupropion and its metabolites to OATP4C1 could possibly increase the transport of digoxin and therefore, increase the renal secretion of digoxin.

#### Other interactions

Milrinone does not alter steady-state serum digoxin levels.

Determination of serum digoxin concentrations with the chemiluminescent microparticle immunoassay (CMIA) while using enzalutamide may cause falsely elevated serum digoxin levels. Results should be confirmed by another type of assay (see section 4.4).

### **4.6 Fertility, pregnancy and lactation**

Category A

#### **Teratogenicity**

No data are available on whether or not digoxin has teratogenic effects

#### **Fertility**

There is no information available on the effect of digoxin on human fertility.

#### **Pregnancy and lactation**

The use of digoxin in pregnancy is not contra-indicated, although the dosage may be less predictable in pregnant than in non-pregnant women, with some requiring an increased dosage of digoxin during pregnancy. As with all medicines, use should be considered only when the expected clinical benefit of treatment to the mother outweighs any possible risk to the developing foetus.

Despite extensive antenatal exposure to digitalis preparations, no significant adverse effects have been observed in the foetus or neonate when maternal serum digoxin concentrations are maintained within the normal range. Although it has been speculated that a direct effect of digoxin on the myometrium may result in relative prematurity and low birthweight, a contributing role of the underlying cardiac disease cannot be excluded. Maternally-administered digoxin has been successfully used to treat foetal tachycardia and congestive heart failure.

Adverse foetal effects have been reported in mothers with digitalis toxicity.

Although digoxin is excreted in breast milk, the quantities are minute and breast feeding is not contra-indicated.

### **4.7 Effects on ability to drive and use machines**

Since central nervous system and visual disturbances have been reported in patients receiving Lanoxin, patients should exercise caution before driving, using machinery or participating in dangerous activities.

### **4.8 Undesirable effects**

In general, the adverse reactions of digoxin are dose-dependent and occur at doses higher than those needed to achieve a therapeutic effect. Hence, adverse reactions are less common when digoxin is used within the

recommended dose range or therapeutic serum concentration range and when there is careful attention to concurrent medications and conditions.

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1000$  and  $< 1/100$ ), rare ( $\geq 1/10,000$  and  $< 1/1000$ ), very rare ( $1/10,000$ ), including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Adverse drug reactions identified through post-marketing surveillance were considered to be rare or very rare (including isolated reports).

**Appendix 1. Tabulation of adverse reactions:**

| <u>System organ class</u>                            | <u>Frequency</u> | <u>Adverse reaction</u>   |
|--|------------------|---|
| Blood and lymphatic system disorders                 | Very rare        | Thrombocytopaenia   |
| Metabolism and nutrition disorders                   | Very Rare        | Decreased appetite  |
| Psychiatric disorders                                | Uncommon         | Depression  |
|  | Very rare        | Psychotic disorder, apathy, confusional state   |
| Nervous system disorders                             | Common           | Nervous system disorder, dizziness  |
|  | Very rare        | Headache  |
| Eye disorders  | Common           | Visual impairment (vision blurred or xanthopsia)  |
| Cardiac disorders                                    | Common           | Arrhythmia, conduction disorder, extrasystoles, electrocardiogram PR prolongation, sinus bradycardia  |
|  | Very rare        | Supraventricular tachyarrhythmia, atrial tachycardia (with or without block), (nodal arrhythmia) supraventricular tachycardia, ventricular arrhythmia, ventricular extrasystoles, electrocardiogram ST segment depression |
| Gastrointestinal disorders                           | Common           | Nausea, vomiting, diarrhoea   |
|  | Very rare        | Intestinal ischaemia, gastrointestinal necrosis   |
| Skin and subcutaneous tissue disorders               | Common           | Rash*   |
| Reproductive system and breast disorders             | Very rare        | Gynaecomastia*  |
| General disorders and administration site conditions | Very rare        | Fatigue, malaise, asthenia  |

\* See "Description of selected adverse reactions"

Description of selected adverse reactions

*Skin and subcutaneous tissue disorders*

Skin rashes of urticarial or scarlatiniform character may be accompanied by pronounced eosinophilia.

*Reproductive system and breast disorders*

Gynaecomastia can occur with long term administration.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine.

Healthcare professionals are asked to report any suspected adverse reactions

<https://pophealth.my.site.com/carmreportnz/s/>

## 4.9 Overdose

### Symptoms and signs

The systems and signs of toxicity are generally similar to those described in the Undesirable Effects section but may be more frequent and can be more severe.

Signs and symptoms of digoxin toxicity become more frequent with levels above 3.0 nanograms/mL (3.84 nanomol/L) although there is considerable inter-individual variation. However, in deciding whether a patient's symptoms are due to digoxin, the clinical state, together with serum electrolyte levels and thyroid function are important factors (see section 4.2, Dose and method of administration). In patients undergoing haemodialysis, digoxin use is associated with increased mortality; patients with low pre-dialysis potassium concentrations are most at risk.

### Adults

In adults without heart disease clinical observation suggests that an overdose of digoxin of 10-15mg was the dose resulting in death of half of the patients. If more than 25mg of digoxin was ingested by an adult without heart disease, death or progressive toxicity responsive only to digoxin-binding Fab antibody fragments (DIGIBIND®) resulted.

### Cardiac manifestations

Cardiac manifestations are the most frequent and serious sign of both acute and chronic toxicity. Peak cardiac effects generally occur 3 to 6 hours following overdosage and may persist for the ensuing 24 hours or longer. Digoxin toxicity may result in almost any type of arrhythmia. Multiple rhythm disturbances in the same patient are common. These include paroxysmal atrial tachycardia with variable atrioventricular (AV) block, accelerated junctional rhythm, slow atrial fibrillation (with very little variation in the ventricular rate) and bi directional ventricular tachycardia.

Premature ventricular contractions (PVCs) are often the earliest and most common arrhythmia. Bigeminy or trigeminy also occur frequently. Sinus bradycardia and other bradyarrhythmias are very common. First, second, third degree heart blocks and AV dissociation are also common. Early toxicity may only be manifested by prolongation of the PR interval. Ventricular tachycardia may also be a manifestation of toxicity. Cardiac arrest from asystole or ventricular fibrillation due to digoxin toxicity is usually fatal.

Acute massive digoxin overdosage can result in mild to pronounced hyperkalaemia due to inhibition of the sodium-potassium (Na<sup>+</sup>-K<sup>+</sup>) pump. Hypokalaemia may contribute to toxicity (See section 4.4, Special warnings and precautions for use).

### **Non-cardiac manifestations**

Gastrointestinal symptoms are very common in both acute and chronic toxicity. The symptoms precede cardiac manifestations in approximately half of the patients in most literature reports. Anorexia, nausea and vomiting have been reported with an incidence up to 80%. These symptoms usually present early in the course of an overdose.

Neurologic and visual manifestations occur in both acute and chronic toxicity. Dizziness, various CNS disturbances, fatigue and malaise are very common. The most frequent visual disturbance is an aberration of colour vision (predominance of yellow green). These neurological and visual symptoms may persist even after other signs of toxicity have resolved.

In chronic toxicity, non-specific extracardiac symptoms, such as malaise and weakness, may predominate.

### **Children**

In children aged 1 to 3 years without heart disease, clinical observation suggests that an overdose of digoxin of 6 to 10mg was the dose resulting in death in half of the patients. If more than 10mg of digoxin was ingested by a child aged 1 to 3 years without heart disease, the outcome was uniformly fatal when Fab fragment treatment was not given.

Most manifestations of toxicity in children occur during or shortly after the loading phase with digoxin.

### **Cardiac manifestations**

The same arrhythmias or combination of arrhythmias that occur in adults can occur in paediatrics. Sinus tachycardia, supraventricular tachycardia, and rapid atrial fibrillation are seen less frequently in the paediatric population.

Paediatric patients are more likely to present with an AV conduction disturbance or a sinus bradycardia.

Ventricular ectopy is less common, however in massive overdose, ventricular ectopy, ventricular tachycardia and ventricular fibrillation have been reported.

In neonates, sinus bradycardia or sinus arrest and/or prolonged PR intervals are frequent signs of toxicity. Sinus bradycardia is common in young infants and children. In older children, AV blocks are the most common conduction disorders.

Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should be assumed to be caused by digoxin, until further evaluation proves otherwise.

### **Extracardiac manifestations**

The frequent extracardiac manifestations similar to those seen in adults are gastrointestinal, CNS and visual. However, nausea and vomiting are not frequent in infants and small children.

In addition to the undesirable effects seen with recommended doses, weight loss in older age groups and failure to thrive in infants, abdominal pain due to mesenteric artery ischaemia, drowsiness and behavioural disturbances including psychotic manifestations have been reported in overdose.

## Treatment

Patients with massive digitalis ingestion should receive large doses of activated charcoal to prevent absorption and bind digoxin in the gut during enteroenteric recirculation.

If hypokalaemia is present, it should be corrected with potassium supplements either orally or intravenously, depending on the urgency of the situation. In cases where a large amount of LANOXIN has been ingested hyperkalaemia may be present due to release of potassium from skeletal muscle. Before administering potassium in digoxin overdose the serum potassium level must be known.

Bradyarrhythmias may respond to atropine but temporary cardiac pacing may be required. Ventricular arrhythmias may respond to lignocaine or phenytoin.

Dialysis is not particularly effective in removing digoxin from the body in potentially life-threatening toxicity.

DIGIBIND® is a specific treatment for digoxin toxicity and is very effective. Rapid reversal of the complications that are associated with serious poisoning by digoxin, digitoxin and related glycosides has followed intravenous administration of digoxin-specific (ovine) antibody fragments (Fab). For details, consult the literature supplied with antibody fragments.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic Properties

#### Mode of Action

Digoxin increases contractility of the myocardium by direct activity. This effect is proportional to dose in the lower range and some effect is achieved with quite low dosing; it occurs even in normal myocardium although it is then entirely without physiological benefit. The primary action of digoxin is specifically to inhibit adenosine triphosphatase, and thus sodium-potassium ( $\text{Na}^+\text{-K}^+$ ) exchange activity, the altered ionic distribution across the membrane

resulting in an augmented calcium ion influx and thus an increase in the availability of calcium at the time of excitation- contraction coupling. The potency of digoxin may therefore appear considerably enhanced when the extracellular potassium concentration is low, with hyperkalaemia having the opposite effect.

Digoxin exerts the same fundamental effect of inhibition of the  $\text{Na}^+\text{-K}^+$  exchange mechanism on cells of the autonomic nervous system, stimulating them to exert indirect cardiac activity such as diminished impulse conduction rate through the atria and atrio-ventricular node (vagotonic) and sensitisation of the carotid sinus nerves (sympathomimetic). Indirect cardiac contractility changes also result from changes in venous compliance brought about by the altered autonomic activity and by direct venous stimulation. The interplay between direct and indirect activity governs the total circulatory response, which is not identical for all subjects. In the presence of certain supraventricular arrhythmias, the neurogenically mediated slowing of AV conduction is paramount.

The degree of neurohormonal activation occurring in patients with heart failure is associated with clinical deterioration and an increased risk of death. Digoxin reduces activation of both the sympathetic nervous system and the (renin-angiotensin) system independently of its inotropic actions, and may thus favourably influence survival. Whether this is achieved via direct sympathoinhibitory effects or by re-sensitizing baroreflex mechanisms remains unclear.

## 5.2 Pharmacokinetic properties

Upon oral administration, digoxin is absorbed from the stomach and upper part of the small intestine. When digoxin is taken after meals, the rate of absorption is slowed, but the total amount of digoxin absorbed is usually unchanged. When taken with meals high in fibre, however, the amount absorbed from an oral dose may be reduced. Using the oral route the onset of effect occurs in 0.5 to 2 hours and reaches its maximum at 2 to 6 hours. The bioavailability of orally administered LANOXIN is approximately 63% in tablet form and 75% as paediatric elixir.

The initial distribution of digoxin from the central to the peripheral compartment generally lasts from 6 to 8 hours. This is followed by a more gradual decline in serum digoxin concentration, which is dependent upon digoxin elimination from the body. The volume of distribution is large ( $V_{d_{ss}} = 510$  litres in healthy volunteers), indicating digoxin to be extensively bound to body tissues. The highest digoxin concentrations are seen in the heart, liver and kidney, that in the heart averaging 30-fold that in the systemic circulation. Although the concentration in skeletal muscle is far lower, this store cannot be overlooked since skeletal muscle represents 40% of total body weight. Of the small proportion of digoxin circulating in plasma, approximately 25% is bound to protein.

The major route of elimination is renal excretion of the unchanged medicine.

Digoxin is a substrate for P-glycoprotein. As an efflux protein on the apical membrane of enterocytes, P-glycoprotein may limit the absorption of digoxin. P-glycoprotein in renal proximal tubules appears to be an important factor in the renal elimination of digoxin (See section 4.5 Interaction with other medicines and other forms of interaction).

Following intravenous administration to healthy volunteers, between 60 and 75% of a digoxin dose is recovered unchanged in the urine over a 6 day follow-up period. Total body clearance of digoxin has been shown to be directly related to renal function, and percent daily loss is thus a function of creatinine clearance, which in turn may be estimated from a stable serum creatinine. The total and renal clearances of digoxin have been found to be  $193 \pm 25$  mL/min and  $152 \pm 24$  mL/min in a healthy control population.

In a small percentage of individuals, orally administered digoxin is converted to cardioinactive reduction products (digoxin reduction products or DRPs) by colonic bacteria in the gastrointestinal tract. In these subjects over 40% of the dose may be excreted as DRPs in the urine. Renal clearances of the two main metabolites, dihydrodigoxin and digoxigenin, have been found to be  $79 \pm 13$  mL/min and  $100 \pm 26$  mL/min respectively.

In the majority of cases however, the major route of digoxin elimination is renal excretion of the unchanged medicine.

The terminal elimination half life of digoxin in patients with normal renal function is 30 to 40 hours. It is prolonged in patients with impaired renal function, and in anuric patients may be of the order of 100 hours.

In the newborn period, renal clearance of digoxin is diminished and suitable dosage adjustments must be observed. This is especially pronounced in the premature infant since renal clearance reflects maturation of renal function. Digoxin clearance has been found to be  $65.6 \pm 30 \text{ mL/min/1.73m}^2$  at 3 months, compared to only  $32 \pm 7 \text{ mL/min/1.73m}^2$  at 1 week. Beyond the immediate newborn period, children generally require proportionally larger doses than adults on the basis of body weight and body surface area.

Since most of the medicine is bound to the tissues rather than circulating in the blood, digoxin is not effectively removed from the body during cardiopulmonary by-pass. Furthermore, only about 3% of a digoxin dose is removed from the body during five hours of haemodialysis.

### **5.3 Preclinical safety data**

#### **Mutagenicity, carcinogenicity**

No data are available on whether or not digoxin has mutagenic or carcinogenic effects.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

None

### **6.2 Incompatibilities**

No data

### **6.3 Shelf life**

Tablets 62.5mcg and 250mcg: 60 months

Paediatric Elixir 50mcg/mL: 36 months

### **6.4 Special precautions for storage**

Tablets 62.5mcg and 250mcg Store below 25 °C

Paediatric Elixir 50mcg/mL Store below 25 °C. Protect from light. Do not dilute.

### **6.5 Nature and contents of container (and special equipment for use, administration or implantation)**

#### **Package Quantities**

62.5mcg tablets: Blister pack, PVC/Al foil blisters (240 tablets); glass bottles (250 tablets)

250mcg tablets: Blister pack, PVC/PVDC/Al foil blisters (240 tablets); glass bottles (250 tablets)

Paediatric Elixir 50mcg/mL: Bottle, glass, with polypropylene CRC cap 60mL.

### **6.6 Special precautions for disposal (and other handling)**

#### **DILUTION**

LANOXIN Elixir should not be diluted.

## **7. MEDICINE SCHEDULE**

Prescription Only Medicine

## **8. SPONSOR**

Pharmacy Retailing (NZ) Limited

Trading as Healthcare Logistics

58 Richard Pearse Drive  
Airport Oaks  
Auckland  
New Zealand

**9. DATE OF FIRST APPROVAL**

25 September 2007

**10. DATE OF REVISION OF THE TEXT**

15 September 25

**SUMMARY TABLE OF CHANGES**

| <b>Section Changed</b> | <b>Summary of New Information</b>  |
|------------------------|--|
| Format of Data sheet   | As per new European SmPC style format.   |
| Section 4.5            | Safety related changes   |
| Section 4.8            | Safety related changes   |
| Section 4.5            | Addition of Posaconazole and osimertinib   |
| Section 4.4            | Additional information on direct current cardioversion.<br>Laboratory test interference with enzalutamide. |
| Section 4.5            | Interaction with enzalutamide.   |