LANOXIN TABLETS
Digoxin Tablets IP 0.25 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each uncoated tablet contains:
Digoxin IP 0.25 mg

PHARMACEUTICAL FORM
Uncoated Tablets

CLINICAL PARTICULARS
Therapeutic Indications
For the treatment of:

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 chronic atrial flutter and fibrillation.

Posology 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.

Monitoring
Serum concentrations of digoxin may be expressed in Conventional Units of nanograms/mL or SI Units of nanomol/L. To convert nanograms/mL to nanomol/L, multiply nanograms/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.
Several post hoc analyses of heart failure patients in the Digitalis Investigation Group trial suggest that the optimal trough digoxin serum level may be 0.5 nanograms/mL (0.64 nanomol/L) to 1.0 nanograms/mL (1.28 nanomol/L).

*LANOXIN* toxicity is more commonly associated with serum digoxin concentration greater than 2 nanograms/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 *LANOXIN*, the patient’s clinical state together with the serum potassium level and thyroid function are important factors (*See 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.

**Route of Administration**

For oral use.

**Adults and children over 10 years**

*Adults with chronic cardiac failure in the absence of supraventricular arrhythmia*

No loading dose is required. The usual daily dose is 125 to 250 micrograms (0.125 to 0.25 mg) for patients with normal renal function. A lower dose of 62.5 micrograms (0.0625 mg) should be considered in the elderly.

*For the management of atrial fibrillation or flutter*

**Rapid Oral Loading**

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

750 to 1500 micrograms (0.75 to 1.5 mg) 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, assessing clinical response before giving each additional dose (*See Special Warnings and Special 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 750 micrograms (0.25 to 0.75 mg) daily for 1 week followed by an appropriate maintenance dose. A clinical response should be seen within 1 week.

**NOTE:** The choice between slow and rapid oral loading depends on the clinical state of the patient and the urgency of the condition. (*See Special Warnings and Special Precautions for Use*).
**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:

\[
\text{Maintenance dose} = \text{Peak body stores} \times \text{daily loss in percent} / 100
\]

Where:

- Peak body stores = loading dose
- daily loss (in percent) = 14 + creatinine clearance (\(C_{\text{cr}}\)) / 5

\(C_{\text{cr}}\) is creatinine clearance corrected to 70 kg body weight or 1.73 m² body surface area. If only serum creatinine (\(S_{\text{cr}}\)) concentrations are available, a \(C_{\text{cr}}\) (corrected to 70 kg body weight) may be estimated in men as:

\[
C_{\text{cr}} = \frac{(140 - \text{age})}{S_{\text{cr}} \text{ (in mg/100 ml)}}
\]

**NOTE:** Where serum creatinine values are obtained in \(\mu\text{mol/L}\), these may be converted to mg/100 ml (mg %) as follows:

\[
S_{\text{cr}} \text{ (mg/100 ml)} = \frac{S_{\text{cr}} \text{ (micromol/l)} \times 113.12}{10,000}
\]

\[
= \frac{S_{\text{cr}} \text{ (micromol/l)}}{88.4}
\]

Where 113.12 is the molecular weight of creatinine.

*For women*, this result should be multiplied by 0.85.

**Note:** 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 micrograms (0.125 to 0.25 mg) *LANOXIN* daily; however, in those who show increased sensitivity to the adverse effects of *LANOXIN*, a dose of 62.5 micrograms (0.0625 mg) daily or less may suffice. Conversely, some patients may require a higher dose.

**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 (See Special Warnings and Special Precautions for Use).

Renal impairment

A reduction in both initial and maintenance doses should be considered (See Special Warnings and Special Precautions for Use).

Hepatic impairment

Hepatic impairment has little effect on digoxin clearance.

Contraindications

LANOXIN is contraindicated in:

- patients known to be hypersensitive to digoxin, other digitalis glycosides, or to any component of the preparation,
- intermittent complete heart block or second degree atrioventricular (AV) block, especially if there is a history of Stokes-Adams attacks,
- arrhythmias caused by cardiac glycoside intoxication,
- 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 has been evaluated. If an accessory pathway is known or suspected to be present and there is no history of previous supraventricular arrhythmias, digoxin is similarly contraindicated,
- ventricular tachycardia or ventricular fibrillation,
- hypertrophic obstructive cardiomyopathy, unless there is concomitant atrial fibrillation and heart failure, but even then caution should be exercised if digoxin is to be used.

Special Warnings and Special 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 AV block requires particular care as clinically the rhythm resembles atrial fibrillation.

Many beneficial effects of LANOXIN on arrhythmias result from a degree of AV conduction blockade. However, when incomplete AV 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) LANOXIN may cause or exacerbate sinus bradycardia or cause sinoatrial block.

Myocardial infarction
The administration of LANOXIN in the period immediately following myocardial infarction is not contraindicated. 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. However, 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.

**Heart failure**

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

**Myocarditis**

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

**Beri beri heart disease**

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

**Constrictive pericarditis**

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

**Supraventricular arrhythmias**

LANOXIN 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. However, the benefit of LANOXIN in patients with supraventricular arrhythmias is most evident at rest, less evident with exercise.

**Diuretics, an ACE inhibitor, or diuretics alone**

In patients receiving diuretics and an ACE inhibitor, or diuretics alone, the withdrawal of LANOXIN has been shown to result in clinical deterioration.

**Electrophysiologic effects**

The use of therapeutic doses of LANOXIN may cause prolongation of the PR interval and depression of the ST segment on the electrocardiogram.

LANOXIN 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 coadministration

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.

Elderly

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.

Serum electrolytes and renal function

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

Serum concentration

Determination of the serum digoxin concentration may be very helpful in making a decision to treat with further LANOXIN, but toxic doses of other glycosides may cross-react in the assay and wrongly suggest apparently satisfactory measurements. Observations during the temporary withholding of LANOXIN might be more appropriate.

Respiratory disease

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

Hypokalaemia, Hypoxia, hypomagnesaemia

Hypokalaemia sensitises the myocardium to the actions of cardiac glycosides.

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

Thyroid disease

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.

Thyrotoxicosis

During the course of treatment of thyrotoxicosis, dosage should be reduced as the thyrotoxicosis comes under control.
**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 LANOXIN, 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.

**Chronic congestive cardiac failure**

Although many patients with chronic congestive cardiac failure benefit from acute administration of LANOXIN, there are some in whom it does not lead to constant, marked or lasting haemodynamic improvement. It is therefore important to evaluate the response of each patient individually when LANOXIN is continued long-term.

**Malabsorption syndrome or gastro-intestinal reconstructions**

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

**Interaction with Other Medicaments and Other Forms of Interaction**

Interactions 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.

**Pharmacodynamic Interactions**

**Beta-adrenoceptor blocking drugs**

LANOXIN, in association with beta-adrenoceptor blocking drugs, may increase atrio-ventricular conduction time.

**Diuretics, lithium salts, corticosteroids, carbenoxolone and sennosides**

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

**Hyperkalaemia**
Patients receiving LANOXIN are more susceptible to the effects of suxamethonium-exacerbated hyperkalaemia.

**Calcium**

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

**Sympathomimetics**

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.

**Pharmacokinetic Interactions**

**Inhibitors of P-glycoprotein**

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. Induction of P – glycoprotein can result in decreases in plasma concentrations of digoxin.

**Combinations which can increase effects of digoxin when co-administered:**

Alprazolam, amiodarone, flecainide, gentamicin, indometacin, itraconazole, prazosin, propafenone, quinidine, quinine, spironolactone, macrolide antibiotics (e.g. erythromycin and clarithromycin), tetracycline (and possibly other antibiotics), trimethoprim, propantheline, atorvastatin, ciclosporin, epoprostenol (transient), vasopressin receptor antagonists (tolvaptan and conivaptan), carvedilol, ritonavir/ritonavir containing regimens, taleprevir, dronedarone, ranolazine, telmisartan, lapatinib and ticagrelor.

**Sennosides**

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

**Lapatinib**

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.

**ACEIs, ARBs, NSAIDs, and COX-2 inhibitors**

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 blockers**

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

**Combinations which can decrease the effects of digoxin when co-administered:**

Adrenaline (epinephrine), antacids, kaolin-pectin, some bulk laxatives, colestyramine, acarbose, salbutamol, sulfasalazine, neomycin, rifampicin, some cytostatics, phenytoin, metoclopramide, penicillamine, herbal remedy 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.

**Milrinone**

Milrinone does not alter steady-state serum digoxin levels.

**Pregnancy and Lactation**

**Fertility**

No data are available on whether or not *LANOXIN* has teratogenic effects.

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

**Pregnancy**

The use of *LANOXIN* in pregnancy is not contraindicated, although the dosage may be less predictable in pregnant than in non-pregnant women, with some requiring an increased dosage of *LANOXIN* during pregnancy. As with all drugs, 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 LANOXIN has been successfully used to treat foetal tachycardia and congestive heart failure.

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

**Lactation**

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

**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.

**Undesirable Effects**

**Clinical Trial Data and Post Marketing Data**

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

Frequencies are defined as:

- Very common $\geq 1/10$
- Common $\geq 1/100$ to $<1/10$
- Uncommon $\geq 1/1000$ to $<1/100$
- Rare $\geq 1/10000$ to $<1/1000$
- Very rare $<1/10000$
- Not known (cannot be estimated from the available data).

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).

**Blood and lymphatic system disorders**

- Very rare : Thrombocytopenia

**Metabolism and nutrition disorders**

- Very Rare : Anorexia

**Psychiatric disorders**

- Uncommon : Depression
Very rare : Psychosis, apathy, confusion

**Nervous system disorders**
Common : CNS disturbances, dizziness
Very rare : Headache

**Eye disorders**
Common : Visual disturbances (blurred or yellow vision)

**Cardiac disorders**
Common : Arrhythmia, conduction disturbances, bigeminy, trigeminy, PR prolongation, sinus bradycardia
Very rare : Supraventricular tachyarrhythmia, atrial tachycardia (with or without block), junctional (nodal) tachycardia, ventricular arrhythmia, ventricular premature contraction, ST segment depression

**Gastrointestinal disorders**
Common : Nausea, vomiting, diarrhoea
Very rare : Intestinal ischaemia, intestinal necrosis

**Skin and subcutaneous tissue disorders**
Common : Skin rashes of urticarial or scarlatiniform character may be accompanied by pronounced eosinophilia

**Reproductive system and breast disorders**
Very rare : Gynaecomastia can occur with long term administration

**General disorders and administration site conditions**
Very rare : Fatigue, malaise, weakness

**Overdose**

**Symptoms and Signs**

The symptoms 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 2.0 nanograms/ml (2.56 nanomol/l) although there is considerable interindividual 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 Posology 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 10-15 mg was the dose resulting in death of half of the patients. If more than 25 mg of digoxin
was ingested by an adult without heart disease, death or progressive toxicity responsive only to digoxin-binding Fab antibody fragments 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. LANOXIN 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 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 LANOXIN toxicity is usually fatal. Hypokalaemia may contribute to toxicity (See Special Warnings and Special Precautions for Use).

Non-cardiac manifestations:

Acute massive digoxin overdosage can result in mild to pronounced hyperkalaemia due to inhibition of the sodium-potassium (Na+-K+) pump.

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 10 mg was the dose resulting in death in half of the patients. If more than 10 mg 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 LANOXIN.

**Cardiac manifestations:**

The same arrhythmias or combination of arrhythmias that occur in adults can occur in children. 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 LANOXIN 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 LANOXIN in the gut during enteroenteric recirculation. Hypokalaemia should be corrected. In cases where a large amount of digoxin 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.

If more than 25 mg of digoxin was ingested by an adult without heart disease, death or progressive toxicity responsive only to digoxin-binding Fab antibody fragments resulted.

If more than 10 mg of digoxin was ingested by a child aged 1 to 3 years without heart disease, the outcome was uniformly fatal when Fab fragments treatment was not given.
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.

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).

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Cardiac glycosides, Digitalis glycosides; ATC Code: C01AA05.

Mechanism 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 (Na⁺-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 Na⁺-K⁺ exchange mechanism on cells of the autonomic nervous system, stimulating them to exert indirect cardiac activity. Increases in efferent vagal impulses result in reduced sympathetic tone and diminished impulse conduction rate through the atria and AV node. Thus, the major beneficial effect of digoxin is reduction of ventricular rate.

Pharmacodynamic effects

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-sensitising baroreflex mechanisms remains unclear.
Pharmacokinetic Properties

Absorption

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 digoxin is approximately 63 % in tablet form.

Distribution

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 (Vdss = 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.

Metabolism

The majority of digoxin is excreted by the kidneys as an intact drug, although a small fraction of the dose is metabolised to pharmacologically active and inactive metabolites. The main metabolites of digoxin are dihydrodigoxin and digoxigenin.

Elimination

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

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 Interaction with Other Medicaments and Other Forms of Interaction).

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 ± 25 mL/min and 152 ± 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, dihydridigoxin and digoxigenin, have been found to be $79 \pm 13 \text{ mL/min}$ and $100 \pm 26 \text{ mL/min}$, respectively.

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

Since most of the drug 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 5 hours of haemodialysis.

**Special Patient Populations**

**Renal Impairment**

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.

**Hepatic Impairment**

Hepatic impairment has little effect on digoxin clearance.

**Elderly**

Age-related declines in renal function in elderly patients can result in a lower rates of digoxin clearance than in younger subjects, with reported digoxin clearance rates in the elderly of 53 ml/min/1.73m2.

**Gender**

Digoxin clearance is 12% – 14% less in females than males and may need to be considered in dosing calculations.

**Preclinical Safety Data**

Digoxin showed no genotoxic potential in *in vitro* studies (Ames test and mouse lymphoma). No data are available on whether or not digoxin has mutagenic or carcinogenic effects.

**PHARMACEUTICAL PARTICULARS**

**List of Excipients**

Maize Starch, Lactose, Magnesium Stearate

**Incompatibilities**

No incompatibilities have been identified.
Shelf Life

The expiry date is indicated on the label and packaging.

Special Precautions for Storage

Store protected from light, at a temperature not exceeding 30°C.

Keep out of reach of children.

Nature and Specification of Container

Strips of tablets in a carton.

Instructions for Use / Handling

There are no special requirements for use or handling of the product.

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