Digoxin

QUALITATIVE AND QUANTITATIVE COMPOSITION
Injections containing 25, 50, 100 or 250 micrograms digoxin per ml.
Tablets containing 62.5, 125 or 250 micrograms digoxin.
Oral solutions containing 50 or 500 micrograms digoxin in 1 ml.

PHARMACEUTICAL FORM
Injection.
Tablets.
Oral solution.

CLINICAL PARTICULARS
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 chronic atrial flutter and fibrillation.

Dosage and 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.
The difference in bioavailability between injectable LANOXIN and oral formulations must be considered when changing from one dosage form to another. For example if patients are switched from oral to the i.v. formulation the dosage should be reduced by approximately 33%.

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

Monitoring
Serum concentrations of LANOXIN 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 suggest that 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).

LANOXIN toxicity is more commonly associated with serum digoxin concentration greater than 2 ng/ml. However, toxicity may occur with lower digoxin serum concentrations. In deciding whether a patient's symptoms are due to LANOXIN, the 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.

Dilution of LANOXIN Injection
LANOXIN Injection can be administered undiluted or diluted with a 4-fold or greater volume of diluent. The use of less than a 4-fold volume of diluent could lead to precipitation of digoxin.

LANOXIN Injection, 250 micrograms per ml when diluted in the ratio of 1 to 250 (i.e. one 2ml ampoule containing 500 micrograms added to 500ml of influ-
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 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:
- \(\text{Peak body stores} = \text{loading dose}\)
- \(\text{daily loss (in percent)} = 14 + \text{creatinine clearance (C cr)/5}\)
- \(\text{Ccr is creatinine clearance corrected to 70 kg bodyweight or 1.73 m2 body surface area.}\)

If only serum creatinine (Scr) concentrations are available, a Ccr (corrected to 70 kg bodyweight) may be estimated in men as:

\[
\text{Ccr} = \left(\frac{140 - \text{age}}{\text{S cr (in mg/100 ml)}}\right)
\]

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

\[
\text{S cr (micromol/l)} \times 113.12 = \text{S cr (mg/100 ml)}
\]

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.

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

If cardiac glycosides have been given in the two weeks preceding commencement of digoxin therapy, it should be anticipated that optimum loading doses of digoxin will be less than those recommended below. In the newborn, particularly in the premature infant, renal clearance of LANOXIN 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.

**Parenteral Loading Dose**
The intravenous loading dose in the above groups should be administered in accordance with the following schedule.

- Preterm neonates <1.5 kg - 20 micrograms /kg over 24 hours.
- Preterm neonates 1.5 kg - 2.5 kg - 30 micrograms /kg over 24 hours.
- Term neonates to 2 years - 35 micrograms /kg over 24 hours.
- 2 to 5 years - 35 micrograms /kg over 24 hours.
- 5 to 10 years - 25 micrograms /kg over 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. Each dose should be given by intravenous infusion (see Dilution of LANOXIN Injection above) over 10 to 20 minutes.

**Oral Loading Dose**
This should be administered in accordance with the following schedule.

- Preterm neonates <1.5 kg - 25 micrograms /kg per 24 hours.
- Preterm neonates 1.5 kg to 2.5 kg - 30 micrograms /kg per 24 hours.
- Term neonates to 2 years - 45 micrograms /kg per 24 hours.
- 2 to 5 years - 35 micrograms /kg per 24 hours.
- 5 to 10 years - 25 micrograms /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 (i.v. or oral).
- Term neonates and children up to 10 years:
  - daily dose = 25% of 24-hour loading dose (i.v. or oral).

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

**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 Warnings and Precautions.
**Contraindications**
LANOXIN is contraindicated in intermittent complete heart block or second degree atrioventricular block, especially if there is a history of Stokes-Adams attacks. LANOXIN is contraindicated in arrhythmias caused by cardiac glycoside intoxication. LANOXIN is contraindicated 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 LANOXIN 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 contraindicated. LANOXIN is contraindicated in ventricular tachycardia or ventricular fibrillation. LANOXIN is contraindicated 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 contraindicated in patients known to be hypersensitive to digoxin, other digitalis glycosides or to any component of the preparation.

**Warnings and Precautions**
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 LANOXIN 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) LANOXIN may cause or exacerbate sinus bradycardia or cause sinoatrial block.

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 LANOXIN 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. 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 to control the ventricular rate in patients with cardiac amyloidosis and atrial fibrillation. LANOXIN can rarely precipitate vasoconstriction and therefore should be avoided in patients with myocarditis. Patients with beri beri heart disease may fail to respond adequately to LANOXIN if the underlying thiamine deficiency is not treated concomitantly. 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. 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. In patients receiving diuretics and an ACE inhibitor, or diuretics alone, the withdrawal of LANOXIN has been shown to result in clinical deterioration. 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. 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. 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 LANOXIN 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 LANOXIN, but other glycosides and endogenous digoxin-like substances may cross-react in the assay giving false-positive results. Observations while temporarily withholding LANOXIN might be more appropriate.

The intramuscular route is painful and is associated with muscle necrosis. This route cannot be recommended.

Rapid intravenous injection can cause vasoconstriction producing hypertension and/or reduced coronary flow. A slow injection rate is therefore important in hypertensive heart failure and acute myocardial infarction.

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.

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 gastrointestinal reconstructions may require larger doses of LANOXIN.

**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.

**Interactions**

These may arise from effects on the renal excretion, tissue binding, plasma protein binding, distribution within the body, gut absorptive capacity and sensitivity to LANOXIN. 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.

LANOXIN, 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 LANOXIN; they include some diuretics, lithium salts, corticosteroids and carbenoxolone.

Patients receiving LANOXIN are more susceptible to the effects of suxamethonium-exacerbated hyperkalaemia.
Calcium, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients.

Serum levels of digoxin may be INCREASED by concomitant administration of the following:
- amiodarone, flecainide, prazosin, propafenone, quinidine, spironolactone, macrolide antibiotics e.g. erythromycin and clarithromycin, tetracycline (and possibly other antibiotics), gentamicin, itraconazole, quinine, trimethoprin, alprazolam, indomethacin, propantheline, nefazodone, atorvastatin, cyclosporine, epoprostenol (transient) and carvedilol.

Serum levels of digoxin may be REDUCED by concomitant administration of the following:
- antacids, some bulk laxatives, kaolin-pectin, carbose, neomycin, penicillamine, rifampicin, some cytostatics, metoclopramide, sulphasalazine, adrenaline, salbutamol, cholestyramine, phenytoin, St John’s wort (Hypericum perforatum).

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. Angiotensin converting enzyme inhibitors may also increase or cause no change in serum digoxin levels.

Milorinone does not alter steady-state serum digoxin levels.

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 Pharmacokinetics).

Pregnancy and Lactation

Fertility
There is no information available on the effect of LANOXIN on human fertility.
No data are available on whether or not LANOXIN has teratogenic effects.

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 birth weight, 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.

Adverse Reactions
In general, the adverse reactions of LANOXIN are dose-dependent and occur at doses higher than those needed to achieve a therapeutic effect. Hence, adverse reactions are less common when LANOXIN 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: ≥1 in 10
common: ≥1 in 100 and <1 in 10
uncommon:  ≥1 in 1,000 and <1 in 100
rare:     ≥1 in 10,000 and <1 in 1,000
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).

Blood and lymphatic system disorders
Very rare: Thrombocytopaenia

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 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
The symptoms and signs of toxicity are generally similar to those described in the Adverse Reactions 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). 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 Dosage and Administration).

• Adults
In adults without heart disease, clinical observation suggests that an overdose of LANOXIN of 10-15 mg was the dose resulting in death of half of the patients. If more than 25 mg of LANOXIN 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. 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 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.
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 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**

After recent ingestion, such as accidental or deliberate self-poisoning, the load available for absorption may be reduced by gastric lavage.

Patients with massive digitalis ingestion should receive large doses of activated charcoal to prevent absorption and bind LANOXIN 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 the premature conversion of prostaglandins to the active metabolites.
Thus, the major beneficial effect of digoxin is reduction of ventricular rate.
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.

**Pharmacokinetics**

**Absorption**
Intravenous administration of a loading dose produces an appreciable pharmacological effect within 5 to 30 minutes; this reaches a maximum in 1 to 5 hours. 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 (oral suspension).

**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 to release of potassium from skeletal muscle. Before administering potassium in LANOXIN 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 LANOXIN from the body in potentially life-threatening toxicity.

DIGIBIND™ is a specific treatment for LANOXIN 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.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamics**

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 atrio-ventricular node.
in serum digoxin concentration, which is dependent upon digoxin elimination from the body. The volume of distribution is large (V_dss = 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 main metabolites of digoxin are dihydridogoxin and digoxygenin.

**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 Interactions).

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 ± 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, dihydro digoxin and digoxygenin, have been found to be 79 ± 13 ml/min and 100 ± 26 ml/min, respectively. In the majority of cases however, the major route of digoxin elimination is renal excretion of the unchanged drug.

The terminal elimination half life of digoxin in patients with normal renal function is 30 to 40 hours. 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 five hours of haemodialysis.

### Special Patient Populations

- **Neonates, infants and children up to 10 years of age**
  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 ± 30 ml/min/1.73 m2 at 3 months, compared to only 32 ± 7 ml/min/1.73 m2 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.

- **Renal Impairment**
  The terminal elimination half life of digoxin is prolonged in patients with impaired renal function, and in anuric patients may be of the order of 100 h [190].

### Pre-clinical Safety Data

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

### PHARMACEUTICAL PARTICULARS

**List of Excipients**
As registered locally.

**Incompatibilities**
No data.

**Shelf Life**
The expiry date is indicated on the packaging.

**Nature and Contents of Container**
As registered locally.
Instructions for Use/Handling
LANOXIN Oral Solution, 50 micrograms in 1 ml, is supplied with a graduated pipette and this should be used for measurement of all doses.

Dilution
LANOXIN PG Elixir (Oral Solution) should not be diluted.
LANOXIN Injection can be administered undiluted or diluted with a 4-fold or greater volume of diluent. The use of less than a 4-fold volume of diluent could lead to precipitation of LANOXIN.
LANOXIN Injection, 250 micrograms per ml when diluted in the ratio of 1 to 250 (i.e. one 2 ml ampoule containing 500 micrograms added to 500 ml of infusion solution) is known to be compatible with the following infusion solutions and stable for up to 48 hours at room temperature (20 to 25oC).
- Sodium Chloride Intravenous Infusion, B.P., 0.9% w/v
- Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion, B.P.
- Glucose Intravenous Infusion, B.P., 5% w/v.
Dilution should be carried out either under full aseptic conditions or immediately before use. Any unused solution should be discarded.
Not all presentations are available in every country.
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