For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

LANOXIN TABLETS

1. GENERIC NAME

Digoxin Tablets IP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:
Digoxin IP 0.25 mg

3. DOSAGE FORM AND STRENGTH

Uncoated Tablets

Each uncoated tablet contains:
Digoxin IP 0.25 mg

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

For the treatment of:

Cardiac Failure

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

Supraventricular Arrhythmias

LANOXIN TABLETS is indicated in the management of certain supraventricular arrhythmias, particularly chronic atrial flutter and fibrillation.

4.2 Posology and Method of Administration

The dose of *LANOXIN TABLETS* 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 TABLETS*.

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 TABLETS 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 TABLETS*, the patient's clinical state together with the serum potassium level and thyroid function are important factors (*See 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.

Route of Administration

For oral use.

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 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 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 750 micrograms (0.25 to 0.75 mg) daily for one 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. (*See 4.4 Special Warnings and 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:-

Maintenance dose = Peak body stores x daily loss in percent / 100

Where:-

Peak body stores = loading dose

daily loss (in percent) = 14 + creatinine clearance (C_{cr})/5

C_{cr} is creatinine clearance corrected to 70 kg body weight or 1.73 m^2 body surface area. If only serum creatinine (S_{cr}) concentrations are available, a C_{cr} (corrected to 70 kg body weight) may be estimated in men as:

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

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

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

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

Where 113.12 is the molecular weight of creatinine.

For women, this result should be multiplied by 0.85.

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 TABLETS* daily; however in those who show increased sensitivity to the adverse effects of *LANOXIN TABLETS*, 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 TABLETS* such that high serum digoxin levels and associated toxicity can occur quite readily, unless doses of *LANOXIN TABLETS* lower than those in non-

elderly patients are used. Serum digoxin levels should be checked regularly and hypokalaemia avoided (*See 4.4 Special Warnings and Precautions for Use).*

Renal impairment

A reduction in both initial and maintenance doses should be considered (*See 4.4 Special Warnings and Precautions for Use*).

Hepatic impairment

Hepatic impairment has little effect on digoxin clearance.

4.3 Contraindications

LANOXIN TABLETS 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.

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 *LANOXIN TABLETS* 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 TABLETS* may cause or exacerbate sinus bradycardia or cause sinoatrial block.

Myocardial infarction

The administration of *LANOXIN TABLETS* 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.

Cardiac amyloidosis

Treatment with *LANOXIN TABLETS* 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 TABLETS 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 TABLETS* if the underlying thiamine deficiency is not treated concomitantly.

Constrictive pericarditis

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

Exercise tolerance

LANOXIN TABLETS 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 TABLETS* in patients with supraventricular arrhythmias is most evident at rest, less evident with exercise.

Withdrawal while on diuretics, an ACE inhibitor or diuretics alone.

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

Electrocardiography

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

LANOXIN TABLETS 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 TABLETS* 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 TABLETS*, 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 TABLETS* might be more appropriate.

Respiratory disease

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

Hypokalaemia, Hypoxia, hypomagnesaemia and hypercalcaemia

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 TABLETS* to a patient with thyroid disease requires care. Initial and maintenance doses of *LANOXIN TABLETS* 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 TABLETS*, 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 TABLETS*, 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 TABLETS* is continued long-term.

Malabsorption syndrome or gastro-intestinal reconstructions

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

4.5 Drug Interactions

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

Diuretics, lithium salts, corticosteroids and carbenoxolone

Agents causing hypokalaemia or intracellular potassium deficiency may cause increased sensitivity to *LANOXIN TABLETS*; 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 TABLETS* 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, canagliflozin, daclatasvir, flibanserin, flecainide, gentamicin, indometacin, itraconazole, prazosin, propafenone, quinidine, quinine, spironolactone, macrolide antibiotics (e.g. erythromycin and clarithromycin), tetracycline (and possibly other antibiotics), isavuconazole, ivacaftor, trimethoprim, propantheline, mirabegron, nefazodone, atorvastatin, ciclosporin, epoprostenol (transient), vasopressin receptor antagonists (tolvaptan and conivaptan), carvedilol, ritonavir/ritonavir containing regimens, taleprevir, dronedarone, ranolazine, simeprevir, telmisartan, lapatinib, ticagrelor, vandetanib, velpatasvir, venetoclax and vemurafenib.

Care should be taken when any of the above medicinal products are used in combination with digoxin. Serum digoxin concentrations should be monitored and used titration of digoxin.

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 blocker 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. 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:

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.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Elderly

The tendency to impaired renal function and low lean body mass in the elderly influences the pharmacokinetics of *LANOXIN TABLETS* such that high serum digoxin levels and associated

toxicity can occur quite readily, unless doses of *LANOXIN TABLETS* lower than those in non-elderly patients are used. Serum digoxin levels should be checked regularly and hypokalaemia avoided (*See 4.4 Special Warnings and Precautions for Use).*

Renal impairment

A reduction in both initial and maintenance doses should be considered (*See 4.4 Special Warnings and Precautions for Use*).

Hepatic impairment

Hepatic impairment has little effect on digoxin clearance.

Pregnancy and Lactation

Fertility

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

Pregnancy

The use of *LANOXIN TABLETS* 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 TABLETS* 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 TABLETS* 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.

4.7 Effects on Ability to Drive and Use Machines

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

4.8 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 ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100
Rare ≥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 : 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), supraventricular tachycardia (nodal arrhythmia), 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 (Skin rashes of urticarial or scarlatiniform character may be accompanied by pronounced eosinophilia)

Reproductive system and breast disorders

Very rare : Gynaecomastia (gynaecomastia can occur with long term administration)

General disorders and administration site conditions

Very rare : Fatigue, malaise, asthenia

4.9 Overdose

Symptoms and Signs

The symptoms and signs of toxicity are generally similar to those described in the *4.8 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 4.2 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 to15 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 TABLETS* 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 *LANOXIN TABLETS* toxicity is usually fatal.

Hypokalaemia may contribute to toxicity (*See 4.4 Special Warnings and Precautions for Use). Extra-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 chronic toxicity in children occur during or shortly after *LANOXIN TABLETS* overdose.

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 TABLETS* 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.

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.

Digoxin-specific antibody Fab 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).

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

5. PHARMACOLOGICAL PROPERTIES

5.1 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 atrioventricular node. Thus, the major beneficial effect of digoxin is reduction of ventricular rate.

5.2 Pharmacodynamic Properties:

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

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.

5.3 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 (Vd_{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.

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 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 4.5 Drug Interactions*).

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, dihydrodigoxin 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.

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/1.73m^2.

Gender

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

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

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.

7. DESCRIPTION

Uncoated Tablets

Each uncoated tablet contains:
Digoxin IP 0.25 mg

List of Excipients

Maize Starch, Lactose, Magnesium Stearate, Purified water

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

No incompatibilities have been identified.

8.2 Shelf Life

The expiry date is indicated on the label and packaging.

8.3 Packaging Information

Strips of tablets in a carton or CRSF (Child Resistant Senior Friendly) blisters in a carton.

8.4 Storage and Handling Instructions

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

Keep out of reach of children.

These tablets come in special packaging to prevent children removing them.
To take out a tablet gently push one end of the tablet through the foil layer.
For more information open the link below:
https://www.youtube-nocookie.com/embed/OYXJcPkJrVA

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or patient's caregiver as applicable) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contra-indications of *LANOXIN TABLETS*. Patients (and/or patient's caregiver) may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

The Manufacturing Site details are mentioned on the label and packaging.

For further information please contact:
GlaxoSmithKline Pharmaceuticals Limited.
Registered Office:
Dr. Annie Besant Road, Worli
Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Manufacturing Licence number is indicated on the label and packaging.

12. DATE OF REVISION

29-SEP-2021

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Version - LAN/PI/IN/2021/01

Adapted from Digoxin NCDS 04 dated 22 July 2021.