SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

LANOXIN PG ELIXIR 0.05MG/ML

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of Lanoxin Oral Solution contains 0.05mg Digoxin

3. PHARMACEUTICAL FORM

Oral Solution

A clear, yellow, lime flavoured solution

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cardiac Failure

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

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

Supraventricular Arrhythmias

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

4.2 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.

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 intravenous (I.V.) formulation the dosage should be reduced by approximately 33 %.

LANOXIN, 50 micrograms in 1 ml, 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 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.

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 demonstrated that at low serum digoxin concentrations (0.5 to 0.9 ng/ml), the use of digoxin was associated with reductions in mortality and hospitalization. Patients with higher digoxin levels (> 1 ng/ml) had a higher incidence of morbidity and mortality, although at these concentrations digoxin reduces heart failure hospitalization. Therefore, 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 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.

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 micrograms to 1 500 micrograms (0,75 mg 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, with approximately half the total dose given as the first dose. Clinical response should be assessed before giving each additional dose (see 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 micrograms to 750 micrograms (0,25 mg 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.

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.

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

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:

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

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

$$S_{cr}\ (\text{mg/100 ml}) = \frac{S_{cr}\ (\text{micromol/l}) \times \frac{113{,}12}{10\,000}}{}$$

$$= \frac{S_{cr}\ (\text{micromol/l})}{88{,}4}$$

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 mg 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 2 weeks)

If cardiac glycosides have been given in the 2 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.

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 hours to 8 hours, assessing clinical response before giving each additional dose.

Maintenance dose

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

a. Preterm neonates: daily dose = 20 % of 24hour loading dose (I.V. or oral).
b. Term neonates and children up to 10 years: daily dose = 25 % of 24hour loading dose (I.V. or oral).

These dosage schedules are meant as guidelines and careful clinical observation and monitoring of serum LANOXIN levels (see Special warnings and precautions for use) should be used as a basis for adjustment of dosage in these paediatric 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 Special warnings and precautions for use.

4.3 Contraindications

LANOXIN is contraindicated in:

- 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 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.

- 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 LANOXIN is to be used.
- patients known to be hypersensitive to digoxin, other digitalis glycosides or to any of the excipients listed in *Pharmaceutical particulars - List of excipients*

4.4 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 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.

Sinoatrial Disorder

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 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.

Cardiac Amyloidosis

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.

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.

Exercise Tolerance

LANOXIN improves exercise tolerance in patients with 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.

Withdrawal

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

Electrocardiography

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

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

Renal Impairment

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.

Monitoring

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.

Severe Respiratory Disease

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

- Hypokalaemia
- Hypokalaemia sensitises the myocardium to the actions of cardiac glycosides.
- Hypoxia, hypomagnesaemia and hypercalcaemia
- 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. During the course of treatment of thyrotoxicosis, dosage should be reduced as the thyrotoxicosis comes under control.

Malabsorption

Patients with malabsorption syndrome or gastro-intestinal 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.

4.5 Interaction with Other FPPs and Other Forms of Interaction

Drug 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 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.

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 *Pharmacokinetic properties*). Induction of P-glycoprotein can result in a decrease in the concentration of digoxin in the blood.

Combinations that should be avoided

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

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

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

Combinations requiring caution

Combinations which can increase the effects of LANOXIN when co-administered:

amiodarone, dronedarone, flecainide, prazosin, propafenone, quinidine, spironolactone, macrolide antibiotics e.g. erythromycin and clarithromycin, tetracycline (and possibly other antibiotics), gentamicin, itraconazole, quinine, trimethoprim, alprazolam, indomethacin, propantheline, nefazodone, atorvastatin, cyclosporine, epoprostenol (transient), carvedilol, ritonavir/ritonavir containing regimens,

ranolazine, telmisartan, vasopressin receptor antagonists (tolvaptan, conivaptan), ticagrelor, lapatinib, telaprevir, isavuconazole, daclatasvir, flibanserin, mirabegron, simeprevir, velpatasvir, canagliflozin, ivacaftor and vandetanib.

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

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

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

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

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

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

antacids, some bulk laxatives, kaolin-pectin, acarbose, neomycin, penicillamine, rifampicin, some cytostatics, metoclopramide, sulphasalazine, adrenaline, salbutamol, cholestyramine, phenytoin, St John's wort (Hypericum perforatum), bupropion and supplemental enteral nutrition.

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

Other interactions

Milrinone does not alter steady-state serum digoxin levels.

4.6 Pregnancy and Lactation

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.

Use during 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.

Use during 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, patients should exercise caution before driving, using machinery or participating in dangerous activities.

4.8 Undesirable Effects

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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), 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).

System organ class	Frequency	Adverse reaction
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 (blurred vision or xanthopsia)
Cardiac disorders	Common	Arrhythmia, conduction disorder, bigeminy, trigeminy, 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*
Reproductive system and breast disorders	Very rare	Gynaecomastia*
General disorders and administration site conditions	Very rare	Fatigue, malaise, asthenia

* See “Description of selected adverse reactions”

Description of Selected Adverse Reactions

Skin and subcutaneous tissue disorders

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

Reproductive system and breast disorders

Gynaecomastia can occur with long term administration.

4.9 Overdose

Symptoms and Signs

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) although there is considerable inter-individual variation. However, in deciding whether a patient’s symptoms are due to digoxin, the clinical state, together with serum electrolyte levels and thyroid function are important factors (see *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 LANOXIN of 10 mg to 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 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 bidirectional 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.

Acute massive LANOXIN overdosage can result in mild to pronounced hyperkalaemia due to inhibition of the sodium-potassium (Na+-K+) pump. Hypokalaemia may contribute to toxicity (see *Special warnings and precautions for use*).

Non-cardiac manifestations

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

Neurologic and visual manifestations occur in both acute and chronic toxicity.

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

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

Paediatric population

In children aged 1 to 3 years without heart disease, clinical observation suggests that an overdose of LANOXIN of 6 mg to 10 mg was the dose resulting in death in half of the patients.

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 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 arre st 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. Gastric lavage increases vagal tone and may precipitate or worsen arrhythmias. Consider pre-treatment with atropine if gastric lavage is performed. Treatment with digitalis Fab antibody usually renders gastric lavage unnecessary. In the rare instances in which gastric lavage is indicated, it should only be performed by individuals with proper training and expertise.

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.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic Group: Cardiac therapy, Cardiac glycosides

ATC code:C01C.

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.

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.

5.3 Pharmacokinetic Properties

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 % in oral solution.

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 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 Interaction with other medicinal products and other forms of interaction).

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.

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 5 hours of haemodialysis.

Special Patient Population

- *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 m^2 at 3 months, compared to only 32 ± 7 ml/min/1,73 m^2 at 1 week. Beyond the immediate newborn period, children generally require proportionally larger doses than adults on the basis of body weight and body surface area.

Specific Patient Population

- *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 hours.

5.3 Preclinical Safety Data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Adverse reactions not observed in clinical studies but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

- Mutagenicity - Digoxin showed no genotoxic potential in in vitro studies (Ames test and mouse lymphoma).
- Carcinogenicity - No data are available on the carcinogenic potential of digoxin.
- Developmental Toxicity

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

- Ethanol (96 %)
- Propylene Glycol
- Disodium Phosphate Anhydrous
- Methyl Parahydroxybenzoate
- Citric Acid Monohydrate
- Colour, Quinoline Yellow E104
- Lime flavour No.1 NA, BBA
- Purified Water

6.2 Incompatibilities

None known

6.3 Shelf life

36 Months

6.4 Special Precautions for Storage

Store below 25^0C

6.5 Nature and Contents of Container

Nature of Container

Amber glass bottles

Pack Size

60ml

6.6 Special Precautions for Disposal and Other 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 Oral Solution should not be diluted.

Not all presentations are available in every country.

7 MARKETING AUTHORISATION HOLDER

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8 NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

05803/08739/NMR/2020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2-November-2004

10 DATE OF REVISION OF THE TEXT

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