1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

LANOXIN 0,25 mg TABLETS

LANOXIN PG 0,0625 mg tablets

LANOXIN INJECTION 0,50 mg/2 ml

LANOXIN PAEDIATRIC/GERIATRIC ELIXIR 0,05 mg/1 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LANOXIN 0,25 mg TABLETS:

Each tablet of LANOXIN 0,25 mg TABLETS contains 0,25 mg of digoxin.

Contains sugar: Lactose monohydrate 95,525 mg

LANOXIN PG:

Each tablet of LANOXIN PG contains 0,0625 mg of digoxin.

Contains sugar: Lactose monohydrate 58,131 mg

LANOXIN INJECTION:

Each 2 ml of LANOXIN INJECTION contains 0,50 mg of digoxin.

Contains alcohol: Ethanol 9,98 % *v/v*

Sugar free

LANOXIN PAEDIATRIC/GERIATRIC ELIXIR:

Each 1 ml of LANOXIN PAEDIATRIC/GERIATRIC ELIXIR contains 0,05 mg of digoxin.

Preservative: Methyl parahydroxybenzoate 0,1 % *m/v*

Contains alcohol: Ethanol 9,97 % *v/v*

Contains sugar: Sucrose 300 mg

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets.

LANOXIN 0,25 mg TABLETS is a white, biconvex, round tablet, branded “D025” above the score line on one side, and plain on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Tablets.

LANOXIN PG is a blue, round, biconvex tablet, branded “D06” on one side and plain on the other side.

Solution for injection.

LANOXIN INJECTION is a clear, colourless liquid, practically free from particles.

Elixir.

LANOXIN PAEDIATRIC/GERIATRIC ELIXIR is a clear, bright yellow fluid with a characteristic odour.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

LANOXIN is indicated for:

- The management of chronic cardiac failure including in patients with ventricular dilatation.
- The management of certain supraventricular dysrhythmias such as atrial fibrillation to reduce ventricular rate.

4.2. Posology and method of administration

The dose of LANOXIN for each patient has to be tailored individually according to age, lean body mass, hepatic and renal function. Suggested doses are intended only as an initial guide.
In cases where LANOXIN has 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 difference in bioavailability between injectable LANOXIN and oral formulations must be considered when changing from one dosage form to another, e.g. if patients are switched from the oral to the IV formulation, the dosage should be reduced by approximately 33 %.

Monitoring:

Serum concentration of digoxin may be expressed in conventional units of ng/ml or SI Units of nmol/l. To convert ng/ml to nmol/L, multiply 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 concentration that are most efficacious. Several post hoc analyses of heart failure patients in the Digitalis Investigation Group trial demonstrated that low serum digoxin concentrations (0,5 ng/ml to 0,9 ng/ml) are adequate. Trough levels of > 1,0 ng/ml were associated with increased morbidity and mortality in patients treated with LANOXIN for heart failure.

LANOXIN toxicity is 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 toxicity, the clinical state together with the serum potassium level and thyroid function are important factors (see section 4.9). Other substances, including metabolites of digoxin and spironolactone, 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.

Posology

Adults and children over 10 years:

Rapid Oral Loading: (Only for atrial fibrillation)

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

A total of 750 micrograms to 1500 micrograms (μg) (0,75 mg to 1,5 mg) in a single dose. Where there is less urgency, or greater risk of toxicity e.g. in the elderly, the loading dose should be given in divided doses six hours apart, assessing clinical response before giving each additional dose.

Slow Oral Loading:

In chronic cardiac failure, digitalisation may be initiated with the desired maintenance doses of 0,125 mg per day.

Parenteral Loading:

(For treating atrial dysrhythmias within the preceding two weeks.)

The total loading dose of parenteral LANOXIN is 500 μg to 1 000 μg (0,5 mg to 1,0 mg) depending on age, lean body weight, hepatic and renal function. The total loading dose should be administered in divided doses with approximately half of the total dose given as the first dose and further fractions of the total dose given at intervals of 4 to 8 hours. An assessment of clinical response should be performed before giving each additional dose. Each dose should be given by intravenous infusion (see section 6.6) over 10 to 20 minutes.

Maintenance dose in patients with atrial fibrillation:

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:

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

Where: - Peak body stores = loading dose

$$\% \text{ daily loss} = 14 + \frac{\text{creatinine clearance } (C_{cr})}{5}$$

C_{cr} is creatinine clearance corrected to 70 kg bodymass 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 mass) 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 μmol/l, these may be converted to mg/100 ml (mg %) as follows:

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

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

Where 113,12 is the molecular weight of creatinine.

In 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 adult patients will be maintained on 0,125 mg LANOXIN daily; however in those who show increased sensitivity to the adverse effects of LANOXIN, a dose of 62,5 μg (0,0625 mg) daily or less may suffice. Conversely, some adult patients may require a higher dose. Doses > 0,50 mg/day need blood level determinations.

Special populations

LANOXIN PAEDIATRIC/GERIATRIC ELIXIR is supplied with a graduated pipette and this should be used for measurement of all doses.

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

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 obtained regularly and hypokalaemia avoided.

Dose Recommendations in Specific Patient Groups:

See section 4.4.

Paediatric population

Neonates, infants and children up to 10 years of age:

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 μg/kg over 24 hours
Preterm neonates 1,5 kg to 2,5 kg	30 μg/kg over 24 hours
Term neonates to 2 years	35 μg/kg over 24 hours
2 years to 5 years	35 μg/kg over 24 hours
5 years to 10 years	25 μg/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 section 6.6) over 10 to 20 minutes.

Oral loading dose:

This should be administered in accordance with the following schedule:

Preterm neonates < 1,5 kg	25 μg/kg per 24 hours
Preterm neonates 1,5 to 2,5 kg	30 μg/kg per 24 hours
Term neonates to 2 years	45 μg/kg per 24 hours
2 years to 5 years	35 μg/kg per 24 hours
5 years to 10 years	25 μg/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 (intravenous or oral)

Term neonates and children up to 10 years:

Daily dose = 25 % of the 24 hour loading dose (intravenous or oral)

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

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

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

Method of administration

LANOXIN 0,25 mg TABLETS:

For oral administration

LANOXIN PG:

For oral administration

LANOXIN INJECTION:

For parenteral administration

LANOXIN PAEDIATRIC/GERIATRIC ELIXIR:

For oral administration

4.3. Contraindications

LANOXIN is contraindicated in:

- Patients with known hypersensitivity to digoxin, other digitalis glycosides or to any of the excipients in LANOXIN (see section 6.1).
- Patients with ventricular tachycardia.
- Patients with total or intermittent complete heart block or with second degree atrioventricular block.
- Patients with supraventricular dysrhythmias 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 has been evaluated. If an accessory pathway is known or suspected to be present and there is no history of previous supraventricular dysrhythmias, LANOXIN is contraindicated.
- Patients with hypertrophic obstructive cardiomyopathy and aortic stenosis.

4.4. Special warnings and precautions for use

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 helpful in making a decision to treat with further LANOXIN especially if used at higher dosages. However, spironolactone and endogenous digoxin-like substances may cross-react in the assay causing false-positive results. Observations while temporary withholding digoxin, as in LANOXIN, might be more appropriate.

The following may be important in patient monitoring: ECG monitoring, hepatic and renal function determinations, pulse rate and serum electrolytes, especially potassium, calcium and magnesium concentrations.

Dysrhythmias

Dysrhythmias, including atrioventricular block, may be precipitated by LANOXIN, some of which can resemble dysrhythmias for which LANOXIN 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 dysrhythmias result from a degree of atrioventricular conduction blockade. When incomplete heart block exists, rapid progression of the block may occur with the use of LANOXIN. In complete heart block the idioventricular escape rhythm may be suppressed.

Sinoatrial disorders

In sinoatrial disorders (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 absolutely contraindicated. However, the use of inotropic medicines such as LANOXIN in this setting may result in undesirable increases in myocardial oxygen demand and further ischaemia. Prospective studies have suggested if digoxin blood levels were > 1,0 ng/ml, LANOXIN would be associated with an increased risk of death. The possibility of dysrhythmias arising in patients who are 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 be avoided in patients with heart failure associated with cardiac amyloidosis. However, if alternative treatments are not appropriate, LANOXIN may be used to control the ventricular rate in patients with cardiac amyloidosis and atrial fibrillation.

Myocarditis

LANOXIN can precipitate vasoconstriction and 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 patients with constrictive pericarditis unless it is used to control the ventricular rate in atrial fibrillation or to improve systolic dysfunction.

Exercise tolerance

Digoxin, as in 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 dysrhythmias is most evident at rest, less evident with exercise.

Withdrawal

In patients with heart failure also receiving diuretics and an ACE inhibitor, or diuretics alone, the withdrawal of LANOXIN has been shown to result in clinical deterioration of heart failure. LANOXIN doses should be reduced if patients are elderly or there are other reasons for the renal clearance of digoxin being reduced.

Thyroid disease

Administering digoxin to a patient with thyroid disease requires care. The initial and maintenance dose 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 the LANOXIN dosage should be reduced as the thyrotoxicosis comes under control.

Malabsorption

Patients with malabsorption syndrome or gastrointestinal tract reconstructions may require

larger doses of LANOXIN.

Electrocardiography

The use 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 LANOXIN and are not indicative of toxicity.

Chronic congestive cardiac failure

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

Hypokalaemia

Hypokalaemia sensitises the myocardium to the actions of cardiac glycosides.

Hypoxia, hypomagnesaemia and hypercalcaemia

Hypoxia, hypomagnesaemia and hypercalcaemia increase the myocardial sensitivity to LANOXIN.

Administration of LANOXIN

Rapid intravenous injection of LANOXIN can cause vasoconstriction resulting in hypertension and/or reduced coronary artery blood flow. A slow injection rate is therefore important.

The intramuscular route of administration is painful and is associated with muscle necrosis. This route should not be used.

Severe respiratory disease

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

Direct current cardioversion

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

For elective direct current cardioversion of a patient who is taking LANOXIN, the medicine 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 dysrhythmias thought to be caused by LANOXIN.

Excipients

Lactose warning:

LANOXIN 0,25 mg TABLETS and LANOXIN PG contain lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, total lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take LANOXIN 0,25 mg TABLETS or LANOXIN PG.

Sucrose warning:

LANOXIN PAEDIATRIC/GERIATRIC ELIXIR contain sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take LANOXIN PAEDIATRIC/GERIATRIC ELIXIR.

Alcohol warning:

LANOXIN INJECTION: contains 0,208 ml of alcohol (ethanol 96 %) in each 2 ml ampoule.

The small amount of alcohol in this medicine will not have any noticeable effects.

LANOXIN PAEDIATRIC/GERIATRIC ELIXIR: contains 0,1039 ml of alcohol (ethanol 96 %) in each 1 ml.

The small amount of alcohol in this medicine will not have any noticeable effects.

Propylene Glycol warning:

LANOXIN INJECTION contains 0,8 ml of propylene glycol in each 2 ml ampoule.

LANOXIN PAEDIATRIC/GERIATRIC ELIXIR contains 0,05 ml of propylene glycol in each 1 ml.

4.5. Interaction with other medicines and other forms of interactions

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

concentration is recommended when any doubt exists.

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

Combinations that should be avoided

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

Beta-adrenoceptor blocking medicines: LANOXIN, in association with beta-adrenoceptor blocking medicines, may increase atrioventricular conduction time.

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

Calcium administration: particularly if administered rapidly by the IV route, may produce serious dysrhythmias in digitalised patients.

Sympathomimetics: Sympathomimetic medicines have direct positive chronotropic effects that can promote cardiac dysrhythmias and may also lead to hypokalaemia, which can lead to or worsen cardiac dysrhythmias. Concomitant use of LANOXIN and sympathomimetics may increase the risk of cardiac dysrhythmias

Combinations requiring caution

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

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

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

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

Angiotensin converting enzyme (ACE) inhibitors: medicines that modify afferent and efferent arteriole vascular tone may alter glomerular filtration Concomitant use of ACE inhibitors may also increase serum LANOXIN levels. 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 LANOXIN pharmacokinetics or did not alter pharmacokinetic (PK) parameters in a consistent manner. However, these medicines may modify renal function in some patients, resulting in a secondary increase in LANOXIN levels.

Calcium channel blockers: Calcium channel blocking medicines may either increase or cause no change in serum LANOXIN levels. Verapamil, tiapamil and felodipine increase serum

LANOXIN levels. Nifedipine and diltiazem may increase or have no effect on serum LANOXIN levels. Isradipine causes no changes in serum LANOXIN levels at steady state. Calcium channel blockers are also known to have depressant effects on sinoatrial and atrioventricular nodal conduction, particularly diltiazem and verapamil.

Proton pump inhibitors (PPI): are able to increase plasma levels of digoxin, as in LANOXIN, 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.

Care should be taken when any of the below medicines are used in combination with LANOXIN. Serum levels of digoxin, as in LANOXIN, may be increased by concomitant administration of the following:

Amiodarone, canagliflozin, daclatasvir, flibanserin, captopril, flecainide, prazosin, propafenone, quinidine or quinine, spironolactone, tetracycline, macrolide antibiotics e.g. erythromycin, clarithromycin (and possibly other antibiotics), gentamicin, isavuconazole, ivacaftor, itraconazole, mirabegron, nefazodone, vasopressin receptor antagonists (tolvaptan and conivaptan), taleprevir, trimethoprim, alprazolam, indomethacin, propantheline, atorvastatin, ciclosporin, epoprostenol (transient), carvedilol, vandetanib, velpatasvir, venetoclax, vemurafenib, ritonavir/ritonavir containing antiretroviral treatment regimens, dronedarone, ranolazine, simeprevir, telmisartan, lapatinib and ticagrelor.

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

Serum levels of digoxin may be decreased by concomitant administration of the following:

Antacids, kaolin-pectin, some bulk laxatives and cholestyramine, acarbose, diphenoxylate, sulphasalazine, neomycin, rifampicin, cytostatics, adrenaline, salbutamol, phenytoin,

metoclopramide, penicillamine and St. John's Wort *(Hypericum perforatum),* bupropion and supplemental enteral nutrition.

Bupropion and its major circulating metabolite, with and without digoxin, as in LANOXIN, stimulated Organic Anion Transporter Polypeptide (OATP) 4C1-mediated digoxin transport. Digoxin, as in LANOXIN, has been identified as a substrate for OATP 4C1 in the basolateral side of the proximal renal tubules. Binding of bupropion and its metabolites to OATP 4C1 may increase the transport of digoxin, as in LANOXIN, and therefore, increase the renal secretion of digoxin, as in LANOXIN.

Other interactions

Milrinone does not alter steady-state serum digoxin levels.

4.6. Fertility, pregnancy and lactation

LANOXIN should be with caution in pregnancy and lactation.

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.

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 LANOXIN on the myometrium may result in relative prematurity and low birthweight, a contributing role of the underlying cardiac disease cannot be excluded.
Maternally-administered LANOXIN has been used to treat foetal tachycardia and congestive heart failure.
Adverse foetal effects have been reported in mothers with LANOXIN toxicity.

Breastfeeding

Although digoxin, as in LANOXIN, is excreted in breastmilk, the quantities are minute and breastfeeding is not contraindicated.

Fertility

There are no fertility data available on the effect of digoxin, as in LANOXIN, on human fertility.
No data are available on whether or not digoxin, as in LANOXIN, has teratogenic effects.

4.7. Effects on ability to drive and use machines

LANOXIN has major influence on the ability to drive or operate machinery.
Since adverse reactions such as dizziness and visual disturbances have been reported in patients using LANOXIN, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that LANOXIN does not adversely affect their ability to do so (see section 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

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 medicines and conditions.

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1 000 and < 1/100), rare (≥ 1/10 000 and < 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).

b) Tabulated list of adverse events

System organ class	**Common**	**Uncommon**	**Very Rare**
Blood and the lymphatic system disorders			Thrombocytopenia
Metabolism and nutrition disorders			Decreased appetite
Psychiatric disorders		Depression	Psychotic disorder, apathy, confusional state
Nervous system disorders	Nervous system disorders, dizziness		Headache
Eye disorders	Visual impairment (blurred vision or xanthopsia)		

Cardiac disorders	Dysrhythmia, conduction disorder, bigeminy, trigeminy, PR prolongation, sinus bradycardia		Supraventricular tachydysrhythmia, atrial tachycardia (with or without block), supraventricular tachycardia (nodal dysrhythmia) tachycardia, ventricular dysrhythmia, ventricular extrasystoles, electrocardiogram ST segment depression
Gastrointestinal disorders	Nausea, vomiting, diarrhoea		Intestinal ischaemia, gastrointestinal necrosis
Skin and subcutaneous tissue disorders	Urticaria, scarlatiniform, eosinophilia, rash		
Reproductive system and breast disorders			Gynaecomastia
General disorders and administrative site conditions			Fatigue, malaise, asthenia

c) Description of selected adverse reactions

Skin and subcutaneous tissue disorders

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

Reproductive system and breast disorders

Gynaecomastia can occur with long-term administration.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It

allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting From”. Found online under SAHPRA’s publications:

SAHPRA: https://www.sahpra.org.za/Publications/Index/8

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088/+27 (0)11 239 6200

4.9. Overdose

Symptoms

The symptoms and signs of toxicity are generally similar to those described under section 4.8 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 LANOXIN, the clinical state, together with serum electrolyte levels and thyroid function are important factors (see section 4.2). In patients undergoing haemodialysis, digoxin, as in LANOXIN, 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 resulted 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 fragment 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 dysrhythmia. 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 dysrhythmia. Bigeminy or trigeminy also occur frequently.

Sinus bradycardia and other bradydysrhythmias are very common.

First, second, third degree heart blocks and AV dissociation are also common.

Early toxicity may only be manifested by prolongation of the PR interval.

Ventricular tachycardia may also be a manifestation of toxicity.

Cardiac arrest from asystole or ventricular fibrillation due to digoxin toxicity is usually fatal.

Acute massive 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 section 4.4).

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, nonspecific extracardiac symptoms, such as malaise and weakness, may predominate.

Paediatric population:

In children aged 1 year 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. If more than 10 mg of LANOXIN was ingested by a child aged 1 year 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 overdose.

Cardiac manifestations:

The same dysrhythmias or combination of dysrhythmias 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 dysrhythmia or alteration in cardiac conduction that develops in a child taking LANOXIN should be assumed to be caused by LANOXIN, until further evaluation proves otherwise.

Non-cardiac 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 large doses of repeated activated charcoal administrations within 120 minutes.

Treatment with digitalis Fab antibody usually renders gastric lavage unnecessary.

Patients with massive digoxin (as in LANOXIN) ingestion should receive large doses of activated charcoal to prevent absorption and bind digoxin in the gut during enteroenteric recirculation. Emesis may be indicated especially if ingestion has occurred within 30 minutes of the patient's presentation at the hospital. Emesis should not be induced in patients who are

obtunded. If a patient presents more than 2 hours after ingestion or already has toxic manifestations, it may be unsafe to induce vomiting or attempt passage of a gastric tube, because such manoeuvres may induce an acute vagal episode that can worsen digitalis-toxic dysrhythmias.

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

Bradydysrhythmias may respond to atropine but cardiac pacing may be required.

Ventricular dysrhythmias may respond to lignocaine or phenytoin.

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

Digoxin-specific antibody Fab is a specific treatment for digoxin toxicity and is very effective. The decision to administer Digibind before the onset of toxic manifestations will depend on the likelihood that life-threatening toxicity will occur (see above). Rapid reversal of the complications that are associated with serious poisoning by digoxin, digitoxin and related glycosides has followed I.V. administration of digoxin-specific (ovine) antibody fragments (Fab).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 6.3 Cardiac glycosides

Pharmacotherapeutic group: Cardiac therapy, cardiac glycosides, digitalis glycosides

ATC code: C01AA05

Mechanism of action

Digoxin is a positive inotropic medicine, it increases the force and velocity of myocardial contraction. A decrease in the conduction rate and increase in the effective refractory period of the atrioventricular node is predominantly due to an indirect effect caused by enhancement of parasympathetic tone and decrease in sympathetic tone.

5.2. 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.

Distribution

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. Using the oral route the onset of effect occurs in 30 minutes to 2 hours and reaches its maximum at 2 to 6 hours.

Elimination

The terminal elimination half-life of digoxin in patients with normal renal function is 36 to 48 hours.

Digoxin is a substrate for P-glycoprotein. As an efflux protein on the apical membrane of enterocytes, P-glycoprotein may limit the absorption of digoxin. P-glycoprotein in renal

proximal tubules appears to be an important factor in the renal elimination of digoxin (see section 4.5).

Special 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 three months, compared to only 32 ± 7 ml/min/1,73 m2 at one 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.

6. PHARMACUETICAL PARTICULARS

6.1. List of excipients

LANOXIN 0,25 mg TABLETS:

Lactose monohydrate, magnesium stearate, maize starch, modified maize starch, rice starch.

LANOXIN PG:

Indigo Carmine FD&C Blue No. 2 (C.I. 73015), lactose monohydrate, magnesium stearate, maize starch, modified maize starch, povidone, rice starch.

LANOXIN INJECTION:

Citric acid monohydrate (for pH adjustment), ethanol, propylene glycol, sodium phosphate dodecahydrate (for pH adjustment), water for injection.

LANOXIN PAEDIATRIC/GERIATRIC ELIXIR:

Citric acid monohydrate (for pH adjustment), disodium phosphate anhydrous (for pH adjustment), ethanol, lime flavour, methyl parahydroxybenzoate, propylene glycol, purified water, quinolone yellow (C.I. 47005), sucrose.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

LANOXIN 0,25 mg TABLETS: 24 months

LANOXIN PG (tablet): 24 months

LANOXIN INJECTION: 24 months

LANOXIN PAEDIATRIC/ GERIATRIC ELIXIR: 36 months

6.4. Special precautions for storage

Store at or below 25℃.

Protect from light.

Keep in original packaging until required for use.

6.5. Nature and contents of container

LANOXIN 0,25 mg TABLETS:

100, 120 or 500 tablets are packed in a type III, amber, glass bottle fitted with a white low density polyethylene snap-fit cap. The bottle is packed into an outer cardboard carton.
30, 100, 120 or 500 tablets are packed in push-through strips of white opaque thermoforming polyvinylchloride film backed by an aluminium lidding foil with a heat seal coating. The blister strips are packed into an outer cardboard carton.

LANOXIN PG:

90, 100 or 120 tablets are packed in an amber, glass bottle sealed with a white low density polyethylene cap. The bottle is packed into an outer cardboard carton.
90, 100 or 120 tablets are packed in push-through strips of white opaque thermoforming polyvinylchloride/polyvinylidene chloride film backed by an aluminium lidding foil with a heat seal coating. The blister strips are packed into an outer cardboard carton.

LANOXIN INJECTION:

LANOXIN INJECTION is packed into Type I, clear, glass ampoules. Five ampoules are packed together in a printed cardboard carton.

LANOXIN PAEDIATRIC/GERIATRIC ELIXIR:

50 ml or 60 ml is packed into an amber, glass bottle and sealed with a white polypropylene or metal roll-on pilfer proof cap, fitted with a sealing wad. The bottle is packed together with a graduated 1 ml polyethylene dropper into an outer cardboard carton.
Not all packs and pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Dilution of LANOXIN INJECTION:

LANOXIN INJECTION, 250 μg per ml when diluted in the ratio of 1 to 250 (i.e. one 2 ml ampoule containing 500 μg 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 °C to 25 °C):

Sodium chloride intravenous infusion, B.P. 0,9 % *m/v*

Sodium chloride (0,18 % *m/v*) and glucose (4 % *m/v*) intravenous infusion, B.P.

Glucose intravenous, B.P. 5 % *m/v*

Dilution should be carried out either under full aseptic conditions or immediately before use.

Any unused solution should be discarded.

Dilution of LANOXIN PAEDIATRIC/GERIATRIC ELIXIR:

LANOXIN PAEDIATRIC/GERIATRIC ELIXIR should not be diluted.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead

2191

8. REGISTRATION NUMBERS

LANOXIN 0,25 mg TABLETS: G2846 (Act 101/1965)

LANOXIN PG: J/6.3/302

LANOXIN INJECTION: G2848 (Act 101/1965)

LANOXIN PAEDIATRIC/GERIATRIC ELIXIR: G2847 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION

LANOXIN 0,25 mg TABLETS: Old Medicine

LANOXIN PG: 22 March 1978

LANOXIN INJECTION: Old Medicine

10. DATE OF REVISION OF TEXT

06 October 2023

Die Afrikaanse Profesionele Inligting is op versoek beskikbaar.

Mediese Blitslyn 0800 118 088

Botswana: S2

LANOXIN 0,25 mg TABLETS: BOT1702978

LANOXIN PG: BOT1702977

LANOXIN INJECTION: B9317290

Namibia: NS2

LANOXIN 0,25 mg TABLETS: 14/6.3/0272

LANOXIN PG: 90/6.3/00581

LANOXIN INJECTION: 14/6.3/0271

LANOXIN PAEDIATRIC/GERIATRIC ELIXIR: 14/6.3/0131

Zimbabwe: P.P.10

LANOXIN 0,25 mg TABLETS: 2017/12.4/5421

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