SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lanoxin 250 microgram Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 micrograms Digoxin.

Excipients with known effect:
Each tablet contains 95.525mg of Lactose Monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

They are white, round, biconvex tablets bisected and debossed "DO25" on the same side and plain on the other side.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cardiac failure
Digoxin 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.

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

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

4.2 Posology and method of administration

Posology:
The dose of digoxin 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.

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

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

Adults and paediatric populations over 10 years

Rapid oral loading:
If medically appropriate, rapid digitalisation may be achieved in a number of ways, such as 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 six hours apart, with approximately half the total dose given as the first dose.
Clinical response should be assessed before giving each additional dose (see Section 4.4).

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.

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:

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

Where: Peak body stores = personalised loading dose
daily loss (in percent) = 14 + creatinine clearance (C_{cr})/5

Ccr is creatinine clearance corrected to 70 kg bodyweight or 1.73 m^2 body surface area. If only serum creatinine (S_{cr}) concentrations are available, a C_{cr} (corrected to 70 kg bodyweight) 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:

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

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

Where 113.12 is the molecular weight of creatinine.

For women, this result should be multiplied by 0.85.

N.B. 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) digoxin daily; however in those who show increased sensitivity to the adverse effects of digoxin, 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 paediatric populations up to 10 years of age

If cardiac glycosides have been given in the two weeks preceding commencement of digoxin therapy, it should be anticipated that optimum loading doses of digoxin will be less than those recommended below.

In the newborn, particularly in the premature infant, renal clearance of digoxin 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 ten 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 less than 1.5 kg	-	25 micrograms/kg per 24 h.
Preterm neonates 1.5 kg to 2.5 kg	-	30 micrograms/kg per 24 h.
Term neonates to 2 years	-	45 micrograms/kg per 24 h.
2 to 5 years	-	35 micrograms/kg per 24 h.
5 to 10 years	-	25 micrograms/kg per 24 h.

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 h, assessing clinical response before giving each additional dose.

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

Preterm neonates:
daily dose = 20 % of 24 h loading dose .

Term neonates and children up to 10 years:
daily dose = 25 % of 24 h loading dose .

These dosage schedules are meant as guidelines and careful clinical observation and monitoring of serum digoxin levels (see Section 4.4) should be used as a basis for adjustment of dosage in these paediatric patient groups.

Elderly
The possibility of reduced renal function and lower lean body mass should be taken into account when dealing with elderly patients. If necessary, the dosage should be reduced and adjusted to the changed pharmacokinetics to prevent elevated serum digoxin levels and the risk of toxicity. The serum digoxin levels should be checked regularly and hypokalaemia should be avoided.

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 (See Section 4.4).

Method of administration:
For oral use only.

4.3 Contraindications

Digoxin is contraindicated in:

- intermittent complete heart block or second degree atrioventricular 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 have 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.

- hypersensitivity to the active substance, other digitalis glycosides, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

Serum concentrations of digoxin may be expressed in conventional units of nanograms/ml or SI units of nanomol/l . To convert nanograms/ml to nmol/l, multiply ng/ml by 1.28.

The serum concentration of digoxin can be determined by radioimmunoassay.

Blood should be taken six hours or more after the last dose of digoxin.

There are no rigid guidelines as to the range of serum concentrations that are most efficacious. 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).

Digoxin toxicity is more commonly associated with serum digoxin concentrations 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 digoxin, the clinical state together with the serum potassium level and thyroid function are important factors (see Section 4.9).

Determination of the serum digoxin concentration may be very helpful in making a decision to treat with further digoxin, but other glycosides and endogenous digoxin-like substances, 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. Observations while temporary withholding digoxin might be more appropriate.

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 digoxin 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) digoxin may cause or exacerbate sinus bradycardia or cause sinoatrial block.

Myocardial infarction
The administration of digoxin 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. 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 digoxin 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
Digoxin 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 digoxin if the underlying thiamine deficiency is not treated concomitantly.

Constrictive pericarditis
Digoxin 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
Digoxin 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 digoxin 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 digoxin has been shown to result in clinical deterioration.

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

Digoxin 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.

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 digoxin to a patient with thyroid disease requires care. Initial and maintenance doses of digoxin 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 digoxin.

Chronic congestive cardiac failure
Although many patients with chronic congestive cardiac failure benefit from acute administration of digoxin, 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 digoxin is continued long-term.

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 digoxin, the drug should be withheld for 24 h 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.

Laboratory Test Interference
Falsely elevated serum levels of digoxin may occur when samples from patients receiving enzalutamide or apalutamide are analysed using the chemiluminescent microparticle immunoassay (CMIA), independently of being treated with digoxin. In case of doubtful results, it is recommended to confirm digoxin serum levels with an alternative assay without known interference, in order to avoid any unnecessary discontinuation or decrease in the dose of digoxin (see section 4.5).

Digoxin tablets contain lactose.
Patients with rare hereditary problems of galactose intolerance, the total lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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 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.

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 Section 5.2). Induction of P-glycoprotein can result in decreases in plasma concentrations of digoxin.

Combinations that should be avoided

Combinations which can increase effects of digoxin when co-administered:
Digoxin, in association with beta-adrenoceptor blocking drugs, may increase atrio-ventricular conduction time.

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

Calcium, particularly if administered rapidly by the I.V. route, may produce serious arrhythmias in digitalised patients.

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.

Combinations requiring caution

Combinations which can increase the effects of digoxin when co-administered:
amiodarone, canagliflozin, daclatasvir, flibanserin, flecainide, prazosin, propafenone, quinidine, spironolactone, macrolide antibiotics e.g. erythromycin and clarythromycin, tetracycline (and possibly other antibiotics), gentamicin, isavuconazole, itraconazole, posaconazole, ivacaftor, quinine, trimethoprim, alprazolam, indomethacin, propantheline, mirabegron, nefazodone, atorvastatin, ciclosporine, epoprostenol (transient), vasopressin receptor antagonists (tolvaptan and conivaptan), carvedilol, ritonavir/ritonavir containing regimens, taleprevir, dronedarone, ranolazine, simeprevir, telmisartan, ticagrelor, velpatasvir, venetoclax, lapatinib, vandetanib, vemurafenib and osimertinib. 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 for titration of digoxin.

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

Patients receiving digoxin 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 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 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.

Proton pump inhibitors (PPI) are able to increase plasma levels of digoxin. Absorption of unchanged digoxin is enhanced and 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:
antacids, some bulk laxatives, kaolin-pectin, acarbose, neomycin, penicillamine, rifampicin, some cytostatics, metoclopramide, sulfasalazine, 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 aOATP4C1 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.

Determination of serum digoxin concentrations with the chemiluminescent microparticle immunoassay (CMIA) while using enzalutamide or apalutamide may cause falsely elevated serum digoxin levels. Results should be confirmed by another type of assay (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of digoxin 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 digoxin 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 digoxin has been successfully used to treat foetal tachycardia and congestive heart failure.
Adverse foetal effects have been reported in mothers with digitalis toxicity.

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
In general, the adverse reactions of digoxin are dose-dependent and occur at doses higher than those needed to achieve a therapeutic effect.

Hence, adverse reactions are less common when digoxin is used within the recommended dose range or therapeutic serum concentration range and when there is careful attention to concurrent medications and conditions.

Tabulated list of adverse reactions

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 ≥ 1/1000 and < 1/100
Rare ≥ 1/10,000 and < 1/1000
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**	**Side effects**
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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

Symptoms and signs
The symptoms and signs of toxicity are generally similar to those described in 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 digoxin, the clinical state, together with serum electrolyte levels and thyroid function are important factors (see Section 4.2). 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 to 15 mg was the dose resulting in death of half of the patients. If more than 25 mg of digoxin was ingested by an adult without heart disease, death or progressive toxicity responsive only to digoxin-binding Fab antibody fragments resulted.

Cardiac manifestations
Cardiac manifestations are the most frequent and serious sign of both acute and chronic toxicity. Peak cardiac effects generally occur 3 to 6 hours following overdose and may persist for the ensuing 24 hours or longer. Digoxin 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 digoxin toxicity is usually fatal. Acute massive digoxin overdose 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, non-specific non-cardiac symptoms, such as malaise and weakness, may predominate.

<u>Paediatric population</u>

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 digoxin overdose.

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 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 digoxin should be assumed to be caused by digoxin, until further evaluation proves otherwise.

Non-cardiac manifestations
The frequent non-cardiac manifestations are 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 digoxin in the gut during enteroenteric recirculation.
If hypokalaemia is present, it should be corrected with potassium supplements either orally or intravenously, depending on the urgency of the situation. In cases where a large amount of 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 I.V. administration of digoxin-specific (ovine) antibody fragments (Fab). For details, consult the literature supplied with antibody fragments.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, cardiac glycosides, digitalis glycosides.

ATC code: C01AA05

Mechanism of action

Digoxin increases contractility of the myocardium by direct activity. This effect is proportional to dose in the lower range and some effect is achieved with quite low dosing; it occurs even in normal myocardium although it is then entirely without physiological benefit. The primary action of digoxin is specifically to inhibit adenosine triphosphatase, and thus sodium-potassium (Na^+-K^+) exchange activity, the altered ionic distribution across the membrane resulting in an augmented calcium ion influx and thus an increase in the availability of calcium at the time of excitation-contraction coupling. The potency of digoxin may therefore appear considerably enhanced when the extracellular potassium concentration is low, with hyperkalaemia having the opposite effect.

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

Intravenous administration of a loading dose produces an appreciable pharmacological effect within 5 to 30 mins, while using the oral route the onset of effect occurs in 0.5 to 2 hours.

Pharmacodynamic effects

The PROVED trial designed to determine the effectiveness of digoxin in 88 patients with chronic, stable mild to moderate heart failure. Withdrawal of digoxin or its continuation was performed in a prospective, randomised, double-blind, placebo-controlled multicentre trial of patients with chronic, stable mild to moderate heart failure secondary to left ventricular systolic dysfunction who had normal sinus rhythm and were receiving long-term treatment with diuretic drugs and digoxin. Patients withdrawn from digoxin therapy showed worsened maximal exercise capacity ($p = 0.003$) an increased incidence of treatment failures ($p = 0.039$) and a decreased time to treatment failure ($p = 0.037$). Patients who continued to receive digoxin had a lower body weight ($p = 0.044$) and heart rate ($p = 0.003$) and a higher left ventricular ejection fraction ($p = 0.016$). The overall percentage of participants having one or more adverse event was similar in the two groups: 59 % in the placebo group and 69 % in the digoxin group. The types of adverse event were unspecified

The RADIANCE trial examined the effects of discontinuation of digoxin in stable NYHA class II and III patients who were receiving diuretics and ACE inhibitors. The 178 patients were initially stabilised on a combination of captopril or enalapril, diuretics and digoxin, then randomised to continue digoxin therapy or change to placebo. The relative risk of worsening disease in the placebo group was 5.9 compared to the digoxin group. Withdrawal of digoxin was accompanied by worsening symptoms, reduced exercise tolerance, and a deteriorating quality of life, indicating that patients with CHF were at considerable risk from discontinuation of the drug in spite of the continuation of therapy with diuretics and ACE inhibitors. Approximately 56 % in the placebo group and 49% in the digoxin group experienced unspecified side effects.

In the DIG trial, 6800 patients with heart failure were randomised to receive digoxin or placebo. No difference was found in all-cause mortality between patients who were treated with digoxin and those who were given placebo. In the digoxin group, there was a trend toward a decrease in the risk of death attributed to worsening heart failure (risk ratio, 0.88; 95% confidence interval, 0.77 to 1.01; $p = 0.06$). However, the patients who received digoxin had significantly ($p<0.001$) fewer hospital admissions when the drug was given in addition to diuretics and ACE inhibitors. Digoxin therapy was most beneficial in patients with ejection fractions of ≤25%, patients with enlarged hearts (cardiothoracic ratio of >0.55), and patients in NYHA functional class III or IV. In the DIG study, 11.9 % of patients in the digoxin arm and 7.9 % of patients in the placebo arm

were suspected of having digoxin toxicity, the most common symptoms being new episodes of ventricular fibrillation, supraventricular arrhythmia, tachycardia, or advanced atrioventricular block.

The AFFIRM study involved a total of 4060 patients recruited to a randomised, multicentre comparison of two treatment strategies in patients with atrial fibrillation and a high risk of stroke or death. The primary end point was overall mortality. There were 356 deaths among the patients assigned to rhythm-control therapy (amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, and combinations of these drugs) and 310 deaths among those assigned to rate-control [β-blockers, calcium-channel blockers (verapamil and diltiazem), digoxin, and combinations of these drugs) therapy (mortality at five years, 23.8% and 21.3%, respectively; hazard ratio, 1.15 [95% confidence interval, 0.99 to 1.34]; p=0.08). More patients in the rhythm-control group than in the rate-control group were hospitalised, and there were more adverse drug effects in the rhythm-control group as well.

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.

5.2 Pharmacokinetic properties

Absorption
The T_{max} following IV administration is approximately 1 to 5 hours, while the T_{max} for oral administration is 2 to 6 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.

The bioavailability of orally administered digoxin is approximately 63 % in tablet form and 75 % as oral solution.

Distribution
The initial distribution of digoxin from the central to the peripheral compartment generally lasts from 6 to 8 h. 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.

Biotransformation
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 Section 4.5).

Following I.V. administration to healthy volunteers, between 60 and 75 % of a digoxin dose is recovered unchanged in the urine over a six day follow-up period. Total body clearance of digoxin has been shown to be directly related to renal function, and percent daily loss is thus a function of creatinine clearance. 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.

The terminal elimination half-life of digoxin in patients with normal renal function is 30 to 40 h.

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 h of haemodialysis.

Special patient populations

Paediatric population
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/1.73m^2 at three months, compared to only 32 ± 7 ml/min/1.73m^2 at one week. By 12 months digoxin clearance of 88 ± 43 ml / min / 1.73m^2 has been reported. 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.

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.

5.3 Preclinical safety data

Carcinogenesis, mutagenesis
Digoxin showed no genotoxic potential in in vitro studies (Ames test and mouse lymphoma). No data are available on the carcinogenic potential of digoxin.

PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Modified maize starch
Magnesium stearate
Rice starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package protected from light.

6.5 Nature and contents of container

Amber glass bottles with low density polyethylene snap fit closures or white opaque thermoform blisters with aluminium lidding.

Pack sizes: 30, 500, 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive,
Citywest Business Campus,
Dublin 24,
Ireland

8. MARKETING AUTHORISATION NUMBER

MA 955/00702

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

09/2026