SUMMARY OF PRODUCT CHARACTERISTICS

NAME OF THE MEDICINAL PRODUCT

Digoxin KERN PHARMA 0.25 mg tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Digoxin KERN PHARMA 0.25 mg tablets

Each tablet contains:
Digoxin. . . . . 0.25 mg
Lactose monohydrate 95.52 mg, maize starch, hydrolysed maize starch, rice starch and other excipients.

For a full list of excipients, see section 6.1

PHARMACEUTICAL FORM

Digoxin KERN PHARMA 0.25 mg tablets:
Round, biconvex, white tablets scored on both sides. The purpose of the score line is to facilitate breaking of the tablet for ease of swallowing or, if necessary, for dividing into equal doses .

CLINICAL PARTICULARS:

Therapeutic indications

Cardiac failure:

Digoxin KERN PHARMA is indicated for the treatment of chronic cardiac failure where the principal cause is systolic dysfunction. The greatest therapeutic benefit is achieved in patients with ventricular dilatation.

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

Supraventricular arrhythmias:

Digoxin KERN PHARMA is indicated for the treatment of certain supraventricular arrhythmias, particularly atrial fibrillation and flutter, where its principal beneficial effect is to reduce the ventricular rate.

Posology and method of administration

The dose of Digoxin KERN PHARMA for each patient must be tailored individually according to age, lean body weight, and renal function. The suggested doses are intended only as an initial guide.

Adults and children over 10 years:

Rapid oral administration:

0.75 to 1.5 mg as a single dose.

In less urgent cases, or when there is a major risk of toxicity, for example in the elderly, the oral loading dose should be administered in divided doses at intervals of 6 hours, with approximately half of the total dose given as the first dose. The clinical response should be assessed before giving each additional dose (see Special warnings and precautions for use).

Slow oral administration:

0.25 to 0.75 mg should be administered daily for 1 week followed by a suitable maintenance dose. A clinical response should be observed within a week.

NOTE: The choice of a slow or rapid oral digitilisation regimen will depend on the clinical status of the patient and on the urgency of the clinical indication.

Maintenance Dose:

The maintenance dose should be based on the percentage of the body stores lost each day through elimination. The following formula has had wide clinical use:

$$\text{Maintenance dose} = \text{Peak body stores} \times \frac{\text{dailyloss}(\%)}{100}$$

Where:
-Peak body stores = loading dose
Daily loss (%) = 14 + creatinine clearance (Ccr)/5

Ccr is creatinine clearance corrected to 70 kg body weight or 1.73 m² body surface area. If only serum creatinine (Scr) concentrations are available, Ccr (corrected to 70 kg body weight) may be estimated in men as:

$$\text{Ccr} = \frac{(140-\text{age})}{\text{Scr (mg/100 ml)}}$$

NOTE: Where serum creatinine values are obtained only in mcmol/l, these can be converted into mg/100 ml (mg%) as follows:

$$\text{Scr (mg/100 ml)} = \frac{\text{Scr(mcmol/l)} \times 113.12}{10{,}000}$$

$$= \frac{\text{Scr(mcmol/l)}}{88.4}$$

- Where 113.12 is the molecular weight of creatinine.
- For women, this result should be multiplied by 0.85.
- These formulae cannot be used for creatinine clearance in children.

In practice this will mean that most patients will be maintained on 0.125 to 0.25 mg of digoxin per day. However, in those who show greater sensitivity to the adverse effects of digoxin, a dosage of 0.0625 mg per day or less may be sufficient.

Newborns, infants, and children under 10 years of age (if cardiac glycosides have not been given in the preceding two weeks):

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

Beyond the immediate newborn period, children generally require proportionally higher 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 doses in proportion to their body weight.

The loading dose for the preceding groups should be administered according to the following schedule:

Pre-term newborns < 1.5 kg	0.025 mg/kg over 24 hours.
Pre-term newborns 1.5 kg-2.5 kg	0.030 mg/kg over 24 hours.
Full-term newborns to age 2 years	0.045 mg/kg over 24 hours.
Age 2 to 5 years	0 . 0 35 mg/kg over 24 hours.
Age 5 to 10 years	0.025 mg/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 4-8 hours, assessing the clinical response before giving each additional dose.

Maintenance Dose:

The maintenance dose should be administered according to the following schedule:

Pre-term newborns:
- daily dose = 20% of 24-hour loading dose.

Full-term newborns and children up to 10 years:
- daily dose = 25% of 24-hour loading dose.

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 adjusting the dosage in these paediatric patient groups.

In patients who have received a cardiac glycoside within the preceding two weeks, it should be expected that the optimum loading doses of digoxin will be less than those recommended above.

Digitalis glycosides are a significant cause of accidental poisoning in children. Newborn tolerance of digitalis glycosides is variable since renal clearance of the medicine is reduced. Premature newborns and immature infants are especially sensitive.

The elderly:

In the elderly, the tendency for impaired renal function and a low lean body mass affects the pharmacokinetics of Digoxin KERN PHARMA such that high serum digoxin levels and associated

toxicity can occur unless reduced doses of Digoxin KERN PHARMA are used. Serum levels should be checked regularly and hypokalaemia should be avoided.

Recommended Doses in Specific Groups of Patients:

See Special warnings and precautions for use

Monitoring:
In order to ensure the continuity of different products of digoxin in individual patients it should be emphasized that if patients are changed from one digoxin tablet to another it should be done only with monitoring . Serum digoxin concentrations may be expressed in Conventional Units of ng/ml or in SI units of nmol/l (Multiply ng/ml by 1.28 to convert to nmol/l).

Digoxin serum concentrations can be determined by radioimmunoassay. Blood must be taken at least 6 hours after the last dose of Digoxin KERN PHARMA. There are no strict guidelines on the most effective range of serum concentrations, but the majority of patients will benefit, from concentrations of digoxin between 0.8ng/ml (1.02 nmol/1) and 2.0 ng/ml (2.56 nmol/1), with limited risk of developing signs and symptoms of toxicity. Above this range, signs and symptoms of toxicity may be more frequent, and it is very probable that levels above 3.0 ng/ml (3.84 nmol/1) are toxic.

However, clinical status along with potassium serum levels and thyroid function are important factors to take into account when determining whether symptoms are due to digoxin.

Other glycosides, including digoxin metabolites, can interfere with the available assays and one should be cautious of values that are not compatible with the clinical status of the patient.

Contraindications

Digoxin KERN PHARMA is contraindicated in patients with intermittent complete heart block or second-degree atrioventricular block, especially if there is a history of Stokes-Adams syndrome.

Digoxin KERN PHARMA is contraindicated in patients with arrhythmias caused by cardiac glycoside intoxication.

Digoxin KERN PHARMA is contraindicated in patients with supraventricular arrhythmias associated with an accessory atrioventricular pathway, as in Wolff-Parkinson-White syndrome, unless the electrophysiological characteristics of the accessory pathway and any possible harmful effects 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 KERN PHARMA is similarly contraindicated.

Digoxin is contraindicated in patients with ventricular tachycardia or ventricular fibrillation.

Digoxin is contraindicated in patients with hypertrophic obstructive cardiomyopathy, unless there is concomitant atrial fibrillation and heart failure, but even then caution should be exercised if Digoxin KERN PHARMA is to be used.

Digoxin is contraindicated in patients with known hypersensitivity to digoxin, to other digitalis glycosides or to any component of the preparation.

Special warnings and precautions for use

Digoxin intoxication produces a variety of cardiac dysrhythmias, some of which can resemble those for which the product was intended (e.g. atrial tachycardia with intermittent atrioventricular block requires particular care as the rhythm clinically 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.

In some cases of sinoatrial disorder (i.e. Sick Sinus Syndrome) digoxin may cause or exacerbate sinus bradycardia or cause sinoatrial block.

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. However, the possibility of arrhythmias arising in patients who may be hypokalaemic after myocardial infarction and are likely to be cardiologically unstable must be born in mind. The limitations imposed thereafter on cardioversion must also be remembered.
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 with caution to control the ventricular rate in patients with cardiac amyloidosis and atrial fibrillation.

Digoxin can rarely precipitate vasoconstriction and therefore should be avoided in patients with myocarditis.

Patients with beri beri heart disease may fail to respond adequately to digoxin if the underlying thiamine deficiency is not treated concomitantly. There is also some published information indicating that digoxin may inhibit the uptake of thiamine in myocytes in beri beri heart disease.

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.

Digoxin 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 patients with supraventricular arrhythmias is most evident at rest, less evident with exercise. In patients receiving diuretics and an ACE inhibitor, or diuretics alone, the withdrawal of digoxin has been shown to result in clinical deterioration

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 chang es on the electrocardiogram during exercise testing. These electrophysiological effects reflect an expected effect of the drug and are not indicative of toxicity.

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

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

Determination of the serum digoxin concentration can be very helpful in making a decision to increase the digoxin dose, although other glycosides and endogenous substances similar to digoxin may cross-react in the assay leading to false-positive results. Observations during the temporary withholding of digoxin might be more appropriate.

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

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.

Hypokalaemia sensitizes the myocardium to the actions of cardiac glycosides. Hypokalaemia may also accompany malnutrition, diarrhea, vomiting and long standing wasting disease and the dose may need to be reduced in such patients. Hypoxia, hypomagnesaemia and marked hypercalcaemia increase myocardial sensitivity to cardiac glycosides.

Administering digoxin to a patient with thyroid disease requires caution. Initial and maintenance doses of Digoxin KERN PHARMA should be reduced when thyroid function is deficient. 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 is brought under control.

Patients with malabsorption syndrome or gastrointestinal reconstruction may require larger doses of digoxin.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose galactose malabsorption should not take this medicine.

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 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 caused by cardiac glycosides.

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 and sensitivity to Digoxin KERN PHARMA. Consideration of the possibility of an interaction whenever concomitant therapy is contemplated is the best precaution and a check on serum digoxin level is recommended when any doubt exists.

• *Antiarrhythmics*

Amiodarone*:** plasma levels of digoxin are considerably increased by concurrent administration of amiodarone. This is due to a decrease in the renal and non-renal clearance of digoxin, a prolongation of its half life and a possible increase in absorption. Children are especially sensitive. The dose of digoxin should be reduced by a third to a half when it is given concurrently with amiodarone. ***Disopyramide may modify the cardiovascular effects of digoxin and reduce its volume of distribution. The loading dose of digoxin should be reduced in patients who are also receiving disopyramide. ***Flecainide:*** plasma levels of digoxin are increased by concurrent administration of flecainide. This is likely to be clinically significant only in patients with high plasma levels of digoxin or those with atrioventricular nodal dysfunction. ***Moracizine:*** digoxin and moracizine have additive effects on cardiac conduction. ***Propafenone:*** plasma levels of digoxin are increased by concurrent administration of propafenone. There is considerable interindividual variation in the extent of this interaction but the dose of digoxin should be reduced and patients monitored for signs of digoxin toxicity. ***Quinidine:*** the renal and non-renal excretion of digoxin is reduced by co-administration of digoxin. Excretion in bile and tissue binding of digoxin may also be reduced Significant effects occur as soon as quinidine is given to a patient stabilised on digoxin and plasma levels of digoxin are usually doubled within 5 days. The dose of digoxin should be halved when quinidine is added to therapy and the possibility of an alternative anti-arrhythmic should be examined.

• *Anti-infective drugs*

Macrolides, tetracycline: presystemic metabolism of digoxin to inactive metabolites in the gastrointestinal tract occurs in about 10% of patients. Co-administration of macrolide antibiotics (*azithromycin, clarithromycin, erythromycin, telithromycin*) or *tetracycline* to this sub-group of patients can result in a clinically significant increase in plasma digoxin levels. ***Neomycin:*** absorption of digoxin from the gastrointestinal tract is inhibited by neomycin and plasma levels are reduced. ***Rifampicin:*** the metabolism of digoxin may be increased by co-administration with rifampicin. The interaction may be enhanced in patients with renal impairment. ***Trimethoprim:*** the renal excretion of digoxin is decreased by concurrent administration with trimethoprim. The interaction is more significant in elderly patients or those with renal impairment and digoxin plasma levels should be monitored**.** ***Amphotericin:*** hypokalaemia due to amphotericin administration may potentiate digoxin toxicity. Patients should be monitored and given potassium supplements when necessary. ***Itraconazole*** can cause a marked increase in plasma digoxin levels and toxicity may occur if the dose of digoxin is not reduced. Itraconazole may also oppose the positive inotropic effects of digoxin. ***Quinine, hydroxychloroquine*** **and** ***chloroquine*** can increase plasma levels of digoxin by decreasing non-renal clearance.

• *Calcium channel blockers*

Diltiazem and digoxin co-administration can result in increased or no effect on digoxin plasma levels and toxicity and patients should be monitored. ***Nifedipine*** may increase or have no effect on digoxin plasma levels but there is considerable interindividual variation. Patients taking high doses of digoxin or those with renal impairment are most at risk. ***Nisoldipine*** may also increase plasma levels of digoxin but ***amlodipine, felodipine, isradipine, lercanidipine, nicardipine, nimodipine*** **and** ***nitrendipine*** do not appear to have significant effects on digoxin plasma levels but it is prudent to monitor the effects of co-administration. ***Verapamil,*** **felodipine and tiapamil** increase plasma digoxin levels by inhibiting the active tubular secretion and non-renal clearance of digoxin. The dose of digoxin should be reduced and plasma levels monitored. Verapamil may also increase atrioventricular block and tachycardia in patients taking digoxin.

• *Calcium salts and vitamin D analogues*

Intravenous administration of *calcium salts* to patients taking digoxin can result in dangerous cardiac arrhythmias and should be avoided. *Vitamin D analogues* can also increase digoxin toxicity due to elevations in plasma calcium concentrations.

• *Cardiovascular drugs*

ACE inhibitors and angiotensin II antagonists may cause hyperkalaemia which can reduce tissue binding of digoxin resulting in higher serum levels. These drugs may also cause a deterioration in renal function resulting in elevated serum levels of digoxin because of impaired renal excretion. Concurrent administration of ***captopril*** has been associated with increases in plasma digoxin levels but this may only be clinically significant in patients with impaired renal function or severe congestive heart failure. ***Telmisartan*** administration has been associated with increases in plasma digoxin levels and patients receiving both drugs should be monitored. No clinically significant interactions have been noted with other ACE inhibitors or angiotensin II antagonists examined (*cilazapril, enalapril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril* and *trandolapril; candesartan, eprosartan, irbesartan, losartan* and *valsartan*)) but it is prudent to monitor the effects of co-administration. There is an increased risk of atrio-ventricular block, increasing atrio-ventricular conduction time and bradycardia when digoxin and **beta blockers** are taken concomitantly. ***Nitroprusside*** **and** ***hydralazine*** increase the renal clearance of digoxin by increasing renal blood flow and tubular secretion and lowering plasma digoxin levels.

• *Central nervous system drugs*

St John's wort: co-administration of digoxin with St John's wort should be avoided because plasma levels are significantly reduced. ***Nefazodone, trazodone****:* Plasma levels of digoxin are increased by concomitant administration of nefazodone or trazodone and it may be necessary to reduce the dose of digoxin. ***Phenytoin*** increases total clearance of digoxin and reduces its elimination half-life, resulting in a decrease in plasma levels. Intravenous phenytoin should not be used to treat digitalis induced arrhythmias or in patients with a high degree of heart block or marked bradycardia because of the risk of cardiac arrest. ***Topiramate:*** co-administration of digoxin and topiramate reduces the bioavailability of digoxin and patients should be monitored. ***Alprazolam*** **and** ***diazepam*** can decrease digoxin clearance, resulting in increased plasma concentrations. Patients should be monitored for digoxin toxicity, especially those aged over 65. Digoxin may have detrimental effects on the short term control of bipolar disorder in patients treated with ***lithium*****.** Lithium may also cause hypokalaemia or intracellular potassium deficiency and therefore may cause increased sensitivity to Digoxin KERN PHARMA.

• *Diuretics*

Potassium depletion due to ***acetazolamide****, loop diuretics* and ***thiazide*** *diuretics* potentiates the effects of digoxin on the myocardium and may also have a small effect on reducing the renal tubular secretion of digoxin. Patients should be monitored for hypokalaemia and given potassium supplements when necessary. ***Spironolactone*** decreases renal excretion of digoxin, increasing plasma levels. The dose of digoxin should be decreased in susceptible patients.

• *Gastrointestinal drugs*

Antacids and adsorbents, such as **kaolin**, can inhibit the absorption of digoxin from the gastrointestinal tract, resulting in a fall in digoxin plasma levels. The interaction can be prevented by separating the doses by about 2 hours. ***Carbenoxolone*** may cause fluid retention and hypokalaemia which can increase susceptibility to digoxin toxicity. Metabolism of digoxin in the gastrointestinal tract is inhibited by ***omeprazole***, resulting in increased plasma levels of digoxin. Smaller effects have been seen with ***pantoprazole*** **and** ***rabeprazole*****.** ***Sucralfate*** decreases the absorption of digoxin from the gastrointestinal tract, lowering plasma levels. Plasma levels of digoxin may be reduced by co-administration with ***sulfasalazine*** because of decreased absorption. Patients receiving both drugs should be monitored. No interaction has been seen between digoxin and another mesalazine prodrug, ***balsalazide***.

• *Lipid regulating drugs*

Increases in plasma levels of digoxin have been observed in patients taking ***atorvastatin*** and it may be necessary to reduce the dose of digoxin. Although ***fluvastatin, pravastatin*** **and** ***simvastatin*** do not appear to cause significant increases in plasma digoxin levels it is prudent to monitor the effects of co-administration. ***Colestipol*** **and** ***colestyramine*** bind to digoxin in the gastrointestinal tract, reducing its absorption and lowering plasma digoxin levels. The interaction can be prevented by separating the doses of digoxin and anion exchange resin by about 2 hours.

• *Muscle relaxants*

Edrophonium should not be given to patients with atrial flutter and tachycardia who are taking digoxin as the combination may cause excessive bradycardia and atrioventricular block. Serious cardiac arrhythmias can develop in patients taking digoxin if they are given ***suxamethonium*** **and** ***pancuronium*** due to rapid removal of potassium from myocardial cells. Concomitant use should be avoided. ***Tizanidine*** may potentiate hypotension and bradycardia when administered concurrently with digoxin.

• *NSAIDs*

NSAIDs have the potential to cause renal impairment, reducing the renal clearance of digoxin with a subsequent increase in plasma levels. ***Aspirin, azapropazone, diclofenac, fenbufen, ibuprofen, indometacin*** **and** ***tiaprofenic acid*** have all been shown to increase plasma concentrations of digoxin but this may only be clinically significant in patients with impaired renal function. ***Etoricoxib, ketoprofen, meloxicam, piroxicam*** **and** ***rofecoxib*** do not appear to increase plasma digoxin levels. Patients being treated with digoxin often need to take NSAIDs and digoxin plasma concentrations should be monitored whenever an NSAID is initiated or discontinued. ***Phenylbutazone*** stimulates hepatic metabolism of digoxin so plasma levels should be monitored in these drugs are given concurrently.

• *Other drugs*

Acarbose inhibits the absorption of digoxin in the gastrointestinal tract, resulting in lower plasma levels. Plasma levels of digoxin are increased by concomitant administration of ***prazosin. Carbimazole*** **or** ***penicillamine*** may reduce plasma levels of digoxin. Changes in thyroid function may affect sensitivity to digoxin independently of plasma levels. Increased plasma digoxin levels have been reported when ***ciclosporin*** has been administered to patients taking digoxin due to reduced renal elimination. Patients should be monitored closely and the digoxin dose adjusted when required. ***Corticosteroids*** cause potassium loss and sodium and water retention which increase the risk of digoxin toxicity and heart failure. Patients taking prolonged courses of corticosteroids should be monitored closely. Many ***cytotoxic drugs*** damage the intestinal lining, impairing the absorption of digoxin and decreasing plasma levels. The effect is reversed shortly after discontinuing cytotoxic drug administration**. Selective beta$_2$ agonists** may cause hypokalaemia which can increase susceptibility to digoxin induced arrhythmias. Concurrent administration of ***salbutamol*** has also been associated with decrease in plasma digoxin levels.

Serum digoxin levels may be INCREASED also by concomitant administration of the following: ***gentamicin, diphenoxylate and atropine, propantheline.***

Serum digoxin levels may be REDUCED also by concomitant administration of the following: ***Some laxatives, metoclopramide, adrenaline***.

Milrinone does not alter steady-state serum digoxin levels.

Digoxin is a substrate of P-glycoprotein. Thus, inhibitors of P-glycoprotein may increase blood concentrations of digoxin by enhancing its absorption and/or by reducing its renal clearance.

Fertility, pregnancy and lactation

Teratogenicity

There are no data on whether or not digoxin has teratogenic effects.

Fertility

There is no information available on the effect of digoxin on human fertility.

Pregnancy and Lactation

The use of digoxin during pregnancy is not contraindicated, although the dosage may be less predictable in pregnant than in non-pregnant women, with some requiring an increased dose 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 newborn 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 used successfully to treat foetal tachycardia and congestive heart failure.

Adverse foetal effects have been reported in mothers with digitalis toxicity.

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES.

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

UNDESIRABLE EFFECTS

In general, the adverse effects produced by digoxin depend on the dosage and occur at doses higher than those required to achieve a therapeutic effect. As a result, adverse effects are less common when digoxin is being used within the recommended dosage range or within the range of therapeutic serum concentrations and close attention is paid to concomitant conditions and medication.

The side effects of digoxin in infants and children differ from those observed in adults in various aspects. Although digoxin can cause anorexia, nausea, vomiting, diarrhoea and CNS disturbances in young patients, these are rarely the initial symptoms of an overdose. Instead, the earliest and most frequent manifestation of an excessive dose of digoxin in infants and children is the appearance of cardiac arrhythmias, including sinus bradycardia.

In children, digoxin can cause any variety of arrhythmia. The most common are conduction abnormalities or supraventricular tachyarrhythmias such as atrial tachycardia (with or without block) and atrioventricular nodal re-entrant tachycardia. Ventricular arrhythmias are less common. Sinus

bradycardia may be a sign of imminent digoxin intoxication, especially in children, including in the absence of first-degree heart block. It must be assumed that any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin is caused by digoxin until further evaluation proves otherwise.

Cardiac disorders:

Digoxin toxicity may be the cause a variety of arrhythmias and conduction abnormalities. Premature ventricular contractions are often an early sign of digoxin toxicity; they can progress to bigeminy or even trigeminy. Atrial tachycardia, for whose treatment digoxin is frequently indicated, can appear with excessive doses of the drug. Atrial tachycardia with a certain degree of atrioventricular block is particularly indicative, and is not necessarily accompanied by a rapid pulse (see also Special warnings and precautions for use). Digoxin causes prolongation of the PR interval and depression of the ST segment which, in themselves, should not be considered as toxic effects of digoxin. Cardiac toxicity may also appear with therapeutic doses in patients with conditions that alter their sensitivity to digoxin (see Special warnings and precautions for use).

Non-cardiac disorders:

Hypersensitivity reactions have been reported rarely in patients taking digoxin. These include pruritus, erythematous, rashes, papules, vesicles and angioedema.

Other non-cardiac disorders are primarily found related to an overdose but may appear due to temporarily high blood levels caused by rapid absorption. They include anorexia, nausea, and vomiting, and usually disappear a few hours after having taken the drug. Diarrhoea may also occur. It is not advisable to consider nausea as an early warning of an excessive dose of digoxin.

Orally administered digoxin has also been linked to intestinal ischaemia and, rarely, to intestinal necrosis.

Long-term administration can cause gynaecomastia.

Central nervous system disorders reported include weakness, apathy, fatigue, malaise, headache, drowsiness, bad dreams, restlessness, nervousness, agitation.

It was found that taking regular doses of Digoxin can cause dizziness (common) and in very rare cases can cause confusion.

Psychiatric disorders associated with digoxin are disorientation, mental confusion, amnesia and depression. Acute psychosis, delirium, visual and auditory hallucinations have been reported rarely, especially in elderly patients. Epilepsy has been reported rarely.

Visual disturbances (including blurred vision and photophobia, color vision may be affected infrequently with objects appearing yellow or less frequently green red blue brown or white).

Urticaria or scarlatiniform-type skin rashes are rare reactions to digoxin and can be accompanied by pronounced eosinophilia.

Very rarely, digoxin can cause thrombocytopenia.

OVERDOSE

Signs and symptoms

The symptoms and signs of toxicity are generally similar to those described in the Undesirable Effects section but may be more frequent and can be more severe (see Undesirable Effects).

Signs and symptoms of digoxin toxicity become more frequent with levels above 2.0 nanograms/mL (2.56 nanomol/L) although there is considerable interindividual variation. However, in deciding whether a patient's symptoms are due to digoxin, the clinical state, together with serum electrolyte levels and thyroid function are important factors.

Treatment

Adults:

In adults without heart disease, clinical observation indicates that an overdose of digoxin of 10 to 15 mg was the dose that resulted in death in half of the patients. If more than 25 mg of digoxin was ingested by an adult without heart disease, the result would be death or progressive toxicity responsive only to digoxin-binding antibody fragments.

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. 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 disocciation 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.
Hypokalaemia may contribute to toxicity (see *Warnings and Precautions)*.
Non-cardiac manifestations
Acute massive digoxin overdosage can result in mild to pronounced hyperkalaemia due to inhibition of the sodium-potassium (Na+-K+) pump.
Gastrointestinal symptoms are very common in both acute and chronic toxicity. The symptoms precede cardiac manifestations in approximately half of the patients in most literature reports. Anorexia, nausea and vomiting have been reported with an incidence up to 80%. These symptoms usually present early in the course of an overdose.
Neurologic and visual manifestations occur in both acute and chronic toxicity. Dizziness, various CNS disturbances, fatigue and malaise are very common. The most frequent visual disturbance is an aberration of colour vision (predominance of yellow green). These neurological and visual symptoms may persist even after other signs of toxicity have resolved.
In chronic toxicity, non-specific extracardiac symptoms, such as malaise and weakness, may predominate.

Children:

In children aged 1 to 3 years without heart disease, clinical observation indicates that an overdose of digoxin of 6 to 10 mg was the dose that resulted 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 result would invariably be fatal unless antibody fragments were administered.
Most manifestations of toxicity in children occur during or shortly after the loading phase with digoxin.

Cardiac manifestations
The same arrhythmias or combination of arrhythmias that occur in adults can occur in children. Sinus tachycardia, supraventricular tachycardia, and rapid atrial fibrillation are seen less frequently in the paediatric population.

Paediatric patients are more likely to present with an AV conduction disturbance or a sinus bradycardia.
Ventricular ectopy is less common, however in massive overdose, ventricular ectopy, ventricular tachycardia and verntricular fibrillation have been reported.
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.
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.

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

In cases of massive digitalis ingestion, patients should receive large doses of activated charcoal to prevent absorption and bind digoxin in the gastrointestinal tract during enterohepatic recirculation.

If hypokalaemia presents, 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 KERN PHARMA has been ingested, hyperkalaemia may occur due to release of potassium from skeletal muscle. The serum potassium level must be known before administering potassium in digoxin overdose.

Bradyarrhythmias may respond to atropine but temporary cardiac pacing may be required. Ventricular arrhythmias may respond to lidocaine or phenytoin.

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

Rapid reversal of the complications associated with severe poisoning by digoxin, digitoxin and related glycosides has followed intravenous administration of digoxin-specific (ovine) antibody fragments.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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 very low doses; it occurs even in normal myocardium although it is then entirely without physiological benefit. The principal 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 be 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 such as slowing the speed of conduction of the impulse across the sinoatrial and the atrioventricular nodes (vagotonic effect) and sensitising the carotid sinus nerves (sympathomimetic). 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 atrioventricular 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 independent 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.

When administered orally, digoxin is absorbed in the stomach and in the upper part of the small intestine. Food decreases the rate but not the extent of absorption. Following an oral dose, the onset of effects occurs within 0.5 to 2 hours and reaches its peak after 2 to 6 hours. The bioavailability of digoxin administered orally is 63% in tablet form.

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 that digoxin is extensively bound to body tissues. The highest digoxin concentrations are seen in the heart, liver, and kidney, with concentration in the heart averaging 30 times that found 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.

The principal route of elimination is renal excretion of the unchanged drug.

Total body clearance of digoxin has been shown to be directly related to renal function, and percent daily loss is thus a function of creatinine clearance, which in turn may be estimated from a stable serum creatinine.

In a small percentage of individuals, orally-administered digoxin is metabolised into cardio-inactive metabolites by bacterial flora in the gastrointestinal tract. In these individuals, more than 40% of the dose may be excreted as digoxin reduction products 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 principal route of digoxin elimination is renal excretion of the unchanged drug.
The terminal elimination half-life of digoxin is 30 to 40 hours in patients with normal renal function. This may be longer in patients with impaired renal function, and in anuric patients, will be in the order of 100 hours.

In the newborn, renal clearance of digoxin is diminished and suitable dosage adjustments must be considered. 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.

Since most of the drug is bound to the tissues rather than circulating in the blood, digoxin is not effectively removed from the body during cardiopulmonary by-pass. Furthermore, only about 3% of a digoxin dose is removed from the body during five hours of haemodialysis.

PRECLINICAL SAFETY DATA

Mutagenicity and carcinogenicity

There is no information available on whether or not digoxin presents carcinogenic or mutagenic effects.

PHARMACEUTICAL PARTICULARS

List of excipients

Lactose monohydrate
Maize starch
Rice starch
Hydrolyzed maize starch
Magnesium stearate

INCOMPATIBILITIES

No information available

SHELF LIFE

3 years

SPECIAL PRECAUTIONS FOR STORAGE

Maintain at temperature below 30°C.

NATURE AND CONTENTS OF CONTAINER (and special equipment for use, administration or implantation)

PVC/aluminium blister. Packages contain 50 tablets.

MANUFACTURER:

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MARKETING AUTHORISATION HOLDER

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