PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

DigoKern tablets 0.25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of DigoKern 0.25 mg tablets contains 0.25 mg of digoxin.
Excipient(s) with known effect: Each tablet contains 95.52 mg of lactose, 13.68 mg of maize starch, 1.82 mg of hydrolysed maize starch.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, round, biconvex tablets, scored on both sides. The score is used to split and facilitate swallowing but not to divide the tablet into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cardiac failure:

Digoxin is indicated in the treatment of chronic heart failure where systolic dysfunction is the main problem. The greatest therapeutic benefit is obtained in patients with ventricular dilatation.

Digoxin is specifically indicated when heart failure is accompanied by atrial fibrillation.

Supraventricular arrhythmias:

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

4.2 Dosage and Administration

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. The score is used to split and facilitate swallowing but not to divide the tablet into equal doses.

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

Monitoring

Serum concentrations 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 ng/ml by 1.28. The serum concentration of digoxin can be determined by radioimmunoassay. Blood should be taken 6 hours or more after the last dose of digoxin.

There are no rigid guidelines as to the range of serum concentrations that are most efficacious. A post hoc analysis of heart failure patients in the Digitalis Investigation Group trial demonstrated that at low serum digoxin concentrations (0.5-0.9 ng/ml), the use of digoxin was associated with reductions in mortality and hospitalisation. Patients with higher digoxin levels (> 1ng/ml) had a higher incidence of morbidity and mortality, although at these concentrations digoxin reduces heart failure hospitalisation. Therefore, the optimal trough digoxin serum level may be 0.5 ng/mL (0.64 nanomol/L) to 1.0 ng/mL (1.28 nanomol/L).

Digoxin toxicity is more commonly associated with serum digoxin concentration greater than 2 ng/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 Overdose)*.

Other glycosides, including metabolites of digoxin, can interfere with the assays that are available and one should always be wary of values which do not seem commensurate with the clinical state of the patient.

Populations

- **Adults and children over 10 years**

Rapid Oral Loading:

If medically appropriate, rapid digitalisation may be achieved in a number of ways, such as the following: 750 to 1500 micrograms (0.75 to 1.5 mg) as a single dose.

Where there is less urgency, or greater risk of toxicity, e.g. in the elderly, the oral loading dose should be given in divided doses 6 hours apart, with approximately half the total dose given as the first dose. Clinical response should be assessed before giving each additional dose (*see Special warnings and precautions for use*).

Slow Oral Loading:

In some patients, for example those with mild heart failure, digitalisation may be achieved more slowly with doses of 250 to 750 micrograms (0.25 to 0.75 mg) daily for 1 week followed by an appropriate maintenance dose. A clinical response should be seen within one week.

NOTE: The choice between slow and rapid oral loading depends on the clinical state of the patient and the urgency of the condition.

Maintenance Dose:

The maintenance dose should be based on 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 = loading dose
daily loss (in percent) = 14 + creatinine clearance (C_{cr})/5

C_{cr} 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, C_{cr} (corrected to 70 kg bodyweight) may be estimated in men as:

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

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

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

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

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

In practice this will mean that most patients with heart failure will be maintained on 125 to 250 micrograms (0.125 to 0.25 mg) of digoxin per day. 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 children up to 10 years of age**
  (if cardiac glycosides have not been given in the preceding two weeks)

An age-appropriate formulation should be used in this patient population.

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 10 years of age require adult doses in proportion to their body weight.

Oral Loading Dose:

This should be administered in accordance with the following schedule:

Pre-term neonates < 1.5 kg	-	25 micrograms/kg per 24 hours.
Pre-term neonates 1.5 kg to 2.5 kg	-	30 micrograms/kg per 24 hours.
Term neonates to 2 years	-	45 micrograms/kg per 24 hours.
2 to 5 years	-	35 micrograms/kg per 24 hours.
5 to 10 years	-	25 micrograms/kg per 24 hours.

The loading dose should be administered in divided doses with approximately half of the total dose given as the first dose and further fractions of the total dose given at intervals of 4 to 8 hours, assessing the clinical response before giving each additional dose.

Maintenance

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

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

Term neonates 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* above) should be used as a basis for adjusting the dosage in these paediatric patient groups.

- **Elderly**

The tendency to impaired renal function and low lean body mass in the elderly influences the pharmacokinetics of digoxin such that high serum digoxin levels and associated toxicity can occur quite readily, unless doses of digoxin lower than those in non-elderly patients are used. Serum digoxin levels should be checked regularly and hypokalaemia avoided.

- **Dose Recommendations in Specific Patients Groups**

See Special warnings and precautions for use.

4.3 Contraindications

DigoKern is contraindicated in intermittent complete heart block or second-degree atrioventricular block, especially if there is a history of Stokes-Adams Syndrome.

DigoKern is contraindicated in arrhythmias originating through intoxication with cardiac glycosides.

DigoKern is contraindicated in supraventricular arrhythmias associated with an atrioventricular accessory pathway, as in the Wolff-Parkinson-White syndrome, unless the electrophysiological characteristics of the accessory pathway and any harmful effects of digoxin on these characteristics have been assessed. If the existence of an accessory pathway is confirmed or suspected, and there is no history of prior supraventricular arrhythmias, DigoKern is similarly contraindicated.

DigoKern is contraindicated in ventricular tachycardia or in ventricular fibrillation.

DigoKern is contraindicated in 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.

DigoKern is contraindicated in patients known to be hypersensitive to digoxin, to other digitalis glycosides or to any of the excipients listed in Section 6.1.

4.4 Special warnings and precautions for use

Arrythmias may be precipitated by digoxin toxicity, some of which can resemble arrhythmias for which the drug could be advised. For example, atrial tachycardia with variable atrioventricular block requires special care given that, clinically, the rhythm is similar to that of 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. 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.

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.

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.

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 digoxin in patients with supraventricular arrhythmias is most evident at rest, less evident with exercise.

In patients receiving diuretics and an ACE inhibitor, or diuretics alone, stopping 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 changes on the electrocardiogram during exercise testing. These electrophysiological effects reflect an expected effect of the drug and are not indicative of toxicity.

If patients have taken cardiac glycosides in the preceding two weeks, the initial posology recommendations of the patient should be reconsidered, and a reduced dose is recommended.
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 the initial dose and maintenance dose should be considered.

Patients receiving digoxin should periodically monitor their serum electrolytes and kidney function (serum creatinine concentration); the frequency of assessments will depend on the clinical setting.

Determination of the serum digoxin concentration can be very helpful in making a decision to treat with further digoxin, but other glycosides and endogenous digoxin-like substances 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 an increased myocardial sensitivity to digitalis glycosides. Hypokalaemia sensitises the myocardium to the actions of cardiac glycosides.

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 should be reduced when thyroid function is deficient. For hyperthyroidism, there is a relative resistance to digoxin, and the dose may need to be increased. During the course of treatment of thyrotoxicosis, dosage should be reduced as the thyrotoxicosis comes under control.

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

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 thought to be caused by cardiac glycosides.

DigoKern tablets 0.25 mg contain lactose

This medicine contains lactose. Patients with hereditary galactose intolerance, Lapp lactase deficiency (deficiency observed in certain populations from Lapland) or glucose/galactose malabsorption should not take this medicine.

4.5 Interactions 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 a decrease in the concentration of digoxin in the blood.

Combinations that should be avoided:

Combinations which can increase effects of digoxin when co-administered:
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 intravenous route, may produce serious arrhythmias in digitalized patients.

Sympathomimetic drugs have direct positive chronotropic effects that can promote cardiac arrhythmias and may also lead to hypokalemia, 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, flecainide, prazosin, propafenone, quinidine, spironolactone, macrolide antibiotics e.g. erythromycin and clarythromycin, tetracycline (and possibly other antibiotics), gentamicin, itraconazole, isavuconazole, quinine, trimethoprim, alprazolam, indomethacin, propantheline, nefazodone, atorvastatin, cyclosporine, epoprostenol (transient), vasopressin receptor antagonists (tolvaptan and conivaptan), carvedilol, ritonavir/ritonavir containing regimens, telaprevir, dronedarone, ranolazine, telmisartan, lapatinib, ticagrelor, daclatasvir, flibanserin, mirabegron, simeprevir, velpatasvir, canagliflozin, ivacaftor, vandetanib, venetoclax and vemurafenib.

Proton pump inhibitors (PPI) are able to increase plasma levels of digoxin by inhibiting its efflux. Metabolism of digoxin in the gastrointestinal tract is inhibited by omeprazole, resulting in increased plasma levels of digoxin. Similar effects have been reported with pantoprazole and rabeprazole to a lesser extent.

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 nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 enzyme (COX-2) inhibitors decrease prostaglandin-mediated afferent arteriole vasodilation. ARBs, ACEIs, NSAIDs, and COX-2 inhibitors did not significantly alter digoxin pharmacokinetics or did not alter PK parameters in a consistent manner. However, these drugs may modify renal function in some patients, resulting in a secondary increase in digoxin.

Calcium channel blocking agents may either increase or cause no change in serum digoxin levels.

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

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

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

Bupropion and its major circulating metabolite, with and without digoxin, stimulated OATP4C1-mediated digoxin transport. Digoxin has been identified as a substrate for 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.

4.6 Fertility, pregnancy and lactation

Fertility

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

Pregnancy

The use of digoxin in pregnancy is not contraindicated, although the dose of digoxin may be less predictable in pregnant women than in women who are not pregnant, with some requiring a higher dose of digoxin during pregnancy. As with all drugs, use should be considered only when the expected clinical benefit of treatment for the mother outweighs any possible risk to the developing foetus.

Despite extensive prenatal exposure to digitalis preparations, there were no significant undesirable effects in the foetus or newborn when maternal serum digoxin concentrations are maintained within the normal range. Although there has been speculation as to whether a direct effect of digoxin on the myometrium can give rise to a relative premature birth and a low birth weight, the contribution of underlying heart disease cannot be ruled out. Digoxin administered maternally has been successful in treating congestive heart failure and tachycardia in the foetus.

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

Lactation

Although digoxin is excreted in breast milk, the amounts are minimal and breast feeding is not contraindicated.

4.7 Effects on the 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 Adverse reactions

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 used within the recommended dosage range or within the range of therapeutic serum concentrations and close attention is paid to concomitant conditions and medication.

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).

Tabulation of adverse reactions

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Very rare	Thrombocytopaenia
Metabolism and nutrition	Very rare	Decreased appetite
Psychiatric disorders	Uncommon	Depression
	Very rare	Psychotic disorder, apathy, confusional state
Nervous system disorders	Common	Nervous system disorder, dizziness
	Very rare	Headache
Eye disorders	Common	Visual impairment (vision blurred or xanthopsia)
Cardiac disorders	Common	Arrhythmia conduction disorder, extrasystoles, electrocardiogram PR prolongation, sinus bradycardia
	Very rare	Supraventricular tachyarrhythmia, atrial tachycardia (with or without block) nodal arrhythmia supraventricular tachycardia, 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 administrative site conditions	Very rare	Fatigue, malaise, asthenia

*See “Description of selected adverse reactions”.

Description of selected adverse reactions

Skin and subcutaneous tissue disorders
Skin rashes of urticarial or scarlatiniform character may be accompanied by pronounced eosinophilia.

Reproductive system and breast disorders
Gynaecomastia can occur with long term administration.

4.9 Overdose

Signs and symptoms

The symptoms and signs of toxicity are generally similar to those described in the Section 4.8 Adverse Reactions 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 Dosage and Administration). In patients undergoing haemodialysis, digoxin use is associated with increased mortality; patients with low predialysis potassium concentrations are most at risk.

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, death or progressive toxicity responsive only to digoxin-binding Fab antibody fragments resulted.

Cardiac manifestations:

Cardiac manifestations are the most frequent and serious sign of both acute and chronic toxicity. Peak cardiac effects generally occur 3 to 6 hours following overdosage and may persist for the ensuing 24 hours or longer. 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 overdosage can result in mild to pronounced hyperkalaemia due to inhibition of the sodium-potassium (Na^+-K^+) pump. Hypokalaemia may contribute to toxicity (*see Special warnings and precautions for use*).

Non-cardiac manifestations:

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

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

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

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 outcome was uniformly fatal when DIGIBIND Fab fragment treatment was not given.

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 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.

Extracardiac manifestations:

The frequent extracardiac manifestations similar to those seen in adults are gastrointestinal, CNS and visual. However, nausea and vomiting are not frequent in infants and small children.

In addition to the undesirable effects seen with recommended doses, weight loss in older age groups and failure to thrive in infants, abdominal pain due to mesenteric artery ischaemia, drowsiness and behavioural disturbances including psychotic manifestations have been reported in overdose.

Treatment

Gastric lavage is not recommended as a routine measure in digitalis intoxication. 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.

DIGIBIND™ is a specific treatment for digoxin toxicity and is very effective. Rapid reversal of the complications that are associated with serious poisoning by digoxin, digitoxin and related glycosides has followed intravenous administration of digoxin -specific (ovine) antibody fragments (Fab). 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 the dose in the lower range, achieving a certain effect with quite low dosing. This occurs even in normal myocardium, although there is no physiological benefit. The main action of digoxin specifically consists of inhibiting adenosine triphosphatase and therefore sodium-potassium exchange activity (Na^+ - K^+). The altered ion distribution across the membrane leads to a greater calcium ion influx and increased calcium availability during 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. 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.

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 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.

5.2 Pharmacokinetic properties

Absorption

Upon oral administration, digoxin is absorbed in the stomach and in the 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.

Following an oral dose, the onset of effect occurs within 0.5 to 2 hours and reaches its peak after 2 to 6 hours.

The bioavailability of digoxin administered orally is approximately 63% in tablet form.

Distribution

The initial distribution of digoxin from the central to the peripheral compartment generally lasts from 6 to 8 hours. This is followed by a more gradual decline in serum digoxin concentration, which is dependent upon digoxin elimination from the body. The volume of distribution is large (V_{dss} = 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.

Metabolism

The main metabolites of digoxin are dihydrodigoxin and digoxygenin.

Elimination

The principal 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 Interactions with other medicinal products and other forms of interaction).

Following intravenous administration to healthy volunteers, between 60% and 75% of a dose of digoxin was recovered unchanged in the urine over a 6-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, which in turn may be estimated from a stable serum creatinine. The total and renal clearances of digoxin have been found to be 193 ± 25 ml/min and 152 ± 24 ml/min in a healthy control population.

In a small percentage of individuals, orally-administered digoxin is metabolised into cardio-inactive reduction products (digoxin reduction products or DRPs) by colonic bacterial 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.

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.

Special Patient 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/1.73m^2 at 3 months, compared to only 32 ± 7 ml/min/1.73m^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.

- **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.

5.3 Preclinical safety data

Mutagenicity and carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, maize starch, hydrolysed maize starch and magnesium stearate.

6.2 Incompatibilities

No information available.

6.3 Shelf life

The expiry date is indicated on the packaging.

6.4 Special precautions for storage

Store below 30ºC.

6.5 Nature and contents of pack

Opaque PVC/aluminium blister. Packs containing 50 tablets.

6.6 Special precautions for disposal and other handling

Not applicable.

7. MANUFACTURER

Kern Pharma, S.L.
Venus, 72 - Pol. Ind. Colón II
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Spain

8. DATE OF REVISION OF THE TEXT

July 2024