

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Digoxin Tablets BP 0.125mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient

Digoxin Ph.Eur 0.125mg

Excipients with known effect: Also contains Lactose spray dried

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

White, round, biconvex, uncoated tablets embossed with '125' on one face and 'BL' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

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

4.2. Posology and method of administration

The dose of 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 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 with chronic cardiac failure in the absence of supraventricular arrhythmia:

No loading dose is required. The usual daily dose is 125 to 250 micrograms (0.125 to 0.25 mg) for patients with normal renal function. A lower dose of 62.5 micrograms (0.0625 mg) should be considered in the elderly.

For the management of atrial fibrillation or flutter in adults and children over 10 years:

Rapid Oral Loading:

If medically appropriate, rapid digitalization 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, assessing clinical response before giving each additional dose (*See Special Warnings and Precautions for Use*).

Slow Oral Loading:

Digitalisation may be achieved more slowly with doses of 250 to 750 micrograms (0.25 to 0.75 mg) given 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 dosage should be based upon the percentage of the peak body stores lost each day through elimination. The following formula has had wide clinical use:

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

Where:

$$\text{Peak Body Stores} = \text{Loading Dose}$$

$$\% \text{ Daily Loss} = 14 + \text{Creatinine Clearance } (C_{cr})/5.$$

C_{cr} is creatinine clearance corrected to 70 kg body weight or 1.73 m² body surface area. If only serum creatinine (S_{cr}) concentrations are available, a C_{cr} (corrected to 70 kg body weight) may be estimated in men as

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

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

$$\begin{aligned} S_{cr} \text{ (mg/100 ml)} &= \frac{S_{cr} \text{ (micromol/L)} \times 113.12}{10,000} \\ &= \frac{S_{cr} \text{ (micromol/L)}}{88.4} \end{aligned}$$

-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 will be maintained on 0.125 to 0.25 mg digoxin daily; however in those who show increased sensitivity to the adverse effects of digoxin, a dosage of 62.5 microgram (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):

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 dosages in proportion to their body weight.

Oral loading dose:

This should be administered in accordance with the following schedule:

Preterm neonates < 1.5 kg	25 microgram/kg over 24 hours
Preterm neonates 1.5 kg to 2.5 kg	30 microgram/kg over 24 hours
Term neonates to 2 years	45 microgram/kg over 24 hours
2 to 5 years	35 microgram/kg over 24 hours
5 to 10 years	25 microgram/kg over 24 hours

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

Maintenance Dose:

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

Preterm neonates:

daily dose = 20% of 24-hour loading dose (intravenous or oral)

Term neonates and children up to 10 years:

daily dose = 25% of 24-hour loading dose (intravenous or oral)

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

If 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 above.

Use in the 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 renal disorder or with diuretic therapy:

See *Special Warnings and Precautions for Use*.

Monitoring:

Serum concentrations of digoxin may be expressed in conventional units of nanogram/ml (ng/ml) or SI Units of nanomol/L (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 but most patients will benefit, with little risk of toxic symptoms and signs developing, with digoxin concentrations from 0.8 nanogram/ml, ng/ml (1.02 nanomol/litre, nm/L) to 2.0ng/ml (2.56nm/L). Above this range toxic symptoms and signs become more frequent and levels above 3ng/ml (3.84nm/L) are quite likely to be toxic. However, toxicity may occur with lower digoxin serum concentrations. In deciding whether a patient's symptoms are due to digoxin, the patient's clinical state together with the serum potassium level and thyroid function are important factors.

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.

Renal impairment

Loading and maintenance doses of digoxin should be reduced as outlined above in patients with impaired renal function because the major route of elimination is renal excretion of unchanged drug.

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.

Gastrointestinal disease

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

Method of Administration

For oral administration.

4.3. Contraindications

Digoxin is contra-indicated in intermittent complete heart block or second degree atrioventricular block, especially if there is a history of Stokes-Adams attacks.

Digoxin is contra-indicated in arrhythmias caused by cardiac glycoside intoxication.

Digoxin is contra-indicated in 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 contra-indicated.

Digoxin is contra-indicated in ventricular tachycardia or ventricular fibrillation.

Digoxin is contra-indicated 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.

Digoxin is contra-indicated in patients known to be hypersensitive to digoxin, other digitalis glycosides, or to any component of the preparation.

4.4. Special warnings and precautions for use

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.

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

Determination of the serum digoxin concentration may be very helpful in making a decision to treat with further digoxin, but toxic doses of other glycosides may cross-react in the assay and wrongly suggest apparently satisfactory measurements. Observations during the temporary withholding of digoxin might be more appropriate.

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 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.

Hypokalaemia sensitises the myocardium to the actions of cardiac glycosides. Digoxin should be used with caution in patients taking drugs that may cause hypokalaemia (see section 4.5). Hypokalaemia may also accompany malnutrition, diarrhoea, vomiting and long standing wasting disease and the dose may be 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 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.

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

Direct current cardioversion is the preferred method of treatment for atrial flutter. 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, the lowest effective energy should be applied when attempting cardioversion. Direct current cardioversion is inappropriate in the treatment of arrhythmia thought to be caused by cardiac glycosides.

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.

The administration of digoxin in the period immediately following myocardial infarction is not contra-indicated. 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 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 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 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 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 changes on the electrocardiogram during exercise testing. These electrophysiologic effects reflect an expected effect of the drug and are not indicative of toxicity.

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.

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.

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency 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 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 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 digoxin plasma levels and toxicity and patients should be monitored. *Nifedipine* may increase 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* increases 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 atrioventricular block 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*.

- *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 beta₂ agonists may cause hypokalaemia which can increase susceptibility to digoxin induced arrhythmias. Concurrent administration of *salbutamol* has also been associated with increases in plasma digoxin levels.

4.6 Pregnancy and lactation

Pregnancy

No data available on whether or not digoxin has teratogenic effects.

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

The use of digoxin in pregnancy is not contra-indicated, although the dosage and control 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.

Lactation

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

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

The adverse effects produced by digoxin are frequently due to the narrow margin between therapeutic and toxic doses. Plasma levels in excess of 2nmol.L^{-1} indicate that the patient is at special risk, although there is considerable interindividual variation. Special care should be taken in patients at high risk of developing digoxin toxicity, such as the elderly and those with renal impairment or thyroid disease (see Special warnings, above). In addition, care should be taken when digoxin is taken with other medications as many have the potential to affect plasma digoxin concentrations or electrolytes and cause toxicity (see section 4.5). Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ 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).

Blood and lymphatic system disorders

Thrombocytopenia has been reported in patients taking digoxin. Agranulocytosis has been reported rarely.

• Immune system disorders

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

• Endocrine disorders

Digoxin has oestrogenic activity and is associated with gynaecomastia in men following prolonged administration.

• Psychiatric disorders

Digoxin is associated with 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.

• Nervous system disorders

Neurological effects are also common symptoms of excessive digoxin dosage. They include headache, fatigue, weakness, dizziness, drowsiness, bad dreams, restlessness, nervousness, agitation and apathy.

• Eye disorders

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

- *Cardiac disorders*

The most serious adverse effects of digoxin are on the heart. Usually an early stage of digoxin toxicity is the occurrence of ventricular premature contractions; they can proceed to bigeminy or even trigeminy. Toxic doses may cause or aggravate heart failure. Supraventricular or ventricular arrhythmias and defects of conduction are common and may be an early indication of excessive dosage. The underlying heart condition influences the occurrence and severity of arrhythmias. Supraventricular tachycardia, especially atrioventricular node junctional tachycardia and atrial tachycardia with block are particularly indicative of digoxin toxicity. Ventricular arrhythmias, including extrasystoles, sinoatrial block, sinus bradycardia and atrioventricular block, may also occur.

- *Gastrointestinal disorders*

Centrally mediated anorexia, nausea and vomiting may be early signs of an excessive dose of digoxin. Abdominal pain and diarrhoea may occur, particularly in elderly patients. Intestinal ischaemia which responds to verapamil has been reported rarely.

Undesirable effects in children

Children are especially sensitive to the effects of digoxin (see section 4.2). Anorexia, nausea, vomiting, diarrhoea and CNS disturbances may occur but they are rarely the initial symptoms of overdose. Cardiac arrhythmias are the most frequent sign of excessive dosing with digoxin. The most common are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia with or without block. Ventricular arrhythmias are less common. Sinus bradycardia may indicate digoxin toxicity, especially in infants.

Reporting of side effects

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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

4.9. Overdose

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.

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 (see *Dosage and Administration*).

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.

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 suggests that an overdose of digoxin of 6 to 10 mg was the dose resulting in death in half of the patients.

Most manifestations of toxicity in children occur during or shortly after the loading phase with 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 ventricular 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.

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.

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 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 (Digibind[®]) resulted. 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.

Hypokalaemia should be corrected. 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.

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) when other therapies have failed. Digibind[®] is the only specific treatment for digoxin toxicity.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mode of Action:

Digoxin has a positive inotropic effect on the heart when in failure, increasing myocardial contraction and cardiac output. Digoxin depresses heart conduction by a direct action on the AV node and bundle of His leading to a slowing of the ventricular rate and improved cardiac efficiency. Digoxin acts quickly but has a short duration 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.

A direct action on the contractile protein may supplement this primary action of glycosides, digoxin included. This appears to improve transformation of chemical energy into mechanical work but does not increase energy production.

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

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

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. Food decreases the rate but not the extent of absorption. Using the oral route the onset of effect occurs in 0.5 to 2 hours and reaches its maximum after 6 hours following the oral dose. Digoxin is incompletely (about 70%) absorbed from the gastrointestinal tract. The generally accepted therapeutic plasma level is 0.8 to 2 nmol.L⁻¹ but there are wide interindividual variations.

Distribution

Digoxin has a large volume of distribution and is widely distributed in tissues, including the heart, brain, erythrocytes and skeletal muscles, and it crosses the blood brain barrier. The concentration of digoxin in the myocardium is considerably higher than in plasma. From 20 to 30% of a dose is bound to plasma proteins. The volume of distribution is decreased in patients with renal impairment and hypothyroidism and it is increased in patients with hyperthyroidism.

Metabolism and Elimination

Most of a dose of digoxin is excreted unchanged by the kidneys, although some of the dose is metabolised to pharmacologically active and inactive metabolites. It is subject to glomerular filtration and to active secretion and passive resorption by the renal tubules. The balance between these two mechanisms results in a close relationship between renal clearance of digoxin and creatinine. Bacterial flora in the gastrointestinal tract metabolise digoxin to cardio-inactive metabolites in about 10% of patients. The elimination half-life of digoxin is about 40 hours in patients with normal renal function but it can be prolonged to 96 hours in severe renal impairment.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Spray Dried
Industrial Methylated Spirit
Maize Starch
Magnesium Stearate
Stearic Acid

6.2. Incompatibilities

None

6.3 Shelf life

Container: 36 months
Al/PVC blisters in outer cartons: 36 months.

6.4. Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

A rectangular 60ml amber-glass bottle with polypropylene cap.
Pack size: 500

Or a rectangular 30ml amber-glass bottle with polypropylene cap.
Pack size: 28

Or Al/PVC blister in outer carton. Pack size 28 tablets.

6.6 Special precautions for disposal

None

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

PL 17907/0115

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/06/2005

10 DATE OF REVISION OF THE TEXT

04/02/2014