1.3	Summary of Product characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Digoxin Injection BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains

Digoxin BP 0.25 mg

Ethanol BP 0.125 ml

3. PHARMACEUTICAL FORM

Solution for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Digoxin is indicated in the management of chronic cardiac failure. The therapeutic benefit of Digoxin is greater in 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 atrial fibrillation and flutter, where its major beneficial effect is to reduce the ventricular rate. Digoxin injection is indicated when emergency parenteral digitilisation is required in patients who have not been given cardiac glycosides within the preceding two weeks

4.2 Posology and Method of Administration

Digoxin Injection BP is for administration by slow intravenous infusion.

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.

Emergency parenteral digitalisation (in patients who have not been given cardiac glycosides within the preceding two weeks):

Adults: 500 to 1,000 micrograms (0.5 to 1.0mg) depending on age, lean body weight and renal function.

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 - 8 hours, assessing the clinical response before giving each additional dose. Each dose should be given by intravenous infusion (see *Dilution*) over a period of 10 - 20 minutes.

- *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:

Peak Body Stores = Loading Dose

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

C_{cr} is creatinine clearance corrected to 70 kg body weight or 1.73 m^2 body surface area.

If only serum creatinine (S_{cr}) concentrations are available, a C_{cr} (corrected to 70 kg body weight) may be estimated in men as

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

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

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

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 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 & 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.

Parenteral Loading:

The Parenteral loading dose should be administered according to the following schedule:

Pre- term neonates < 1.5kg	20 micrograms/kg over 24 hours
Pre-term neonates 1.5 - 2.5kg	30 micrograms/kg over 24 hours
Full-term neonates To age 2 years	35 micrograms/kg over 24 hours
Age 2 - 5 years	35 micrograms/kg over 24 hours
Age 5 - 10 years	25 micrograms/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. Each dose should be given by intravenous infusion (see *Dilution*) over a period of 10 - 20 minutes.

Note: 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.

-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.

Elderly patients: In the elderly, the tendency towards impaired renal function and a low lean body mass affects the pharmacokinetics of Digoxin so that high serum Digoxin levels and associated toxicity can occur unless reduced doses are used. Serum levels should be checked regularly, and hypokalaemia should be avoided.

Dosage in renal impairment or with concurrent Diuretic therapy: See (*Precautions & Interactions)*.

Dilution: Digoxin Injection BP may be diluted with the following solutions:

Sodium Chloride Intravenous Infusion BP 0.9% w/v

Glucose Intravenous Infusion BP 5.0% w/v

Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion BP

When diluted in the ratio of 1 to 250 (i.e. one 2ml ampoule containing 500 micrograms digoxin added to 500ml of infusion solution), Digoxin Injection B.P. is known to be compatible with the above mentioned infusion solutions and stable for up to 48 hours at room temperature (20 - 25°C).

Dilution should be carried out either under full aseptic conditions or immediately prior to use. Any unused solution should be discarded.

Monitoring: Serum Digoxin concentrations may be expressed in Conventional Units of ng/ml or in SI units of nM/L (Multiply ng/ml by 1.28 to convert to nM/L).

Serum Digoxin concentration can be determined by radioimmunoassay. Blood samples for Digoxin assay should be taken at least 6 hours after the last dose to allow for distribution.

Several post hoc analyses of heart failure patients in the Digitalis Investigation Group trial suggest that the optimal trough Digoxin serum level may be 0.5 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, toxicity may occur with lower Digoxin serum concentrations.

When deciding whether symptoms are due to Digoxin toxicity, the patient's clinical state together with the serum potassium level and thyroid function are important factors to be considered.

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 state of the patient.

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 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 or other digitalis glycosides or to any component of the preparation.

4.5 Interaction with other Medicinal products and other forms of Interaction

These may arise from effects on the renal excretion, tissue binding, plasma protein binding and distribution within the body, gut absorptive capacity and sensitivity to Digoxin. The best precaution is to consider the possibility of an interaction whenever concomitant therapy is contemplated and to check on serum Digoxin concentration when any doubt exists.

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 diuretics, lithium salts, corticosteroids and carbenoxolone.

Patients receiving Digoxin are more susceptible to the effects of suxamethonium-exacerbated hyperkalaemia.

Calcium, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients.

Serum levels of Digoxin may be increased by concomitant administration of the following:

Alprazolam, amiodarone, flecainide, gentamicin, indometacin, itraconazole, prazosin, propafenone, quinidine, quinine, spironolactone, macrolide antibiotics (e.g. erythromycin and clarithromycin), tetracycline (and possibly other antibiotics), trimethoprim, propantheline, atorvastatin, ciclosporin, epoprostenol (transient) and carvedilol.

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

Adrenaline (epinephrine), antacids, kaolin-pectin, some bulk laxatives, colestyramine, acarbose, salbutamol, sulfasalazine, neomycin, rifampicin, some cytostatics, phenytoin, metoclopramide, penicillamine and the herbal remedy St John's wort (Hypericum perforatum).

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. Isradipine causes no change in serum digoxin levels. Angiotensin converting enzyme (ACE) inhibitors may also increase or cause no change in serum digoxin concentrations.

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.

4.6 Pregnancy and Lactation

No data are 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 of Digoxin should be considered only when the expected clinical benefit to the mother outweighs any possible risk to the 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 birth weight, 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.

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

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).

Blood and lymphatic system disorders	
Very rare:	Thrombocytopenia
Metabolism and nutrition disorders	
Very Rare:	Anorexia
Psychiatric disorders	
Uncommon:	Depression
Very rare:	Psychosis, apathy, confusion
Nervous system disorders	
Common:	CNS disturbances, dizziness
Very rare:	Headache
Eye disorders	
Common:	Visual disturbances (blurred or yellow vision)
Cardiac disorders	
Common:	Arrhythmia, conduction disturbances, bigeminy, trigeminy, PR prolongation, sinus bradycardia
Very rare:	Supraventricular tachyarrhythmia, atrial tachycardia (with or without block), junctional (nodal) tachycardia, ventricular arrhythmia, ventricular premature contraction, ST segment depression
Gastrointestinal disorders	
Common:	Nausea, vomiting, diarrhoea
Very rare:	Intestinal ischaemia, intestinal necrosis
Skin disorders	
Common:	Skin rashes of urticarial or scarlatiniform character may be accompanied by pronounced eosinophilia
Reproductive system and breast disorders	
Very rare:	Gynaecomastia can occur with long term administration
General disorders and administration site conditions	
Very rare:	Fatigue, malaise, weakness

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 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.

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 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 antibody fragments (Fab) when other therapies have failed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mode of Action:-

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

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

Intravenous administration of a loading dose produces an appreciable pharmacological effect within 5 to 30 minutes; this reaches a maximum in 1 to 5 hours.

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 (Vd_{ss} = 510 litres in healthy volunteers), indicating Digoxin to be extensively bound to body tissues. The highest Digoxin concentrations are seen in the heart, liver and kidney that in the heart averaging 30- fold that in the systemic circulation. Although the concentration in skeletal muscle is far lower, this store cannot be overlooked since skeletal muscle represents 40% of total body weight. Of the small proportion of Digoxin circulating in plasma, approximately 25% is bound to protein.

Elimination-

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

Digoxin is a substrate for P-glycoprotein. As an efflux protein on the apical membrane of enterocytes, P-glycoprotein may limit the absorption of Digoxin. P-glycoprotein in renal proximal tubules appears to be an important factor in the renal elimination of Digoxin (See 4.5 Interaction with other medicinal products and other forms of interaction).

Following intravenous administration to healthy volunteers, between 60 and 75% of a Digoxin dose is 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 mil/min in a healthy control population.

In a small percentage of individuals, orally administered Digoxin is converted to cardioinactivate reduction products (Digoxin reduction products or DRPs) by colonic bacteria in the gastrointestinal tract. In these subjects over 40% of the dose may be excreted as DRPs in the urine. Renal clearances of the two main metabolites, dihydrodigoxin and digoxygenin, have been found to be 79

± 13 ml/min and 100 ± 26 ml/min respectively. In the majority of cases however, the major route of Digoxin elimination is renal excretion of the unchanged drug.

The terminal elimination half life of Digoxin in patients with normal renal function is 30 to 40 hours. It will be prolonged in patients with impaired renal function, and in anuric patients will be of the order of 100 hours.

In the newborn period, renal clearance of Digoxin is diminished and suitable dosage adjustments must be observed. This is specially 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/1.73 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.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf Life

Shelf-life of the medicinal product as packaged for sale: 36 months.

6.2 Special Precautions for Storage

Store below 30°C. Protect from light.

6.3 Nature and Contents of Container

2ml USP Type I flint ampoule

6.4 Special Precautions for Disposal and Other Handling

For slow intravenous infusion.

Use as directed by the physician.

Keep out of reach of children.

7. MARKETING AUTHORISATION HOLDER

Ciron Drugs & Pharmaceuticals Pvt. Ltd.

8. MARKETING AUTHORISATION NUMBER(S)

None

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable