DIGOXIN 62.5 MICROGRAMS TABLETS

PL 17907/0186 & 0222

UKPAR

TABLE OF CONTENTS

Lay Summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 12
Summary of Product Characteristics Page 13
Product Information Leaflet Page 24
Labelling Page 26
DIGOXIN 62.5 MICROGRAMS TABLETS

PL 17907/0186 & 222

LAY SUMMARY

The MHRA granted Bristol Laboratories Limited a Marketing Authorisation (licence) for the medicinal product Digoxin 62.5 micrograms Tablets (PL 17907/0186) and its duplicate application Digoxin 62.5 micrograms Tablets (PL 17907/0222) on 20 January 2011. These products are prescription-only medicines (POM).

Digoxin 62.5 micrograms Tablets are used to treat certain heart problems such as:

- heart failure
  This is when your heart muscle can’t pump strongly enough to supply blood around your whole body. It is not the same as a heart attack and does not mean that your heart stops

- certain types of irregular heart beats
  These include ‘partial flutter’ or fibrillation’. They are caused by problems in the way the upper chambers of your heart send electrical signals. They cause your heart to beat too fast or in an uneven way.

The active ingredient digoxin belongs to a group of medicines called ‘cardiac glycosides’ which work by slowing down the rate while increasing the force of your heart when it beats.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Digoxin 62.5 micrograms Tablets outweigh the risks, hence Marketing Authorisations have been granted.
DIOGOXIN 62.5 MICROGRAMS TABLETS

PL 17907/0186 & 222

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 5
Non-clinical assessment Page 8
Clinical assessment Page 9
Overall conclusions and risk benefit assessment Page 11
INTRODUCTION

The UK granted a Marketing Authorisation for the medicinal product Digoxin 62.5 micrograms Tablets (PL 17907/0186) and its duplicate application Digoxin 62.5 micrograms Tablets (PL 17907/0222) to Bristol Laboratories Limited on 20 January 2011. These products are available as prescription-only medicines (POM) and are indicated for:

- Management of chronic cardiac failure where the dominant problem is systolic dysfunction. Its therapeutic benefit is greatest in those patients with ventricular dilatation.
- Cardiac failure accompanied by atrial fibrillation
- Management of certain supraventricular arrhythmias, particularly chronic atrial flutter and fibrillation.

Digoxin belongs to a group of medicines called ‘cardiac glycosides’. 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.

These are national applications for a line extension ((PL 17907/0186 and duplicate licence PL 17907/0222) to the existing marketing authorisations Digoxin 0.125mg and 0.25mg Tablets (PL 17907/0115 and 0114 respectively) authorised to Bristol Laboratories Limited, UK. The applications were submitted as abridged standard applications according to Article 10(1) (a) iii of Directive 2001/83/EC, as amended, claiming to be generic products of the reference product Lanoxin PG Tablets (The Welcome Foundation Limited) first authorised in the UK in February 1987.

No new non-clinical studies were performed, which is acceptable given that the proposed products are generic medicinal products of an originator product that has been licensed for over 10 years.

A single-dose, bioequivalence study under fasting conditions was submitted to support the applications. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the proposed products are generic medicinal products of an originator product that has been licensed for over 10 years

No new or unexpected safety concerns arose during the assessment of these applications and it was, therefore, judged that the benefits of taking Digoxin 62.5 micrograms Tablets outweigh the risks, hence Marketing Authorisations have been granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
INN: Digoxin
Chemical Name: 3b-[(O-2,6-dideoxy-b-D-ribo-hexopyranosyl-(1→4)-O-2,6-dideoxy-b-D-ribo-hexopyranosyl-(1→4)-2,6-dideoxy-b-D-ribo-hexopyranosyl)oxy]-12b, 14-dihydroxy-5b-card-20(22)-enolide
Molecular Formula: C_{41}H_{64}O_{14}
Structure:

Molecular weight: 491.1
Appearance: A white or almost white powder or colourless crystals, practically insoluble in water, freely soluble in a mixture of equal volumes of methanol and methylene chloride and slightly soluble in alcohol.

Digoxin is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance digoxin are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability

MEDICINAL PRODUCT
Other ingredients
Other ingredients consist of the pharmaceutical excipients lactose monohydrate, maize starch, magnesium stearate, industrial methylated spirit and stearic acid.

All excipients comply with their respective European Pharmacopoeia monograph with the exception of industrial methylated spirit which complies with the British Pharmacopoeia. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph/specification.

With the exception of lactose monohydrate, none of the excipients are of animal or human origin. An assurance has been provided that the lactose used to produce lactose monohydrate is sourced from healthy animals under the same conditions as milk for human consumption. None of the excipients are sourced from genetically modified organisms.

Pharmaceutical Development
The objective of the development programme was to produce safe, efficacious products containing 0.0625 mg digoxin that could be considered generic medicinal products of Lanoxin PG Tablets (The Welcome Foundation Limited).
A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

**Manufacturing Process**
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation on three batches of product has been provided.

**Finished product specification**
The finished product specifications are satisfactory. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Container Closure System**
The finished product is packaged in aluminium/polyvinylchloride opaque blister strips in pack sizes of 14, 28, 56 and 84 tablets.

The MAH has stated that not all pack sizes may be marketed and has committed to submit mock-ups for all packaging for assessment before those pack sizes are commercially marketed.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials suitable for contact with food.

**Stability of the Product**
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months, with the special storage conditions ‘Do not store above 25ºC.’

**Bioequivalence/Bioavailability**
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence studies.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPCs, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA Forms**
The MAA forms are satisfactory.
Expert Report
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
No new non-clinical studies were performed, which is acceptable given that the proposed products are generic medicinal products of an originator product that has been licensed for over 10 years.

NON-CLINICAL EXPERT REPORT
The non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT
An environmental risk assessment was not submitted and none is required for these applications. This is acceptable given that these products are intended for generic substitution with the market leaders and, as such, will be used instead of not additional to other such products on the market (thus not increasing any environmental impact).

CONCLUSION
The grant of Marketing Authorisations is recommended.
CLINICAL ASSESSMENT

PHARMACOKINETICS
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

A randomised, open-label, single-dose, two-period crossover study comparing the pharmacokinetics of the test product digoxin 4 x 0.0625 mg tablets versus the reference product Lanoxin-PG 4 x 0.0625 mg tablets (GlaxoSmithKline, UK) in healthy subjects under fasting conditions.

Subjects were dosed with either treatment after at least a 10-hour fast. Blood sampling was performed pre- and up to 144 hours post dose in each treatment period. The washout period between the two treatment arms was at least 21 days. Pharmacokinetic parameters were measured from plasma and statistically analysed.

The pharmacokinetic results for digoxin (presented as log-transformed data, mean ± Standard Deviation (SD), ratios and 90% confidence intervals) are presented below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-1}$ ng/ml/h</th>
<th>AUC$_{0-\infty}$ ng/ml/h</th>
<th>C$_{\text{max}}$ ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>11.726 ± 4.7089</td>
<td>14.783 ± 5.6955</td>
<td>1.4454 ± 0.5072</td>
</tr>
<tr>
<td>Reference (mean)</td>
<td>11.784 ± 5.3813</td>
<td>16.130 ± 9.3855</td>
<td>1.5025 ± 0.4833</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>93.60-108.96%</td>
<td>87.31-102.56%</td>
<td>88.03-102.97%</td>
</tr>
</tbody>
</table>

AUC$_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC$_{0-1}$ area under the plasma concentration-time curve from time zero to t hours
C$_{\text{max}}$ maximum plasma concentration

The 90% confidence intervals of the relative mean AUC$_{0-1}$, AUC$_{0-\infty}$ and C$_{\text{max}}$ of the test to reference product are within the accepted range 80-125% in line with CPMP/EWP/QWP/1401/98 Note for guidance on the investigation of bioavailability and bioequivalence. Thus, the data support the claim that the test product, Digoxin 62.5 micrograms Tablets is bioequivalent to the reference product Lanoxin PG Tablets.

EFFICACY
No new data on the efficacy have been submitted and none are required for these types of applications.

SAFETY
No new or unexpected safety issues were raised by the bioequivalence data.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELS
The SmPCs, PIL and labels are medically acceptable. The SmPCs are consistent with those for the originator product.
CLINICAL EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

CONCLUSION
The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Digoxin 62.5 micrograms Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Digoxin 62.5 micrograms Tablets and the respective reference product.

SAFETY
No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant’s products and the originator product are interchangeable. Extensive clinical experience with digoxin is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
### STEPS TAKEN FOR ASSESMENT

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 29/07/2005.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 16/11/2005.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications, the MHRA requested further information relating to the quality dossiers on 21/04/2006, 10/05/2006, 02/04/2009, 15/07/2009, 15/03/2010 and 14/05/2010 and the clinical dossiers on 19/02/2009.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 20/01/2011.</td>
</tr>
</tbody>
</table>
### SUMMARY OF PRODUCT CHARACTERISTICS

1 **NAME OF THE MEDICINAL PRODUCT**

Digoxin 62.5 micrograms Tablets

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>mg/tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin Ph.Eur.</td>
<td>0.0625</td>
</tr>
</tbody>
</table>

Contains 62.0865mg of lactose per tablet.
For a full list of excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**

Tablets

White, round, biconvex, unscored tablet with BL embossed on one side of the tablet

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 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, 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) should be 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:
Where:

\[
\text{Peak Body Stores} = \frac{\text{Loading Dose} \times \% \text{ Daily Loss}}{100}
\]

\[
\% \text{ Daily Loss} = 14 + \frac{\text{Creatinine Clearance (C}_{\text{cr}})}{5}.
\]

\text{C}_{\text{cr}} \text{ is creatinine clearance corrected to 70 kg body weight or 1.73 m}^2 \text{ body surface area. If only serum creatinine (S}_{\text{cr}}) concentrations are available, a C}_{\text{cr}} \text{ (corrected to 70 kg body weight) may be estimated in men as}

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

\text{NOTE: Where serum creatinine values are obtained in micromol/L these may be converted to}

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

\[
= \frac{S_{\text{cr}} \text{ (micromol/L)}}{88.4}
\]

\text{Where 113.12 is the molecular weight of creatinine.}

\text{For women, this result should be multiplied by 0.85.}

\text{NOTE: These formulae cannot be used for creatinine clearance in children.}

\text{In practice, this will mean that most patients will be maintained on 0.125 to 0.25 mg digoxin daily;}

\text{however in those who show increased sensitivity to the adverse effects of digoxin, a dosage of 62.5}

\text{microgram (0.0625 mg) daily or less may suffice. Conversely, some patients may require a higher}

\text{dose.}

\text{Neonates, infants and children up to 10 years of age (if cardiac glycosides have not been given}

\text{in the preceding two weeks):}

\text{In the newborn, particularly in the premature infant, renal clearance of digoxin is diminished and}

\text{suitable dose reductions must be observed, over and above general dosage instructions.}

\text{Beyond the immediate newborn period, children generally require proportionally larger doses than}

\text{adults on the basis of body weight or body surface area, as indicated in the schedule below. Children}

\text{over 10 years of age require adult dosages in proportion to their body weight.}

\text{Oral loading dose:}

\text{This should be administered in accordance with the following schedule:}

\begin{align*}
\text{Preterm neonates < 1.5 kg} & \quad 25 \text{ microgram/kg over 24 hours} \\
\text{Preterm neonates 1.5 kg to 2.5 kg} & \quad 30 \text{ microgram/kg over 24 hours} \\
\text{Term neonates to 2 years} & \quad 45 \text{ microgram/kg over 24 hours} \\
\text{2 to 5 years} & \quad 35 \text{ microgram/kg over 24 hours} \\
\text{5 to 10 years} & \quad 25 \text{ microgram/kg over 24 hours}
\end{align*}

\text{The loading dose should be administered in divided doses with approximately half the total dose}

\text{given as the first dose and further fractions of the total dose given at intervals of 4 to 8 hours,}

\text{assessing clinical response before giving each additional dose.}

\text{Maintenance Dose:}

\text{The maintenance dose should be administered in accordance with the following schedule:}

\text{Preterm neonates:}

\[
daily \text{ dose} = 20\% \text{ of 24-hour loading dose (intravenous or oral)}
\]
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. 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. 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.

### 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 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. 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.

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.

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 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, 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, as it contains lactose.

4.5 Interaction with other medicinal products and other forms of interaction

These may arise from effects on the renal excretion, tissue binding, plasma protein binding, distribution within the body, gut absorptive capacity 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, 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, diphenoxylate with atropine, flecainide, gentamicin, indomethacin, itraconazole, prazosin, propafenone, quinidine, quinine, spironolactone, macrolide antibiotics (e.g. erythromycin, clarithromycin, neomycin), tetracycline (and possibly other antibiotics), trimethoprim and 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 and cholestyramine, acarbose, salbutamol, sulphasalazine, 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 substance 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 5.2 Pharmacokinetic properties).
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 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 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.
eurologic 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 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. Upon oral administration, digoxin is absorbed from the stomach and upper part of the small intestine. Absorption is delayed by taking a meal although the total amount absorbed is unchanged. When taken with meals with high fibre, the amount absorbed from an oral dose may be reduced. Using the oral route the onset of effect occurs in 0.5 to 2 hours and reaches its maximum at 2 to 6 hours. The bioavailability of orally administered Digoxin is approximately 63% in tablet form and 75% as paediatric elixir.

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 (Vdα = 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
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 ml/min in a healthy control population.

In a small percentage of individuals, orally administered digoxin is converted to cardio inactive 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 is prolonged in patients with impaired renal function, and in anuric patients may 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 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.

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.

5.3 Preclinical safety data
No data are available on whether or not digoxin has mutagenic or carcinogenic effects.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose Monohydrate Ph Eur
Maize Starch Ph Eur
Magnesium Stearate Ph Eur
Industrial Methylated Spirit BP
Stearic Acid Ph.Eur.

6.2 Incompatibilities
None known

6.3 Shelf life
36 months

6.4 Special precautions for storage
Blisters: Do not store above 25°C.

6.5 Nature and contents of container
Al/PVC Opaque blister, pack sizes of 14, 28, 56 and 84 tablets.
Not all pack sizes may be marketed
6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Bristol Laboratories Limited,
Unit 3, Canalside,
Northbridge Road,
Berkhamsted, Herts, HP4 1EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 17907/0186
PL 17907/0222

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/01/2011

10 DATE OF REVISION OF THE TEXT
20/01/2011
Module 3

The following Digoxin 62.5 micrograms Tablets leaflet for PL 17907/0186 is included as a representative example leaflet. The leaflet proposed for the other product PL 17907/222 is consistent with this leaflet:

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Take special care with Digoxin if you:

- have had an allergic reaction to the tablets.
- have heart disease or impaired liver or kidney function.
- are taking other medications that may interact with Digoxin.

- severe allergic reaction (anaphylaxis) caused by Digoxin.
- heart disease or impaired liver or kidney function.
- are taking other medications that may interact with Digoxin.

- premature birth or breast feeding.
- have a history of heart disease.
- are taking other medications that may interact with Digoxin.

- hypokalaemia (low potassium).
- heart disease or impaired liver or kidney function.
- are taking other medications that may interact with Digoxin.

- Take Digoxin once daily in the evening.
- Take with food or milk to reduce the risk of side effects.
- Do not take Digoxin if you:
  - have an allergy to Digoxin.
  - are taking other medications that may interact with Digoxin.

- Take Digoxin if you:
  - have an allergy to Digoxin.
  - are taking other medications that may interact with Digoxin.

- Take Digoxin if you:
  - have an allergy to Digoxin.
  - are taking other medications that may interact with Digoxin.

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MHRA PAR – Digoxin 62.5 micrograms Tablets (PL 17907/0186 & 222) - 24 -
Important Information about some of the ingredients of these Tablets

- This medicine contains LACTOSE.
- If you have been told by your doctor that you have intolerance to some sugars (such as lactose), contact your doctor before taking this medicine.

**Always take Digoxin Tablets exactly as prescribed by your doctor.**
- You should check with your doctor or pharmacist if you are not sure.
- Check the label to see how often you should take your tablets.
- Swallow the tablets whole with a glass of water or milk.
- Do not crush or chew the tablets.

Your doctor will have decided how much digoxin is right for you.

- It depends on what heart problem you have and how serious it is.
- It also depends on your age, weight and how well your kidneys work.
- Your dose may go up or down depending on how your body responds to the medicine. Your doctor will do checks to see how well the medicine is working.

These may involve blood and urine tests.

The medicine is usually taken in two stages:

**Stage 1: loading or starting dose**
- The loading dose gets your digoxin levels up to the correct level quickly.
- You will either:
  - take one large dose and then begin your maintenance dose or
  - take a smaller dose each day for a week and then begin your maintenance dose.

**Stage 2: maintenance dose**
- After your loading dose you will take a much smaller dose every day, until your doctor tells you to stop.

**Adults and children over 10 years**

**Loading/Starting dose**
- Usually between 0.25mg and 0.5mg (12 and 24 tablets) as a single dose.
- For some patients, like the elderly, this dose may be reduced or given in divided doses 5 hours apart.
- Alternatively a starting dose between 0.25mg and 0.75mg (4 and 12 tablets) may be given each day for a week.
- You may take a higher strength tablet for the loading dose.

**Maintenance dose**
- Your doctor will decide this depending on your response to digoxin.
- It is usually between 0.125mg and 0.25mg (2 and 4 tablets daily).

**Children under 10 years**

**Loading/Starting dose**
- This is worked out using your child's weight.
- Usually between 0.03mg and 0.06mg per kg of body weight. This should be given in divided doses between 4 and 8 hours apart.

**Maintenance dose**
- The doctor will decide this depending on your child's response to digoxin.
- It is usually 0.1 or 0.15 mg (1/4 or 1/3rd of the loading dose) to be taken daily.

**If you take more Digoxin Tablets than you should**
- If you take too much or if somebody takes your medicine by mistake, go to a hospital casualty department (A&E) immediately. You may get any of the side effects and symptoms listed in Section 4, but these can be serious.
- If you forget to take Digoxin Tablets
  - If you forget to take a dose, take it as soon as you remember. However, if it is almost time for the next dose, skip the missed dose.
  - DO NOT take a double dose to make up for the one you have missed.

**If you stop takingDigoxin Tablets**
- Do not stop taking this medicine suddenly, as your heart may go worse. Talk to your doctor if you want to stop.
- If you have any further questions on the use of this product, ask your doctor or pharmacist.

### 4. Possible side effects

Like all medicines Digoxin can cause side effects, although not everybody gets them.

Tell your doctor immediately:
- You have nausea, chest pain, and shortness of breath or swelling.
- These can be symptoms of a serious heart problem caused by irregular heartbeats. If these happen, tell your doctor immediately.

Other side effects that you should tell your doctor about include:

**Common (affects less than 1 in 10 people)**
- dizziness, being sick or diarrhoea
- skin rash that may be itchy
- drowsiness or dizziness
- visual disturbances, with blurred or yellow-green sight

**Uncommon (affects less than 1 in 100 people)**
- depression
- Very Rare (affect less than 1 in 10,000 people)
- hearing or balance more easily than normal
- weakness, tiredness, or a general feeling of being unwell
- breathlessness in men
- loss of appetite

If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

### 6. How to store Digoxin Tablets

- Keep all medicines out of the reach and sight of children.
- Do not use Digoxin tablets after the expiry date on the bottle. The expiry date refers to the last day of that month.
- Do not store above 25°C.
- If your doctor decides to stop treatment the medicine should not be disposed of via a watercourse or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

### 5. Further information

**What Digoxin Tablets contain:**
- The active ingredient in Digoxin, each tablet contains 62.5 micrograms (0.0625mg) of digoxin.
- The other ingredients are lactose monohydrate, maize starch, microcrystalline cellulose, stearic acid and magnesium stearate.

**What Digoxin tablet looks like and contents of the pack:**
- White, round, blister packed tablet with DL embossed on one side of the tablet.
- The tablets are supplied in blister packs of 14, 28, 56 or 84 tablets.

**Not all pack sizes may be marketed.**

### Marketing Authorisation Holder

**Name and address:**
- Benali Laboratories Ltd
- Unit 3, Canford, Northbridge Road,
  - Basingstoke, Hampshire, United Kingdom, RG24 1GQ

**Telephone:**
- 01256 873717

**Fax:**
- 01256 873717

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**Digoxin 62.5 micrograms Tablets; PL 17907/0166**

This leaflet was last prepared in January 2011

To request a copy of this leaflet in Braille, large print or audio format, please contact the licence holder at the address (or telephone, fax, email) above.

MHRA PAR – Digoxin 62.5 micrograms Tablets (PL 17907/0186 & 222)
Labelling

The following Digoxin 62.5 micrograms Tablets labelling for PL 17907/0186 is included as representative example labelling. The labelling proposed for the other product PL 17907/0222 is consistent with this labelling:

Carton:
<table>
<thead>
<tr>
<th>Blisters:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Digoxin 62.5 micrograms Tablets</strong></td>
<td><strong>Digoxin 62.5 micrograms Tablets</strong></td>
</tr>
<tr>
<td>PL Holder</td>
<td>PL Holder</td>
</tr>
<tr>
<td>Bristol Laboratories Ltd.</td>
<td>Bristol Laboratories Ltd.</td>
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<td>Code BL 501</td>
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MHRA PAR – Digoxin 62.5 micrograms Tablets (PL 17907/0186 & 222)