Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Digoxin 125 microgram Tablets
Digoxin 250 microgram Tablets
digoxin

PL 16363/0744-0745

Milpharm Limited

LAY SUMMARY

Digoxin 125 and 250 microgram Tablets
digoxin

This is a summary of the Public Assessment Report (PAR) for Digoxin 125 and 250 microgram Tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Digoxin tablets in this lay summary for ease of reading.

For practical information about using Digoxin tablets, patients should read the Patient Information Leaflets (PILs) or contact their doctor or pharmacist.

What are Digoxin tablets and what are they used for?
These products are generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised, called Digoxin 0.125 mg and 0.25 mg tablets (previously known as Lanoxin 0.125 mg and 0.25 mg tablets).

Digoxin tablets are used to treat arrhythmias and heart failure. An arrhythmia is an irregularity in the heartbeat, which causes the heart to skip a beat, beat irregularly or beat at the wrong speed.

How do Digoxin tablets work?
Digoxin tablets contain the active substance digoxin, which belongs to a group of medicines called cardiac glycosides. These medicines work by correcting irregular heartbeats to a normal rhythm and strengthens the force of the heartbeat, which is why it is useful in heart failure.

How are Digoxin tablets used?
The pharmaceutical form of these medicines is a tablet, and the route of administration is oral (taken by mouth).

The patient's doctor will have decided how much of this medicine is right for the patient:
- It depends on what heart problem the patient has and how serious it is.
- It also depends on the patient's age, weight and how well their kidneys work.
- While the patient is taking Digoxin tablets, their doctor will take regular blood tests. This is to determine how the patient is responding to treatment.
- The doctor will adjust the patient's dose based on their blood test results and on how they are responding to treatment. This is why the patient must strictly adhere to the treatment course prescribed by their doctor.
- If the patient has taken another cardiac glycoside in the past 2 weeks, their doctor may prescribe a lower dose.
- If the patient feels that the effect of this medicine is too strong or too weak, they should talk to their doctor or pharmacist.

<u>Taking this medicine</u>
The patient usually takes Digoxin tablets in two stages:

- **Stage 1 - loading dose**

The loading dose gets the patient's digoxin levels up to the correct level quickly. The patient will either:
- take one large single dose and then begin their maintenance dose or
- take a smaller dose each day for a week and then begin their maintenance dose.

- **Stage 2 - maintenance dose**

After the patient's loading dose, the patient will take a much smaller dose every day, until their doctor tells them to stop.

Oral administration

Adults and children over 10 years
- loading dose
  - Usually between 750 micrograms and 1500 micrograms as a single dose
  - For some patients, this may be given in divided doses 6 hours apart
  - Alternatively, between 250 micrograms and 750 micrograms may be given each day for a week.

- maintenance dose
  - The doctor will decide this, depending on their patient's response to Digoxin tablets
  - It is usually between 125 micrograms and 250 micrograms daily.

Children under 10 years
- loading dose
  - This is worked out using the child's weight.
  - Usually between 25 micrograms and 45 micrograms 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 the child's response to Digoxin tablets.
  - It is usually a 1/5 (fifth) or a 1/4 (quarter) of the loading dose, to be taken daily.

Elderly

Elderly people may be given a lower dose than the usual adult dose. This is because older people may have reduced kidney function. The patient's doctor will check the levels of Digoxin tablets in their blood and may change the patient's dose if necessary.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

For further information on how Digoxin tablets are used, refer to the PILs and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take these medicines exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Digoxin tablets have been shown in studies?
As Digoxin tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicines. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Digoxin tablets?
For the full list of all side effects reported with these medicines, see Section 4 of the PILs or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PILs that come with these medicines. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of these medicines.

As Digoxin tablets are generic medicines and are bioequivalent to the reference medicines, their possible side effects are considered to be the same as the reference medicines.

Why were Digoxin tablets approved?
It was concluded that, Digoxin tablets have been shown to be bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that it can be approved for use.

Digoxin tablets has been authorised with the condition to perform further studies and/or to provide additional measures to minimise the risk. See section below "What measures are being taken to ensure the safe and effective use of Digoxin tablets?"

What measures are being taken to ensure the safe and effective use of Digoxin tablets?
As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed for Digoxin tablets. The RMP details the important risks of Digoxin tablets, how these risks can be minimised, any uncertainties about Digoxin tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Digoxin tablets:

Summary of safety concerns	
Important identified risks	Arrhythmias
	Digoxin Toxicity and Over dosage
Important potential risks	None
Missing information	None

The information included in the SmPCs and the PILs is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Digoxin tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Digoxin tablets
Marketing authorisations for Digoxin tablets were granted in the United Kingdom (UK) on 04 May 2023.

The full PAR for Digoxin tablets follows this summary.

This summary was last updated in August 2023.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Digoxin 125 and 250 microgram Tablets (PL 16363/0744-0745) could be approved.

The products are approved for the following indications:

- Cardiac failure
  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.

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

The active substance, 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 atrio-ventricular node. Thus, the major beneficial effect of digoxin is reduction of ventricular rate.

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Digoxin 0.125 mg and 0.25mg tablets (previously known as Lanoxin 0.125 mg and 0.25 mg tablets) that have been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing authorisations for Digoxin 125 and 250 microgram Tablets were granted in the United Kingdom (UK) on 04 May 2023.

II QUALITY ASPECTS

II.1 Introduction

These products contain 125 or 250 micrograms of digoxin in each tablet.

In addition to digoxin, these products also contain the excipients lactose monohydrate, starch, pregelatinised maize starch, maize starch and magnesium stearate.

The finished products are packaged in white, opaque, round high-density polyethylene containers, each closed with a white, opaque, polypropylene child resistance closure with wad having induction sealing liner. The products are available in a pack size of 28 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

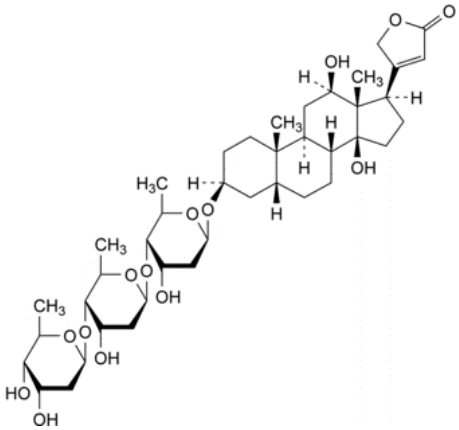
II.2 ACTIVE SUBSTANCES

rINN: Digoxin

Chemical Name: 3β-[(2,6-Dideoxy-β-D-ribo-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12β,14-dihydroxy-5β-card-20(22)-enolide

Molecular Formula: $C_{41}H_{64}O_{14}$

Chemical Structure:



Molecular Weight: 781 g/mol

Appearance: White or almost white powder, or colourless crystals.

Solubility: Practically insoluble in water, soluble in a mixture of equal volumes of methanol and methylene chloride, slightly soluble in ethanol (96 per cent).

Digoxin is the subject of a European Pharmacopoeia monograph.

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

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution profiles were provided for the proposed and reference products.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis were provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with the storage conditions Store below 25°C, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of marketing authorisations was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of digoxin are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the marketing authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of digoxin are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for applications of this type. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of the applications, the applicant submitted the following bioequivalence study:

Bioequivalence study 1 (single dose fasted conditions)
This study was an open-label, randomised, two-treatment, two-sequence, two-period, crossover, single-dose, oral bioequivalence study comparing the test product Digoxin Tablets B.P 0.25 mg versus the reference product Lanoxin 0.25 mg Tablets in healthy, adult, human subjects under fasted conditions.

After an overnight fast of at least 10 hours, subjects were administered a single dose of either treatment with approximately 240 ml of water. Blood samples were taken pre-dose and up to 72 hours post-dose, with a washout period of 14 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 1 Geometric Least Square Mean, Ratios, 90% Confidence Interval and Intra-Subject Coefficient of Variation (ISCV%) for Digoxin

Parameter (Unit)	(Ln-transformed) Geometric Least Square Mean			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product (T)	Reference Product (R)	Ratio (T/R)%			
C_{max} (pg/mL)	1568.9712	1539.0476	101.94	96.59-107.59	17.3	100
AUC_{0-72} (hr. pg/mL)	15334.8097	14864.8887	103.16	100.55-105.84	8.2	100

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional 0.125 mg (125 microgram) product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 0.25 mg (250 microgram) product strength can be extrapolated to the 0.125 mg strength.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications, and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns.

This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations was recommended for these applications.

V USER CONSULTATION

Full colour mock-up of the Patient Information Leaflets (PILs) were provided with the applications in accordance with legal requirements.

The PILs has been evaluated via a user consultation with target patient groups, in accordance with legal requirements, on the basis of a bridging report making reference to:

1. Lanoxin 0.125 mg and 0.25 mg Tablets (PL 39699/0009-0010; Aspen Pharma Trading Limited), with respect to content and key messages.
2. Metoprolol Aurobindo 50 mg & 100 mg film-coated tablets (SE/H/120l/001-002/DC; Aurobindo Pharma Limited), with respect to layout and design.

The bridging report submitted by the applicant is acceptable.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. 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.

The Summaries of Product Characteristics (SmPCs), PIls and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, is recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**