Part VI: Summary of the risk management plan by product

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Copy table from Part I: SVIII

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

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable. There are no proposed post authorisation efficacy studies for digoxin.

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable. There are no proposed post authorisation efficacy studies for digoxin.

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Arrhythmias	Text in SmPC	None
Digoxin Toxicity and Overdosage	Text in SmPC	None

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Heart Failure

The prevalence of heart (cardiac) failure can be estimated at 1-2% in the developed world and incidence at 5-10 per 1000 persons per year. The prevalence and incidence of heart failure increases with age and persons over 50 years are most at risk of developing heart failure. Risk factors for heart failure include past heart attack, hypertension, abnormal heart valves, heart muscle diseases (dilated cardiomyopathy,

hypertrophic cardiomyopathy) or inflammation (myocarditis), congenital heart defects, severe lung disease, diabetes mellitus, chronic anaemia and sleep apnoea. Lifestyle factors that increase the risk of heart attack and stroke – smoking, being overweight, foods high in fat and cholesterol and physical inactivity – can also increase the risk of heart failure. In the US and England, studies have shown one year survival rates of 63-70% one year following onset of heart failure. Five year follow-up showed a survival rate of 35%.

Supraventricular arrhythmias

Digoxin is indicated in the management of certain supraventricular arrhythmias, particularly chronic atrial flutter and fibrillation. Supraventricular tachycardia (arrhythmia) is a condition presenting as a rapid heart rhythm originating at or above the atrioventricular node. A study in the US showed an incidence of atrial fibrillation to range of 3.68 per 1000 person years which was consistent those reported from other countries including Canada, Scotland, and the United Kingdom. The current estimate of the prevalence of atrial fibrillation (AF) in the developed world is approximately 0.95 - 2.1% of the general population, with the average age of patients with this condition steadily rising, such that it now averages between 75 and 85 years. The arrhythmia is associated with a five-fold risk of stroke and a three-fold incidence of congestive heart failure, and higher mortality. While atrial fibrillation is rare in patients age less than 60 years (prevalence >1%), prevalence increases significantly with age. Notable risk factors for the onset of atrial fibrillation include blood pressure, hypertension and obesity. Others include ageing, some heart diseases and defects, diabetes, sleep apnoea in association with hypertension and chronic renal disease.

VI.2.2 Summary of treatment benefits

The goals of treatment in patients with established HF are to relieve symptoms and signs (e.g. oedema), prevent hospital admission, and improve survival. Digoxin therapy is used to treat heart failure patients for more than 200 years. Digoxin is an effective drug for patients with heart failure, and can be used as a first-line therapy in association with angiotensin-converting-enzyme (ACE) inhibitors and β-blockers for patients with clinical heart failure and left ventricular dysfunction, with LVEF ≤ 45%. The drug has been shown to have a large morbidity benefit, certainly at least as large as that seen for ACE inhibitors in heart failure.

Management of atrial fibrillation patients is aimed at reducing symptoms and at preventing severe complications associated with atrial fibrillation in particular stroke. As a result antithrombotic treatment of atrial fibrillation is fundamental. Treatment for correction of arrhythmias can include cardioversion, antiarrhythmic drug therapy, or ablation therapy.

VI.2.3 Unknowns relating to treatment benefits

Digoxin has been used to treat patients globally since 1930. It has been used to patients in all age groups (paediatric patients through to the elderly), in pregnant and lactating women and with careful monitoring in patients with hepatic and renal impairment during which time the efficacy of the product has been well established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Irregular heart beat	Digoxin increases the ability of heart muscle to contract by complex mechanisms involving sodium, potassium and calcium ions. Any changes in the to the calcium ion mobility can therefore impact on heart beat regulation.	Yes, by monitoring for early symptoms and notifying your doctor immediately
Poisoning/toxicity and overdosing	Digoxin has a narrow therapeutic range (dose at which drug is effective). Multiple drugs can affect it availability in the blood stream and each person has to be assessed for the correct dosage based on age, lean body wright and kidney function. For these reasons, there is a risk of digoxin toxicity (poisoning) or overdosage where the levels of digoxin in the blood are too high and can cause harm. The symptoms and signs of toxicity are generally nonspecific: fatigue, blurred vision, change in colour vision (e.g. "yellow vision"), weight loss, nausea (feeling sick), vomiting, diarrhoea, abdominal pain, headache, dizziness, confusion, and delirium. It is also associated with irregular heartbeats.	Yes, by monitoring for early symptoms and notifying your doctor immediately and Ensuring that you do not exceed the prescribed dosage

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
None	Not applicable

Missing information

Risk	What is known
None	Not applicable

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures. The Summary of Product Characteristics and the Package leaflet for digoxin can be found in the packaging of the product. This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

There are no planned post authorisation studies for digoxin.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	At time of authorisation	Not applicable	First version