Summary Public Assessment Report

Generics

Phloroglucinol ELC 80 mg orodispersible tablets
Phloroglucinol Dihydrate

MT/H/0263/001/DC

Date: 18/09/2019

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Phloroglucinol Dihydrate; orodispersible tablets; 80 mg

This is a summary of the public assessment report (PAR) for Phloroglucinol ELC 80 mg orodispersible tablets. It explains how Phloroglucinol ELC was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Phloroglucinol ELC.

For practical information about using Phloroglucinol ELC, patients should read the package leaflet or contact their doctor or pharmacist.

What is Phloroglucinol ELC and what is it used for?

Phloroglucinol ELC is a 'generic medicine'. This means that Phloroglucinol ELC is similar to a 'reference medicine' already authorised in the European Union (EU) Spasfon Lyoc 80 mg, lyophilisat oral (Teva, Sante, France).

This medicine is indicated in the treatment of pain caused by spasms (cramps) in the intestines, biliary tract, bladder and uterus.

How does Phloroglucinol ELC work?
Phloroglucinol ELC belongs to a group of medicines known as antispasmodic. Phloroglucinol reduces smooth muscle fibre spasms and relieves pain.

How is Phloroglucinol ELC used?
The pharmaceutical form of Phloroglucinol ELC is an orodispersible tablets and the route of administration is oral.

Please read section 3 of the PL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

The recommended dose is:

Adults: 2 tablets, to be taken when the pain occurs. to be repeated if there are severe spasms, with a minimum interval of 2 hours between each dose without exceeding 6 tablets per 24 hours.

Use in children over 2 years: 1 tablet to be taken when the pain occurs, to be repeated if there are severe spasms with a minimum interval of 2 hours between the previous dose without exceeding 2 tablets per 24 hours.

Method of administration

Adults: The tablets should be dissolved under the tongue for a fast effect or in a glass of water.

Children: The tablets should be dissolved in a glass of water. The reconstituted solution should be drunk immediately.

If more Phloroglucinol ELC than the recommended dose is taken the nearest hospital casualty department, or a doctor must be contacted immediately.

The medicine can be obtained without a prescription.

What benefits of Phloroglucinol ELC have been shown in studies?
Because Phloroglucinol ELC is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Spasfon Lyoc 80 mg, lyophilisat oral. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Phloroglucinol ELC?

Because Phloroglucinol ELC is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

Why is Phloroglucinol ELC approved?

It was concluded that, in accordance with EU requirements, Phloroglucinol ELC has been shown to have comparable quality and to be bioequivalent to Spasfon Lyoc 80 mg, lyophilisat oral. Therefore, the Malta Medicines Authority decided that, as for Spasfon Lyoc 80 mg, lyophilisat oral, the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Phloroglucinol ELC?

A risk management plan has been developed to ensure that Phloroglucinol ELC is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Phloroglucinol ELC, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Phloroglucinol ELC

The marketing authorisation for Phloroglucinol ELC was granted on 20th August 2019.

The full PAR for Phloroglucinol ELC can be found on the website http://medicinesauthority.gov.mt/advanced-search. For more information about treatment with

Phloroglucinol ELC, read the package leaflet (*http://medicinesauthority.gov.mt/advanced-search*) or contact your doctor or pharmacist.

This summary was last updated in 09-2019.

Public Assessment Report

Scientific discussion

Phloroglucinol ELC 80mg orodispersible tablets
Phloroglucinol Dihydrate

MT/H/0263/001/DC

Date: 18/09/2019

This module reflects the scientific discussion for the approval of Phloroglucinol ELC 80mg orodispersible tablet. The procedure was finalised at Day 210. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Phloroglucinol ELC 80mg orodispersible tablet, from ELC GROUP s.r.o.

The product is indicated for:

- Symptomatic treatment of pain associated with functional gastrointestinal tract and bile duct disorders
- Treatment of acute painful spasmodic urinary tract problems: renal colic
- Symptomatic treatment of painful spasmodic gynaecological problems
- Adjuvant treatment of contractions during pregnancy in combination with rest

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The drug product is an orodispersible tablet containing phloroglucinol dihydrate (API) and lactose monohydrate, microcrystalline cellulose, povidone, aspartame, crospovidone and magnesium stearate as excipients. The product is packed in a PVC-PVDC/Aluminium blister pack as well as an HDPE bottle pack. The excipients and container closure systems are common for this type of dosage form.

II.2 Drug Substance

The active substance phloroglucinol dihydrate is described in the European Pharmacopoeia, reference 01/2017:2302. For the drug substance a Certificate of Suitability issued by EDQM was included in this MAA submission.

Phloroglucinol dihydrate is a white or almost white powder which is sparingly soluble in water, freely soluble in ethanol (96 per cent) and practically insoluble in methylene chloride.

The control tests and specifications for drug substance product are adequately drawn up.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period is of 3 years if stored in double polyethylene bags (outer black) placed in a paperboard drum.

II.3 Medicinal Product

The applicant has applied the principles of Quality by Design (QbD) throughout the pharmaceutical development. The development of the product has been described and the formulation studies and optimisation are suitable.

The excipients are common pharmacopoeial excipients. They are in accordance with the Ph. Eur. The choice of excipients in adults is justified.

The applicant provided a multimedia dissolution report comparing the bioequivalence batches. Dissolution profiles were provided at 0.01N (QC medium), 0.1N, pH 4.5 and pH 6.8. Dissolution was more than 85% in 15 minutes for both formulations at all pHs. As a result, no F2 calculations were considered necessary and the dissolution profiles can be considered similar.

The tablets are manufactured by direct compression. The applicant has carried out validation studies on commercial scale batches. Since manufacturing process development also used QbD principles, the applicant carried out risk assessments throughout. This was considered acceptable by the RMS.

The conditions used in the stability studies are according to the ICH stability guideline. A bulk stability study of 45 days was conducted together with a photostability study and an in-use stability study. The applicant presented accelerated (6 months), intermediate (36 months) and long-term data (36 months). All results are well within specifications and no trends of concern are observed. As a result, the proposed shelf life of 36 months is granted. The proposed storage condition, "Store below 30°C", is also acceptable, and the product information also contains information on protection from moisture.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of this Marketing Authorisation is recommended.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The applicant has provided a non-clinical overview and summary documents based on scientific literature data. This is adequate in view of the generic legal basis applied for this product. The non-clinical overview and summary are written by a company expert and are dated 14 May 2019. For the overview and summary, the applicant refers to 18 publications the latest of which is dated 2017.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Phloroglucinol 80mg orodispersable is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

The application is made under reference to article 10(1) of Directive 2001/83/EC as amended. Abridged applications avoid the need for repetitive tests on animals and humans.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application for marketing authorisation is based on the Art 10(1) of the 2001/83/EC which allows the generic applicant to reference the clinical and non-clinical data from the originator.

To support the application, the applicant has submitted one bioequivalence study.

IV.2 Pharmacokinetics

Bioequivalence studies

The applicant has performed bioequivalence study of Phloroglucinol orodispersible tablets 80 mg (Test product) with Phloroglucinol oral lyophilisates 80 mg (Reference product). The study results demonstrated that Phloroglucinol orodispersible tablets 80 mg (Test product) is bioequivalent with that of Phloroglucinol oral lyophilisates 80 mg (Reference product). Hence, rate and extent of absorption of Test product is in-line with Reference product.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for Phloroglucinol (fasting,n=36)

Parameter (Unit)	Mean ± SD (Based on un-transformed data)	
	Reference Product (R)	Test Product (T)
C_{max} (ng/mL)	277.889 ± 120.6726	269.139 ± 96.1553
AUC_{0-t} (hr. ng/mL)	283.491 ± 57.4501	284.465 ± 62.9912
$AUC_{0-\infty}$ (hr. ng/mL)	297.796 ± 56.8414	297.329 ± 61.4419
$AUC_{\%Extrapolation}$	5.040 ± 2.5576	4.688 ± 2.5617
T_{max} (hr)*	0.50 (0.25-2.00)	0.50 (0.20-1.50)
K_{el} (hr^{-1})	0.49971 ± 0.082278	0.50090 ± 0.096974
$t_{½}$ (hr)	1.424 ± 0.2369	1.447 ± 0.3893

**For T_{max} Median has been represented instead of Mean and Range instead of SD.*

Table 2. ANOVA 90% CI (Log transformed) and CV% for primary parameters of Phloroglucinol (fasting, n=36).

Parameter (Unit)	(Ln-transformed) Geometric Least Square Mean		Ratio (T/R)%	90% Confidence Interval T vs R	Intra Subject CV (%)	Power (%)
	Test Product (T)	Reference Product (R)				
C_{max}	250.2049	253.0945	98.86	86.41-113.11	34.8	86
AUC_{0-t}	276.6135	277.4155	99.71	95.35-104.27	11.2	100

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study Phloroglucinol orodispersible tablets 80 mg is considered bioequivalent with Phloroglucinol oral lyophilisates 80 mg (Reference) of Spasfon-Lyoc, Teva, Sante, France.

IV.3 Risk Management Plan

The applicant has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Phloroglucinol 80mg orodispersable tablet.

The following safety specifications have been proposed by the applicant;

List of important risks and missing information	
Important identified risks	• Hypersensitivity to phloroglucinol or to any of the excipients • Use in patients with phenylketonuria • Concomitant use with major analgesics such as morphine or morphine derivatives • Use in patients with rare hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption
Important potential risks	• Use during pregnancy • Severe cutaneous adverse reactions; especially DRESS, TEN, and AGEP
Missing information	• Use during breastfeeding • Use in children • Use in patients with renal and liver failure

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are required.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are required.

Summary of the RMP
The submitted Risk Management Plan, is considered acceptable.

Periodic Safety Update Report (PSUR)
For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

IV.4 Discussion on the clinical aspects

The application is made under reference to article 10(1) of Directive 2001/83/EC as amended. Abridged applications avoid the need for repetitive tests on animals and humans.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of the user testing the PIL was English.

The test was carried out by ELC Group including participants with English as their first language. The targeted demographic group were potential users of the medication. The protocol and questionnaire used in the study are provided in the documentation. A pilot study with 4 subjects and then testing over 2 rounds with 10 different subjects in each round was carried out. Based on quantitative and qualitative results from the second round, no changes were made to the PIL after testing

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

From a quality point of view all issues have been resolved and the marketing authorisation can be granted.

From a non-clinical and risk management perspective, the documentation provided is adequate and there are therefore no objections for the granting of a marketing authorisation for this product.

The clinical issues have been addressed. There are no concerns for approval from a clinical point of view.