LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lidokain GALENpharma
(lidocaine)

SE/H/2279/01/DC

This module reflects the scientific discussion for the approval of Lidokain GALENpharma. The procedure was finalised on 2023-08-22. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Lidokain GALENpharma, 50 mg/g, rectal ointment.

The active substance is lidocaine. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Lidokain GALENpharma, 50 mg/g, rectal ointment, is submitted according to Article 10a of Directive 2001/83/EC. The applicant, GALENpharma GmbH, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE as concerned member state (CMS).

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology
Lidocaine is a well-known substance with local anaesthetic properties. Topical anesthetics reversibly block nerve conduction near their site of administration, thereby producing temporary loss of sensation in a limited area. Absorption of local anaesthetics requires a lipid state conferred by the aromatic portion which allows diffusion across the lipoprotein cell membrane.

Pharmacokinetics
The pharmacokinetic properties of lidocaine are also well-known. Lidocaine rectal ointment, 50 mg/g is intended for relief of pain in the anal region before proctological examination, and pain relief of symptoms associated with anorectal conditions. Lidocaine in the topical formulation is expected to be absorbed and exert a local effect.

Toxicology
At high doses, lidocaine can result in central nervous system depression, which causes behavioural effects such as tonic extension, clonic convulsions, a loss of righting reflex and motor ataxia, which also can produce respiratory depression resulting in cardiovascular collapse and death. The severity of acute adverse effects increases with increased systemic availability of lidocaine and is therefore dependent on the route of administration.

Lidocaine is not reported to be genotoxic *in vitro* or *in vivo.*

The lidocaine metabolite 2,6-xylidine showed weakly positive responses in some bacterial mutagenicity tests using *Salmonella typhimurium* strain TA100 (and once in TA1535) in the presence of S9 in some tests, while, in other tests, the results were negative. The weight of evidence indicates that 2,6-xylidine is a non-direct acting (metabolic threshold-dependent) genotoxin. In a carcinogenicity study of rats exposed to 2,6-xylidine *in utero*, postnatally and throughout their lifetime, tumours in the nasal cavity, subcutaneous tumours and liver tumours were observed. No NOEL has been established for carcinogenicity. Overall, 2,6-xylidine is a genotoxic carcinogen in rats and it is assumed that no threshold exists for genotoxicity. The clinical relevance of tumour findings in relation to short-term/intermittent use of lidocaine in humans is unknown.

There are limited data available on the reproductive and developmental toxicity of lidocaine. No data are available on effects on fertility and early embryonic development and pre- and post-natal development.

In vivo studies on embryo-foetal development rats and rabbits suggest low potential for adverse reproductive and teratogenic effects of lidocaine at subcutaneous doses up to 60 mg/kg/day.

Environmental Risk Assessment (ERA)
A log Kow value for lidocaine of 2.26 at pH 7.4 (derived from QSAR analysis) is referenced to. This is not a valid determination of the log Kow. The calculation of the predicted environmental concentration in surface water revealed concentrations above the trigger value of 0.01 µg/L indicating that a phase II environmental fate and effect analysis would be required. On the other hand, the Applicant has also submitted a justification for omitting ERA studies based on sales data in SE and DE during years 2018-2022. The presented sales data indicate that the consumption of lidocaine in the period 2018 to 2022 is subject to fluctuations. However, the sales data indicate no significant increase in the release of lidocaine during the last five years. Thus, the introduction of Lidokain GALENpharma into the market is not likely to result in any significant increase in the environmental exposure for lidocaine. The absence of an environmental risk assessment is thus considered to be acceptable.

A final conclusion on potential risk of Lidokain GALENpharma to the environment cannot be drawn as the applicant did not provide any ERA studies in this procedure.

IV. CLINICAL ASPECTS

Pharmacokinetics
Lidokain GALENpharma is a locally acting, locally applied medicinal product. Reported systemic exposure of lidocaine after rectal administration corresponding to the maximum proposed dose for Lidokain GALENpharma is below therapeutic levels and systemic PK is therefore of limited value.

Several products containing lidocaine alone or in combination with other active ingredients are approved in EU with indications related to anorectal complaints, including haemorrhoids. Most of these products are formulated as ointments, creams and suppositories, and in most of them the concentration of lidocaine varies between 2% and 5%. Bridging to the literature is based on quality data, see quality AR.

The clinical overview has been updated and the pharmacokinetic proposerties of lidocaine has in general been sufficiently described and supported by adequate references.

Pharmacodynamics
Topical anesthetics reversibly block nerve conduction near their site of administration, thereby producing temporary loss of sensation in a limited area. Absorption of local anaesthetics requires a lipid state conferred by the aromatic portion which allows diffusion across the lipoprotein cell membrane.

Clinical efficacy
The application for Lidokain GALENpharma is submitted according to Article 10a of Directive 2001/83/EC. This means that it is a stand-alone application where efficacy and safety should be sufficiently characterised by published literature data in the dossier, and reference cannot be made to other approved products for that purpose. In this type of application, the submitted data should in principle meet two different objectives regarding the clinical parts:

- Well-established use in the specific indication(s) applied for, within the EU for more than 10 years, should be documented.
- Efficacy and safety should be sufficiently characterised to fully support the product information.

The justification for well-stablished use within the EU for more than 10 years should preferably be supported by data. Support can be provided from sales data, treatment guidelines, textbooks, review articles, and/or drug utilisation studies or surveys documenting well-stablished use within the EU for more than 10 years. These publications should therefore preferably be older than 10 years. That a product has been approved for marketing authorisation does not automatically mean that it has been marketed and used to such an extent in routine care that it can be characterised as *well-established*.

For characterisation of the efficacy and safety profile of the product, the requirements on the literature data submitted differ from the requirements to demonstrate well-established use. For characterisation of efficacy and safety, preference should be given to more recent and well-designed interventional studies with a low risk for bias and adequate sample size. Narrative reviews have low relevance. If used, the supporting literature that is mentioned in the review, and that the Applicant wishes to refer to, should be provided as full text references and be critically discussed individually. For characterisation of safety also well-designed, comparative observational studies are relevant.

The literature provided for characterisation of efficacy in the current application is very limited.

- For the indication "*Relief of pain in the anal region before proctological examination"* the supporting literature is limited to the study Skriapas 2011. It is accepted that the study provides evidence for efficacy of topical lidocaine before proctological examination. The study was non-interventional and published >10 years ago within the EU, and therefore also provides support for WEU for the proctological examination indication.
- For the indication "*Relief of itching in the anal region"* the supporting literature is limited to the randomised controlled trial Rothhaar 2014. The magnitude of effect compared to placebo,

as determined in a subgroup analysis when the overall primary efficacy measure fails to show a meaningful difference, is quite modest and the risk for random error remains high due to the high P-value and lack of supporting evidence to increase the prior probability. The study provides some support for efficacy and safety in treatment of itching, but notably restricted to adult patients with a haemorrhoid-specific medical history.

There is consequently some support for efficacy in the proposed indications "*Relief of pain in the anal region before proctological examination"*. There is insufficient support for the broad indication "*Relief of itching in the anal region"*. The wording of the indication has therefore been revised to the previously approved – "*Symptomatic treatment in adults of itching and pain in the anal area caused by, for example, haemorrhoids*" – which is approvable.

Alignment with current wording of indications notably facilitates the assesment of potential OTC status.

Clinical safety
The safety of the substance lidocaine is well characterised and most importantly related to the risk for effects from systemic exposure. While the exposure documented in published studies, to a relevant formulation, dose and treatment duration is very limited in the submitted data, the pharmacokinetic characterisation available is reassuring regarding the risk for systemic exposure. The risk for local intolerance raises no major concerns.

Risk Management Plan
The MAH 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 Lidokain GALENpharma.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 1.1 signed 11.05.2021 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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 user testing the package leaflet was English.
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

The application for Lidokain GALENpharma, 50 mg/g, rectal ointment, is an application submitted according to Article 10a of Directive 2001/83/EC. The substance lidocaine is a well-known substance with local anaesthetic properties. Lidocaine in the topical formulation it is expected to be absorbed and exert a local effect.

Lidocaine rectal ointment, 50 mg/g is not intended to treat and cure haemorrhoidal nor other anal disorders. It is only intended for relief of symptoms associated with anorectal conditions.

The scientific interest, as judged by the reviewed literature, is very low. For the indication "*Relief of pain in the anal region before proctological examination*" the supporting literature is limited but provides at least some support for well-established use for this indication.

There is currently insufficient support for efficacy in the broad indication "*Relief of itching in the anal region*". The wording of the indication has therefore been revised to the previously approved – "*Symptomatic treatment in adults of itching and pain in the anal area caused by, for example, haemorrhoids*" – which is approvable.

The benefit-risk balance is favourable and Lidokain GALENpharma, 50 mg/g, rectal ointment is recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Lidokain GALENpharma, 50 mg/g, rectal ointment was positively finalised on 2023-08-22.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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