CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Lidocaine Claris 10 and 20 mg/ml solution for injection
Claris Lifesciences (UK) Limited, United Kingdom

lidocaine hydrochloride

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2539/001-002/DC
Registration number in the Netherlands: RVG 111018- 111019

26 August 2014

Pharmacotherapeutic group:	Anaesthetics, local; Amides
ATC code:	N01BB02
Route of administration:	intravenous, intramuscular and subcutaneous
Therapeutic indication:	Local and regional anaesthesia, minor and major nerve blocks.
Prescription status:	prescription only
Date of authorisation in NL:	6 February 2014
Concerned Member States:	Decentralised procedure with AT, BG, EE, FI, LT, LV, PT and UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Lidocaine Claris 10 and 20 mg/ml solution for injection, from Claris Life sciences (UK) Limited. The date of authorisation was on 6 February 2014 in the Netherlands.

The product is indicated for local and regional anaesthesia, minor and major nerve blocks.

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

Lidocaine is a short-acting amide-type local anesthetic. The mechanism of action is based on a decreased permeability of the membrane of the neuron for sodium ions. As a consequence of this, the depolarization rate is decreased and the threshold of excitation is increased, resulting in a reversible local numbness. Lidocaine is used to provide anaesthesia by nerve blockade at various sites in the body and in the control of dysrhythmias.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Lidocaine Hydrochloride Injection BP 1 and 2%w/v (NL License RVG 07828- 07829) which has been registered in the United Kingdom by AstraZeneca B.V. since 1986 (original product). In addition, reference is made to Lidocaine Hydrochloride BP authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Lidocaine Claris 10 and 20 mg/ml solution for injection is a product for parenteral use, it is exempted for bioequivalence study (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is lidocaine hydrochloride, an established active substance described in the European (Ph.Eur.*). The active substance is a white or almost white, crystalline powder which is very soluble in water for injections, freely soluble in ethanol (96%).

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality

of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification of the MAH is in accordance with the Ph.Eur. and the CEP. It contains additional requirements for identification, bacterial endotoxins, and microbial count. The drug substance specification of the Applicant is acceptable.
Batch analytical data was provided for one commercial scale batch demonstrating compliance with the proposed drug substance specification.

Stability of drug substance
This aspect is covered by the CEP. The re-test period of the substance is 5 years.

** Ph.Eur. is official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Medicinal Product

Composition
Lidocaine Claris 10 and 20 mg/ml is a clear and colourless or almost colourless solution. The pH of the solution is between 5.00 and 7.00 and osmolarity of the solution is 276.49 mosmol/kg for Lidocaine Claris 10 mg/ml and 313.42 mosmol/kg for Lidocaine Claris 20 mg/ml.

Lidocaine 10mg/ml solution for injection is packed in 2ml, 5ml, 10ml clear glass ampoules and 20ml clear glass vials with rubber closures and flip off seal.
Lidocaine 20mg/ml solution for injection is available in 2ml, 5ml clear glass ampoules and 20ml clear glass vial with rubber closures and flip off seal.

The excipients are: sodium chloride (as a tonicity agent), hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The drug product contains the same excipients as the reference product. As the drug product is applied as aqueous intravenous solution, no bioequivalence study was carried out. The product at issue is considered to be comparable to the reference product from a chemical-pharmaceutical point of view.
The drug product is terminally sterilised. The manufacturing process additionally contains a prefiltration and two sterile filtration steps. The aim of these filtration steps is to reduce particulate contamination and bioburden and to assure aseptic conditions during filling.
Compared to the indicated reference product, the Applicant additionally uses glass vials as container closure system. The drug product was shown to be compatible with this additional container closure system. The Applicant investigated in use stability after dilution of the drug product with common infusion solutions e.g. a saline solution, and no incompatibilities were observed.

Manufacturing process

The manufacturing process involves mixing, sterile filtration, filling, and terminal sterilisation by steam. Although the manufacturing process involves sterile filtration steps, it is regarded to be a standard process. Overall, the manufacturing process was sufficiently described.
Process validation was carried out with the minimum proposed commercial batch size. Validation of the mixing step included three batches of each strength. Validation of the filling and terminal sterilisation step included two batches of each container closure system of both strengths. In addition, validation data were provided for container closure integrity of the vials, for the depyrogenation tunnel for all container closure systems, and for the steam sterilisation of the rubber closures. Overall, the manufacturing process was sufficiently validated at the intended commercial manufacturing site. A process validation protocol for full scale batches was provided.

Control of excipients
All excipients comply with the European Pharmacopoeia. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification of the drug substance, extractable volume, pH, particulate matter, assay, 2,6-dimethylaniline, related substances, bacterial endotoxins, and sterility. The release and shelf life specifications differ with regard to the limits for assay. The drug product specification is acceptable.
The analytical methods were adequately described. Batch analysis data was provided on two batches of the minimum proposed commercial batch size of each container closure system of both strengths. All batches complied with the proposed release specification.

Stability of drug product
Stability data on the product was provided on two batches of the minimum proposed commercial batch size of each container closure system of both strengths stored at 25°C/60% RH (24 months), 30°C/65% RH (24 months), and 40°C/75% RH (six months). The condition used in the stability study is according to the ICH stability guideline. The batches were stored in the proposed commercial packaging. No significant changes were observed. The claimed shelf life of 24 months is acceptable.
The drug product was shown to be photostable in the primary packaging. On the basis of the provided stability data, no temperature storage condition is needed. However in order to harmonise the storage condition with the reference product the storage condition is claimed as: “Do not store above 25°C. Do not refrigerate or freeze”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Lidocaine Hydrochloride Injection BP 1 and 2%w/v, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of <active substance> released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Lidocaine Claris 10 and 20 mg/ml solution for injection is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is of the same type of solution, contains the same active substance in the same concentration and has the same or comparable excipients as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Lidocaine Claris 10 and 20 mg/ml solution for injection is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Risk management plan

Lidocaine hydrochloride was first approved in 1986, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of lidocaine hydrochloride can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for other lidocaine hydrochloride containing products.

Readability test

A readability test has been performed. A Preliminary Study and a Main Study consisting of two rounds were carried out with respectively 2, 10 and 10 participants. During the whole test no changes to either the leaflet or the questionnaire were deemed necessary. Both in the 1st and the 2nd round of testing showed that, for each question, 100% of participants were able to find the correct information, and 100% of participants were able to answer the questions correctly.

Overall, it can be concluded that the readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. In the test it was easy to determine which results are linked to which conclusions. The conclusions are clear, concise and clearly presented. Furthermore, the following areas have been sufficiently covered: traceability, comprehensibility and applicability.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Lidocaine Claris 10 and 20 mg/ml solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Lidocaine Hydrochloride Injection BP 1 and 2%w/v. Lidocaine Hydrochloride Injection BP is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other lidocaine hydrochloride containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Lidocaine Claris 10 and 20 mg/ml solution for injection with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 17 January 2013. Lidocaine Claris 10 and 20 mg/ml solution for injection is authorised in the Netherlands on 6 February 2014.

The date for the first renewal will be: 17 January 2018.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached