LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lidokain Aguettant
(lidocaine hydrochloride)

SE/H/1975/01/DC

This module reflects the scientific discussion for the approval of Lidokain Aguettant. The procedure was finalised on 2020-10-06. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Lidokain Aguettant, 20 mg/ml, Solution for injection/infusion.

The active substance is lidocaine hydrochloride. 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 Aguettant. 20 mg/ml, solution for injection/infusion, is submitted according to Article 10(3) of Directive 2001/83/EC. The applicant, Laboratoire Aguettant, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, DE, DK, ES, FI, IE, IT, LU, NL, NO, UK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Xylocain utan konserveringsmedel, 20 mg/ml, solution for injection, authorised in Sweden since 1987, with ASPEN Pharma trading Ltd as marketing authorisation holder.

European Reference Product (ERP)
The reference medicinal product in the RMS, Xylocain utan konserveringsmedel, 20 mg/ml, solution for injection, is used as a European Reference Product in CMS FI, IE, LU, ES and UK.
The justification to use this product is based on RMS's own files.

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

Pharmacodynamic, pharmacokinetic and toxicological properties of the active substance lidocaine are well known. As lidocaine is a widely used, well-known active substance, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate.

Pharmacology
The pharmacological mode of action of lidocaine is well established. As reflected in the literature, lidocaine is a local anaesthetic agent of the amide type and is widely used for different kinds of local anaesthesia. Lidocaine binds reversibly to primarily voltage-gated Na^+ channels and blocks the conduction of excitable structures such as sensor, motor and autonomic nerve fibres and the cardiac impulse conducting systems by decreasing or preventing the large transient increase in the permeability of the cell membrane to Na^+. In addition, lidocaine can also block Ca^{2+} and K^+ channels, at higher concentrations. The effect of lidocaine is use-dependent, and its effect is markedly increased when the membrane is depolarised (e.g. in case of hyperkalaemia), when pH is reduced, or when the frequency of excitation is increased. Lidocaine must enter the cell before reaching its site of action. Its effect depends on its pKa and on the environmental pH, i.e. on the proportion of the free base which is the moiety predominantly migrating through the lipophilic membranes of nerve fibres. Local anaesthetics affect the sensory functions in a predicable order: the sense of pain usually disappears first, followed by cold, warmth, touch, deep pressure and finally motor function.

In animal studies in vivo, intravenous administration of lidocaine has demonstrated dose-dependent anti-nociceptive effects in various acute pain models, such as postoperative pain. Furthermore, studies in laboratory animals (rats, rabbits) showed that lidocaine anaesthesia may accelerate recovery of gastrointestinal motility after abdominal surgery. It is thought that lidocaine improves smooth muscle contractility and basic cell function by cellular repair mechanisms that are still unknown. The results of these studies may be considered supportive for the applied indications.

Following systemic absorption, lidocaine may also affect cardiac sodium channels. As a consequence, the duration of the action potential is decreased and the functional refractory period is prolonged, thereby preventing ventricular arrhythmias. Lidocaine has anti-arrhythmic properties. Lidocaine may also affect the CNS, producing initially light-headedness, dizziness, sensory disturbances, restlessness, disorientation, and tremor, including convulsions. Central stimulation may be followed by depression and death due to respiratory failure.

In conclusion, based on published non-clinical studies there is extensive primary pharmacodynamic experience from the use of lidocaine in the applied indications. The literature-based data provided by the Applicant is considered to cover the necessary aspects of lidocaine primary pharmacodynamics.

Pharmacokinetics
No non-clinical pharmacokinetic studies have been conducted with lidocaine by the Applicant. The pharmacokinetics of lidocaine has been reported in the literature.

Orally administered lidocaine is subject to extensive first pass hepatic metabolism (only one third to half of the drug dose enters general circulation). This was demonstrated in dog studies, in which the administration of 31 mg/kg b.w. lidocaine led to mean peak blood levels of 5.8 and 3.2 µg/mL, respectively. Lidocaine is rapidly and almost completely absorbed: following injection in the tongues of rats, 88% of the injected dose was absorbed from the tongue after 8 min.

There is a rapid distribution of lidocaine after i.v. injection, primarily in highly perfused tissues. It has also been established that hepatic function and blood flow are primary determinants of the rate of clearance. Lidocaine is markedly bound to AAG. Lidocaine is subject to extensive hepatic metabolism mainly by CYP1A2 and CYP3A4 enzymes leading to pharmacologically active metabolites MEGX (which is further metabolised) and GX. The major primary metabolite, MEGX, still possesses some of the pharmacological properties of lidocaine.

Lidocaine undergoes first-pass metabolism in the liver. Lidocaine is largely metabolised in the liver by cytochrome P450 enzymes; only 3% is found unchanged in the urine. Neither drug nor metabolite has been detected in the bile and there is no entero-hepatic circulation. The main metabolic pathway involves the following steps:
1. N-De-ethylation of lidocaine to monotheylglycinexylidide (MEGX, active metabolite)
2. N-de-ethylation of MEGX to glycinexylidide (GX, active metabolite).
3. Hydrolysis of glycinexylidide to 2,6-xylidine
4. Hydroxylation of 2,6-xylidine to give 4-hydroxy-2,6-xylidine (or 4-Hydroxy-2,6-dimethylaniline).

In mice more than 50% of a 10 mg/kg b.w. i.p. injection of lidocaine was metabolised after 10 min. In man approximately 90% of the lidocaine dose is dealkylated by the microsomal enzyme system to form two active metabolites; MEGX and GX. MEGX is the main metabolite in dogs, and MEGX and GX are also produced from lidocaine in rats, where the elimination half-life of lidocaine is less than 30 min. Monoethylglycinexylidide, the major primary metabolite, is further metabolised in the liver to GX and 2,6-xylidine, which is hydroxylated to 4-hydroxy-2,6-xylidine. It is noted that the lidocaine metabolite 2,6 xylidine may present safety concerns since 2,6-xylidine is a genotoxic metabolite.

After the metabolism of lidocaine in the liver (cytochrome P450 3A4), metabolites and unchanged drug (approx. 10%) are excreted by the kidneys. More than the 98% of an absorbed dose of lidocaine can be recovered in the urine. Lidocaine has an elimination half time (t1/2) of 1.6 h in adults. The elimination half-life in neonates (3.2 hours) is approximately twice that of adults. The half-life may be increased in cardiac and hepatic dysfunction. Renal impairment does not affect the clearance of lidocaine but accumulation of its active metabolites can occur and may lead to toxicity.

The excretion of lidocaine has been reported in breast milk, as is its primary metabolite, monoethylglycinexylidide. The potential transfer of the metabolite 2,6-xylidine from nursing mother to infant is of toxicological concern, as xylidine has been shown to be a genotoxic metabolite.

In conclusion, the non-clinical pharmacokinetics of lidocaine have been reported in published literature, where the studies were partly performed in animals, and were discussed in the non-clinical overview.

Toxicology
The toxicology of both lidocaine as well as its metabolites, is well known and it is well documented in the scientific literature. The lidocaine can have serious effects on the central nervous and cardiovascular systems. An overdosage of lidocaine can result in severe hypotension, asystole, bradycardia, apnoea, seizures, coma, cardiac arrest, respiratory arrest, and death.

<u>Single-dose toxicity</u>
Following single dose administration of lidocaine, the LD50 dose for s.c. and i.p. lidocaine in mice has been reported to be in the range of 100 to 350 mg/kg b.w. (22- to 77-fold the MRHD of 4.5 mg/kg b.w.). In rats the i.v. LD50 dose varied from 21 to 25 mg/kg b.w. (4.7- to 5.6-fold the MRHD), in rabbits i.v. LD50 was 41 mg/kg b.w. (8.9-fold the MRHD). In man toxic reactions to lidocaine are usually encountered at plasma concentrations in excess of 5-10 mg/l. However, some patients may tolerate concentrations between 5 and 10 mg/l without signs of toxicity. Lidocaine´s pharmacological principle of preventing nerve impulse generation and conduction may trigger CNS and cardiovascular toxicity at toxic doses. Animal studies demonstrated lidocaine´s cardiotoxicity at high doses.

Repeat-dose toxicity

Oral administration of the lidocaine metabolite, 2,6-xylidine, to dogs in doses of 2, 10 or 50 mg/kg b.w./d for 4 weeks induced fatty degeneration of the liver, however, in rats doses of 400 – 500 mg/kg b.w. (administered for 4 weeks) were less hepatotoxic and only caused liver enlargement. In rats, hyperkeratosis of the forestomach was observed, probably due to stomach irritation. Repeated administration of 100 mg/kg b.w. 2,6-xylidine was found to induce gastric ulcers in dogs. A dose-related leukocytosis and an increase in the number of nucleated erythrocytes occurred in male rats fed diets containing 2,6-xylidine for 2 weeks.

In order to define the concentration of lidocaine, which result in convulsions in awake newborn pigs, 18 landrace piglets aged 12 – 60 h were administered lidocaine infusion at the dose of 2 mg/kg/min i.v. (n=5) and repeated bolus doses of 15 mg/kg (n=4) until electroencephalogram-confirmed the seizures appeared. Piglets of the repeated bolus doses group started to convulse after a cumulative dose of lidocaine from 30 to 60 mg was given. The lidocaine plasma concentration was 41.3 ± 17.8 mg/l at the start of the convulsions.

In summary, high doses of the metabolite 2,6-xylidine have been shown to cause liver damage in dogs after repeat dosing but the effects were less pronounced in rats. No repeat dose toxicity studies were submitted for lidocaine.

Genotoxicity

In vitro

The lidocaine metabolite 2,6-xylidine was found to be mutagenic in Salmonella typhimurium strain TA100 in the presence of S9 activator. Mutagenic effects were not found for 2,6-xylidine in the absence of S9 activator. In the presence of S9 activator doses of 2,6-xylidine from 33 to 3,333 µg/plate increased the number of revertants per plate.

In vivo

In a study investigating chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells, 2,6-xylidine was found to promote sister chromatid exchange at concentrations of 301 µg/mL without rat liver S9 mix stimulation and 1,100 µg/mL with S9 activation. These doses induced cell cycle delay. Chromosome aberrations were found at concentrations of 1,000 µg/mL without S9 stimulation and at concentrations of 1,200 µg/mL with S9 stimulation. The doses required for chromosome aberration were cytotoxic. No in vivo mutagenicity studies in accordance with ICH S2 have been reported.

Carcinogenicity

In a study on rats the oral administration of high doses (50 mg/kg b.w. or 3,000 ppm of the diet) of the lidocaine metabolite, 2,6-xylidine, induced the growth of carcinomas and papillary adenomas in the nasal cavity. Carcinomas occurred in 28/56 (50%) of high-dose males, 24/56 (43%) high-dose females and 1/56 (2%) medium dose (1,000 ppm) females. Papillary adenomas occurred in 10/56 (18%) of high-dose males, 6/56 (11%) of high-dose females, and 2/56 (4%) of medium-dose males. The incidence of nasal cavity carcinomas was significantly ($p<0.001$) increased compared to controls. Rhabodomyosarcomas (a rare type of tumour) were diagnosed in two male and two female rats treated with 3,000 ppm 2,6-xylidine. Studies with labelled 2,6-xylidine revealed that the concentration of radioactivity in the nasal tissue, 24 h after rats had received 63 mg/kg b.w.[14C]2,6-xylidine by gavage, was 2.5 times greater than that in the liver.

Taken together, studies in rats show that both DNA binding and the development of carcinomas in the nasal cavity of the animals only occur following continuous oral treatment of animals with very high doses of the lidocaine metabolite 2,6-xylidine. It was reported that the occurrence of carcinoma in the nasal cavity might be related to a topical effect of 2,6-xylidine due to inhalation of the compound (low vapour pressure of the compound and considerable loss

from the feeding by evaporation). Furthermore, clinical pharmacokinetic studies have demonstrated that following therapeutic doses of lidocaine, the levels of this metabolite were low. Even though one of the metabolites of lidocaine, 2,6-xylidine has been shown to be a rat carcinogen, no signal appears to have been raised from the vast clinical experience of lidocaine.

Reproductive and developmental toxicity

The reproductive and teratogenic effects of lidocaine were studied in 155 Sprague-Dawley rats chronically implanted with osmotic minipumps. Three different lidocaine doses were used as follows: a low dose (100 mg/kg/ b.w./d); an intermediate dose (250 mg/kg b.w./d); and a high dose (500 mg/kg/ b.w./d). In the low and intermediate dose groups, lidocaine was administered for two weeks before mating and throughout pregnancy to evaluate reproductive and teratogenic effects. In the high-dose group, lidocaine was administered from Days 3 to 17 of pregnancy to evaluate teratogenic effects. On Day 21, caesarean section was performed and all of the 1,040 offspring, including those from control and positive control (retinoic acid) groups, were preserved and subsequently examined microscopically to detect external, visceral, and skeletal abnormalities. None was found in lidocaine-treated groups; reproductive indices also were normal. The only treatment effect was a reduction in mean foetal weight in the high-dose group. In a subsequent experiment this was found to be secondary to slightly delayed foetal development. The results showed that lidocaine appears to be devoid of significant adverse reproductive and teratogenic effects in Sprague-Dawley rats.

Pregnant Long-Evans hooded rats were dosed via injections into the gum with 3, 6, or 9 mg/kg lidocaine, or vehicle, or were uninjected, on gestational day 4 (GD4), GD11, or GD18. Offspring (8 – 11 litters/group) were tested on a variety of tests of behavioural development and adult behaviour. No effects of any dose at any time of administration were found upon maternal weight gain in gestation, litter size, or initial birth weight or weight gain of the pups. Administration at GD4 produced few effects; only footshock sensitivity showed a significant effect of dosing, although there were trends toward dosing effects on spontaneous alternation. For administration on GD11, lidocaine was associated with slight but significant alterations in sex ratios, and a trend toward drug effects on development of spontaneous alternation. Vehicle administration at this age reduced barbiturate sleep time in offspring and slightly altered footshock sensitivity. Lidocaine dosing on GD18 was associated with a number of significant alterations of behaviour, including visual discrimination, shuttlebox avoidance, tail flick, and water maze errors; there were also both vehicle and lidocaine effects on water maze latencies.

Sprague-Dawley rat embryos in vitro were explanted on GD 9 and were cultured in medium containing various concentrations of lidocaine. Controls were cultured in medium without lidocaine. After 50 h of culture, they were evaluated for growth size and morphology, including the neural tube closure. In the presence of 250 µM of lidocaine, embryos showed an increased incidence of situs inversus compared with control group but were otherwise normal. At 375 µM, embryos showed slight growth retardation but no significant morphologic abnormalities. At 500µM, all viable embryos showed severe morphologic abnormalities. However, morphologic abnormalities were so-called non-specific types and neural tube closure defects were not observed. Lidocaine may cause teratogenic effects in vitro in rats only at concentrations much higher than clinically relevant concentrations.

In summary, studies in rats did not reveal any obvious embryotoxic or teratogenic effects of lidocaine. In one study a reduction in mean foetal weight was observed in rats treated with high-dose lidocaine. The applicant did not present reproductive toxicity studies in rabbits. However, its known that embryotoxic or fetotoxic effects of lidocaine is detected in rabbits at high doses of 25 mg/kg, SC. When administered to pregnant rats at doses almost as high as the therapeutic maximum doses applied in humans, lidocaine resulted in significant alterations of behaviour of the offspring. The SmPC text in section 4.6 and 5.3 is acceptable.

Local tolerance

No specific literature study that investigated the local tolerance of lidocaine was submitted.

In conclusion, toxicological studies with lidocaine have identified that high single doses are primarily CNS toxic and cardiotoxic. Toxic doses produce CNS symptoms such as confusion, drowsiness, but particularly seizures, coma and respiratory arrest. Cardiotoxicity of lidocaine is associated with cardio-depression, arrhythmias and cardiac arrest. Such findings are primarily related to higher plasma levels of lidocaine, which may occur if high doses of lidocaine are applied at fast rates. In addition, based on the submitted toxicity studies, there was no evidence of any reproductive, mutagenic, or oncogenic toxicity of lidocaine. The lidocaine metabolite 2,6-xylidine has, however, been shown to be mutagenic in bacteria (TA 100 strain) and Chinese hamster ovary cells, and carcinogenic in rats.

Environmental Risk Assessment (ERA)
The applicant has provided an updated ERA including a study report for experimental determination of Log Kow value using a HPLC method. The applicant has refined the Fpen value based on prevalence data for the sought indications. The provided ERA is considered to be acceptable.

IV. CLINICAL ASPECTS

Pharmacokinetics
No bioequivalence study was submitted with this application and no formal biowaiver justification could be found besides the statement *"The pharmaceutical form does not require a demonstration of bioequivalence"*.

Even though no formal biowaiver justification could be found beside the statement above it is agreed in this case that no bioequivalence study is considered necessary.

The applied product could be administrated intravenously as well as via other parenteral routes. Both the applied product and the reference product are aqueous solutions and contain the same concentration of the same active substance. There are small differences in excipients between the applied product and the reference product. However, these differences are assessed as having no impact on the viscosity of the solution and thus, no bioequivalence study is considered necessary according to the guideline on the investigation of bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1).

Pharmacodynamics
No formal studies have been performed. Literature data is provided to support some of the pharmacodynamic aspects of the product. The Clinical Overview discusses mainly interactions in the Clinical Pharmacodynamics section. Further aspects on pharmacodynamics are discussed in the section "Mechanism of action" which even includes "Mechanism of action related to safety" This is deemed sufficient for an abridged application as the applied for indication is identical to that of the reference product.

Clinical efficacy
Only literature data is provided. The Applicant presented literature data for Efficacy of lidocaine in local and regional anaesthesia but not for Efficacy in intravenous regional anaesthesia and epidural anaesthesia. This was nevertheless deemed acceptable because 1. the reference product has been approved for those indications in Sweden and are therefore, in principle, approvable in other CMS countries in the EU and 2. in view of the Bioequivalence between Lidokain Aguettant and the reference product. Because intravenous regional anaesthesia and epidural anaesthesia are not registered as indications of the reference product in some CMSs the applicant provided an update of the clinical overview discussing these indications which is deemed satisfactory.

Efficacy has been sufficiently shown for the applied for indication which is identical to that of the reference product. The benefit/risk balance is considered positive. The application is therefore recommended for approval.

Clinical safety
Only literature Safety data is provided, and no new Safety studies have been performed.
The safety profile of Lidocaine 20 mg/ml solutions for injections is relatively well-known for the indication's infiltration anaesthesia, intravenous regional anaesthesia, nerve blocks and epidural anaesthesia and considered sufficiently described in the Clinical Overview.

Safety has been sufficiently shown for the applied for indication which is identical to that of the reference product. The benefit/risk balance is considered positive. The application is therefore recommended for approval.

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 Aguettant. 20 mg/ml, solution for injection/infusion.

Safety specification

Summary of safety concerns	
Important identified risks	Central nervous or cardiovascular reactions following overdose/medication error
Important potential risks	None
Missing information	Use in patients < 2 years of age

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 1.4 with DLP 26 April 2019 and signed 24 September 2020 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

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Lidocain Aguettant, DE/H/4804/001-002/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lidokain Aguettant, with the indications approved for the reference product Xylocain *utan konserveringsmedel*, 20 mg/ml, solution for injection, is recommended for approval as the product is of adequate quality and the bridge to the reference product is established.

No bioequivalence study has been performed and no bioequivalence study is considered necessary in this case.

There are no objections to approval of Lidokain Aguettant, from a non-clinical and clinical point of view. The benefit risk of this product is positive. The product information is acceptable. The application is therefore 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 Aguettant, 20 mg/ml, Solution for injection/infusion was positively finalised on 2020-10-06.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se