Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Covonia Medicated Sore Throat 5mg/1mg Lozenges Menthol Flavour

Covonia Medicated Sore Throat 5mg/1mg Lozenges Lemon Flavour

(chlorhexidine dihydrochloride and lidocaine hydrochloride)

UK Licence Number: PL 00240/0395-0396

Thornton & Ross Ltd

LAY SUMMARY

Covonia Medicated Sore Throat 5mg/1mg Lozenges Menthol Flavour
Covonia Medicated Sore Throat 5mg/1mg Lozenges Lemon Flavour
(chlorhexidine dihydrochloride and lidocaine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Covonia Medicated Sore Throat 5mg/1mg Lozenges Menthol Flavour (PL 00240/0395) and Covonia Medicated Sore Throat 5mg/1mg Lozenges Lemon Flavour (PL 00240/0396). For ease of reading, these medicinal products will be referred to as Covonia Lozenges in this Lay Summary.

This summary explains how Covonia Lozenges were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about using Covonia Lozenges, patients should read the package leaflets or contact their doctor or pharmacist.

What are Covonia Lozenges and what are they used for?

Covonia Lozenges are medicines with 'well established use'. This means that the medicinal use of the active substances of Covonia Lozenges have been in well-established use in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Covonia Lozenges are compressed lozenges for local action in the mouth and the pharynx.

Covonia Lozenges are recommended for the treatment of the symptoms of a sore throat, red throat, and disorders of the pharynx accompanied by irritation.

In case of bacterial infection accompanied by fever, an additional treatment is necessary.

Covonia Lozenges are sugar-free and are therefore also suited for diabetic patients

How are Covonia Lozenges used?

Covonia Lozenges are taken by mouth. The patient must allow the lozenge to dissolve in the mouth slowly.

The patient should use this medicine exactly as the doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

This medicine must not be used for long periods. The patient must consult a doctor, if the symptoms worsen or do not improve after 3 to 4 days.

The recommended dose is in adults is 6 to 10 lozenges per day.

The recommended dose in children from 12 years old is 3 to 5 lozenges per day.

This medicinal product can be obtained from a pharmacy.

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

How do Covonia Lozenges work?
Covonia Lozenges contain the active ingredients chlorhexidine dihydrochloride which is an antiseptic, and lidocaine hydrochloride which is a local anaesthetic which relieves pain.

What benefits of Covonia Lozenges have been shown in studies?
As Covonia Lozenges contain well-known substances, and their uses as a disinfectant and local pain-killer are well established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of the use of chlorhexidine dihydrochloride and lidocaine hydrochloride for the proposed indications.

What are the possible side effects of Covonia Lozenges?
Like all medicines, Covonia Lozenges can cause side effects, although not everybody gets them.

For the full list of all side effects reported with these medicines, see section 4 of the package leaflets or the Summaries of Product Characteristics (SmPC) available on the MHRA website.

Why were Covonia Lozenges approved?
The MHRA decided that the benefits of Covonia Lozenges are greater than the risks and recommended that they were approved for use.

What measures are being taken to ensure the safe and effective use of Covonia Lozenges?
A Risk Management Plan has been developed to ensure that Covonia Lozenges are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflets for Covonia Lozenges, 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.

Other information about Covonia Lozenges
Marketing Authorisations were granted in the UK on 12 October 2018.

The full PAR for Covonia Lozenges follows this summary.

This summary was last updated in December 2018.

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I INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Thornton & Ross Ltd Marketing Authorisations for the medicinal products Covonia Medicated Sore Throat 5 mg/1 mg Lozenges Menthol Flavour (PL 00240/0395) and Covonia Medicated Sore Throat 5mg/1mg Lozenges Lemon Flavour (PL 00240/0396) on 12 October 2018. These products are available from a pharmacy (P), and are indicated for the symptomatic and local treatment at the pharynx. Proposed as disinfectant and local pain-killer of sore throat and disorders of the pharynx and mouth accompanied by irritation, the presence of lidocaine causes a quick alleviation of the symptoms.

In case of a bacterial infection accompanied by fever, a supplementary treatment is required.

These products are sugar free and can therefore also be used in diabetic patients.

These applications were made under Article 10a of Directive 2001/83/EC, as amended, claiming to be applications for products containing active substances of well-established use.

The active substances are chlorhexidine dihydrochloride and lidocaine hydrochloride.

Lidocaine is a local anaesthetic of the amide type. Like other local anaesthetics, lidocaine impairs the generation and conduction of the nerve impulses by slowing depolarisation. This results from blocking of the large transient increase in permeability of the cell membrane to sodium ions that follows initial depolarisation of the membrane. Lidocaine also reduces the permeability of the resting axon to potassium and to sodium ions.

Chlorhexidine is a cation-active antiseptic agent. It possesses a powerful bactericidal effect against both gram-positive and gram-negative bacteria and an antimycotic effect on dermatophytes and yeasts.

No new non-clinical or clinical studies were necessary for these applications, which is acceptable given that these are bibliographic applications for products containing active substances of well-established use.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products.

A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with these applications, and these are satisfactory.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Covonia Medicated Sore Throat 5mg/1mg Lozenges Menthol/Lemon Flavour outweigh the risks and Marketing Authorisations were granted.

II QUALITY ASPECTS

II.1 Introduction

The finished product is presented as a compressed lozenge. One compressed lozenge contains 5 mg chlorhexidine dihydrochloride and 1 mg lidocaine hydrochloride as active ingredients. Other excipients present in Covonia Medicated Sore Throat 5 mg/1 mg Lozenges Menthol Flavour (PL 00240/0395) are sorbitol (E420), magnesium stearate, anhydrous citric acid and levomenthol. Other excipients present in Covonia Medicated Sore Throat 5 mg/1 mg Lozenges Lemon Flavour (PL 00240/0396) are sorbitol (E420), magnesium stearate, aspartame (E951), lemon aroma 501050 AP0551 and acesulfame K.

All excipients comply with their respective European Pharmacopoeia monographs, except for the lemon flavour. Satisfactory Certificates of Analysis have been provided for these excipients.

The finished products are available in a box with 12, 24 or 36 compressed lozenges in a perforated unit dose blister. Not all pack sizes may be marketed.

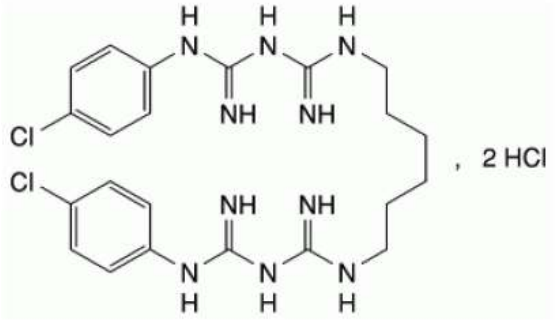
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2. Drug Substances

INN: Chlorhexidine dihydrochloride

Chemical name(s): 1,1-(Hexane-1,6-diyl)bis[5-(4-chlorophenyl)biguanide] dihydrochloride

Structure:



Molecular formula: $C_{22}H_{30}Cl_2N_{10}.2HCl$

Molecular weight: 578.4 g/mol

Appearance: A white or almost white, crystalline powder.

Solubility: Chlorhexidine dihydrochloride is sparingly soluble in water, in propylene glycol and very slightly soluble in alcohol

The active substance is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, chlorhexidine dihydrochloride, are covered by either an Active Substance Master File or by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory

specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

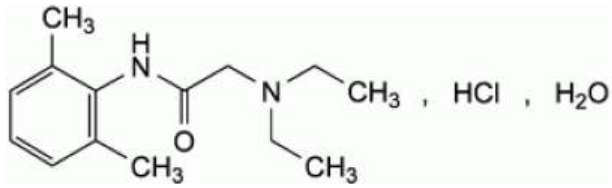
Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification limits. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

INN: Lidocaine hydrochloride
Chemical name(s): Lidocaine hydrochloride
Structure:



Molecular formula: $C_{14}H_{22}N_2O.HCl, H_2O$

Molecular weight: 288.8 g/mol
Appearance: A white or almost white, crystalline powder.
Solubility: Lidocaine hydrochloride is very soluble in water and freely soluble in ethanol (96 %).

Lidocaine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, lidocaine hydrochloride, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious lozenges containing 5 mg of chlorhexidine dihydrochloride and 1 mg lidocaine hydrochloride.

A satisfactory account of the pharmaceutical development has been provided.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing processes. The manufacturing processes have been validated with commercial-scale batches and have shown satisfactory results.

Finished Product Specification
The proposed finished product specification is acceptable. The test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 3 years for Covonia Medicated Sore Throat 5 mg/1 mg Lozenges Menthol Flavour (PL 00240/0395) and 2 years for Covonia Medicated Sore Throat 5 mg/1 mg Lozenges Lemon Flavour (PL 00240/0396) with storage conditions 'Keep this medicine out of the sight and reach of children', 'Store below 25°C' and 'Do not use [Covonia Lozenges Menthol][Covonia Lozenges Lemon] after the expiry date which is stated on the box/the blister after "EXP"'.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of chlorhexidine dihydrochloride and lidocaine hydrochloride are well-known, and the applicant has provided an acceptable overview from limited literature sources. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier. No new non-clinical data have been supplied with these applications. This is acceptable.

III.2 Pharmacodynamics
The pharmacology of both chlorhexidine dihydrochloride and lidocaine hydrochloride is well-known and the published literature has been reviewed and discussed in the applicant's non-clinical overview.

Lidocaine hydrochloride:
The combination of an hydrophobic (aromatic ring) and hydrophilic (tertiary amine) moiety enables lidocaine to cross the cell membrane readily and to reach the intracellularly located receptor site of voltage-dependent sodium channels. The hydrophilic or charged form is responsible for the direct interaction with the ionic channel. Since lidocaine is a weak base, the local pH influences the ratio of the charge/uncharged form and, thus the effectiveness of the entry of lidocaine into the channel.

The consequence of the blockade of Na^+ entry by lidocaine through voltage-dependent sodium channels is the interruption of nerve conduction. Its action is restricted to the site of application and rapidly reverses upon diffusion from the site of action. In addition, lidocaine can also block K^+ channels, at higher concentrations. More recently lidocaine has also been shown to affect a variety of additional ion channels and receptors such as K^+ channels, Ca^{2+} channels, transient receptor potential

vanilloid 1 (TRPV1) channels, NMDA receptors, AMPA receptors and GTP-binding protein coupling receptors.

After topical application, lidocaine targets nerve endings in the dermis, prevents the propagation of nerve impulses such as pain and temperature sensations, thereby providing analgesia.

Chlorhexidine dihydrochloride
Chlorhexidine is a cationic compound and the antibacterial activity of the drug is believed to be the result of attraction between positively charged chlorhexidine and negatively charged bacterial cell surfaces. Chlorhexidine becomes adsorbed onto the cell surfaces of susceptible organisms, with specific and strong adsorption to certain phosphate-containing compounds. This disrupts the integrity of the cell membrane and results in increased permeability whereby essential cellular contents are lost.

Chlorhexidine acts though bacteriostatic or bactericidal means, depending on the concentration of the drug attained at the site and the susceptibility of the organism.

- At low concentrations, the drug usually exerts a bacteriostatic effect as the result of efflux of small molecular weight substances (e.g. potassium, phosphorus). The bacteriostatic effect may be reversible; removal of excess chlorhexidine by neutralizers may allow the bacterial cell to recover.

- Higher concentrations of chlorhexidine promote irreversible bactericidal activity as the result of precipitation or coagulation of the cytoplasm, possibly caused by the interaction of chlorhexidine and phosphate entities such as adenosine triphosphate (ATP) and nucleic acids within the cytoplasm.

The applicant has presented some data based upon *in vitro* use of chlorhexidine lozenges (3 mg chlorhexidine as an antiseptic and 0.2 mg tetracaine as a local anaesthetic) on bacterial and virucidal activity in relation to the main microorganisms responsible for upper respiratory tract infections. These lozenges presented an antibacterial activity inducing significant (> 90%) destruction of the main upper respiratory tract pathogens after a 5-minute contact time at high concentration and after a 3-hour contact time after dilution. These lozenges also exerted an antiviral activity inducing 2 log (99%) destruction of the H1N1 virus after a 5-minute contact time at high concentration, with maintenance of this activity after dilution. Another study confirmed that chlorhexidine and a series of its analogues demonstrated antimicrobial activity against the Gram-negative and Gram-positive oral bacteria.

Resistance to chlorhexidine
A brief discussion of the acquired resistance to chlorhexidine in previously susceptible organisms has been provided in the overview and summary. Results of *in vitro* studies of the oral flora of patients receiving chlorhexidine gluconate topical oral solution in a clinical study indicated that after 6 months of treatment there are no clinically important changes in bacterial resistance or other adverse changes in oral flora and no evidence of overgrowth of potentially opportunistic organisms in the oral microbial ecosystem. At 3 months after discontinuance of the drug, bacterial counts in dental plaque returned to baseline levels and the extent of chlorhexidine-resistance in dental plaque bacteria was equal to baseline.

Safety Pharmacology
A brief discussion on the implications on non-clinical safety pharmacology with lidocaine hydrochloride, chlorhexidine dihydrochloride, and its combination in the literature in line with guidance in ICH S7A was provided. It is acknowledged that there is extensive clinical experience with both components of the final drug product.

Pharmacodynamic Drug Interactions
Lidocaine hydrochloride:
Lidocaine enhances cocaine seizure activity in rats and diazepam pre-treatment successfully antagonises the seizures induced by cocaine and lidocaine and raises the seizure threshold dose for the combination treatment by approximately four-fold. The results suggest that cocaine and lidocaine interact synergistically to increase seizure activity and that the nature of this response occurs in part through a depression of inhibitory neuronal transmission.

Pre-treatment with diazepam and clonazepam completely protect rats against lidocaine-induced convulsions. Phenobarbital also significantly decreases the incidence of both convulsions and prolongs their latencies. Carbamazepine does not completely repress both convulsions, but it prolongs their latencies.

Phenytoin and primidone markedly enhance both local anaesthetic-induced convulsions, as shown by shortening of latency and increase in mortality. Valproate protects against procaine-induced convulsions, while it strongly enhances lidocaine-induced convulsions.

Male Sprague Dawley rats weighing 200 to 300 g received intraperitoneal (i.p.) injections of cocaine and lidocaine, either alone or in combination. At doses of 30 or 40 mg/kg, lidocaine did not induce seizures or death. Lidocaine dramatically increased the incidence of both seizures and death caused by cocaine.

Lithium increases in potency of lidocaine-induced block of voltage-gated Na+ channels.

Dextromethorphan blocks sodium channels, the site of action of local anaesthetics administered dextromethorphan, and its active metabolite dextrorphan, and lidocaine subcutaneously to rats and tested them for cutaneous anaesthesia and drug-drug interactions. Dextromethorphan and dextrorphan had a local anaesthetic effect after cutaneous infiltration. A combination of dextromethorphan or dextrorphan with lidocaine produced an additive effect.

Chlorhexidine dihydrochloride
Nicotinic acid but not nicotinamide annulled the biocidal action of chlorhexidine.

Overall conclusion on pharmacology
The primary pharmacology of lidocaine and chlorhexidine has been reviewed adequately in the applicant's non-clinical overview. Limited discussion was provided to support potential secondary pharmacology and safety pharmacology effects, however given the extensive clinical experience with both components of the final drug product, the requirement for this data are largely superseded.

III.3 Pharmacokinetics
Lidocaine hydrochloride:
Absorption
Lidocaine is absorbed following topical administration to mucous membranes. The rate and extent of absorption is dependent upon concentration and total dose administered the specific site of application, and duration of exposure. In general, the rate of absorption of local anaesthetic agents following topical application occurs most rapidly after intratracheal administration.

When applied to the skin of rats in a vehicle consisting of 45% water, 45% isopropyl alcohol, and 10% glycerin, adequate cutaneous analgesia can be obtained.

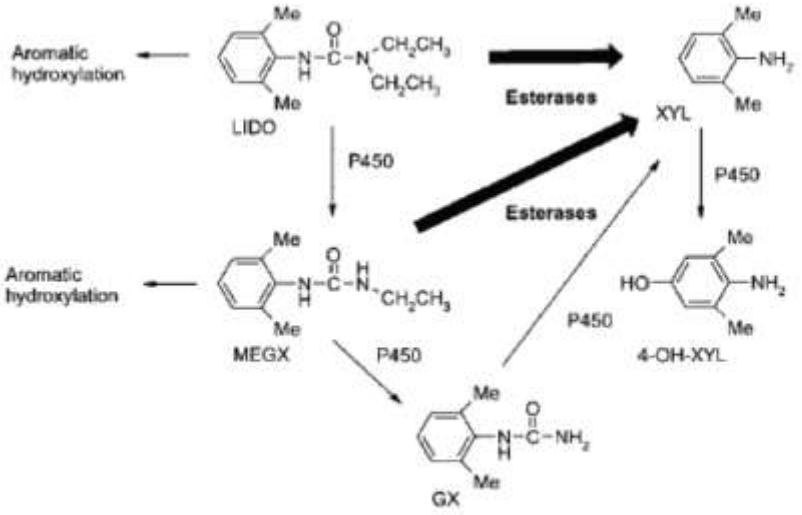
Distribution
When lidocaine hydrochloride was administered by intravenous (i.v.) injection over 60 seconds, the volume of the central compartment was greater in pregnant than in non-pregnant ewes, as was the volume of distribution at steady state. The volume of distribution during the terminal exponential phase of drug elimination and total clearance of lidocaine were also higher in pregnant animals.

Following administration of lidocaine in pregnant guinea pigs, it rapidly crosses the placenta. High concentrations are found in the foetal liver, heart and brain. High myocardial levels of drug in the fetus may possibly account for marked depressant effects that local anaesthetics produce.

The CSF binding of lidocaine is linear in a range from 50 to 500 μg/ml, and the mean unbound CSF fraction at a concentration of 100 μg/ml is 75.8 ± 7.7%. After intrathecal administration, the plasma concentrations are below the limit of quantitation.

Metabolism
Lidocaine is metabolised by the liver. Using microsomes isolated from male rat liver, it was shown that lidocaine is mainly metabolised by deethylation to N-(N-ethylglycyl)-2,6-xylidine (MEGX), and MEGX is mainly metabolised to N-glycyl-2,6-xylidine, also by deethylation. 3-Hydroxylidocaine is the major metabolite recovered from equine urine.

Figure 7: Hypothetical scheme for the metabolism of lidocaine (LIDO).



Abbreviations used are 4-OH-XYL, 4-hydroxy-2,6-xylocaine; MEGX, N-(N-ethylglycyl)-2,6-xylidine; GX, N-glycyl-2,6-xylidine. Bold arrows indicate deamidation via esterases. Taken from Alexson et al. 2002.

When deethylation of lidocaine by human and rat liver, lung, kidney and small intestine slices was compared on a protein basis, the activity was highest in liver slices, followed by the small intestine.

Samples of milk were obtained from bovines administered lidocaine during surgery. A breast milk sample was also obtained from a human donor who received 36 mg lidocaine during dental work. 2,6-dimethylaniline (2,6-DMA) was present at levels ranging from 14.5 to 66.0 ppb in bovine milk and was detected at 1.6 ppb in the human milk sample

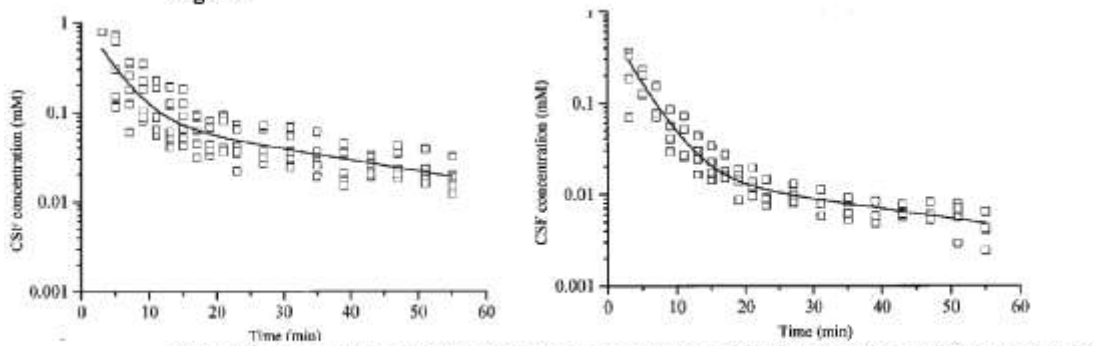
Excretion

After a 2 mg/kg i.v. bolus injection of lidocaine in newborn pigs the elimination half-life was 0.87-5.44 hours. Lidocaine pharmacokinetics in newborn pigs were dose-dependent at high plasma concentrations. At lower plasma concentrations, lidocaine pharmacokinetics were linear.

Intrinsic clearance of lidocaine was consistently reduced in the dog after repeated administration: from 1224 ± 859 ml/ min/kg at day 1 to 285 ± 104 ml/min/kg at day 10. Furthermore, hepatic tissue uptake of lidocaine and/or its metabolites was less on day 10 than on day 1.

Epidural and intrathecal disposition of intrathecally administered lidocaine in rabbits shows a biexponential decline:

Figure 8



Measured and population-predicted intrathecal concentrations of bupivacaine (left) and lidocaine (right) after separate intrathecal administration of equimolar dose (0.2 µM: 0.060 mg of BUP and 0.049 mg of LID) in rabbits. Taken from Clement et al. 1999.

Pharmacokinetic drug interactions
Interactions are reported with epinephrine (adrenaline) which potentiates and prolongs peripheral nerve block. In rats, lidocaine concentrations in serum were significantly increased after either paracetamol or propranolol administration. The combined therapy of propranolol and lidocaine resulted in a significant decrease in the total concentration and the percent protein binding of lidocaine in tissues.

Thilamylal is a moderate competitive inhibitor of lidocaine metabolism. Pentobarbital, diazepam and cimetidine weakly inhibit lidocaine metabolism formation in a concentration-dependent manner.

When studied in rabbits, mexiletine seemed to decrease the total plasma clearance of lidocaine, resulting in increased plasma lidocaine concentrations. Mexiletine significantly reduced the tissue distribution of lidocaine to the kidneys and lungs. A strong displacing effect of mexiletine on the binding of lidocaine to phosphatidylserine was observed *in vitro*.

Chlorhexidine dihydrochloride
Absorption
Although no accurate data have been published regarding the transdermal or oral bioavailability of the compound, it is known that chlorhexidine is virtually not absorbed when administered topically or when given orally. Following administration of chlorhexidine gluconate 0.12% topical oral solution as a mouthwash or rinse, approximately 30% of the drug is retained in the oral cavity.

It has been suggested that chlorhexidine is bound to the tooth surface, saliva, and oral mucosa and that the bacteriostatic and bactericidal effects of the drug in the oral cavity occur as the result of contact with bacteria that attach to these areas (tooth surface, saliva, and oral mucosa).

Distribution
No information on the distribution of chlorhexidine in animal models has been found in the published scientific literature. Therefore, human data are given as these are much more relevant to these applications.

Results of a pharmacokinetic study indicate that peak plasma chlorhexidine concentrations of 0.206 µg/ml are attained 30 minutes after ingestion of a 300-mg dose of chlorhexidine gluconate; however, the drug is undetectable in plasma 12 hour after the dose. Chlorhexidine binds tightly to saliva proteins.

Metabolism
No information on the metabolism of chlorhexidine is reported.

Excretion
Results of a pharmacokinetic study indicate that following ingestion of a 300 mg dose of chlorhexidine gluconate, approximately 90% of the dose is excreted in faeces via biliary elimination and less than 1% is eliminated in urine.

Pharmacokinetic drug interactions
There are no known pharmacokinetic drug interactions with chlorhexidine.

Overall conclusion on pharmacokinetics
The pharmacokinetic properties of both components have been reviewed adequately in the applicant's non-clinical overview. As these drug substances have been used extensively in the clinic the findings from non-clinical species are generally superseded by the human findings. There is a general lack of identification of combination study data from the literature, although this has been supported by relevant clinical use data.

III.4 Toxicology

The toxicology properties of lidocaine and chlorhexidine are discussed in detail in the applicant's non-clinical overview. The summaries of these findings are presented below.

Lidocaine hydrochloride:
General toxicity:
Acute toxicity studies are reported in rats and mice suggested the development of cardiovascular changes, central nervous system (CNS) effects (seizures, functional impairment, tonic-colonic seizures, shivering, neck extension and nystagmus). LD_{50}s range from 25 mg/kg (iv rat) to 335 mg/kg (subcutaneous rat).

Administration of 5-10 mg/kg of 2% lidocaine hydrochloride per day for 16 weeks intramuscular (i.m.) showed no toxic effect in dogs. In a 6-months study in rats, lidocaine hydrochloride 2% has been administered via i.m. injections at dosages of 5, 10, and 20 mg/kg once a day, five times a week. The trial showed that the 6-months treatment is well tolerated by rat; only the highest dosage (20 mg/kg) provokes an increase in the weight of the surrenal glands.

Mutagenicity:
The Ames test (*Salmonella* strains TA100 and TA98) with or without metabolic activation did not reveal any mutagenic potential of lidocaine. This was replicated in TA158 strain. The substance and metabolites do not exhibit mutagenic activity (in presence and absence of S9).

Carcinogenicity:
One of lidocaine's breakdown products in humans-2,6-dimethylaniline (2,6- DMA) has been identified as being "clearly carcinogenic" in experimental animals. Almost half a group of 112 rats exposed to the substance *in utero* and then fed 3 mg/kg food /day developed cancers in the nasal cavity and in other tissues.

In the hands of the references, lidocaine effectively inhibited the invasive ability of human cancer (HT1080, HOS, and RPMI-7951) cells at concentrations used in surgical operations (5-20 mM). The relevance of these findings in clinical practice remains to be established.

The oncogenic potential lidocaine when administered weekly via topical application to the dorsal skin of Tg.AC mice for 26 weeks was assessed. Lidocaine at a dose level of 162 mg/kg and at an application rate of 40.5 mg/cm^2/kg/week did not display any evidence of increase in dermal masses. Based on these results, lidocaine should be considered non-oncogenic in the Tg.AC mouse dermal model.

Reproductive toxicity:
Lidocaine has been shown not to be teratogenic when administrated at any stage of pregnancy. Epidural analgesia in pregnant women immediately prior to delivery with lidocaine 1.5% caused no adverse effect on baseline fetal heart rate, uterine activity, neonatal acid-base status and neuronal adaptive capacity.

The effects of lidocaine on fetal murine CNS development in pregnant mice has been investigated. Lidocaine was administered i.p. at gestational day 9 under light ether anaesthesia. On day 13 of gestation, the animals were killed by cervical dislocation. The dilation of the fourth ventricle was the most frequent anomaly observed with lidocaine, however doses up to 40 mg/kg did not reveal a major teratogenic effect.

The reproductive and teratogenic effects of lidocaine were studied in 155 Sprague- Dawley rats with subcutaneously implanted osmotic minipumps. Rats were exposed for 2 weeks to 3 different doses of lidocaine (100, 250 and 500 mg/kg per day). Only a reduction in mean fetal weight was observed upon of the highest dose (500 mg/kg) and was considered to be secondary to delayed fetal development. No significant adverse reproductive and teratogenic effects were found. These findings were further supported by other studies; however, it is also suggested that prenatal exposure to lidocaine may result in behavioural changes of offspring.

Pregnant Long-Evans hooded rats were dosed via injections into the gum. Offspring 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 gestational day 4 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 gestational day 11, 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 gestational day 18 was associated with a number of significant alterations of behaviour, including visual discrimination, shuttle box avoidance, tail flick, and water maze errors; there were also both vehicle and lidocaine effects on water maze latencies. These data suggest that lidocaine may be a behavioural teratogen and suggest that administration in later gestation in the rat may alter a broader range of behaviours than earlier in gestation.

An *in vitro* study was conducted to examine the teratogenic effects of lidocaine in rat embryos. Sprague-Dawley rats were explanted on gestational day 9 and were cultured in medium containing various concentrations of lidocaine. After 50 hour of culture they were evaluated for growth size and morphology, including neural tube closure. The results of the study indicated that lidocaine only causes teratogenic effects *in vitro* at concentrations much higher than clinically relevant.

Local tolerance:
No significant changes and concerns were raised from previous treatment of lidocaine from a variety of routes of administration, including topical (eyedrops, ointment), rectal, parenteral.

Chlorhexidine dihydrochloride
General toxicity:
Chlorhexidine, even at low concentrations, is toxic for a variety of eukaryotic cells. Acute pulmonary toxic effects of chlorhexidine were observed following intratracheal instillation in rats. Rats were exposed either to chlorhexidine at concentrations of 0.02% and 0.2% or to distilled water at a volume of 500 ml/kg body weight (bw). Chlorhexidine at concentration of 0.2% caused changes in haematological and biochemical values including white blood cell count, total protein, albumin, lactate dehydrogenase, blood urea nitrogen and creatinine, and induced inflammatory reactions including intra-alveolar oedema and haemorrhages, as well as resulted in the target organ concentration in lungs at the level of about 1.0 mg/g and maintained for more than one week, when administered intratracheally in rats.

Chlorhexidine diacetate was administered as an aerosol at concentrations of 0.10, 0.46 and 5.09 mg/l to rats for 4 hours for the low and mid concentrations. Complete mortality occurred at the high dose within 2 hours. Mortality was 100% (within 2 hours), 90% and 0% for high, mid, and low-doses, respectively. All surviving animals were observed for 14 days and recovered from the treatment related clinical effects. All test animals had discoloured lungs and in addition, for those that died, tracheas filled with mucous, corneal opacity, discoloured and gaseous distention of the gastrointestinal tract. LC_{50} was 0.30 mg/l and 0.43 mg/l for males and females, respectively. Direct lung effects are observed in a further study in which higher concentrations of chlorhexidine (0.1% and 1%), severe congestion to the alveoli and capillaries and perivascular and intra-alveolar haemorrhages were observed 1 day after exposure.

Sub-chronic toxicity data were submitted from a 13-week dermal toxicity study on New Zealand White rabbits that were treated topically. Minimal dermal irritation (erythema, oedema, desquamation and/or fissuring) was evident at the lowest dose tested. In addition, the finding of decreased enzyme activity, coupled with microscopically-observed degenerative changes in the liver are indicative of a hepatic effect in females at this dose level.

Mutagenicity:
A number of studies have been presented examining the potential mutagenicity effects of chlorhexidine. Mutagenic effects were not observed in 2 mammalian *in vivo* mutagenesis studies evaluating chlorhexidine gluconate. The highest daily dosages of chlorhexidine used in a mouse dominate lethal assay and a hamster cytogenetics test were 1000 and 250 mg/kg respectively. The results of several mutagenicity studies, including an Ames *in vitro* assay, a chromosomal aberration assay in Chinese hamster ovary cells, and an *in vivo* mouse micronucleus assay, did not show evidence that chlorhexidine has the potential to cause genetic toxicity.

Carcinogenicity:
No carcinogenicity has been reported with chlorhexidine during long-term toxicity studies in rats. The carcinogenic of chlorhexidine gluconate was studied in a 2-year drinking water study. Groups of 112 male and 112 female Wistar-derived specific pathogen-free rats were given chlorhexidine gluconate-dosed drinking water in concentrations of 5, 25, and 50 mg of chlorhexidine per kg of body weight per day. Chlorhexidine gluconate did not induce an increase in neoplasms.

Reproductive toxicity:
No published information on the effects on animal fertility is available, although the prescribing information of Periogard suggests that dosages up to 100 mg/kg daily have not revealed any evidence of impaired fertility in rats.

Developmental toxicity data were provided in a study using Sprague-Dawley rats that were dosed by gavage. From this study a maternal toxicity no observed effect level (NOEL) for orally-administered chlorhexidine diacetate was established at 15.63 mg/kg/day. Higher doses resulted in dose-related reduced body weight gain, rales, and increased salivation (lowest observed effect level [LOEL] of 31.25 mg/kg/day, and a highest dose tested [HDT] of 62.5 mg/kg/day). No observable malformations or developmental toxicity were found at any dose level tested. Assessment of the teratogenic effects of chlorhexidine in rat embryonic limb bud tissue cells *in vitro* showed that the fetal cells were highly susceptible to the toxic effects of chlorhexidine, but that there was no evidence of teratogenicity.

Local tolerance:
When applied topically, chlorhexidine has been shown to cause dermal irritation (erythema, oedema and dry skin). There is a linear, positive and strong association between concentrations of chlorhexidine and its irritant effects on rabbit nasal mucosa. It has been shown that 0.20 and 0.12% concentrations of chlorhexidine cause excess irritation on the nasal cavity; however, 0.06 and 0.03% concentrations of chlorhexidine gluconate are better tolerated.

Other toxicity studies
Studies on impurities
No discussion of the implication of impurities and excipients is provided in the non-clinical overview, and so much of the information discussed below originates from review of Modules 2.3 and 3.

Drug Substance:
No Class 1 solvents are used by the drug substance manufacturer during the manufacture of chlorhexidine dihydrochloride. Only ICH Class 2 solvent methanol is likely to be present, and the amount of methanol present in the final product is always well below the ICH limit for this solvent under option 1 which is 3000 ppm. An assessment of the route of synthesis, process controls and impurity profile has been performed in order to detect potential genotoxic impurities that can be formed during the synthesis of chlorhexidine dihydrochloride. It is concluded that impurities derived from manufacture of chlorhexidine dihydrochloride is in line with ICH M7 and CHMP guidance for genotoxic impurities.

Drug Product:
All excipients are controlled to the relevant Ph. Eur specifications/monographs, with the exception of lemon flavouring (501050 AP0551). The composition of the lemon flavour is supplied. There are no novel excipients used.

No toxicological concerns are raised in respect to use of excipients.

Elemental impurities:
No concerns are raised in respect of impurities arising from the drug substances, lidocaine hydrochloride or chlorhexidine dihydrochloride, the manufacturers are compliant with respective Ph Eur monographs and impurity limits and residual solvents are adequately justified.

Concerning the drug product, a number of impurities for both active substances produce impurities at levels above qualification thresholds. The use of excipients has been adequately justified and raises no new concerns for safety.

The applicant has supplied *in silico* assessments for impurities. The results of this analysis were negative for potential genotoxicity. In addition, a risk assessment on Elemental Impurities for the drug product was provided in accordance with the ICH Q3D guideline on elemental impurities.

III.5 Ecotoxicity/environmental risk assessment (ERA)
A satisfactory environmental assessment has been provided.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that these are bibliographic applications for products containing active ingredients of well-established use.

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS
IV.1 Introduction
Chlorhexidine dihydrochloride and lidocaine hydrochloride are well-established active substances. The details of the pharmacokinetics of the two active substances are documented in various publicly accessible sources that the applicant has adequately summarised in the clinical overview. The applicant did not conduct any new research or provide any new data. This is acceptable.

The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
Chlorhexidine
Absorption
Although no accurate data have been published regarding the transdermal or oral bioavailability of the compound, it is known that chlorhexidine is poorly absorbed when administered topically or when given orally.

Following administration of chlorhexidine gluconate 0.12% topical oral solution as a mouthwash or rinse, approximately 30% of the drug is retained in the oral cavity. Chlorhexidine gluconate is bound to phosphate groups principally on the coatings of mucous membrane surfaces and is then gradually released into oral fluids for up to 24 hours. After topical application to intact skin, chlorhexidine gluconate is adsorbed onto the outer layers of the skin resulting in a persistent (residual) antimicrobial effect on the skin.

Distribution
Peak plasma chlorhexidine concentrations of 0.206 μg/ml were attained 30 minutes after ingestion of a 300 mg dose, but the drug was undetectable in plasma 12 hours after the dose.

Chlorhexidine tightly binds to saliva proteins. It was shown that chlorhexidine is stable in the oral cavity for at least 9 hours and high concentrations of the drug (2 μg/ml total) are still present in saliva even after 8 hours from mouth rinsing.

Metabolism and Elimination
Chlorhexidine does not accumulate in the body and is only minimally metabolised. The known chemical breakdown product of chlorhexidine, p-chloroaniline, could not be detected in any urine sample examined from species treated orally with [14C]-chlorhexidine, including a human volunteer. Any chlorhexidine absorbed percutaneously following topical application to the skin appears to be mainly excreted unchanged in faeces.

Following ingestion of a 300 mg dose of chlorhexidine gluconate, approximately 90% is excreted in faeces via biliary routes and less than 1% is eliminated into urine.

Lidocaine
Absorption
Lidocaine is readily absorbed from the gastrointestinal tract, from mucous membranes and through damaged skin. Absorption through intact skin is poor. Pharmacologically active plasma concentrations are not achieved after oral administration of 250 or 500 mg of the drug, but toxic effects may appear, probably due to the toxicity of the metabolites. Toxicity has been associated with plasma lidocaine concentrations greater than 5 μg/ml. A study investigated the pharmacokinetic profile of a lidocaine-containing gel used for pain relief in association with periodontal probing and scaling/root planning. The total dose applied per adult patient was 0.9 to 3.5 g of lidocaine/prilocaine 5% gel. The absorption of lidocaine was rapid, with peak plasma concentrations occurring 20–40 minutes, after the start of application of the gel. The lidocaine C_{max} was in the range of 99–266 ng/ml.

Applications of high lidocaine concentrations on the oral mucosa during topical lidocaine spray anaesthesia can lead to significant plasma concentrations in children or when applied repeatedly as a viscous solution. However, it has to be mentioned that in a study applied mean dose levels of lidocaine ranged from 48 to 720 mg.

Although no plasma concentrations within the therapeutic range (1.5-5.5 μg/ml) were obtained, slightly increased plasma concentrations of lidocaine were seen in bone marrow transplantation patients with high-grade oral mucositis: rinsing the mouth with 5 ml of a 2% lidocaine solution for 1 minute resulted in maximum plasma lidocaine levels of approximately 0.2 μg/ml. In healthy controls, however, no detectable plasma lidocaine levels were noted.

The anaesthetic effect of lidocaine after topical use appears 2 to 5 minutes after application and lasts 30 - 45 minutes. The anaesthetic effect is limited to the surface and does not extend to the submucosal structures. In general treatment with local anaesthetics causes the sensation of pain to disappear first followed by the sensation of temperature, touch, deep pressure, and finally motor function.

Given the amount of lidocaine in medicinal products (oromucosal spray: chlorhexidine gluconate 2 mg/ml / lidocaine HCl 0.5 mg/ml; lozenges: chlorhexidine HCl 5 mg / lidocaine HCl 1 mg) and the limited extent of their application, it seems impossible to reach systemic concentration of lidocaine close to therapeutic levels.

Distribution
Lidocaine that reaches the systemic circulation readily crosses the blood-brain barrier and the placenta and is distributed into milk (from a sample obtained 2 hours earlier).

Lidocaine in the systemic circulation is widely distributed into body tissues, initially into highly perfused tissues such as kidneys, lungs, liver and heart, followed by redistribution into skeletal muscle and adipose tissue. Binding to plasma proteins is variable and concentration dependent.

Metabolism and Elimination
Lidocaine undergoes extensive first-pass hepatic metabolism and bioavailability is about 35% after oral administration. Lidocaine has an initial half-life of 7-30 minutes and a terminal half-life of 1.5-2 hours.

About 90% of a given dose of lidocaine is deethylated to monoethylglycinexylidide (MEGX) and glycinexylidide (GX). Both metabolites are pharmacologically active; there elimination half-lives are 2 hours and 10 hours, respectively. Further cleavage of the amide bond forms the metabolites xylidine and 4-hydroxy-xylidine.

In humans the main metabolic pathway of lidocaine is sequential N-deethylation to MEGX and GX. Both metabolites can be hydrolysed to xylidine, which is then oxidized to 4-hydroxy-xylidine, the main metabolic product found in urine. A second, minor biotransformation pathway involves hydroxylation at the aromatic ring to form 3-hydroxy-lidocaine. Cytochrome P450 (CYP) 1A2 is the enzyme principally responsible for the metabolic disposition of lidocaine in subjects with normal liver functions.

Because CYP3A5 exhibits an overlapping substrate specificity with that of CYP3A4, it may contribute to the metabolic clearance of CYP3A substrates in people carrying the wild-type *CYP3A5*1* allele. Based on the experimental results, CYP3A5 was more active than CYP3A4 in catalysing lidocaine demethylation (1.4-fold). The authors suggest that, under conditions when CYP3A5 content represents a significant fraction of the total hepatic CYP3A pool (represented by the presence of at least one copy of the wild-type *CYP3A5*1* allele), the contribution of CYP3A5 to the clearance of lidocaine be an important source of interindividual variability.

Metabolites are excreted in the urine and less than 10% of a dose is excreted unchanged. Renal impairment does not affect the clearance of lidocaine, but accumulation of its active metabolites can occur.

No bioequivalence studies have been submitted. The Applicant is not claiming essential similarity to other products. This is acceptable.

The pharmacokinetics of lidocaine and chlorhexadine are well known and a satisfactory description of the individual components has been provided. The pharmacokinetics of special populations has been discussed.

IV.3 Pharmacodynamics

Chlorhexidine is regarded as the oral antiseptic par excellence. One of its principal advantages, in addition to its powerful antimicrobial action, is its ability to bind to a variety of substrates while maintaining its antibacterial activity; it is then slowly released, leading to the persistence of effective concentrations. This property is called substantivity.

Chlorhexidine is a bisbiguanide antiseptic and disinfectant that is bactericidal or bacteriostatic against a wide range of Gram-positive (e.g. *Micrococcus* sp., *Staphylococcus* sp., *Streptococcus* sp., *Bacillus* sp.*)* and Gram-negative bacteria. It is more effective against Gram-positive than Gram-negative

bacteria, and some species of *Pseudomonas* and *Proteus* have low susceptibility. It is relatively ineffective against mycobacteria and inactive against bacterial spores at room temperature.

Chlorhexidine is active against some fungi and inhibits some viruses. Chlorhexidine appears to have antiviral activity against viruses that have a lipid component in their outer coat or have an outer envelope. Although the clinical importance is unclear, there is some evidence that chlorhexidine has *in vitro* activity against i.e. human immunodeficiency virus (HIV), herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and influenza virus (AHFS 2011). In addition, it has an antimycotic activity against dermatophytes and yeasts.

One study confirmed that the value of chlorhexidine lozenges (Drill®lozenges containing 3 mg chlorhexidine digluconate as an antiseptic and 0.2 mg tetracaine as a local anaesthetic) in the treatment of upper respiratory tract infections such as sore throat. The short-term (5 minutes) and long-term (3 hours) bactericidal activities against the main pathogens responsible for upper respiratory tract infections were determined according to the guidelines of NF EN 1040 and 14476, which defines a logarithmic reduction for a defined contact time. The test product concentrations corresponded to 90%, 50%, 10% and 1% (v/v) of stock solution prepared in artificial saliva to mimic the conditions of use without the effect of the antimicrobial agents present in saliva. The results are presented in Table 3.

Table 3: Antimicrobial and antiviral efficacy of lozenges containing chlorhexidine and tetracaine as a local anaesthetic.

	5 minutes	3 hours
S. aureus	90 % > 90 %	–
	50 % < 90 %	50 % > 99.999 %
	–	10 % < 90 %
S. pneumoniae	90 % > 99.99 %	–
	50 % > 99.99 %	50 % > 99.99 %
	–	10 % > 99.99 %
S. pyogenes	90 % > 99.99 %	–
	50 % > 99.99 %	50 % > 99.999 %
	–	10 % < 90 %
F. nucleatum	90 % > 99.999 %	–
	50 % > 99.99 %	50 % > 99.999 %
	–	10 % > 99.99 %
H. influenzae	90 % > 99.999 %	–
	50 % > 99.999 %	50 % > 99.999 %
	–	10 % > 99.9 %
B. catarrhalis	90 % > 99.99 %	–
	50 % > 99 %	50 % > 99.999 %
	–	10 % > 99.999 %
H1N1 virus	80% > 99%	–
	50% > 99%	50% > 99.99%
	–	10% > 99%

The results obtained in artificial saliva showed percentage reductions greater than 90% after only 5 minutes of contact with the highest concentration (90%) and greater than 99% for five of the six microorganisms tested when with the 50% solution. The limiting microorganism was *S. aureus*. When the stock solution was diluted to 50% (simulation of dissolution in the mouth) and after 3 hours of contact, an intense bactericidal activity (> 4 log reduction) was observed for the 6 test microorganisms and the bactericidal activity was still detectable in relation to four microorganisms with the 10% solution. The results obtained on the H1N1 strain indicated reductions greater than 99% (> 2 log) in the presence of 80% and 50% solutions for a contact time of 5 minutes. A greater than 99.99%

reduction (> 4 log) was observed at the 50% concentration with a 3-hour contact time. The antiviral activity (greater than 99% reduction) was maintained with the 10% solution by increasing the contact time to 3 hours. These *in vitro* tests indicate a significant and homogeneous antibacterial activity on all microorganisms tested, both Gram+ and Gram− species, and confirm the value of chlorhexidine lozenges in the treatment of upper respiratory tract infections such as sore throat. On the basis of the very similar composition, Chlorhexidine hydrochloride 5 mg / lidocaine hydrochloride 1 mg lozenges and Drill®lozenges and should have identical activity profiles.

The antibacterial activity is the result of attraction between positively charged chlorhexidine and negatively charged bacterial cell surfaces. Chlorhexidine becomes adsorbed onto the cell surfaces of susceptible organisms, with specific and strong adsorption to certain phosphate containing compounds. This disrupts the integrity of the cell membrane and results in increased permeability.

At low concentrations, chlorhexidine usually exerts a bacteriostatic effect as the result of efflux of small molecular weight substances (e.g. potassium, phosphorus). This effect may be reversible as removal of excess chlorhexidine by neutralizers may allow the bacterial cell to recover. In this regard, a combination of 3% Tween 80 and 0.3% L-alpha-lecithin has been found the most effective inactivating agent, allowing full recovery of the test organisms (*Enterococcus faecalis*) in the presence of chlorhexidine.

Higher concentrations of chlorhexidine promote irreversible bactericidal activity. Studies confirmed that outer membrane disruption is the lethal event in chlorhexidine action. The inner membrane was not ruptured, but its functionality was breached and there was an inhibition of active uptake of small molecules.

The anti-infective activity of chlorhexidine varies depending on pH; the drug is most active at a neutral or slightly acidic pH (i.e., 5.5–7). Unlike iodine-containing disinfectants, the anti-infective activity of chlorhexidine is not reduced by the presence of organic matter.

In addition to immediate anti-infective activity against susceptible organisms, chlorhexidine has persistent or residual anti-infective activity when used topically (e.g. on the skin, in the oral cavity). Chlorhexidine gluconate is bound to phosphate groups principally on the coatings of mucous membrane surfaces and is then gradually released into oral fluids for up to 24 hours. It has been suggested that chlorhexidine is bound to the tooth surface, saliva, and oral mucosa and that the bacteriostatic and bactericidal effects of the drug in the oral cavity occur as the result of contact with bacteria that attach to these areas (tooth surface, saliva, and oral mucosa).

The *in vivo* antimicrobial activity of 0.12% and 0.2% chlorhexidine on the salivary flora was evaluated with 15 volunteers. The 0.2% chlorhexidine mouthwash had the greatest antimicrobial activity on the salivary flora up to 7 hours after its application, with a progressive recovery in bacterial vitality. The differences observed with respect to the 0.12% chlorhexidine mouthwash demonstrate the influence of the concentration on its immediate antimicrobial activity and substantivity.

A study investigated the influence of intrinsic and extrinsic factors on the *in vivo* antimicrobial activity of chlorhexidine gluconate on the salivary flora in 10 volunteers. With regard to the intrinsic factors, comparison of the 0.12% and 0.2% concentrations of chlorhexidine gluconate showed greater substantivity with 0.2% chlorhexidine gluconate; an increase in the volume of the mouthwash (from 10 ml to 15 ml) did not affect the antimicrobial activity on the salivary flora for up to 7 hours after application, whereas increasing the duration of the mouthwash (from 30 seconds to 1 minute) produced a marked increase in substantivity.

One study determined the *in vivo* antimicrobial activity of different forms of application of chlorhexidine digluconate. A group of 10 volunteers performed mouth rinsing with a 0.2% and 0.12% solution of chlorhexidine digluconate and applied chlorhexidine digluconate in the form of a 0.2% gel, a 0.2% and a 0.12% spray and a swab impregnated with a 0.2% solution. The 0.2% solution of chlorhexidine digluconate had the greatest sustained antimicrobial effect on the salivary flora, confirming the influence of the concentration and form of application on chlorhexidine substantivity. Chlorhexidine should be considered not only as an antimicrobial agent, since it has also anti-inflammatory potential in neutrophil inflammatory processes.

Lidocaine
When applied locally to nerve tissue in appropriate concentrations, local anaesthetics such as lidocaine reversibly block the action potentials responsible for nerve conduction. They block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na+ that is normally produced by a slight depolarisation of the membrane. This action of local anaesthetics is due to their direct interaction with voltage-gated Na+ channels.

Local anaesthetics such as lidocaine block the generation and conduction of impulses through all nerve fibers – sensory motor and autonomic. Small nerve fibers are generally more susceptible to the effects of local anaesthetics than are larger ones. In general, autonomic activity is affected first, followed by loss of pain and other sensory functions and, finally, loss of motor activity. Regression of anaesthesia usually occurs in the reverse order.

Typically, the clinically relevant modulators (such as lidocaine) of voltage-gated sodium channels result in a complex inhibition of voltage-gated sodium currents, producing both tonic and phasic (use dependent) block of sodium currents that often involves negative shifts in the voltage-dependence of steady-state inactivation, indicative of enhanced binding to inactivated channels.

Lidocaine hydrochloride is a local anaesthetic of the amide type. Like other local anaesthetics, it blocks conduction of nerve endings impulses in a reversible way by interfering with processes fundamental to generation of nerve action potential, namely, large transient increase in permeability of membrane to sodium ions that is produced by slight depolarisation of membrane. Local anaesthetics also reduce permeability of resting nerve to potassium as well as to sodium ions. As the anaesthetic action progressively develops in nerve, the threshold for electrical excitability gradually increases and the safety factor for conduction decreases; when this action is sufficiently well developed, block of conduction is produced. In addition to blocking conditions in nerve axons in peripheral nervous system, local anaesthetics interfere with function of all organs in which conduction or transmission of impulses occurs. Effects on central nervous system (CNS), autonomic ganglia, neuromuscular junction, and all forms of muscle fibre can also be observed.

Surface or topical anaesthesia blocks the sensory nerve endings in the skin or mucous membranes. Lidocaine is used in a variety of formulations for surface anaesthesia. Examples of lidocaine containing products include i.e ointments for anaesthesia of skin and mucous membranes, gels for anaesthesia of the urinary tract, or topical solutions/preparations for surface anaesthesia of mucous membranes of the mouth and throat in the case of painful conditions of the mouth and throat. Lidocaine is also a class Ib anti-arrythmic agent.

Description of the PD of the single components and the combination has been provided.

IV.4 Clinical efficacy

No new clinical studies have been submitted. Since these applications have been submitted as a 10a (well-established use), the evidence of use, efficacy and safety of the proposed combination in EU for at least ten years was provided and is considered acceptable.

A number of studies with the individual actives have been presented. However, for the scope of these applications, only studies with the combination of lidocaine and chlorhexidine at the proposed posology are assessed.

SUPPORTIVE STUDIES

The applicant has provided the following supportive studies.

- *Efficacy and safety of chlorhexidine-lidocaine versus placebo in adult patients with acute pharyngitis* (study 1)
- *Echinacea/sage or chlorhexidine/lidocaine for treating acute sore throats: a randomized double-blind trial (study 2)*

Study 1

This was a double-blind, placebo-controlled phase III study to compare the efficacy and safety of a lemon-flavored lozenge formulation (Medica®) containing a combination 5 mg chlorhexidine (dihydrochloride) with 1 mg lidocaine (hydrochloride).

After bacterial infection was ruled out using the McIsaac score and completion of a Rapid Antigen Strep Test (RAST), 209 patients were randomised. The study was registered and approved by the relevant ethical committees (Danish Health and Medicines Authority, French National Drug Safety Agency and the Ministry of Labour, Health and Social Affairs of Georgia). The study was conducted in six centres located in Denmark, France and Georgia, and consisted of: a 2-hour stationary phase followed by a 4-day ambulatory phase. Patients were allowed to take up to a maximum of 10 lozenges per day.

Throat pain and dysphagia were assessed on visual analogue scales (VAS) and therapeutic response was evaluated in terms of reduction in Tonsillopharyngitis Severity Score (TSS). Pain relief and quality of life were also evaluated, as was product safety.

Combined chlorhexidine and lidocaine was found to be superior to placebo regarding several of the parameters investigated, particularly sore throat and erythema. During the ambulatory phase, the significance level was reached for sore throat improvement.

Study population

Patients were recruited by an ear, nose & throat (ENT) specialist, a general practitioner in Paris (France), and ENT specialists at four investigational centres in Tbilisi (Georgia). The study was registered and approved by the relevant ethical committees (Danish Health and Medicines Authority, French National Drug Safety Agency and the Ministry of Labour, Health and Social Affairs of Georgia). The study was carried out in accordance with the ethical requirements of the Declaration of Helsinki.

Inclusion criteria were age >18 years; acute non-bacterial pharyngitis or an erythematous viral sore throat within 72 hours before the inclusion date, absence of bacterial infection (McIsaac score < 2 and Rapid Strep Test (RST) negative), TSS ≥ 5, and provision of written informed consent.

Non-inclusion criteria included the presence of peritonsillar or retro-pharyngeal abscess, pseudomembranous pharyngitis, other causes of dysphagia or pharyngitis, and pregnancy or lactation. Non-inclusion criteria relating to treatment comprised: use of oral or local steroidal or non-steroidal anti-inflammatory drugs, of analgesic or anaesthetic agents during the 48 hours prior to enrolment, or of antibiotic therapy during the 14 days before the inclusion date.

Efficacy Endpoints

The efficacy endpoints for the study were as follows: area under the change-over-baseline curve (AUC) for throat soreness and dysphagia from 0 to 2 hours. Change over baseline in sore throat relief (on a 7-point scale) at 120 minutes after the first dose; comparison between the two groups from day 1 to day 4 for change in VAS score for sore throat and dysphagia; comparison of therapeutic response (reduction at D4 by 50% versus baseline TSS score) between the two groups; quality-of-life score (total score by adding up each 4-point score for the following parameters: soreness, swallowing, talking, sleeping, eating, reading, speaking) noted in the patients' self-assessment questionnaires.

Efficacy results

VAS evaluation of sore throat

At baseline, the mean VAS score for sore throat was 61.7 ± 15.5 in the active treatment group versus 62.5 ± 14.1 in the placebo group. After 120 minutes, throat soreness significantly improved in the active treatment group versus the placebo group (42.4 ± 20.8 versus 48.5 ± 17.2), as did the mean change over baseline (19.3 ± 20.0 vs. 14.0 ± 16.8; $p<0.05$) (Figure 3).

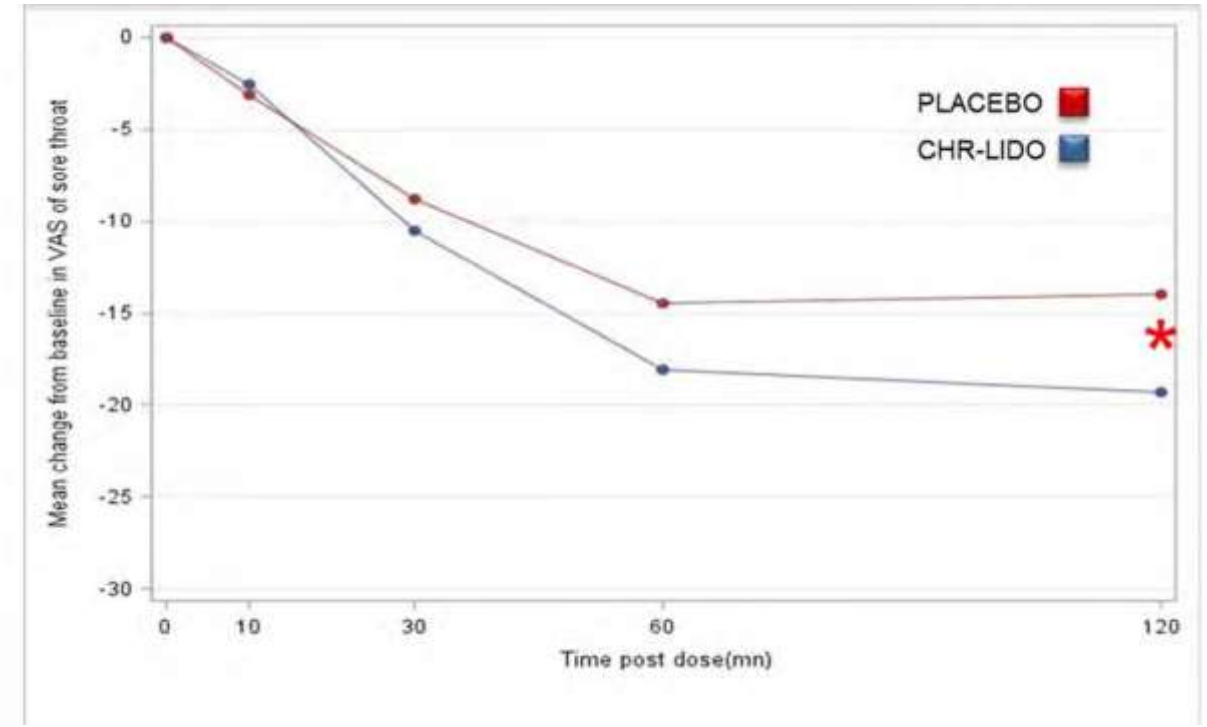


Figure 3. Sore throat – Visual Analogue Scale Mean changes from baseline to 120' (* significant p =0.05)

The AUC for change over baseline between 0 and 120 minutes showed improvement close to significance in the active treatment group versus placebo (1694.6 ± 1867.5 versus 1339.7 ± 1660.3; p=0.09).

The mean AUC for change over baseline between D1 and D4 was significantly improved in the active treatment group compared to the placebo group (92.0 ± 60.8 vs. 74.4 ± 84.6; p=0.04). At D4, mean change over baseline showed significant improvement in the active treatment group versus placebo (51.4 ± 21.0 versus 44.0 ± 23.1; p<0.002).

VAS evaluation of dysphagia

At baseline, the mean VAS score for dysphagia was 53.6 ± 18.3 in the active treatment group versus 52.9 ± 18.5 in the placebo group. There was no significant difference between the active treatment group versus. the placebo group (34.2 ± 21.4 vs. 37.7 ± 19.3), either after 120 minutes or in terms of mean change over baseline (19.1 ± 21.8 vs. 15.1 ± 18.3). The AUC of change over baseline between 10 and 120 minutes showed no significant improvement in the active treatment group versus placebo (1816.9 ± 2200.3 versus 1452.8 ± 1885.7).

The mean AUC for change over baseline between D1 and D4 was almost significantly improved in the active treatment group compared to the placebo group (89.8 ± 63.0 versus 70.8 ±79.9; p=0.08). At D4, mean change over baseline showed significant improvement in the active treatment group versus the placebo group (46.5 ± 21.8 versus 40.9 ± 23.7; p=0.05).

Tonsillopharyngitis Severity Score (TSS)

At baseline, distribution was not significantly different between the two groups for overall score or for any component of TSS.

The mean change in total TSS score between baseline and D4 demonstrated a significant improvement in the active treatment group compared to the placebo group (5.4 ± 2.3 vs. 4.4 ± 2.5; p<0.002).
The mean change in sore throat between baseline and D4 showed significant improvement in the active treatment group versus the placebo group (1.7 ± 0.8 vs. 1.4 ± 0.8; p<0.001) as evidenced by dysphagia (1.7 ± 0.7 vs. 1.4 ± 0.9; p<0.02) and erythema (1.6 ± 0.9 vs. 1.2 ± 0.9; p<0.001) (Figure 4).
There was no difference regarding secretions.

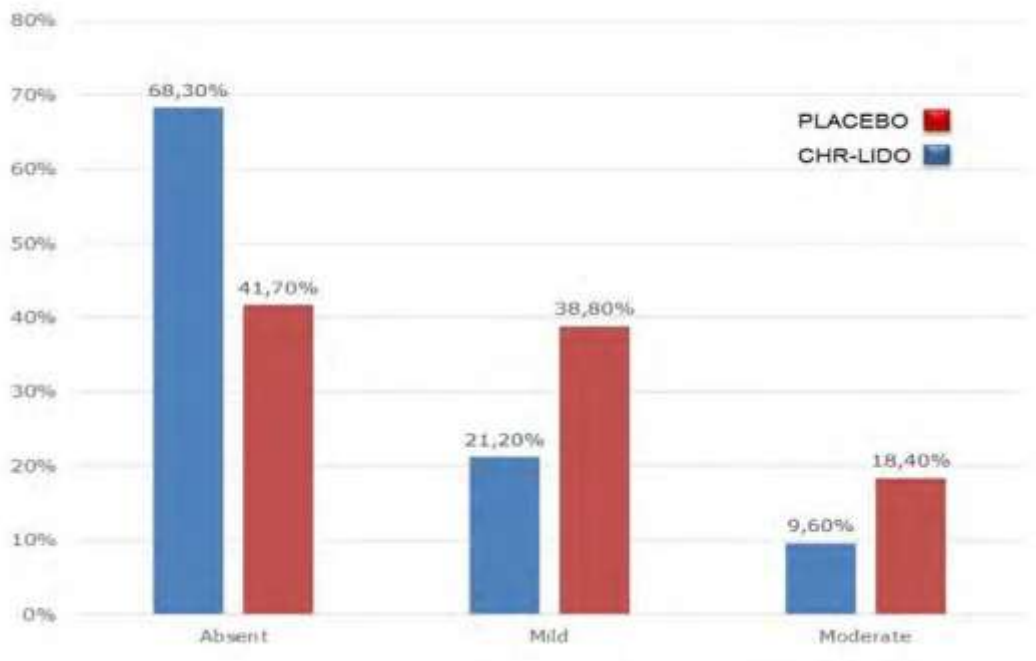


Figure 4. TSS - Evaluation of Throat erythema at day 4.

Pain attenuation

Pain attenuation was evaluated at day 1, 120 minutes after administration of the first dose of study drug. The active treatment significantly reduced pain compared to the placebo; 53.9% of patients presented moderate or total pain attenuation in the active treatment group versus 35.6% in the placebo group (p<0.01) (Figure 5).

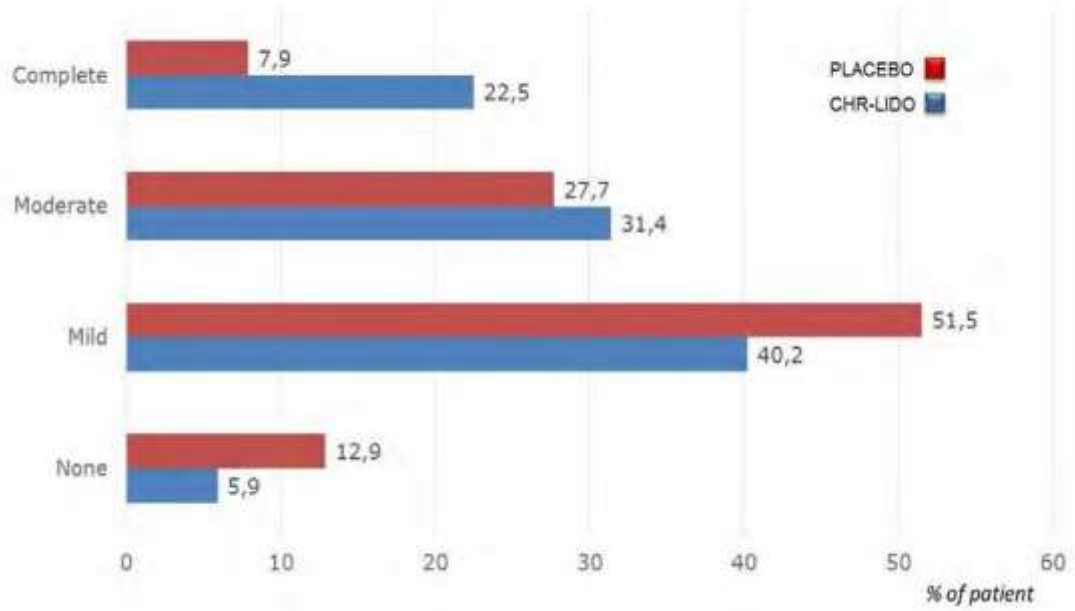


Figure 5. Evaluation of pain attenuation at day 1.

Quality of Life

The mean of change over baseline in total score (Figure 4) showed significant superiority in the active treatment group versus placebo at Day 2 (2.4 ± 2.2 vs 1.9 ± 2.0, p=0.01), Day 3 (4.8 ± 3.1 vs 4.2 ± 2.9, p<0.02) and Day 4 (6.2 ± 3.6 vs 5.5 ± 3.7, p<0.005). At day 4, all quality-of-life parameters evaluated exhibited improvement (p < 0.05).

Figure 6: Total score improvement of quality of life Mean change of the total score D2, D3 and D4 compared to baseline.

Assessor's comment
The results of the study presented above showed statistical differences for the chlorhexidine/lidocaine (5mg/1mg) combination compared to placebo between D1 and D4 for sore throat (no statistically difference was noted at 120), at D4 for dysphagia and general pain attenuation for the combination compared to placebo.

This study supported the efficacy of the combination lidocaine/chlorhexidine for the treatment of sore throat, dysphagia or pharingytis in adults affected by acute non-bacterial pharyngitis or an erythematous viral sore throat.

Study 2
This was a multi-centered, randomised, double blind, double-dummy controlled trial carried out in eleven general practices in Switzerland. A total of 154 patients (133 analysed in per protocol collective) at least 12 years old with acute sore throat present for not more than 72 hours prior to inclusion and with a throat score ≥6 participated in the study. They used either an echinacea/sage spray or a chlorhexidine/ lidocaine spray with two puffs every 2 hours, in a double dummy blinded manner, up to 10 times daily until they were symptom-free, for a maximum of 5 days. The main outcome measures were the comparison of response rates during the first three days. A response was defined as a decrease of at least 50% of the total symptoms compared to baseline.

Results: The echinacea/sage treatment exhibited similar efficacy to the chlorhexidine/lidocaine treatment in reducing sore throat symptoms during the first 3 days ($P(x<Y) = 0.5083$). Response rates after 3 days were 63.8% in the echinacea/sage group and 57.8% in the chlorhexidine/lidocaine group. For all secondary parameters, such as time to becoming symptom free, throat pain, and global assessments of efficacy by the physician and patient, no difference between the two treatments was seen. They were both very well tolerated.

Conclusion
An echinacea/sage preparation is as efficacious and well tolerated as a chlorhexidine/lidocaine spray in the treatment of acute sore throats.

Assessor's comment
Patients were followed for 5 days and showed no differences between the 2 formulations. However, in 5 days a simple viral sore throat could resolve spontaneously. Without a placebo arm it is impossible to comment on the efficacy of the 2 proposed treatments. Therefore, this study is not considered supportive for these applications.

Clinical studies in special populations
Studies in special population have not been presented.

Overall conclusion on clinical efficacy
Evidence of efficacy of the combination chlorhexidine/lidocaine (5mg/1mg) at the proposed posology in the treatment of sore throat, dysphagia or pharingytis in adults affected by acute non-bacterial pharyngitis or an erythematous viral sore throat has been demonstrated.

IV.5 Clinical safety

Combination chlorhexedine/lidocaine
No serious adverse events (SAE) were reported during the study. Of the 209 treated patients, 33 (15.8%) reported at least one adverse event suspected to be related to the investigational product, i.e.

17 (16.2%) in the active treatment group and 16 (15.4%) in the placebo group, but without any statistically significant differences between the groups.

Chlorhexidine

Generalised Reactions

Allergic reactions, hypersensitivity and anaphylaxis to chlorhexidine have been reported but are extremely rare. Hypersensitivity reactions including anaphylactic shock have been reported following topical applications of chlorhexidine. Reactions may occur via contact with the (damaged) skin and mucous membranes, from the use of chlorhexidine-containing lubricants for urinary catheterization or cystoscopy, impregnated central venous catheters, or from chlorhexidine impregnated medical devices including implanted surgical mesh. Routinely allergy testing is recommended when symptoms during medical interventional procedures, e.g. local and general anaesthesia, are investigated.

The incidence of skin sensitivity to chlorhexidine is estimated at 2% in various patient groups. A case of urticaria due to oral use of chlorhexidine has been reported. Occupational asthma has been attributed to an alcoholic chlorhexidine spray.

Irritative Skin Reactions

Chlorhexidine is poorly absorbed from skin. Therefore, most effects noted have been primarily local. If a low concentration solution applied to the skin, mild local irritation can be seen. Contact dermatitis, urticaria, and anaphylaxis have followed repeated skin exposures to this agent. Allergic contact dermatitis from chlorhexidine is rare.

Discoloration

The use of chlorhexidine dental gel and mouthwash has been associated with reversible discoloration of the tongue, teeth and silicate or composite restorations. Chlorhexidine used in mouthwashes may also enhance dental staining by tea.

Taste

Transient disturbance of taste sensation and a burning sensation of the tongue-tip irritation may occur on initial use of chlorhexidine gluconate mouth rinses.

Oral Desquamation and Parotid Gland Swelling

Oral desquamation and occasional parotid gland swelling have been reported with chlorhexidine containing mouthwash. If desquamation occurs, 50% dilution of the mouthwash with water and less vigorous rinsing may allow continued use.

Other Effects

The oral LD50 of chlorhexidine gluconate exceeds 3 g/kg in male and female rats and 2.5 or 2.6 g/kg in male or female mice, respectively. The i.v. LD50 of chlorhexidine gluconate is 21 mg/kg in male rats, 23 mg/kg in female rats, 25 mg/kg in male mice, and 24 mg/kg in female mice. The subcutaneous LD50 of chlorhexidine gluconate exceeds 1 g/kg in male and female rats, 637 mg/kg in male mice, and 632 mg/kg in female mice. The estimated oral LD50 for chlorhexidine gluconate in humans is 2 g/kg. Chlorhexidine is one of the most effective antiseptics currently in use for the prevention of damaged skin infection. However, *in vitro* data have suggested that chlorhexidine inhibit normal cell proliferation (and this may also be true for other less effective antiseptics).

There have been reports of patients who suffered burns following uncontrolled ignition of chlorhexidine-alcohol during surgery and of corneal damage in patients after accidental ocular exposure to chlorhexidine solution.

Sensorineural deafness has been reported in patients who received direct application of a 0.05% chlorhexidine solution in 70% alcohol for perioperative disinfection of the ear prior to vascular myringoplasty. The solution apparently penetrated into the inner ear, causing damage to the cochlea.

Lidocaine
Adverse experiences following the administration of lidocaine are similar in nature to those observed with other amide local anaesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by excessive dosage or rapid absorption, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature.

A study investigated a lidocaine-containing gel used for pain relief in association with periodontal probing and scaling/root planning. Peak plasma concentrations of lidocaine (99–266 ng/ml) were low compared to those reported to cause initial signs of CNS toxicity (5000-6000 ng/ml). Side effects reported were mild local effects of short duration; no signs of systemic toxicity or mucosal irritation were seen.

Despite its widespread and frequent use, adverse effects to lidocaine are uncommon. A study reported that the global tolerability of a newly developed lidocaine 8 mg lozenge formulation was rated as "good" or "very good" in the majority of cases and that the number of study drug related adverse events was low and evenly distributed to both treatment group and placebo group. Medications recommended as first-line treatments for neuropathic pain include topical lidocaine. The primary advantage of this treatment approach is that it is very well tolerated—the most common side effects are mild local reactions, and systemic side effects are unusual.

Adverse effects of the drug mainly involve the CNS and are dose-related and usually short of duration. Taking into account a bioavailability of only 3% when applied as a patch or as a gel, systemic absorption and toxicity of lidocaine after topical administration seems not to be a significant risk. In general, hypersensitivity to local anaesthetics are rare. Hypersensitivity seems to occur almost exclusively with local anaesthetics of the ester type. Agents of the amide type – such as lidocaine – are essentially free of this problem.

Effects on the Skin and Hypersensitivity Reactions
Lidocaine is a well-known allergen. Nevertheless, reports of allergic contact dermatitis and delayed hypersensitivity reactions to this "amide" anaesthetic are limited. Moreover, when the product is applied topically in the recommended dosage and as transdermal resorption is low, only mild dermatological reactions are expected to occur.

Delayed hypersensitivity to lidocaine may present as "suture allergy", treatment failure, typical contact allergy or other local skin or dental reactions.

From 30 patients with a known hypersensitivity to local anaesthetics, few were truly allergic to these substances and some of the hypersensitivity reactions have been attributed to excipients present in the finished product such as para-hydroxybenzoate esters. Severe allergic reactions to lidocaine and contact dermatitis are rarely seen.

Although cross-hypersensitivity between lidocaine and other local anaesthetics is not always observed, caution should be used when lidocaine is given to patients that are allergic or hypersensitive to this class of drugs. One study reported a case of anaphylaxis to multiple local anaesthetics (groups 1 and 2), possibly via an IgE-mediated mechanism. Another study described in a case report an IgE-

mediated hypersensitivity reaction to lidocaine. A 7-year-old girl developed ipsilateral left facial swelling immediately after lignocaine injection to the upper anterior region of her mouth. Hypersensitivity reactions due to lidocaine have been rarely reported in children. There are a limited number of paediatric case reports describing allergic reactions to lidocaine. However, in these cases lidocaine was used as an injected local anaesthetic. As such, a study reported erythema and pigmentation of the upper lip in a child after local dental infiltration of lidocaine. One study postulated a type III hypersensitivity reaction as the cause of a highly unusual skin reaction after the local administration of lidocaine observed in a 6-year old Hispanic child. In this particular case the probable offending agents were the methyl paraben and bisulphite preservatives. A study reported the case of a 7-year-old girl who developed ipsilateral left facial swelling immediately after lidocaine injection that was indicative of a type I hypersensitivity reaction.

Gastrointestinal Effects
Gastrointestinal effects with lidocaine are expected to occur only in very exceptional cases with Chlorhexidine digluconate 20 mg/10 ml / lidocaine hydrochloride 5 mg/10 ml oromucosal spray and Chlorhexidine hydrochloride 5 mg/lidocaine hydrochloride 1 mg lozenges. A study described nausea/vomiting as uncommon gastrointestinal side effect (experienced by about 6.5% of subjects).

CNS Effects
CNS effects with lidocaine have been reported in the scientific literature but are expected to occur only in very exceptional cases with Chlorhexidine digluconate 20 mg/10 ml / lidocaine hydrochloride 5 mg/10 ml oromucosal spray and Chlorhexidine hydrochloride 5 mg/lidocaine hydrochloride 1 mg lozenges.

Adverse CNS reactions may be manifested by drowsiness, dizziness, disorientation, confusion, light-headedness, tremulousness, psychosis, nervousness, apprehension, agitation, euphoria, tinnitus, visual disturbances including blurred or double vision, nausea, vomiting, paraesthesia, sensations of heat, cold or numbness, difficulty swallowing, dyspnoea and slurred speech. Muscle twitching or tremors, seizures, unconsciousness, coma and respiratory depression and arrest may also occur.

Although peak plasma lidocaine levels after nebulisation occurring 30 minutes are an order of magnitude below the accepted toxic threshold of 5 mg/l, a study described three patients who showed CNS toxicity from locally administered lidocaine during transoesophageal echocardiography.

The rare neurological complications of subarachnoid anaesthesia with lidocaine are irrelevant for Chlorhexidine digluconate 20 mg/10 ml / lidocaine hydrochloride 5 mg/10 ml oromucosal spray and Chlorhexidine hydrochloride 5 mg/lidocaine hydrochloride 1 mg lozenges.

Cardiovascular Effects
Hypotension, arrhythmias, heart block, cardiovascular collapse and bradycardia that may lead to cardiac arrest have been reported in the scientific literature but are considered irrelevant for Chlorhexidine digluconate 20 mg/10 ml / lidocaine hydrochloride 5 mg/10 ml oromucosal spray and Chlorhexidine hydrochloride 5 mg / lidocaine hydrochloride 1 mg lozenges.

Methaemoglobinaemia
Methaemoglobinaemia may occur in sensitive individuals after the administration of various drugs, including some local anaesthetics. Isolated use of lidocaine is generally considered safe, although rare reports associated it with methaemoglobinaemia.

Safety and Adverse Effects of Chlorhexidine and Lidocaine in Children

Chlorhexidine
Since there are no clinical study reports, in which chlorhexidine was administered to children as spray or lozenges, safety of chlorhexidine use in paediatric population has to be based on the results of clinical studies, in which mouth washes and gels were tested.

Safety measures were investigated in the studies described in the clinical overview, in which the efficacy of chlorhexidine was described. No adverse events were recorded during these studies. Moreover, the use of chlorhexidine gel was found not to cause any inconvenience by 85% of children, who participated in the trial.

Given similar application site and the extent of action of products containing chlorhexidine in the form of mouth washes and gels, results of these studies can be extrapolated to Chlorhexidine digluconate 2 mg/ml / lidocaine hydrochloride 0.5 mg/ml oromucosal spray and Chlorhexidine hydrochloride 5 mg / lidocaine hydrochloride 1 mg lozenges. Moreover, children using mouth washes are more prone to swallow large amounts of the medicinal product than when it is used as a throat spray or lozenges. The lack of adverse drug reactions in the clinical studies described above indicated that chlorhexidine is safe in paediatric patients.

This safety is further supported by a clinical trial in which children aged from 3 months to 17 years (mean age of 6.8 years) have been bathed with the use of cloths soaked with 2% chlorhexidine. The study took place in the intensive care unit. Analysis of blood samples taken from these children demonstrated that chlorhexidine administered apically is not absorbed to systemic circulation. Although some amounts of this substance could be seen in serum samples, their level was in the majority of cases below the lower limit of quantitation (LLOQ) of the analytical method. This confirms the data presented in the clinical overview, where it was stated that the absorption of chlorhexidine after topical or oral administration is poor.

Furthermore, LD50 value for oral administration of chlorhexidine determined based on animal acute toxicity studies is 5 g/kg in rats, and 2.5 g/kg in male or 2.6 g/kg in female mice, respectively. Assuming that chlorhexidine toxicity can be linearly extrapolated to humans, and taking the body weight of a 2 and a half year old child to be 13 kg, he/she would have to swallow 32.5 g of chlorhexidine. Taking into account the amount of the active substance in Chlorhexidine digluconate 2 mg/ml / lidocaine hydrochloride 0.5 mg/ml oromucosal spray, this means swallowing more than 16 litres of the medicinal product. Similarly, assuming that a child of 6 years of age weights approximately 20 kg, he/she would have to ingest 50 g of the active substance. Taking into account the amount of the active substance in Chlorhexidine hydrochloride 5 mg / lidocaine hydrochloride 1 mg lozenges, this means taking 10.000 lozenges.

Lidocaine
Clinical studies of lidocaine conducted in paediatric patients consist mainly in demonstrating its efficacy and safety in numerous dental procedures. However, there are some data supporting its use in the treatment of local infections of the oral cavity and throat. In the studies described in the clinical overview, lidocaine was found effective in diminishing the pain accompanying primary herpetic gingivostomatitis and as a local anaesthetic acting within the oral cavity. In all of these studies, lidocaine was well tolerated by children and no serious adverse events were reported.

The safety of lidocaine use in children was further analysed in the study, in which the plasma levels of this substance after oral topical administration were measured. The DentiPatch™ lidocaine transoral delivery system containing 46.1 mg of lidocaine (20% concentration) was used in this study. The sample in this study was 11 children aged 2-7 years requiring general anaesthesia for comprehensive

dental care. Blood samples were drawn before placing the DentiPatch™ and at various time intervals after removing it and plasma concentrations of lidocaine and its major metabolite, MEGX were evaluated. The results of this study demonstrated that, even though plasma concentrations of lidocaine and MEGX absorbed from the DentiPatch™ were high enough to require inclusion in the calculation of total lidocaine administered to a paediatric patient, they did not reach toxic levels. This proves that lidocaine use in children is safe.

In another study, safety of topical lidocaine anaesthesia was evaluated in children undergoing bronchoscopy. Children were aged from 3 months to 9.5 years. Total lidocaine doses administered in this study were 3.2-8.5 mg/kg and proved to be safe when administered over a period of time. Taking into account the dosing regimen proposed for the medicinal products Chlorhexidine digluconate 2 mg/ml / lidocaine hydrochloride 0.5 mg/ml oromucosal spray (children > 6 years: 2 to 3 sprays per time, 3 to 5 times per day) and Chlorhexidine hydrochloride 5 mg / lidocaine hydrochloride 1 mg lozenges (children > 6 years: 3 to 5 lozenges per day), the maximal daily dose of lidocaine in spray formulation would be 1.125 mg (assuming the volume of each spraying to be about 0.15 ml) and for lidocaine in lozenges 5 mg. These values are well below the 8.5 mg/kg concentration, which was proven clinically not to cause any adverse drug reactions.

LD50 value for oral administration of lidocaine determined based on animal acute toxicity studies is 292 mg/kg in mice and 317 mg/kg in rats. Assuming that animal toxicity data for lidocaine can be extrapolated to humans in a linear way, a child weighting 13 kg would have to ingest up to 4.12 g of lidocaine to reach this dose and the child weighting 20 kg up to 6.34 g. Such amounts would be present in either about 8.2 or 12.7 litres of Chlorhexidine digluconate 2 mg/ml / lidocaine hydrochloride 0.5 mg/ml oromucosal spray and in 4120 or 6340 lozenges.

Lidocaine - chlorhexidine combination
A pharmaceutical product was marketed in Australia for 'teething' in an almost identical container to a popular paediatric paracetamol preparation. The product contained lidocaine and chlorhexidine. The similarity of the packaging resulted in large number of therapeutic errors in which the 'teething' preparation was given in error for paracetamol. In addition to these cases, all other previously reported cases of lidocaine and chlorhexidine ingestion were identified using a systematic review of the literature. There were 28 cases with complete follow up where the product was given in therapeutic errors (10 girls and 18 boys; median age 11 months; range 2 months-4 years). The mean ingested dose of lidocaine was 2.7 mg/kg (standard deviation 1.3 mg) and chlorhexidine was 0.06 mg/kg (standard deviation 0.03 mg). The largest ingested lidocaine dose was 5.9 mg/kg. Two children developed minor symptoms: one vomited twice and the other was reported to have increased salivation and difficulty with solid food for 20 minutes. No other adverse effects were reported. The literature review suggested that severe effects occurred with doses more than 15 mg/kg. No major adverse effects occurred with lidocaine ingestions of less than 6 mg/kg, chlorhexidine did not appear to cause clinical effects in this low concentration.

In conclusion, there are no data describing adverse effects of chlorhexidine-lidocaine oromucosal spray or lozenges in children. In general, the available data indicate that both lidocaine and chlorhexidine very rarely induce hypersensitivity or other adverse reactions in children.

Safety in special populations
Pregnancy and breast feeding
In the UK, the combination chlorhexidine/lidocaine is recommended to be used in pregnancy and breast feeding only under the direction of a physician, since there is inadequate evidence of the safety

of lidocaine and chlorhexidine in human pregnancy. However, these have been in wide use for many years without apparent ill consequence.

IV.6 Risk Management Plan (RMP)

The Marketing Authorisation Holder (MAH) has submitted a risk management plan (RMP), 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 Covonia Medicated Sore Throat 5 mg/1 mg Lozenges Menthol/Lemon Flavour.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified risk: impaired swallowing	(proposed) text in SmPC Section 4.4 Special warnings and precautions for use: The use of a too high dose (more than 20 tablets) can cause a small risk on too great	none

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	insensitivity of the glottis area, which can cause a diminished control on the swallowing reflex and food aspiration in the airways can occur.	
Important identified risk: local skin reactions (dermatitis, pruritus, erythema, eczema, rash, urticaria, skin irritation, blisters)	(proposed) text in SmPC Section 4.8 Undesirable effects: Allergic skin reactions such as dermatitis, pruritus, erythema, eczema, rash, urticaria, skin irritation, blisters.	none
Important Missing information: pregnancy, breast feeding and fertility	(proposed) text in SmPC Section 4.6 Fertility, pregnancy and lactation There is inadequate evidence of the safety of lidocaine and chlorhexidine in human pregnancy but they have been in wide use for many years without apparent ill consequence. Covonia Sore Throat Spray should only be used in pregnancy and breast feeding under the direction of a physician.	none

Routine risk minimisation is provided through the summaries of product characteristics (SmPC) and the package leaflet (PL). No additional risk minimisation measures are planned for these products.

IV.7 Discussion on the clinical aspects

The grant of Marketing Authorisations is recommended for these applications.

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 PIL 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 quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with chlorhexidine dihydrochloride and lidocaine hydrochloride is considered to have demonstrated the therapeutic value of the compounds. The benefit risk is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Covonia Medicated Sore Throat 5mg/1mg Lozenges Menthol/Lemon Flavour is presented below:


Covonia Medicated Sore Throat
5mg/1mg Lozenges
Menthol Flavour
Chlorhexidine Dihydrochloride
Lidocaine Hydrochloride
Lot:
Exp:
Thornton & Ross Ltd
9279511710


COVONIA
SUGAR FREE
MEDICATED Sore Throat
5mg/1mg LOZENGES
LEMON FLAVOUR
36
NEW
Chlorhexidine Dihydrochloride
Lidocaine Hydrochloride
DUAL ACTION
Fights Infection & Numbs Pain
36 Compressed Lozenges

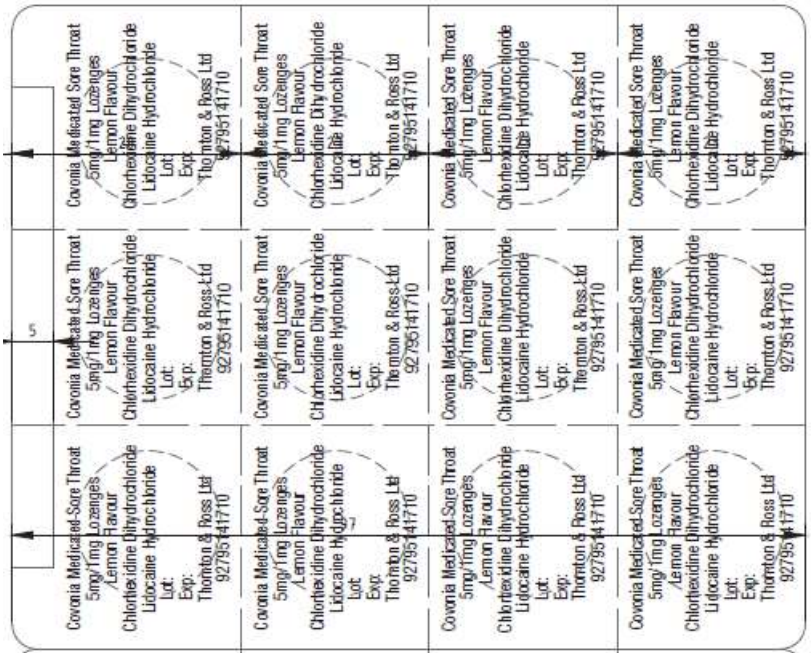

5
Covonia Medicated Sore Throat
5mg/1mg Lozenges
Lemon Flavour
Chlorhexidine Dihydrochloride
Lidocaine Hydrochloride
Lot:
Exp:
Thornton & Ross Ltd
9279514 1710

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Date submitted	Application type	Scope	Outcome