Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rapydan 70 mg/70 mg medicated plaster

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each medicated plaster contains 70 mg of lidocaine and 70 mg of tetracaine.

Excipients: 0.35 mg methyl parahydroxybenzoate, 0.07 mg propyl parahydroxybenzoate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Medicated plaster.

Oval, light brown plaster (approximate dimensions: 8.5 cm x 6.0 cm) with a removable opaque plastic tray.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Surface anaesthesia of the skin in connection with needle puncture and in cases of superficial surgical procedures (such as excision of various skin lesions and punch biopsies) on normal intact skin in adults.

Surface anaesthesia of the skin in connection with needle puncture on normal intact skin in children from 3 years of age.

4.2 Posology and method of administration

Adults (including elderly): 1 or at most 4 plasters simultaneously. Maximum 4 plasters per 24 hours.

Children from 3 years of age: 1 or at most 2 plasters simultaneously. Maximum 2 plasters per 24 hours.

Application time: 30 minutes. The plaster should be applied for the duration of 30 minutes before needle puncture or a superficial surgical procedure is conducted as a shorter duration may result in a decreased efficacy.

Please note that the medicated patch contains a heat-releasing component that may reach a maximum temperature of 40°C, with a mean temperature of 26-34°C.

If considered necessary, hairs in the affected area can be cut off (not shaved) before the plaster is applied to ensure that there is adequate contact between the skin and the plaster.

Rapydan medicated plasters are for single use only, and should be used immediately once the sachet has been opened.

Used plasters should be discarded carefully in accordance with instructions given in section 6.6.

Children under 3 years of age:
Use of Rapydan is strongly discouraged for children under the age of 3 years due to insufficient clinical experience (see section 4.4).

Patients with hepatic, renal and cardiac impairment:
Rapydan should be used with caution in patients with severe hepatic, renal and cardiac impairment (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substances, to sodium borate or to any of the other excipients.

Hypersensitivity to local anaesthetics of the amide or ester type or to para-aminobenzoic acid (by-product in tetracaine metabolism).

Rapydan should not be used on mucous membranes or on areas with a compromised skin barrier.

4.4 Special warnings and precautions for use

A prolonged application time or application of more plasters than recommended can lead to increased absorption of lidocaine and tetracaine into the systemic circulation with accompanying serious systemic effects.

The plaster should be used with caution in patients with hepatic, renal or cardiac impairment, and in subjects with increased sensitivity to systemic circulatory effects of lidocaine and tetracaine, such as the acutely ill or debilitated.

Allergic or anaphylactoid reactions associated with lidocaine, tetracaine or other ingredients in Rapydan can occur. Tetracaine may be associated with a higher incidence of such reactions than lidocaine.

Caregivers are recommended to avoid direct contact with the patch or the skin exposed to the patch, in order to avoid contact dermatitis.

Rapydan contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

Rapydan should be used with caution in the proximity of the eyes, as severe corneal irritation was observed in animal studies with similar products. If Rapydan comes into contact with the eye, the eye should be rinsed immediately with water or sodium chloride solution and the eye protected until feeling returns.

Lidocaine has bactericidal and antiviral properties in concentrations above 0.5-2%. Therefore the result of intradermal injections of live vaccine (e.g. BCG) should be closely monitored.

Rapydan contains a heat-releasing component that may reach a maximum temperature of up to 40°C, with a mean temperature of 26-34°C.

Rapydan should not be used under occlusive dressings due to the heat-releasing nature of the plaster.

Use in children below 3 years of age is strongly discouraged based on limited clinical experience. The available pharmacokinetic data suggest that lidocaine exposure (AUC and C_{max}) is inversely correlated with age. In the single paediatric study which included children under 3 years, the maximum peak lidocaine concentration seen in a single child under 3 years was 331 ng/ml compared to 63.3 ng/ml and 12.3 ng/ml for children aged 3-6 and 7-12 years, respectively. Variability is seen in the exposure levels obtained with Rapydan, and as a concentration of approximately 1000 ng/ml is known to have anti arrhythmic activity, it is possible that children under 3 could be exposed to concentrations of lidocaine associated with this activity (see section 5.2). Plasma levels of tetracaine in this age group were so low after application of one or two plasters that there was no discernable effect of age or dose.

Care should be taken when using the medicated plaster with children to ensure that the medicated plaster remains in position on the skin, in order to decrease the risk of ingestion or contact with the eyes, which could occur with handling of the plaster by a child.

Used plasters
For environmental and safety reasons, used plasters should be disposed of in accordance with the instructions given in section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

The risk of additional systemic toxicity should be considered when Rapydan medicated plasters are applied to patients receiving Class I antiarrhythmic medicinal products (such as quinidine, disopyramide, tocainide and mexiletine) and class III antiarrhythmic medicinal products (e.g. amiodarone) or other products containing local anaesthetic agents.

Should Rapydan be used concomitantly with other products containing lidocaine and/or tetracaine, cumulative doses from all formulations must be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy
Data on a limited number of exposed pregnancies indicate no adverse effects of lidocaine and tetracaine on pregnancy or on health of the fetus/newborn child. Animal studies are insufficient with respect to the effects of lidocaine on pregnancy, embryonal/fetal development, parturition or postnatal development (see section 5.3). Animal studies do not indicate direct or indirect harmful effects of tetracaine with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see section 5.3). Caution should be exercised when prescribing to pregnant women.

Lactation
Lidocaine and probably tetracaine are excreted in human milk (the plasma/milk ratio of lidocaine is 0.4 and has not been determined for tetracaine) but the risk of affecting the child appears low when using recommended doses. Breast-feeding may therefore continue during Rapydan therapy.

4.7 Effects on ability to drive and use machines

Rapydan has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The most commonly reported adverse drug reactions are erythema, oedema and blanching, occurring in 71%, 12% and 12% of patients respectively (see below). These reactions were generally mild and transient, and disappeared after discontinuation of treatment.

Undesirable effects seen in clinical trials are reported below according to the MedDRA convention on frequency and organ system classification.

Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to ≤ 1/1,000); very rare (≤ 1/10,000).

Nervous system disorders

Rare: Pain, taste perversion

Skin and subcutaneous tissue disorders

Very common: Erythema, blanching
Common: Rash
Uncommon: Vesiculobullous rash, pruritus, contact dermatitis

Rare: Urticaria, maculopapular rash, skin discolouration

General disorders and administration site conditions

Very common: Oedema
Uncommon: Application site reaction

Allergic or anaphylactoid reactions associated with lidocaine, tetracaine or other ingredients in Rapydan may occur. Tetracaine may be associated with a higher incidence of such reactions than lidocaine.

Systemic adverse reactions following appropriate use of Rapydan are unlikely, due to the small dose absorbed (see section 5.2).

4.9 Overdose

Systemic toxicity is very unlikely with normal use of Rapydan. In the event of any toxicity the symptoms are expected to be similar to those seen after other local anaesthetic treatment, i.e. excitatory CNS symptoms and in severe cases CNS depression and myocardial depression.

Severe neurological symptoms (seizures, CNS depression) require symptomatic treatment such as assisted ventilation and spasmolytic agents. Due to slow systemic absorption, a patient with symptoms of toxicity should be observed for several hours following any treatment of these symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: local anaesthetic; amides; lidocaine, combinations
ATC code: NO1BB52.

Rapydan medicated plaster contains lidocaine, a local anaesthetic of the amide type, and tetracaine, a local anaesthetic of the ester type. Dermal anaesthesia occurs following application through release of lidocaine and tetracaine to the epidermal and dermal parts of the skin in the vicinity of dermal pain receptors and nerve endings. Thus a block is achieved of the sodium ion channels required for the initiation and conduction of nerve impulses, resulting in local anaesthesia. The degree of anaesthesia depends on the application time.

5.2 Pharmacokinetic properties

Absorption:

The systemic exposure of the two active substances depends on the dose, the duration of the application, the thickness of the skin (varying between different parts of the body) and the skin condition. Simultaneous application of two or four Rapydan medicated plasters for 60 minutes produced peak plasma concentrations of lidocaine of less than 9 ng/ml, while tetracaine plasma concentrations were below the limit of quantification in all subjects (n = 22). Sequential 30-minute applications of four Rapydan medicated plasters at 60−minute intervals produced peak plasma concentrations of lidocaine of less than 12 ng/ml, while tetracaine plasma concentrations were below the limit of quantification (n = 11) in adults.

The medicated plaster contains a heat-releasing component that may reach a maximum temperature of 40°C, with a mean temperature of 26-34°C. The pharmacokinetic studies have not shown evidence of increased or faster absorption owing to the heat component.

Distribution:

Following intravenous administration to healthy volunteers, the steady-state volume of distribution is approximately 0.8 to 1.3 l/kg. Approximately 75% of lidocaine is bound to plasma proteins (primarily alpha-1-acid glycoprotein). The volume of distribution and protein binding have not been determined for tetracaine due to rapid hydrolysis in plasma.

Metabolism and Elimination:

Lidocaine is mainly eliminated by metabolism. Conversion to monoethylglycinexylidide (MEGX) and further to glycinexylidide (GX) is mediated mainly by CYP1A2 and to a lesser extent by CYP3A4. MEGX is also metabolised to 2,6-xylidine. 2,6-xylidine is further metabolised by CYP2A6 to 4-hydroxy-2,6-xylidine that constitutes the main metabolite in urine (80%) and is excreted as conjugate. MEGX has a pharmacological activity similar to lidocaine while GX has less pharmacological activity.

Tetracaine undergoes rapid hydrolysis by plasma esterases. Primary metabolites of tetracaine include para-aminobenzoic acid and diethylaminoethanol, both of which have an unspecified activity.

The extent to which lidocaine and tetracaine are metabolised in the skin is not known. Lidocaine and its metabolites are excreted by the kidneys. More than 98% of an absorbed dose of lidocaine can be recovered in the urine as metabolites or parent drug. Less than 10% of lidocaine is excreted unchanged in adults and approximately 20% is excreted unchanged in neonates. The systemic clearance is approximately 8 – 10 ml/min/kg.

The half-life of lidocaine elimination from plasma after intravenous administration is approximately 1.8 hours. The half-life and clearance for tetracaine has not been established for humans, but hydrolysis in plasma is rapid.

Paediatric Subjects:

Pharmacokinetic data in children are limited, especially in children below the age of 3 years. In the single paediatric study conducted to date, only nine children under 3 years received Rapydan; of these only 4 had complete pharmacokinetic sampling and one child had no samples taken. Risk of higher systemic exposure in children below 3 years of age cannot be excluded. The available pharmacokinetic data suggest that lidocaine exposure (AUC and C_{max}) is inversely correlated with age. In general, toxicity may be observed at lidocaine blood levels above 5000 ng/ml and concentrations as low as 1000 ng/ml have been associated with antiarrhythmic activity.

The following table provides the available C_{max} data for lidocaine and tetracaine by age and treatment group. No firm safety conclusions can be drawn from the data in children under 3 years of age due to the limited number of exposed patients.

Parameter	4 months to 2 years		3 to 6 years		7 to 12 years	
	1 plaster	2 plasters	1 plaster	2 plasters	1 plaster	2 plasters
Lidocaine C_{max} (ng/ml) Mean Range n	 14.3 6.6 – 22.1 2	 141 4.6 – 331 6	 13.4 2.0 – 63.3 7	 16.8 5.0 – 33.8 7	 4.7 0 – 12.3 9	 2.1 0 – 4.9 5
Tetracaine C_{max} (ng/ml) Mean Range n	 <0.9 2	 0.2 0 – 1.33 6	 0.7 0 – 3.97 7	 <0.9 7	 7.2 0 – 64.9 9	 <0.9 6

Elderly:

After simultaneous application of two Rapydan medicated plasters for 60 minutes to elderly subjects (>65 years of age, n = 12), the maximum peak lidocaine concentration was 6 ng/ml but tetracaine was not detectable (<0.9 ng/ml) in the plasma. In intravenous studies, the half-life for elimination of lidocaine was statistically significantly longer in elderly patients (2.5 hours) than younger ones (1.5 hours).

Special populations:

Cardiac, Renal and Hepatic Impairment: No specific pharmacokinetic studies have been conducted. The half-life of lidocaine may be increased in cardiac or hepatic dysfunction. There is no established half-life for tetracaine due to hydrolysis in plasma.

5.3 Preclinical safety data

Reproductive toxicology

Lidocaine: In studies of embryonal/fetal development in rats and rabbits with dosing during organogenesis, no teratogenic effects were observed. However, animal studies are incomplete with respect to effects on pregnancy, parturition or postnatal development.

Tetracaine: No effects on fertility were observed in rats at a toxic dose. In studies of embryo/fetal development in rats and rabbits with dosing during organogenesis, no teratogenic effects were observed. No effects were observed in the offspring of rats treated with a maternally toxic dose during late pregnancy and lactation. As there are no data for systemic exposure in rats, no comparison with exposure in humans can be made.

Lidocaine and tetracaine: In studies of embryo/fetal development with dosing during organogenesis, no teratogenic effects were observed.

Genotoxicity and carcinogenicity

Genotoxicity studies for lidocaine and tetracaine were negative. The carcinogenicity of lidocaine and tetracaine has not been studied. The lidocaine metabolite 2,6-xylidine has genotoxic potential in vitro. In a carcinogenicity study in rats with exposure to 2,6 xylidine in utero and postnatally and throughout their lifetime, tumours in the nasal cavity, the subcutis and the liver were seen. The clinical relevance of the tumour findings in short-term/intermittent/topical use of lidocaine is unknown. However, taken into account the short treatment duration with Rapydan, carcinogenic effects are not anticipated..

There are no further preclinical data of relevance for an evaluation of safety other than what has already been mentioned in this summary of product characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing layer: polyethylene film, covered on one side with acrylate adhesive.

Controlled Heat Assisted Drug Delivery (CHADD) heating pod: iron powder, activated carbon, sodium chloride, and wood flour, encapsulated in a filter paper pouch.

Adhesive film: polyethylene and acrylate adhesive.

Heat sealable foil: polyethylene and aluminium laminate, covered with polyester urethane adhesive.

Drug layer:
polyvinyl alcohol
sorbitan monopalmitate
purified water
methyl parahydroxybenzoate (E218)
propyl parahydroxybenzoate (E216)
sodium borate-covered fibre coating

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Each medicated plaster is covered with a protective plastic (HDPE) tray, which must be removed before the application of the plaster.

Each plaster is individually packaged in a protective sachet (polyester/aluminium/polyethylene laminate).

1, 2, 5, 10, 25, or 50 sachets are packaged into an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

After use the plasters still contain substantial quantities of active ingredients. Used plasters should be folded together with the adhesive mass inwards (so that the release-regulating membrane is not exposed) and for safety and environmental reasons returned to the pharmacy.

Any unused product or waste material should be disposed of in accordance with local requirements. Used plasters should not be flushed down the toilet, placed in liquid waste disposal systems or thrown into household waste. These measures are to protect the environment.

7 MARKETING AUTHORISATION HOLDER

Eurocept International BV
Trapgans 5
1244 RL Ankeveen
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 1591/001/001

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