LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Rapydan, medicated patch
Lidocaine 70 mg/Tetracaine 70 mg

SE/H/762/01/MR

This module reflects the scientific discussion for the approval of Rapydan, medicated patch 70 mg/70 mg. The procedure was finalised at 2007-10-10. For information on changes after this date please refer to the module 'Update'.

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

I. INTRODUCTION

EUSA Pharma Ltd has applied for a marketing authorisation for a combination product named Rapydan, medicated patch 70 mg/70 mg. The active substances are lidocaine and tetracaine. Local anaesthesia in the dermis is achieved by blockage by these two substances of sodium ion channels, required for the initiation and conduction of nerve impulses. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Rapydan is presented in the form of a medicated plaster containing 70 mg of lidocaine and 70 mg of tetracaine. The plaster consists of the below constituents.

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

Each plaster is covered with a protective plastic (HDPE) tray, and individually packaged in a polyester/aluminium/polyethylene laminate sachet.

II.2 Drug Substance

Lidocaine has a monograph in the European Pharmacopoeia whereas tetracaine has not.

Lidocaine is a white, crystalline powder which is practically insoluble in water. Tetracaine is an off-white crystalline powder with is not very soluble in water. The structure of each of the drug substances has been adequately proven and its physicochemical properties sufficiently described. The respective routes of synthesis have been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substances specifications include relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Rapydan 70 mg/70 mg medicated plaster is formulated using excipients and components which are controlled according to acceptable specifications.

The drug formulation is an emulsion in which the oil phase is a eutectic mixture of lidocaine 70 mg and tetracaine 70 mg. The eutectic mixture has a melting point below room temperature and therefore exists as liquid oil rather than as a crystal.

A Controlled Heat Assisted Drug Delivery (CHADD ®) heating pod has been incorporated to the drug product. This integrated oxygen-activated heating element begins to heat once it is removed from the pouch and is exposed to oxygen in the air. It may reach a maximum temperature of up to 40° C with a mean temperature of 26-34° C.

The product development has taken into consideration the physicochemical characteristics of the active substances.

The manufacturing process has been sufficiently described and critical steps identified. Results from process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored at or below 25°C.

III. NON-CLINICAL ASPECTS

The Applicant has provided data on the local responses of the Rapydan medicated plaster, repeat-dose toxicity, genetic toxicity of each active ingredient, reproductive toxicity of each active ingredient and on a eutectic mixture of the active ingredients, and a summary of the published nonclinical pharmacology/toxicology literature of lidocaine and tetracaine. From a preclinical point of view there is no safety concern that precludes a market authorisation for the Rapydan medicated plaster.

The environmental risk assessment (ERA) was not complete and the Applicant has made a commitment to fulfil the ERA by performing the complete Phase II requirements. Nevertheless, the product information regarding disposal of used and unused plaster is considered as an adequate measure to prevent any undesired environmental impact.

IV. CLINICAL ASPECTS

IV.1 Introduction

The indication for Rapydan is surface anesthesia 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.

In the paediatric population Rapydan is indicated for usage as surface anesthesia of the skin in connection with needle puncture on normal intact skin in children from 3 years of age.

Use of Rapydan is strongly discouraged for children under the age of 3 years due to insufficient clinical experience. In the single pharmacokinetic paediatric study conducted to date, only nine children under 3 years received Rapydan. The available pharmacokinetic data suggest that lidocaine exposure is inversely correlated with age.

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 decreased efficacy.

The clinical development has been performed on 1465 subjects who received at least a single application of the developmental A, B or final formulation of Rapydan.

IV.2 Pharmacokinetics

Four pharmacokinetic studies were submitted that aimed to evaluate the pharmacokinetics in children, adults and elderly. The doses studied were one, two, three or four patches administered simultaneously or repeatedly for 30 or 60 minutes in adults. In children, the highest dose studied was two patches applied simultaneously for 30 minutes. Study SC-25-01 was considered inaccurate, due to blood sampling from the vein that drained the patch, which most likely caused the high systemic levels observed in that study. In studies SC 26-01 and SC-51-04 similar results were obtained, and showed that the systemic availability is low, also in elderly (study SC-51-04). Study SC-30-01 was burdened with many protocol violations, namely incomplete blood sampling and samples collected from the patch site, while the pharmacokinetic results, due to the lack of data and indications of high concentrations, are considered insufficient in the youngest age group. The pharmacokinetic data submitted only supports the indication for children from 3 years of age.

The pharmacokinetic studies have not been able to show increased or faster systemic absorption owing to the heat component.

IV.3 Pharmacodynamics

Rapydan medicated plaster provides local dermal anaesthesia by release of lidocaine and tetracaine from the medicated plaster into the epidermal and dermal layers of the skin and from accumulation of lidocaine and tetracaine in the vicinity of dermal pain receptors and nerve endings.
Specifically, they block nerve impulse conduction by interfering with voltage dependent sodium channels and inhibiting the ionic fluxes. By inhibiting sodium influx, the threshold for nerve excitation increases and finally the ability to generate an action potential is lost.
The anaesthetic effect achieved by the medicated plaster depends upon how long the medicated plaster is left on the skin.

IV.4 Clinical efficacy

The efficacy of Rapydan medicated plaster has been investigated in fourteen clinical trials using 3 different formulations. In 7 of the studies the final formulation of the medicated plaster was used.

Five studies (SC-09-99, SC-10-00, SC-20-01, SC-21-01, and SC-04-99) have been conducted in paediatric patients aged 3-17 years, a further study was conducted in children aged 4-6 month, prior to routine immunisation, but this was primarily designed as a safety study.

Three of the paediatric studies evaluated the plaster prior to a vascular access procedure and according to the applicant two studies were intended to evaluate the medicated plaster prior to minor dermatological procedure. The applicant's definition of minor dermatological procedure is not agreed with. In those two studies, one of the studies evaluated the medicated plaster prior to a lidocaine injection and one to a pin-prick test representing a rather low pain stimulus. The efficacy measures used in all those paediatric studies are considered adequate and relevant for pain evaluation in children aged 3-17 years.
The results of the pivotal paediatric studies (prior to vascular access and prior to lidocaine injection), are somewhat inconsistent. Both studies showed that Rapydan medicated plaster was statistically significantly more effective than placebo in younger paediatric patients using the photographic version of the Oucher scale. In older children using the numerical version of the Oucher scale, no statistically significant difference was seen between placebo and active plaster
However the secondary endpoint; the investigator and independent observer's ratings were overall in favour for the Rapydan medicated plaster compared with placebo plaster.
In the supportive studies, performed in children aged 7-18 years, different developmental formulations were used but all comprised of a eutectic mixture of lidocaine 70 mg and tetracaine 70 mg and the results of the supportive studies were also overall in favour for the active plaster.
It is therefore agreed that the submitted documentation supports the efficacy claims regarding anaesthesia prior to vascular access, in children aged 3-17 years.
Regarding anaesthesia in the paediatric population, prior to minor dermatological procedure, no conclusion can be drawn on the basis of the submitted study results, thus the submitted study results does not support a usage prior to a minor dermatological procedure in paediatric patients.

In the adult population 2 studies (SC-23-01, SC-24-01) were considered pivotal. One study evaluated the Rapydan medicated plaster prior to vascular access procedure and one prior to minor dermatological procedure.
The efficacy endpoints used in those studies are considered adequate for pain evaluation. In both studies patient/study subject, investigator and independent observer's evaluation all point in the same direction by significantly favour the Rapydan medicated plaster over placebo, with overall low pain ratings.
Unsatisfactory is, that in spite of the overall low pain ratings, nearly 1/4 of patients receiving Rapydan medicated plaster, required a rescue lidocaine injection to reach satisfactory anaesthesia for a minor dermatological procedure.

Further, two studies were performed in the geriatric population (SC-31-01, SC-22-01). The primary efficacy evaluation, median patient rating of pain, showed significantly lower VAS

scores with Rapydan medicated plaster compared with placebo plaster supporting the superiority of Rapydan medicated plaster compared with placebo. None of the secondary efficacy endpoints showed a statistically significant difference between the active and placebo treatment and again an unsatisfactory amount of patients in the active group, required a rescue lidocaine injection for a minor dermatological procedure.
In adults this is considered acceptable since it most certainly will not influence the adult patient's participation in the actual surgical procedure and a rescue lidocaine injection could be administered at any time. In children on the other hand, the anaesthetic agent must provide predictable and reliable anaesthesia since for the child intolerable pain could result in a non co-operative manner, not only with consequences for the actual procedure but also as negative expectations of pain in future procedures. Consequently the efficacy data available, all in all, supports the efficacy for Rapydan medicated plaster prior to minor dermatological procedures only in the adult population.

One supportive study compared the efficacy of Rapydan medicated plaster with the active comparator EMLA (SC-40-02). Patients were not blinded to treatment, and differences between EMLA cream and Rapydan patch (with heating effect) were obvious for the subjects. The primary endpoint was subjective pain VAS (Visual Analogue Scale).After 30 minutes application, median VAS scores were 2mm for Rapydan and 13mm for EMLA cream ($p=0.001$). Since the design of the active comparator study was not adequate the result does not allow conclusions.
The study investigator was blinded to treatment and the investigator's evaluation of efficacy showed no statistically significant differences between the treatments at any application times.

One study (SC-41-03) compared the Rapydan medicated plaster with placebo and each of the active components separately. The primary efficacy endpoint showed significantly lower VAS scores for the Rapydan medicated plaster group compared with the active integrated components separately. The study result confirms that there is a small additive increase in efficacy when combining lidocaine and tetracaine in the same medicated plaster. However the clinical relevance for the additive efficacy increase seems modest since there were overall low pain ratings for all the 3 active treatments.

An application period of 30 minutes was used in the majority of studies and the overall results indicate that a 30 minutes application period is preferable prior to a vascular access procedure.

Finally a number of studies were conducted to investigate the contribution of the heating element to the efficacy of the Rapydan medicated plaster. In the early studies the applicant failed to demonstrate efficacy contribution of the heating component. However the applicant provides a reasonable explanation for this.
A further clinical study (SC-55-04) compared Rapydan medicated plaster with heat to a plaster without heat prior to vascular access procedure. Both treatment groups showed overall low pain ratings but the VAS scores were significantly lower for subjects who received the heated medicated plaster (mean VAS score 14.2 vs 20.5, two-sample t-test, $p=0.006$). The secondary endpoint, subject overall impression of local anaesthetic (71% vs. 53%, Fisher's Exact test $p=0.004$) were in line with the results of the primary endpoint. The clinical relevance of the efficacy contribution of the heating components seems however limited.

IV.5 Clinical safety

The safety database for Rapydan medicated plaster comprises data from 27 studies, including five clinical pharmacokinetic open label and 22 controlled studies. In all the clinical studies the medicated plaster consisted of a eutectic mixture of 70 mg lidocaine and 70 mg of tetracaine. All phase III studies used the final formulation.

The majority of study subjects received a single application of the medicated plaster. In the clinical settings it is though, probably more usual with an exposure of more than one medicated plaster at the same time. The number of study subjects evaluated for a more exceeded exposure is more limited. However six studies evaluated multiple exposures and the number of patients included in the performed trials is considered sufficient for a safety evaluation in the adult population.

The majority (65 %) of individuals who received the Rapydan medicated plaster experienced slight or well defined erythema. One % experienced erythema that was considered moderate in severity. Oedema occurred less frequently, in approximately 10 % of subjects. Localized skin reactions were generally minor, non serious and transient in nature. Data were also collected regarding delayed skin reactions that occurred within 24-48 hours of study treatment
Overall local reactions associated with Rapydan medicated plaster were mild to moderate but tended to occur with greater prevalence with higher doses. Erythema and oedema were significantly greater for combined multiple applications than combined single applications.

The cumulative irritation and contact sensitization potential were evaluated in one study and results of this study indicate that mild cumulative irritation occurs in a small number of adults when the Rapydan is applied for 120 minutes 3 times per week. In addition, this study indicates that the sensitization potential of repeated application in healthy adults is low.
Mild and transient incidences of localised erythema and oedema are reported as expected reactions from topical anaesthetics. Therefore only moderate to severe cases of erythema and oedema were recorded as adverse events.
The overall incidence of adverse events was 5% of subjects who received any of the different formulations in the studies reporting adverse events. Only rash was reported as a common adverse event, in 1.1% of subject. Other uncommon adverse events include application site reaction, pruritus, and contact dermatitis, urticaria and vesiculobullous rash.
Rare adverse events include urticaria, skin discolouration, maculopapular rash, pain and taste perversion. Thus, the reported skin reaction and adverse events does not give rise to any new safety concern in the adult population.
However allergic or anaphylactic reactions associated with lidocaine, tetracaine or other ingredients in Rapydan can occur which is clearly pointed out in the SPC section 4.4. Tetracaine may be associated with higher incidence of such reactions than lidocaine.

Signs of CNS toxicity may occur at a level of 5 microgram/ml. In all these studies peak blood levels of lidocaine have been well below potentially toxic levels. The pharmacokinetic parameters obtained, including maximum concentration and extent of absorption, indicates low systemic availability in adults and elderly.
In the pediatric population the skin reaction seen is similar to those in seen in the adult population.
The majority of children (57%) experienced very slight or well defined erythema. One child experienced erythema that was considered moderate in severity. None of the children experienced severe erythema or any eschar formation. Oedema occurred less frequently than

erythema. With the Final formulation of the medicated plaster the incidence of oedema was 9%, with one child experiencing oedema that was considered moderate in severity.

Overall the submitted safety documentation supports a usage in children above 3 years of age. In children below 3 years, on the other hand, there is limited safety data especially in the youngest children below 1 year. All children included in the pivotal studies were above 3 years and pharmacokinetic sampling in children below 3 years of age has only been obtained in 9 subjects. The pharmacokinetic parameters showed great variability with the highest concentration observed in a child below one year. An effect of age on Cmax was highly significant with higher Cmax values observed for younger subjects. The PK data suggest a higher exposure and maximal concentration in young children compared to adults. With exposure data from only one subject of four month of age, and the remainder 7 around 1 year the submitted documentation does not permit a firm safety evaluation to ensure a safe usage in children below 3 years of age.

IV.6 Discussion on the clinical aspects

As a result of the MRP the MAH was requested to update the Risk Management Plan to include the issue of caregivers' skin reactions, such as contact dermatitis.

In the view of the limited PK data in children less than 3 years of age the applicant was also requested to submit a variation, to modify the of SPC sections on safety in paediatric use when the results from a planned paediatric pharmacokinetic study are available.

User testing of the package leaflet has been performed.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The submitted documentation supports the indication: surface anesthesia of the skin in connection with needle puncture and in cases of superficial surgical procedures on normal intact skin in adults and surface anesthesia of the skin in connection with needle puncture on normal intact skin in children from 3 years of age.
The risk/benefit ratio is considered favourable and Rapydan, medicated patch, 70 mg/70 mg is recommended for approval.

VI. APPROVAL

The Mutual recognition procedure (SE/H/762/01/MR) of Rapydan, medicated patch, 70 mg/70 mg, was successfully finalised on 20071010.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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