HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

14 May 2008

RAPYDAN 70mg / 70mg, medicated plaster
Pack of 25 - CIP code: 383 640-8

Applicant: EUSA PHARMA

Lidocaine / tetracaine

ATC code: N01BB52

List II
Date of Marketing Authorization: 18 February 2008 (mutual recognition procedure; reporting country: Sweden)

Reason for request: Inclusion on the list of medicines approved for use by hospitals.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Lidocaine / tetracaine

1.2. Background

This proprietary product is the only one based on tetracaine combined with lidocaine which has Marketing Authorization (MA) for the indications stated below.
This proprietary product contains a heat-releasing component which can reach a maximum temperature of 40℃, with a mean temperatur e of 26-34℃.

1.3. Indication

- 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.

1.4. Dosage

- 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 decreased efficacy.
  Please note that the medicated patch contains a heat-releasing component that may reach a maximum temperature of 40℃, with a mean te mperature of 26-34℃.
  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.

- 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.

- Patients with hepatic, renal and cardiac impairment:
  RAPYDAN should be used with caution in patients with severe hepatic, renal and cardiac impairment.

2. COMPARABLE MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

N : nervous system
N01 : anaesthetics
N01B : local anaesthetics
N01BB : amides
N01BB52 : lidocaine, combinations

2.2. Medicines in the same therapeutic category

2.2.1 Comparator medicines

- Closely comparable medicinal products

There are currently no medicines with a similar indication to RAPYDAN whose active ingredients are lidocaine combined with tetracaine.

- Medicinal products not closely comparable

Table 1: medicinal products not closely comparable

Proprietary product	Active ingredient:	Pharmaceutical form Route of administration	Indication	Application time
EMLA 5% cream and its generics	Lidocaine / Prilocaine	Cream + dressing Cutaneous administration Mucosal administration	Local anaesthesia of healthy skin, e.g.: - before venepuncture or subcutaneous punctures, - before instrumental or laser-assisted surface skin surgery. Anaesthesia of the genital mucosa in adults, e.g.: - before surface surgery: biopsy or excision of lesions (instrumental or laser-assisted), - before needle infiltration of local anaesthetics, at the dose of 5-10 g for an application time of 5-10 minutes. Local anaesthesia of leg ulcers requiring long and painful mechanical debridement.	Healthy skin: at least 1 hour before surgery Genital mucosa in adults: 5-10 minutes Leg ulcers: 30 minutes
EMLAPATCH	Lidocaine / Prilocaine	5% adhesive dressing Cutaneous administration	Local anaesthesia of healthy skin, e.g.: - before venepuncture or subcutaneous punctures, - before instrumental or laser-assisted surface skin surgery.	At least 1 hour before surgery

2.3. Medicines with a similar therapeutic aim

ENTONOX gas for inhalation (nitrous oxide – oxygen)
KALINOX gas for inhalation (nitrous oxide – oxygen)
NITROUS OXIDE - MEDICAL OXYGEN ALS 125 BAR gas for inhalation (nitrous oxide - oxygen).

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The file supplied by the manufacturer is based on the following trials:

- In adults:
  - two comparative randomized double-blind placebo-controlled clinical trials (trials SC 24 – 01 and SC 23 – 01). The placebo contained the same heat-releasing system as the proprietary product RAPYDAN.
  - a comparative randomized clinical trial against active comparator (EMLA cream) (trial SC 40-02).
- In children:
  - four comparative randomized double-blind placebo-controlled clinical trials (trials SC 10-00, SC 09-99, SC 20-01 and SC 21-01). The placebo contained the same heat-releasing system as the proprietary product RAPYDAN.

Two other comparative randomized trials are included in the dossier. One compared the efficacy of the combination lidocaine 70 mg / tetracaine 70 mg with and without a heat-releasing system, while the other compared the efficacy of RAPYDAN with that of a 70 mg lidocaine patch, a 70 mg tetracaine patch and a placebo. These trials are not detailed in the present document because they are “proof-of-concept” trials, the aim of which was to assess the relevance of the integrated heat-releasing system and the lidocaine / tetracaine combination.

3.1.1 Trials in adults (> 18 years)

The objective of these trials was to compare the anaesthetic efficacy of RAPYDAN with that of a placebo and EMLA cream, applied before a painful procedure.
The primary endpoint was a visual analogue scale (VAS) (100 mm).
One hundred and sixty-six patients were included in these trials: 127 were treated with RAPYDAN, 89 received a placebo, and 82 were treated with EMLA.

Table 2: Randomized double-blind placebo-controlled trials.

	Trial SC 24 - 01	Trial SC 23 – 01
	Placebo / Rapydan	Placebo / Rapydan
Trial schedule	Paired data *	Parallel groups
Painful procedure	venipuncture	surface dermatological procedure †
No. of patients‡	40	49 /45
Duration of application	20 minutes	30 minutes
median VAS and [range] (in mm)	28 [0-95] / 5 [1-96] §	31 [0-95] / 5 [0 – 92] §

*: each patient acted as his/her own control, with simultaneous application of the active product or the placebo on one arm or the other, according to a random distribution; † : surface excision, surface biopsy, resorption of tattoo; ‡ : all patients included in the trial were taken into account in the analysis; § : P<0.001 ;

- Randomized trial to compare the efficacy of RAPYDAN and EMLA cream

Double randomization was used: firstly for allocation of the treatments to one arm or the other, and secondly for allocation in the groups according to the duration of application.
The efficacy of RAPYDAN and EMLA were compared for each treatment period.

Table 3: results of a randomised trial comparing the efficacy of RAPYDAN and EMLA cream

	Trial SC 40 - 02			
Trial schedule	paired data *			
Painful procedure	venipuncture			
Application time	10 minutes	20 minutes	30 minutes	60 minutes
Population (total =82) **	n=20	n=20	n=22	n=20
Products studied	Rapydan / Emla	Rapydan / Emla	Rapydan / Emla	Rapydan / Emla
Median VAS [range] (in mm)	15,5 [0-48] / 33 [0-69] †	15 [0-37] / 22 [0-71] ‡	2 [0-16] / 13 [0-63] §	2[0-27] / 2 [0-35] NS

* : each patient acted as his/her own control, with simultaneous application of the active product or the placebo on one arm or the other, according to a random distribution; ** : all patients included in the trial were taken into account in the analysis; † : p=0.01 ; ‡ : p<0.05 ; § : p=0.001 ;

A statistically significant difference in favour of RAPYDAN was observed 10, 20 and 30 minutes after the application. The greatest effect of RAPYDAN was observed 30 minutes and 60 minutes after application. However, the difference between RAPYDAN and EMLA after 30 minutes (2 mm vs 13 mm) cannot be deemed clinically relevant[1].
After 60 minutes no statistically significant difference was observed between RAPYDAN and EMLA.

3.1.2 Trials in children (3 to 18 years of age)

The objective of these trials was to compare the anaesthetic efficacy of RAPYDAN with that of a placebo, when applied before a painful procedure.
The four trials presented were conducted in parallel groups.
The primary endpoint was a visual analogue scale, differing according to age:

- 3 to 6 years of age: Oucher photographic scale (scale of six faces with numerical correspondence of 0 to 100)
- 7 to 18 years of age: Oucher numerical scale (100 mm)

Two hundred and seventy-two patients were included; 144 were treated with RAPYDAN, and 128 received a placebo.

1 “in adults, it is accepted that a difference of 20 mm in VAS reflects a clinically relevant change in pain level”; see ANAES recommendation - Evaluation and outpatient treatment strategies for acute pain in children aged 1 month to 15 years. March 2000.

Table 4: Trials in which the pain stimulus was a vascular access:

	Trial SC 20 - 01	Trial SC 09 - 99	Trial SC 10 - 00
	Placebo / Rapydan	Placebo / Rapydan	Placebo / Rapydan
Total population 3-6 years of age 7-18 years of age	21/ 43* 10 / 22 11 / 21	30 / 30** 0 30 / 30	30 / 30** 0 30 / 30
Duration of application	20 minutes	30 minutes	20 minutes
Painful procedure	insertion of venous catheter or venipuncture	venipuncture	Venipuncture
Mean age (years) [range]	7,7 ± 4,4 [3-16] / 8 ± 4,6 [3-17]	12,9 ± 3,1 [7-18] /12,5 ± 3 [7-18]	13,3 ± 2,7 [7-17] / 13,5 ± 2,8 [8-17]
Median Oucher photographic score [range]	80 [0-100] / 0 [0-100] †	None.	None.
Median Oucher numerical score [range] (in mm)	50 [0-80] / 7,5 [0-100] NS	35 [0-100] / 0 [0-100] ‡,	20 [0-80]/ 0 [0-20] ‡,

* : number of patients included in efficacy analysis = 20/41, randomization ½ specified in protocol; ** : all patients included were taken into account in the analysis; † : $p<0.01$; ‡ : $p< 0.001$

Table 5: Trial in which the pain stimulus was an injection of lidocaine administered before a minor dermatological procedure

	Trial SC 21 - 01
	Placebo / Rapydan
Total population* 3-6 years of age 7-17 years of age	47 /41 22 / 20 25 / 21
Duration of application	30 minutes
Mean age (years) ± standard deviation [range]	8,2 ± 4,4 [3 -17] / 8,9 ± 4,1 [3 -15]
Median Oucher photographic score [range]	70 [0-100] / 0 [0-100] †
Median Oucher numerical Score (mm)	10 / 10 NS

*all patients included were taken into account in the analysis; † : $p=0.005$;

3.2. Adverse effects

The tolerance data relate to 1848 patients, 1328 of whom received at least one application of RAPYDAN. The other patients received a formula under development (only differing from the final formulation in terms of the composition of the excipients) or the final formulation without the heating component. The adverse events most frequently observed during the clinical development were rash (71% of cases), swelling (12%) and skin bleaching (12%) at the application site. These adverse events were usually of moderate severity and reversible after removal of the plaster. In a comparative trial between RAPYDAN and EMLA, a well-defined rash was observed in 38% of cases, and slight to mark bleaching in 15% of cases, after RAPYDAN; a well-defined rash was observed in 7% of cases, and slight to marked bleaching in 44% of cases, after EMLA. One case of mild or very mild swelling was observed in each group.

It is stated in the Summary of Product Characteristics (SPC) that “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.”

3.3. Conclusion

In adults:

In two placebo-controlled trials, RAPYDAN was significantly more effective in preventing pain caused by a venipuncture or superficial dermatological procedure, for an application period of 20 or 30 minutes, depending on the trial.

Only one trial compared the preventive efficacy of RAPYDAN with that of the reference treatment, EMLA cream. The pain stimulus was a venipuncture. The patients were divided into four groups, each corresponding to an application period (10, 20, 30 and 60 minutes). RAPYDAN was significantly more effective than EMLA cream for the 10, 20 and 30 minute application periods. The lowest median VAS score after RAPYDAN (2 mm vs. 13 mm for EMLA cream) was measured 30 minutes after the application (duration specified in the marketing authorization). However, this difference cannot be deemed clinically relevant[2].

In children:

Three trials compared the efficacy of RAPYDAN with that of a placebo in the prevention of pain caused by a venipuncture or insertion of a venous catheter, after application of the plaster for 20 or 30 minutes according to the trial.

- children aged 3 to 18 years were included in only one of these trials. RAPYDAN was significantly more effective than the placebo only in the subgroup of children aged 3 to 6 years (median scores on the Oucher photographic scale: 0 / 80)[3].
- In the other 2 trials, in which the patients were aged 7 to 18 years, RAPYDAN was significantly more effective than the placebo. The median scores on the Oucher numerical scale were 0 mm /35 mm in trial SC 09-99 and 0 mm / 20 mm in trial SC 10-00[3].

One trial compared the efficacy of RAPYDAN with that of the placebo in preventing pain caused by an injection of lidocaine after application of the plaster for 30 minutes. The children included in the trial were 3 to 17 years old. RAPYDAN was significantly more effective than the placebo only in the subgroup of children aged 3 to 6 years (median scores on the Oucher photographic scale: 0 / 70)[3].

The comparison with the reference product EMLA cream was only performed in adults, after pain caused by venipuncture.

Adverse events:

The adverse events most frequently observed during the clinical development were rash (71% of cases), swelling (12%) and skin bleaching (12%). These adverse events were usually of moderate intensity and reversible after removal of the plaster. In a comparative trial between RAPYDAN and EMLA, a well-defined rash was observed in 38% of cases and slight to marked bleaching in 15% of cases after RAPYDAN; a well-defined rash was observed in 7% of cases, and slight to marked bleaching in 44% of cases, after EMLA. One case of mild or very mild swelling was observed in each group.

2 “in adults, it is accepted that a difference of 20 mm in VAS reflects a clinically perceptible change in pain level”; see ANAES recommendation - Evaluation and outpatient treatment strategies for acute pain in children aged 1 month to 15 years. March 2000.

3 “in children, the immediate objective of analgesic treatment is to reduce the pain, if possible, below the threshold of 3/10 (30 mm) on the VAS scale” see ANAES recommendation - Evaluation and outpatient treatment strategies for acute pain in children aged 1 month to 15 years. March 2000.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The disorder concerned by this treatment is acute pain caused by punctures or injections in children from 3 years old and punctures, injections or surface surgery in adults. This pain can lead to a deterioration in the quality of life, especially in the case of repeated procedures.

This proprietary drug is intended to provide preventive treatment.

The efficacy/adverse effects ratio for this medicinal product is high.

Public health benefit:

Acute pain caused by invasive procedures such as punctures, injections and surface skin surgery, involving surface anaesthesia of the healthy skin, represents a moderate public health burden.

Improving pain management constitutes a public health need which falls within the scope of an identified public health priority (Pain Management Improvement Plan 2006-2010).

Having regard to the available results, RAPYDAN is not expected in practice to have an additional impact in terms of reduced morbidity and/or improved quality of life compared with the existing medicinal products indicated for local contact anaesthesia of the skin.

RAPYDAN is therefore unlikely to provide a supplementary response to the identified public health need.

Consequently, RAPYDAN is not expected to have an impact on public health.

This proprietary product is a first-line treatment.

There are alternative drug treatments that could be used instead of this proprietary product (EMLA cream and its generics, EMLA patch).

The actual benefit of this proprietary product is substantial.

4.2. Improvement in actual benefit

As:
- the comparison with EMLA was only performed in adults after pain caused by a venipuncture,
- and no direct comparison was made between RAPYDAN and EMLA in children,

the Committee considers that RAPYDAN does not provide an improvement in actual benefit (IAB level V) compared with EMLA in the indications specified in the Marketing Authorization.

4.3. Therapeutic use

The aim of the treatment is to prevent pain caused by punctures, injections or surface skin surgery in healthy skin in adults, and punctures or injections in healthy skin in children.
A clinical practice guideline ([4]) specifies as follows:

- In adults, the pain threshold requiring a therapeutic response is 30 mm measured by VAS.
  It is accepted that a difference of 20 mm in VAS reflects a clinically perceptible change in pain level.
- In children, the immediate objective of analgesic treatment is to reduce the pain, if possible, below the threshold of 3/10 (30 mm) on the VAS scale.

In view of its 30-minute action period, RAPYDAN is an interesting additional treatment option, designed for surface anaesthesia of healthy skin before punctures or injections in adults and children, or surface skin surgery in adults.

4.4. Target population

The target population of RAPYDAN is defined as children aged 3 years and upwards and adults treated in hospitals who require pain prevention for punctures and injections (paediatric patients from 3 years old and adults) or surface skin surgery (in adults) on healthy skin. There is no data available to permit the quantification of the target population for RAPYDAN.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the Marketing Authorisation's indications and dosages.
The Committee points out that the manufacturer has not applied for inclusion on the list of medicines reimbursed by National Insurance.

Packaging: Appropriate for the prescription conditions

4 Evaluation and outpatient treatment strategies for acute pain in children aged 1 month to 15 years. ANAES - March 2000.