Report No.: DIET 01

Periodic Safety Update Report DIETHYLAMINE SALICYLATE & DIETHYLAMINE SALICYLATE/MYRTECAINE

01 January 1997 to 31 December 2001

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1. INTRODUCTION

This is the first periodic safety update report (PSUR) on diethylamine salicylate & diethylamine salicylate/myrtecaine compiled by Solvay Pharmaceuticals' Global Drug Safety and Surveillance (GDSS) Unit. Two PSURs have previously been issued by the national drug safety unit of Solvay France. The PSUR is presented in the format proposed in the ICH Guideline for Clinical Safety Data Management E2C: Periodic Safety Update Reports for Marketed Drugs.

The report reviews the adverse drug reaction reports associated with the use of Solvay Pharmaceuticals' diethylamine salicylate & diethylamine salicylate/myrtecaine received by GDSS, from worldwide sources, between 01 January 1997 and 31 December 2001 (data lock point).

Diethylamine salicylate and diethylamine salicylate/myrtecaine are ointments indicated for 'symptomatic relief of rheumatic and muscular pain'.

The reported adverse drug reactions and the reporting rates presented in this report may slightly differ from those presented in previous post marketing surveillance overviews because of reevaluation of the data, the addition of follow-up information as well as the addition of new information.

2. WORLDWIDE MARKET AUTHORIZATION STATUS

Solvay Pharmaceuticals' diethylamine salicylate or diethylamine salicylate/myrtecaine is currently approved in more than 70 countries. A detailed overview of the worldwide market authorization status is presented in Appendix 1.

3. UPDATE OF REGULATORY AUTHORITY OR MARKETING AUTHORIZATION HOLDER ACTIONS TAKEN FOR SAFETY REASONS

During the period of this update, there were no drug suspensions, restrictions on distribution or changes made for safety reasons.

4. CHANGES TO REFERENCE SAFETY INFORMATION

The French Summary of Product Characteristics (SmPC) for diethylamine salicylate (issue date 6 August 1996, amended 17 February 1997) & diethylamine salicylate/myrtecaine (issue date 3 February 1998, amended 20 August 1998) were used as the reference for this safety analysis as they were valid on 31 December 2001, the data lock point. These national SmPCs are presented in Appendix 2.

During the five-year period of this review the following information ***(changes in bold italics)*** was added to the safety section of the diethylamine salicylate SmPC:

Diethylamine salicylate (17 February 1997):

Contraindications:

Linked to the presence of terpene derivatives, as excipients:

- infants less than 30 months old.

- children with a history of convulsions (febrile or otherwise)

Warnings and Special Precautions for Use

This medicine contains terpene derivatives, as excipients, which can lower the epileptogenic threshold and, at excessive doses, lead to neurological accidents such as convulsions in infants and children.
Keep to the recommended dosages and instructions and in particular:
- do not apply to a large area of the body.
- do not apply to the breasts if breastfeeding.

If you have a history of epilepsy, remember that terpene derivates have been used as excipients.

Pregnancy and breastfeeding

If breastfeeding, it is preferable not to use this medicine because of:

- the lack of kinetic data on the passage of terpene derivatives into milk.

- their potential neurological toxicity to infants.

Adverse reactions

Because of the presence of terpene derivatives as excipients and if the recommended doses have not been kept to:

- there is a risk of convulsions in infants and children.

- there is a possibility of agitation and confusion in elderly subjects.

The Company Core Safety Information (CCSI) is a document recommended in the ICH E2C guideline. Based on the existing national SmPCs from France, the literature, and the results of this safety analysis, a CCSI was newly established. The newly established CCSI was approved on 06 February 2002 and is presented in Appendix 3.

5. PATIENT EXPOSURE

Clinical trials

Within the five-year period of this safety update, there were no newly analyzed clinical trials.

Market experience

A crude estimate of the number of patients exposed to diethylamine salicylate & diethylamine salicylate/myrtecaine during the period covered by this report was calculated from worldwide sales volumes, as an equivalent of 100 g tubes (= one unit), in the period 01 January 1997 to 31 December 2001. The sales data are presented in Table 1.

Table 1 Sales volumes (worldwide): 01 January 1997 to 31 December 2001

	1997	1998	1999	2000	2001*	Total
# units	2 098 031	2 222 258	1 789 834	1 913 565	1 406 705	**9 430 393**

* Figures for 2001 were estimated

For the purpose of this estimate, it has been assumed that each patient received an average of one tube (100 g). The number of patients exposed to diethylamine salicylate and/or diethylamine salicylate/myrtecaine is calculated as follows:

Table 2 Calculation of patient exposure

Assuming a total dose of one tube (100 g) per patient (= one unit)	
Units sold (total)	9 430 393
Cumulative units per patient	1
Number of patients	**9 430 393**

Total exposure

Thus, it is estimated that more than nine million patients were exposed to diethylamine salicylate and/or diethylamine salicylate/myrtecaine during the period covered by this report

6. PRESENTATION OF INDIVIDUAL CASE HISTORIES

6.1 Definitions and limitations

Definitions

The definitions and criteria applied throughout the generation of this safety update report are in line with the ICH Clinical Safety Data Management Guidelines E2A: Definitions and Standards for Expedited Reporting, and E2C: Periodic Safety Update Reports for Marketed Drugs.

Limitations

When interpreting the data provided in this report the following limitations inherent to the science of pharmacovigilance must be acknowledged.

Adverse event reports submitted to the Global Drug Safety and Surveillance Unit in many instances describe no more than suspicions which have arisen from the observation of an event. In most reports, it can not be proven that a pharmaceutical product or ingredient is the cause of an event.

The number of adverse event reports received in association with a particular product may be influenced by many factors, such as the extent of the use of the product, publicity, nature of events, and other factors which may vary over time, from product to product, and from country to country. Spontaneous reporting of AEs tends to underestimate the frequency of a particular event. Events common to a disorder may be assumed to be secondary to the condition, rather than due to an adverse drug effect. Rare or unusual events that are not expected to occur as part of the natural history of the condition under treatment are preferentially reported by prescribers. Thus, spontaneous adverse event reporting can identify an infrequent or rare adverse drug effect, but cannot accurately reflect the true incidence. Clinical trials with comparison to placebo or other agents

provide the best estimate of the AE incidence if the event is not uncommon or rare (≤ 1/10 000).

For these reasons, reporting rates do not reflect incidence rates; low reporting rates do not indicate that the occurrence of an event is rare, nor do high reporting rates indicate that an event occurs frequently.

6.2 Cases presented as line listings

This report reviews all adverse drug reaction reports associated with Solvay Pharmaceuticals' diethylamine salicylate and/or diethylamine salicylate/myrtecaine. The following types of cases are included:

- all serious and non serious adverse drug reactions spontaneously reported from the market;
- all serious adverse drug reactions (attributable to diethylamine salicylate and/or diethylamine salicylate/myrtecaine by either investigator or sponsor), available from studies or named-patient ("compassionate") use;
- all serious and non-serious adverse drug reactions from the literature;
- all serious and non-serious adverse drug reactions from regulatory authorities.

6.3 Presentation of the line listing report

All individual adverse drug reaction reports meeting the criteria defined above and received by the Global Drug Safety and Surveillance Unit of Solvay from worldwide sources between 01 January 1997 and 31 December 2001 are presented in Appendix 4. The reports were sorted by seriousness and by COSTART body system and the details tabulated in the CIOMS line listing format.

Where reports of adverse drug reactions affecting more than one body system were received, the clinically most severe adverse drug reaction was assigned to the corresponding body system and the other(s) listed with it.

6.4 Summary tabulations

During the five-year period of this safety report, there were a total of four ADR reports associated with the use of diethylamine salicylate or diethylamine salicylate/myrtecaine and two reports were evaluated as serious. Two reports were spontaneous reports from the market. The remaining two reports originated from health authorities. The distribution per source and over time is shown in Table 3.

Table 3 Distribution of ADR reports per source and over time

Yearly intervals	Total no. of reports received		Report source						
			Market		Health Authority		Literature		Clinical study*
	All	Serious	All	Serious	All	Serious	All	Serious	Serious
01 Jan 1997 – 31 Dec 1997	3	2	1	0	2	2	0	0	0
01 Jan 1998 – 31 Dec 1998	1	0	1	0	0	0	0	0	0
01 Jan 1999 – 31 Dec 1999	0	0	0	0	0	0	0	0	0
01 Jan 2000 – 31 Dec 2000	0	0	0	0	0	0	0	0	0
01 Jan 2001 – 31 Dec 2001	0	0	0	0	0	0	0	0	0
Total in 5 years	4	2	2	0	2	2	0	0	0

* From clinical studies, only serious cases are processed by GDSS.

A frequency list of all COSTART terms (signs, symptoms and diagnoses) associated with the four ADR reports is presented in Appendix 5. In total, these reports contain five adverse drug reactions (COSTART terms).

The five ADR reports were associated with the following COSTART body systems:

- Body as a Whole (1)
- Cardiovascular (1)
- Hemic and Lymphatic (1)
- Skin and Appendages (2).

6.5 Analysis of individual case histories

All unique reports will be analyzed hereafter.

Death

No deaths were reported during the review period.

Thrombocytopenic purpura

DIET018970001: A 55 year-old female patient was treated with diethylamine salicylate for an unknown indication. A month after commencing treatment she suffered from suspected idiopathic thrombocytopenic purpura. Other suspect drugs included: Etioven® (naftazone), Nalgesic® (fenoprofen), aldactazine, Sectral® (acebutolol) and Chondrosulf® (chondroitin). Upon discontinuation of the drugs the symptoms did not improve. Causality was assessed as 'unlikely' by the reporting health authority.

Comment: Thrombocytopenia is not listed in the reference safety information. The reporting frequency of one case in an estimated nine million patients treated is extremely low. The diagnosis remains uncertain since it was reported as suspected only. No laboratory values are available. The patient was concomitantly treated with fenoprofen a drug which is known to inhibit thrombocyte aggregation. In addition, a causative effect of diethylamine salicylate & diethylamine salicylate/myrtecaine is considered unlikely since the symptoms did not improve upon discontinuation of all drugs. This is the only case of thrombocytopenia ever reported to Solvay Pharmaceuticals. Based on the currently available information, no label change or other safety measure is considered necessary.

Hemorrhage

DIET018970002: An 85 year-old male patient was treated with diethylamine salicylate for an unknown indication. He suffered from a hematoma and was hospitalized. Other suspect drugs included: Doliprane® (paracetamol) given until two weeks before the hematoma occurred, and Temesta® (lorazepam). The patient had not yet recovered at the time of reporting. No further information is available. Causality was assessed as 'unlikely' by the reporting health authority.

Comment: Hemorrhage is not listed in the reference safety information. The reporting frequency of one case in an estimated nine million patients treated is extremely low. Due to the poor documentation of the report no reasonable explanation or comment can be made. This is the second case only assigned to the COSTART term hemorrhage ever reported to Solvay Pharmaceuticals. Based on the currently available information, no label change or other safety measure is considered necessary.

Rash and pain

DIET003970001: A 69 year-old female patient was treated with diethylamine salicylate for an unknown indication. She developed a burning sensation and a rash on the upper half of her body. Upon discontinuation of diethylamine salicylate the symptoms abated. No further information is available. Causality was assessed as 'possible' by the reporter.

Rash

DIET018980001: A 67 year-old female patient was treated with diethylamine salicylate/myrtecaine on forearms, sternum and back for an unknown indication. She was treated concomitantly with Topalgic® and Tranxene®. Within a month after commencing therapy she developed a pruriginous eruption on her back. Upon discontinuation of diethylamine salicylate/myrtecaine the symptoms disappeared completely. Causality was assessed as 'highly probable' by the reporter.

Comment: Rash is not explicitly listed in the reference safety information. Rash is considered as a possible symptom of an allergic reaction to diethylamine salicylate and/or diethylamine salicylate/myrtecaine and will be further discussed in section 9.1.1.

7. STUDIES

7.1 Newly analyzed company-sponsored studies

During the period of this update report no trials sponsored by Solvay Pharmaceuticals were newly analyzed.

7.2 Targeted new safety studies

No studies targeting the safety of diethylamine salicylate and/or diethylamine salicylate/myrtecaine are currently planned or conducted by Solvay Pharmaceuticals.

7.3 Published safety studies / literature review

A literature search in Medline® and Embase® was performed for diethylamine salicylate and/or myrtecaine for the period covered by this report. No articles containing important safety findings related to diethylamine salicylate and/or myrtecaine were published.

Overall, information on topical salicylates in the literature is scarce. Most publications contain information on topical NSAIDs (non-steroid anti-inflammatory drugs) in general. The published data on these products indicate that they are indeed safe and well tolerated. Most of the adverse reactions after topical NSAID being a form of allergic contact dermatitis (including rash and pruritus at the site of application). (Chlud K, 1998; Gniadowska B et al., 1999; Gonzalo MA et al., 1996; Kraemer R et al., 2000; Heyneman CA et al., 2000; Moore RA et el., 1998; MacDonald TM. 1995).

The bibliography of these articles is given in Appendix 6.

8. OTHER INFORMATION

8.1 Efficacy-related information

No report regarding lack of effect which represented a significant hazard to the treated population was identified during the period of this review.

8.2 Late-breaking information

Since the closure of the database on 31 December 2001, no important new safety information was received.

9. OVERALL SAFETY EVALUATION

In light of the estimated exposure to diethylamine salicylate and/or diethylamine salicylate/myrtecaine (nine million patients), the reporting rate of adverse events is very low. Diethylamine salicylate and/or diethylamine salicylate/myrtecaine are concluded to be generally safe and well tolerated. The safety issue of allergic reactions will be discussed in section 9.1.1.

The newly established CCSI is based on the existing French SmPC.

The following will be added:

Effects on ability to drive and use machines ***(changes in bold italics):***

There is no indication to restrict driving or use of machinery whilst receiving this therapy.

In the French SmPC diethylamine salicylate a warning is issued for adverse reactions occurring as terpene derivatives (i.e. camphor) are used as excipients in the cream. Terpene derivatives can lower the epileptogenic threshold and, at excessive doses, can lead to neurological accidents such as convulsions in infants and children. Agitation and confusion may occur in elderly subjects. None of the above mentioned adverse reactions were ever reported to Solvay Pharmaceuticals. In the Special Warnings and Precautions for use section of the CCSI it is stated that 'Diethylamine salicylate and/or diethylamine salicylate/myrtecaine should not be used in children under the age of seven. In addition to this an explicit warning will be issued in the section 'Overdose' (see chapter 9.3).

9.1.1 Allergic reactions

During the period covered by this report two ADR reports coded as rash were reported during treatment with diethylamine salicylate and/or diethylamine salicylate/myrtecaine. Throughout the entire life span of the product four ADR reports of rash, four ADR reports of pruritus, two ADR reports of contact dermatitis, one ADR report of allergic reaction (positive patch test) and two ADR reports on urticaria were received. These fourteen ADRs occurred in ten different cases.

Allergic rashes typically occur between eight to ten days after treatment begin whereas reactions like urticaria may develop soon after first administration of the drug.

In seven out of the ten cases where the ADRs occurred no other medication was given to the patient. In the remaining three cases no other 'suspect' drugs were identified by the reporters. Information on time to onset was available in three cases only. Pruritus and urticaria developed in six days, rash developed within one month and urticaria, pruritus and rash developed within one day.

The absence of alternative explanations in the above listed cases combined with the time to occurrence relationship leads to the conclusion that allergic reactions like rash, pruritus and urticaria cannot be excluded as side effects of diethylamine salicylate and/or diethylamine salicylate/myrtecaine therapy. The frequency of these side effects is considered to be very low (in the reporting period two reported cases in an estimated nine million patients treated). It is considered appropriate to include these adverse drug reactions in the Company Core Safety Information.

Undesirable effects ***(changes in bold italics):***

Allergic reactions (rash, pruritus, urticaria) have been reported very rarely.

9.2 Drug interactions

There were no reports of drug interactions with diethylamine salicylate and/or diethylamine salicylate/myrtecaine during the review period.

9.3 Experience with overdose

There were no reports of overdose with diethylamine salicylate and/or diethylamine salicylate/myrtecaine during the review period.

In light of the presence of terpene derivatives as excipients, the following statement will be included in the Company Core Safety Information.

Overdose ***(changes in bold italics):***

Since terpene derivatives (i.e. camphor) are used as excipients there is a risk of convulsions in infants and children and a risk of agitation and confusion in elderly subjects if the recommended doses are exceeded.

9.4 Drug abuse or misuse

There were no reports of abuse or misuse with diethylamine salicylate and/or diethylamine salicylate/myrtecaine during the review period.

9.5 Experience during pregnancy or lactation

There were no reports of diethylamine salicylate and/or diethylamine salicylate/myrtecaine being taken during pregnancy or lactation during the review period.

In light of lacking pre-clinical data and sparse post-marketing information the following statement will be included in the Company Core Safety Information.

Pregnancy and lactation ***(changes in bold italics):***

There are no adequate data from the use of diethylamine salicylate and/or diethylamine salicylate/myrtecaine in pregnant women. No relevant animal or epidemiological data are available.

The use of diethylamine salicylate and/or diethylamine salicylate/myrtecaine is not recommended during pregnancy or lactation.

9.6 Experience in special patient groups

There were three reports that occurred in an elderly (≥ 65 years) during the review period (see section 6.5 for details).

9.7 Effects of long term treatment

There were no reports of long term use of diethylamine salicylate and/or diethylamine salicylate/myrtecaine during the review period.

10. CONCLUSION

Overall, the cumulative experience for the five-year period covered by this safety update report confirms that diethylamine salicylate and/or diethylamine salicylate/myrtecaine were generally safe and well tolerated.

Together with this PSUR, a Company Core Safety Information was newly issued. The document is based on the existing French Summary of Product Characteristics. *Allergic reactions (rash, pruritus, urticaria)* was added to the section 'undesirable effects'. The sections 'pregnancy and lactation', 'effects on ability to drive and use machines' and 'overdose' were updated.

The new Company Core Safety Information, issued 06 February 2002, accurately reflects the present state of knowledge on diethylamine salicylate and/or diethylamine salicylate/myrtecaine.

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Report No.: DIET 01

Periodic Safety Update Report DIETHYLAMINE SALICYLATE & DIETHYLAMINE SALICYLATE/MYRTECAINE

01 January 1997 to 31 December 2001

Appendices

1 - 6

APPENDIX 1

WORLDWIDE MARKET AUTHORIZATION STATUS

SOLVAY Worldwide Market Authorization Status as of October 2001

DIETHYLAMINE SALICYLATE

COUNTRY	FIRST REGISTRATION DATE	LAST REGISTRATION NUMBER	LAST RENEWAL DATE	EXPIRY DATE
SAUDI ARABIA	(40 g) 00.00.86 (100 g) 18.04.92	(40 g) 1/33/82 (100 g) 7/33/92		
AUSTRIA	30.03.79	8.371	20.01.83	
BAHRAIN	23/09/1991	DRN - 860/91	25/09/2000	25/09/2005
BELGIUM		410 IS 155 F 12 410 IS 220 F 7	15.02.94 17.05.99	15.02.99 17.05.04
CYPRUS	01.07.72	2865	30.06.88	29.06.93
IVORY COAST	27/06/1975	E-75-0996	27/06/1995	27/06/2000
U.A.E.		Dossier d'enregistr. en préparation		
FRANCE	31.05.60	40 g : 341 593-1 50 g : 341 594-8 100 g : 341 595-4	06.08.96	06.08.01
FINLAND		2274	29.11.99	29.09.2004
GUINEA	16/04/1986	245/DNPL/95	28/11/1995	28/11/2000
HUNGARY		(50 g) : K 1739	17.03.92	unlimitted
ITALY	21.07.89	009733015	28.02.95	28.02.00
KUWAIT	11.11.69	Enregistr. dem. le 25.04.93		
LEBANON		Renouv. dem. le 04.12.95		
LYBIA				
MALI		23/R/02.95	03.03.95	03.03.00
MALTA			01.01.1998	01.01.2003
MOROCCO		291 SG/42	28.05.93	28.05.98

SOLVAY Worldwide Market Authorization Status as of October 2001

MEXICO	23.06.51	36705	23.06.51	illimitée
OMAN		Enregistr. dem. le 03.06.96		
The NETHERLANDS	28.03.90	Algesal balsem RVG 00436		28.03.05
SLOVAK REP.	30.06.93	85/289/92 C/S	30.06.93	22.04.97
CZECH REP.	22/04/1992	85/289/92 C/S	22.04.92	22.04.97
UNITED KINGDOM	26.01.89	0512/0066	04.02.94	04.02.99
SUDAN	17.03.64	Renouv. dem. le 22.01.96		
SWEDEN	13.02.61	Renouv. dem. le 06.03.97	04.92	04.97
SWITZERLAND	09.01.76	37618		31.12.02
THAILAND	11.03.75	1517/2518	24.06.85	Permanent
TURKEY		105/40	22.07.87	27.02.92

SOLVAY Worldwide Market Authorization Status as of October 2001

DIETHYLAMINE SALICYLATE/MYRTECAINE

COUNTRY	FIRST REGISTRATION DATE	LAST REGISTRATION NUMBER	LAST RENEWAL DATE	EXPIRY DATE
SOUTH AFRICA (Rhodesia)	11.03.77	("Analgen") 5/13-7/396		
ALGERIA		Enregistrement demandé le 14.01.97		
GERMANY	20.03.70	("Algesal-creme" 50g, 100g, 10 x 100g and 10 x 50 g) 0075943/2547		31.12.04
ANGOLA	22.04.66	1.526/66		
SAUDI ARABIA	00.01.86	2/33/82		
ARGENTINA	22.01.73 21.05.73 28.01.84 29.07.91 13.11.91 11.08.94	("Algesal pomada" 40 g) 34.255 ("Algesal pomada" 20 + 40 g) 34.255 ("Algesal pomada" 20 + 40 g) 34.255 ("Algesal pomada" 20 + 40 g) 34.255 ("Algesal pomada" 20 + 40 + 100 g) 34.255 ("Algesal pomada" 20, 40, 50, 100 g) 34.255		22.01.78 22.01.83 22.01.88 22.01.93 22.01.93 22.01.98
AUSTRIA	30.03.79 30.11.95 20.06.00	("Latesyl-creme") 15.343 ("Latesyl-creme") 15.343 - modif. Algesal creme 1-21187		20.06.05
BAHRAIN	20.09.87 04.11.96 25.09.00	13/85 DRN 4063/96 (40 g)		25.09.05
BELGIUM	26.05.78 15.02.94	202 IS 6F7 410 IS 153 F 7		15.02.99 Renouv. dem. le 14.12.98
BENIN	07.07.75 27.12.77	(Ex-Dahomey) NE 0156/75 (Nomenclature) n° ordre		07.07.1980

SOLVAY Worldwide Market Authorization Status as of October 2001

	02.04.80 07.07.80 07.07.85 07.07.90 07.07.95 07/07/00	31 (Nomenclature) n° ordre 32 NE 1609/80 du 13.10.80 NE 2925/85 du 17.07.85 NR 3751/90 du 24.09.90 4433/95 5509/01 du 13 juillet 2001		07.07.80 07.07.80 07.07.85 07.07.90 07.07.95 07.07.05
BRAZIL	06.12.79	("Algesal espuma") 08772/79		06.12.84
BULGARIA	02.10.92	Protocol n° 512		02/10/97
BURKINA FASO	17.04.91 17.04.96	(Ren. 05/93) Nomencl. n° 05902/91 (40 g) 05902/96 (40 g)		17.04.96 17.04.01
CAMEROON	21.03.74 14.03.89 28.03.95	Att. 1641/MSAP/DSP/SDPH-SIV 1788/2/MSP/DS/SDPHET-SIV Att. 95-03-0009-RV/MSP/SG/DPH/SIVIP		14.03.94 28.03.00
CHILE	20.08.81 11.03.87 09.09.87	("Groman pomada" 50 g) 16.531 ("Lemazol pomada" 30, 40 g) 16531 (vrac) 16531		
CYPRUS	21.04.72 30.06.83 30.06.88 Ren. prévu / *Ren. planned* (10.95) - ?	2866 2866 2866		01.07.74 29.06.88 29.06.93
CONGO	15.11 99	99-016-[illegible]35/VC		28.02.2003
IVORY COAST	27.06.75 01.01.87 27.06.90 Dem. ren. / *Ren. applic.* (11.09.96)	E 75-1001 E-75-0997 (40 g)		01.01.92 27.06.95
EGYPT	13.05.75	11972		*13.05.85*
UNITED ARAB EMIRATES	04/07/99	RR 69/19		04.07.04

SOLVAY Worldwide Market Authorization Status as of October 2001

(DUBAI)				
ECUADOR	08.04.91 12.09.96	("Algesal balsamo" - fab. loc. / loc. manuf.) 7.251 "Algesal Suractive" 20.783 - 06-96 (40 g)		08.04.96 12.09.01
SPAIN	07.06.71 00.06.76 00.06.81 00.06.86 00.06.91 Dem. ren. / *Ren. applic.* (01.03.96)	("Algesal activado) 49.339 ("Algesal activado) 49.339 ("Algesal activado) 49.339 ("Algesal activado) 49.339 ("Algesal activado) 49.339		00.06.81 00.06.86 00.06.91 00.06.96
FRANCE	03/02/98	341-597-7 (40 g) 341 598.3 (50 g) 341 600.8 (100 g)		03/02/03
GABON	21/12/95	4275		21/12/00
GREECE	04.10.77 12.12.88 17.11.93 Dem. ren. / *Ren. applic.* (22.09.95)	(40 g) A6/9986/6296 (40 g) 31324/12.12.88 (40 g + 100 g) 21997/17.11.93		31.12.80 31.12.93
GUATEMALA	23.03.93	PF-12,436		23.03.98
GUINEA	28/11/95	245/DNPL/95		28/11/00
HONDURAS	08.05.92	("Algesal balsamo) 16484-05-92		unknown
HONG KONG	30/12/92	HK-18828		29/12/97
HUNGARY	18.11.91 17.03.92	("Algesal Suractive baume" 40 g) K - 1739 ("Algesal creme" 50 g) K - 1739		18.11.92 17.03.97
INDIA	11.03.80	Avis n° 4-8/73-DC		Permanent
INDONESIA	00.00.77	D 6016106		

SOLVAY Worldwide Market Authorization Status as of October 2001

JORDAN	14.06.84	(100 g) 122/84 : (ré-enregistrement demandé le 30.01.97) (40 g : enregistrement demandé le 30.01.97)		
KENYA		Enreg. Demandé le 07.07.98		
KUWAIT	02.02.69 11.02.80	44164-5/35 (Enr. prov. / Temporary reg.) 1040		
LEBANON	24.01.61 19.02.69 06.08.72 Dem. ren. / *Ren. applic.* (04.12.95)	435 18059		24.01.61 19.02.69 06.08.72 Dem. ren. / *Ren. applic.* (04.12.95)
LITHUANIA		Enreg. Demandé le 16.11.98		
LUXEMBOURG	04.04.69 01.12.94	Avis / Inform. n° 459/1 (100 g) Avis / Inform. n° 0191/65/08/0574		01.12.99
MADAGASCAR	19.07.99	13.1.2.442		19.07.04
MALI	07.07.78 08.10.79 31.12.83 17.03.90 28.02.95 10/04/2000	(Dec. 0 216/MSP-AS - 07.07.78) Aut. 086/78 (Dec. 0216/M.S.P-A.S - 07.07.78) 0014/83 AMM 086/78 (Aut. 00072/ISP-AS - 17.03.90) 23/R/02-95 299.870		07.07.85 31.12.88 17.03.95 28.02.00 10/04/2005
MALTA	01.01.98			01.01.03
MOROCCO	20/04/93	(40 g) 192 SG/42		20/04/98
MAURITANIA	11.07.89 Dem. ren. / *Ren. applic.* (09.11.95)	21266/85 2 503 92		11.07.94
MEXICO	23.04.65 25.06.93	("Algesal activado") 63194 S.S.A. ("Algesal crema") 63194 S.S.A.		indéterminé/indefinite

SOLVAY Worldwide Market Authorization Status as of October 2001

NIGER	31/03/95	95-0692-01		31/03/00
NIGERIA	20.09.00	N - 042068		20.09.05
PANAMA	12.07.93	39572		12.07.98
PARAGUAY	09.08.90 27.10.95	("Latesil crema") 27.745/90 35848/95		09.08.95 27.10.00
THE NETHERLAND	16.07.69	("Algesal forte balsem") Avis RVG 05740		08.06.05
PERU	31.10.77 10.08.94	N-11731 ("Algesal activado - 40 g) MS-010434-94		31.10.80 10.08.99
POLOGNE	11.11.88	("Algesal creme") 1349/Z		31/12/1997 Renouv. dem. le 23.01.98
PORTUGAL	20.11.67 11.03.68 26.08.72 15.03.94 06.07.99	("Dermalgin" 30 g) Aut. 2649 - 28.12.67 ("Algesal") ("Algesal superactivado pomada") ("Algesal pomada" 100 g) 8900019 ("Latesil creme"100g) 8507905		11.03.68 26.08.72 15.03.99 06.04.04
CENTRAFRICAN REPUBLIC	11/02/95	Ren. n° 0016/MSPP/CAB/IGSS/ISPH. (40 g)		11/02/2000 Renouv. dem. le 10-11-2000
SLOVAK REPUBLIC	30/06/1993 10/04/1997	("Algesal Suractive" 40 & 50 g) 85/0289/92-C/S		22/04/1997 30/04/2002
EL SALVADOR	02.12.91 Dem. ren. en suspens / *Ren. applic. in abeyance*	("Algesal suractivado pomada") 18,053		01.12.96
SENEGAL	10.02.72 05.12.90 18.03.96 Dem. Ren. Le 22.03.01	Arrêté/Decree 1035/MSPAS/SCPH Att. 00376/MSPAS/BCV 00419 (40 g)		18.03.01
SUDAN	28.03.70 15.04.76 27.12.94	6978 6978 SK/021/19423		28.03.70 15.04.76 27.12.94

SOLVAY Worldwide Market Authorization Status as of October 2001

	Ren. en cours / *Ren. in process* (info EL Nielein - 12.01.96)			Ren. en cours / *Ren. in process* (info EL Nielein - 12.01.96)
SWITZERLAND	09.01.76 09.06.79 09.06.79 16.02.95 16.02.95	(40 g) IKS-Nr. 37 618 012 (40 g) IKS-Nr. 37 618 012 (50 g) IKS-Nr. 37 618 039 (100 g) IKS-Nr. 37 618 020 (100 g) IKS-Nr. 37 618 020 (50 g) IKS-Nr. 37 618 039		31.12.83 31.12.97 31.12.97
TAIWAN	02.04.76 Dem . ren. / *Ren. applic.* (26.03.93)	04156		02.04.81
TOGO	01.08.00	Aut. n° 329/00/MS/DGS/DPLET		01.08.05
TUNISIA	09.11.99 26.12.95 26.12.00	60 g 9003431 (fab° locale) 40 g 5870021		09.11.04 26.12.00 26.12.05
TURKEY	27.07.70 10.04.72 30.06.75 27.02.87 27.02.92	105/39 105/39 105/39 105/39 105/39		(Permanent, examen / 5 ans-years) Permanent, examen / 5 ans-years) Permanent, examen / 5 ans-years) Permanent, examen / 5 ans-years)
URUGUAY	16.04.82 12.07.91 Dem. ren. / *Ren. applic.* (17.06.96)	("Algesal pomada") 25680		12.07.96
VENEZUELA	24.11.72	E.F.17.213		
VIETNAM	1992	VSA-1294-92		1997

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APPENDIX 2

SUMMARY OF PRODUCT CHARACTERISTICS FRANCE

Algesal Baume®

diethylamine salicylate

(issued August 1996, amended February 1997)

(Amendments to the Marketing Authorization of the General Director of the Drug Agency, dated 17 February 1997 are indicated in italics)

Algesal Suractive®

diethylamine salicylate/myrtecaine,

(issued February 1998, amended August 1998)

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ALGESAL BAUME

SUMMARY OF PRODUCT CHARACTERISTICS

6 AUGUST 1996
(including Amendments to the Marketing Authorization of the General Director of the Drug Agency, dated 17 February 1997)

1. NAME

ALGESAL BAUME, crème

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SALICYLIC ACID	6.54 g
DIETHYLAMINE	3.46 g
Light liquid paraffin	18.00 g
Ethylene glycol monosterarate	12.80 g
Stearic acid	6.50 g
Vaseline	6.00 g
Microcrystalline wax	4.00 g
Glycerol monostearate	3.20 g
Trolamine	3.00 g
Lavandin composition*	0.10 g
Purified water	sqf 100 g

*Composition of lavandin composition: Essential oil of lavandin grosso, essential oil and fractions of essential oil of Chinese eucalyptus, linalol, linalyle acetate, racemic camphor.

3. PHARMACEUTICAL FORM

Cream

4. CLINICAL DATA

4.1 Therapeutical indications

Local, secondary treatment of pains of muscular and tendino-ligamentous origin.

4.2 Dosage and mode of administration

FOR ADULTS AND CHILDREN OVER THE AGE OF 7 ONLY.

Apply by local massage into the painful area 2 to 3 times a day, until it has all been absorbed.

Wash your hands after use.

4.3 Contraindications

Allergy to salicylates, to substances with similar activity or to another component.
Do not use on mucous membranes, the eyes, weeping dermatosis, eczema, an infected lesion or a wound or under an occlusive dressing.

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Linked to the presence of terpene derivatives, as excipients:
- *infants less than 30 months old;*
- *children with a history of convulsions (febrile or otherwise).*

4.4 Warnings and special precautions over use

This medicine contains terpene derivatives, as excipients, which can lower the epileptogenic threshold and, at excessive doses, lead to neurological accidents such as convulsions in unweaned infants and children.
Keep to the recommended dosages and instructions and in particular:
- *do not apply to a large area of the body;*
- *do not apply to the breasts if breastfeeding.*

If you have a history of epilepsy, remember that terpene derivatives have been used as excipients.

4.5 Interactions with other medicines and other forms of interaction

4.6 Pregnancy and breastfeeding

If breastfeeding, it is preferable not to use this medicine because of:
- *the lack of kinetic data on the passage of terpene derivatives into milk;*
- *their potential neurological toxicity to infants.*

4.7 Effects on ability to drive and operate machinery

4.8 Adverse reactions

Possible local allergic reaction requiring the withdrawal of treatment.
Because of the presence of terpene derivatives as excipients and if the recommended doses have not been kept to:
- *there is a risk of convulsions in infants and children;*
- *there is a possibility of agitation and confusion in elderly subjects.*

4.9 Overdosage

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Intended for use as an analgesic
(M. LOCOMOTOR SYSTEM)

5.2 Pharmacokinetic properties

5.3 Preclinical safety data

6. PHARMACEUTICAL DATA

6.1 Incompatibilities

6.2 Storage time

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5 years

6.3 Special precautions to be taken over storage

Store at a temperature below or equal to 25º C

6.4 Nature and capacity of container

40, 50 or 100g aluminium tube with epoxyphenol varnish on the inside and a protective cap

6.5 Manner of use, handling instructions

7. PRESENTATION AND ADMINISTRATIVE IDENTIFICATION NUMBER

341 593-1: 40g in varnished aluminium tube
341 594-8: 50g in varnished aluminium tube
341 595-4: 100g in varnished aluminium tube

8. TERMS OF PRESCRIPTION AND ISSUE

9. HOLDER OF MARKETING PERMIT

Laboratoires SOLVAY PHARMA
42 rue Rouget de Lisle BP 22
92151 SURESNES CEDEX

10. DATE OF APPROVAL/REVISION

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ALGESAL SURACTIVE

1. NAME

ALGEASL SURACTIVE, cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SALICYLIC ACID	6.54 g
DIETHYLAMINE	3.46 g
MYRTECAINE	1.00 g
Ethylene glycol monosterarate	10.00 g
Light liquid paraffin	9.30 g
Cetylic alcohol	7.50 g
Polyoxethylenated castor oil	4.30 g
Stearate of macrogol 300	3.70 g
Saturated polyglycosed glycerides	3.20 g
Glycerol monostearate	2.00 g
Lavandin composition*	0.50 g
Hydrochloric acid	0.39 g
Purified water	sqf 100 g

*Composition of the lavandin composition: Essential oil of lavandin grosso, essential oil and fractions of essential oil of Chinese eucalyptus, linalol, linalyle acetate, racemic camphor.

3. PHARMACEUTICAL FORM

Cream

4. CLINICAL DATA

4.1 Therapeutic indications

Local, secondary treatment of pains of muscular and tendino-ligamentous origin.

4.2 Dosage and mode of administration

FOR ADULTS AND CHILDREN OVER THE AGE OF 7 ONLY

Apply by local massage into the painful area 2 to 3 times a day, until it has all been absorbed.

Wash your hands after use.

4.3 Contraindications

Allergy to salicylates, substances with a similar activity or another component (local anaesthetics...).
Do not use on the mucous membranes, the eyes, a weeping dermatosis, eczema, an infected lesion or wound or under an occlusive dressing.

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4.4 Warnings and special precautions over use

Athletes should be aware that this patent medicinal ptoduct contains an active principle which could lead to a positive result in dope tests.

4.5 Interactions with other medicines and other forms of interaction

4.6 Pregnancy and breastfeeding

4.7 Effects on the ability to drive and operate machinery

4.8 Adverse reactions

Local, allergic reaction necessitating stoppage of treatment

4.9 Overdosage

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Used as an analgesic
(M. LOCOMOTOR SYSTEM)

Combination of diethylamine salicylate, used as an analgesic, and myrtecaine, a local anaesthetic.

5.2 Pharmacokinetic properties

5.3 Preclinical safety data

6. PHARMACEUTICAL DATA

6.1 Incompatibilities

6.2 Storage time

5 years

6.3 Special precautions to be taken over storage

Store at a temperature below or equal to 25°C

6.4 Nature and contents of the container:

40, 50 or 100g aluminium tube with epoxyphenol varnish on the inside and protective cap.

6.5 Manner of use, handling instructions

7. PRESENTATION AND ADMINISTRATIVE IDENTIFICATION NUMBER

341 597-7: 40 g in (varnished aluminium) tube

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341 598-3: 50 g in (varnished aluminium) tube
341 600-8: 100 g in (varnished aluminium) tube

8. TERMS OF PRESCRIPTION AND ISSUE

9. HOLDER OF MARKETING PERMIT

Laboratoires SOLVAY PHARMA
42 rue Rouget de Lisle BP 22
92151 SURESNES CEDEX

10. APPROVAL/REVISION DATE

SOLVAY

Report No.: DIET 01

APPENDIX 3

COMPANY CORE SAFETY INFORMATION

(06 February 2002)

Note: The CCSI is a global document which may be different from the nationally approved text. However, the CCSI represents the minimum safety information which should be reflected in all the national labeling.

Issued:
06 February 2002

COMPANY CORE SAFETY INFORMATION

Diethylamine salicylate & Diethylamine salicylate/myrtecaine

Previous issue:
None

Contraindications

Known hypersensitivity to the active ingredient or any of the excipients.

Diethylamine salicylate and/or diethylamine salicylate/myrtecaine should not be used on mucous membranes, the eyes, weeping dermatoses, eczema, an infected lesion, a wound or under an occlusive dressing.

Special warnings and precautions for use

Diethylamine salicylate and/or diethylamine salicylate/myrtecaine should not be used in children under the age of seven.

Interaction with other medicaments and other forms of interaction

No clinically relevant interactions are known.

Pregnancy and lactation

There are no adequate data from the use of diethylamine salicylate and/or diethylamine salicylate/myrtecaine in pregnant women. No relevant animal or epidemiological data are available.

The use of diethylamine salicylate and/or diethylamine salicylate/myrtecaine is not recommended during pregnancy or lactation.

Effects on ability to drive and use machines

There is no indication to restrict driving or use of machinery whilst receiving this therapy.

Undesirable effects

Allergic reactions (rash, pruritus, urticaria) have been reported very rarely.

Overdose

No cases of overdose have been reported.

Since terpene derivatives (i.e. camphor) are used as excipients there is a risk of convulsions in infants and children and a risk of agitation and confusion in elderly subjects if the recommended doses are exceeded.

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APPENDIX 4

CIOMS LINE LISTING OF ADR REPORTS

Solvay Pharmaceuticals 29-JAN-2002
CIOMS Line Listing of Selected Case Histories

Diethylamine Salicylate & Diethylamine Salicylate/Myrtecaine Adverse Reaction Reports received between 01 Jan 1997 and 31 Dec 2001 sorted by Seriousness and Body System

Reporting cases selected from the Case List.

Cross reference: NONE

The Comment column contains: Causality and Company Causality, Protocol Id and Patient Id

The Reaction column contains: Term and Preferred Term

Query:

```
(AES_EVENT.AES$EVENT_ID LIKE 'DIET%')
AND (AES_EVENT.AES$FIRST_RECEIVED BETWEEN TO_DATE('01-JAN-1997', 'DD-MON-YYYY')
AND TO_DATE('31-DEC-2001', 'DD-MON-YYYY'))
AND ((AES_EVENT.AES$SOURCE = 'SP')
OR ((AES_EVENT.AES$SOURCE = 'SS') AND
(AES_EVENT.AES$SERIOUS = 'YES') AND
(AES_EVENT.AES$COMPANY_CAUSAL = 'Suspect'))
OR ((AES_EVENT.AES$SOURCE = 'SS') AND
(AES_EVENT.AES$SERIOUS = 'YES') AND
(AES_EVENT.AES$COMPANY_CAUSAL IS NULL))
OR ((AES_EVENT.AES$SOURCE = 'US') AND
(AES_EVENT.AES$SERIOUS = 'YES') AND
(AES_EVENT.AES$COMPANY_CAUSAL IS NULL))
OR ((AES_EVENT.AES$SOURCE = 'US') AND
(AES_EVENT.AES$SERIOUS = 'YES') AND
(AES_EVENT.AES$COMPANY_CAUSAL = 'Suspect'))
OR (AES_EVENT.AES$SOURCE IS NULL))
ORDER BY AES_EVENT.AES$EVENT_ID DESC
```

Company Ref. Num.	Country	Source	Age	Sex	Daily Dose	Time to onset	Description of reaction(s)	Outcome	Comment
Serious CV - Cardiovascular System									
–									
DIET018970 002	FR	Auth.	85 yrs	M	(DIETHYLAMINE SALICYLATE)		HAEMATOMA/HEMORRHAGE	Not yet recovered	Causality:Unlikely/Suspect Additional drugs: SD:PARACETAMOL 3 DF, SD:LORAZEPAM 1 DF
Serious HAL - Hemic and Lymphatic System									
–									
DIET018970 001	FR	Auth.	55 yrs	F	(DIETHYLAMINE SALICYLATE)	1 month	THROMBOCYTOPENIA WITH PURPURA/THROMBOCYTOPENIC PURPURA	Not yet recovered	Causality:Unlikely/Suspect Additional drugs: SD:NAFTAZONE 40 mg, SD:FENOPROFEN CALCIUM NI, SD:ALDACTAZINE NI, SD:ACEBUTOLOL HYDROCHLORIDE NI, SD:CHONDROITIN SULFATE SODIUM NI
Non-serious SKIN - Skin and Appendages									
–									
DIET003970 001	UK	Spont.	69 yrs	F	unk (DIETHYLAMINE SALICYLATE)		RASH/RASH, BURNING SENSATION/PAIN	Abating	Causality:Possible/Suspect
–									
DIET018980 001	FR	Spont.	67 yrs	F	(DIETHYLAMINE SALICYLATE/ MYRTECAINE)	1 month	PRURIGINOUS ERUPTION/RASH	Recovered completely	Causality:Highly Probable/Suspect Additional drugs: CD:TRAMADOL 2 DF, CD:CLORAZEPATE DIPOTASSIUM 2 DF

Company Ref. Num.	Country	Source	Age	Sex	Daily Dose	Time to onset	Description of reaction(s)	Outcome	Comment

Number of cases selected from Case List: 4
Number of cases reported in Line Listing: 4

APPENDIX 5

FREQUENCY LIST OF REPORTED SIGNS, SYMPTOMS AND DIAGNOSES

Report Date : 16-JAN-2002 Page 1

Diethylamine Salicylate & Diethylamine Salicylate/Myrtecaine
Frequency Report
(excluding non-suspect study cases) For 01 Jan 1997 To 31 Dec 2001
Case Selection Criteria : DIET%

Body System/COSTART Term	Total Terms Reported	Market	Clinical Study	Health Authority	Literature
Body as a Whole					
PAIN	1	1	0	0	0
Total	1	1	0	0	0
Cardiovascular System					
HEM	1	0	0	1	0
Total	1	0	0	1	0
Digestive System					
Total	0	0	0	0	0
Endocrine System					
Total	0	0	0	0	0
Hemic and Lymphatic System					
PURPURA THROMBOPEN	1	0	0	1	0
Total	1	0	0	1	0
Metabolic and Nutritional Disorders					
Total	0	0	0	0	0
Musculoskeletal System					
Total	0	0	0	0	0
Nervous System					
Total	0	0	0	0	0
Respiratory System					
Total	0	0	0	0	0
Skin and Appendages					
RASH	2	2	0	0	0
Total	2	2	0	0	0
Special Senses					
Total	0	0	0	0	0
Urogenital System					
Total	0	0	0	0	0
GRAND TOTAL	5	3	0	2	0

* Individual reports may contain more than one sign or symptom.
Reports may have been obtained from more than one source.

Report Date : 16-JAN-2002 Page 2

Diethylamine Salicylate & Diethylamine Salicylate/Myrtecaine Frequency Report
(excluding non-suspect study cases) For 01 Jan 1997 To 31 Dec 2001
Case Selection Criteria : DIET%

Body System/COSTART Term	Total Terms Reported	Market	Clinical Study	Health Authority	Literature
Body as a Whole	0	0	0	0	0
Cardiovascular System	1	0	0	1	0
Digestive System	0	0	0	0	0
Endocrine System	0	0	0	0	0
Hemic and Lymphatic System	1	0	0	1	0
Metabolic and Nutritional Disorders	0	0	0	0	0
Muscloskeletal System	0	0	0	0	0
Nervous System	0	0	0	0	0
Respiratory System	0	0	0	0	0
Skin and Appendages	2	2	0	0	0
Special Senses	0	0	0	0	0
Urogenital System	0	0	0	0	0
TOTAL UNIQUE REPORTS	4	2	0	2	0

* Individual reports may contain more than one sign or symptom. Reports may have been obtained from more than one source.

APPENDIX 6
BIBLIOGRAPHY

SOLVAY

Report No.: DIET 01

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