



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/HMPC/706537/2014
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Matricaria recutita* L., aetheroleum (EMA/HMPC/278814/2010)

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Matricaria recutita* L., aetheroleum as released for public consultation on 24 July 2014 until 31 October 2014.

	Organisations and/or individuals
1	Alpinia Laudanum Institute of Phytopharmaceuticals Sciences AG, Switzerland
2	Herbresearch, Germany
3	MEDA Pharma GmbH & Co. KG, Germany
4	Robugen GmbH, Germany



Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
Alpinia Institute	<u>Comment:</u> 1, Chamomile oil contains active ingredients with positive pharmacological activities (e.g. anti-peptic, spasmolytic, anti-ulcer, anti-phlogistic, epithelisation, granulation, fungistatic activities). <u>Rational:</u> Literature based information (in vitro and in vivo animal models): <u>(-) alpha-bisabolol:</u> - anti-peptic activity in in vitro model (Isaac and Thieme, 1975) - spasmolytic action in in vitro isolated guinea pig ileum model (Achterath et al., 1980) - anti-ulcer activity (protective and curative) in rat ulcer models (Szelenyi et al., 1979) - anti-phlogistic effect (Isaac, 1979; Jakovlev et al. 1983) - promotion of epithelisation and granulation (Isaac, 1979) - fungistatic effect (Hitziger et al., 2003) <u>Chamazulene</u> - anti-phlogistic effect (Isaac, 1979, Jakovlev et al. 1983) <u>(-)-alpha-bisabolol oxide A and B</u> - spasmolytic action in in vitro isolated guinea pig ileum model (Achterath-Tuckermann et al., 1980)	The comment is not endorsed. The monograph will not be extended to a monopreparation of <i>matricaria aetheroleum</i> in semisolid dosage form. The changes in the history of the product are substantial. The product contained thirty years ago 10 active substances (homeopathic preparations, vitamins and <i>Matricaria aetheroleum</i>) and was diminished to a monopreparation because some ingredients were declared as excipients, some were extinguished due to a lacking combination rationale, some due to toxicological reasons. The herbal medicinal product is a monopreparation only since 2006. The plausibility of efficacy for the monopreparation cannot be concluded with reference to the combination product.

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	<u>Comment:</u> 2, Chamomile oil has very good toxicological features: <u>Rational:</u> Literature based information: <u>Acute toxicity:</u> LD50 (oral and dermal): 5 g/kg in rabbits (Opdyke, 1974). <u>Irritation:</u> In mice undiluted chamomile oil produced no irritating effect (Opdyke, 1974). On intact or abraded rabbit skin (24 h) full strength chamomile oil under occlusion was moderately irritating. 4 % chamomile oil in petroleum induced no irritation after 48 h closed-patch test (Opdyke, 1974). <u>Sensitization:</u> In human (n = 25, maximization test), 4 % chamomile oil in petroleum produced no sensitization (Opdyke, 1974). <u>Phototoxicity:</u> No phototoxicity effects of chamomile oil were reported (Opdyke, 1974). <u>Comment:</u> 3, Alpinia Institute recommends the extension of the Community Herbal Monograph on <i>Matricaria recutita</i> L., aetheroleum in the field of traditional use: Additional pharmaceutical form: semi-solid dosage forms (e.g. ointment) <u>Rational:</u> An ointment under the name of Hewekzem novo Heilsalbe N (Marketing Authorization	

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	Holder: Hevert-Arzneimittel GmbH & Co. KG; Registration number [Eingangsnummer]: 0886191) was marketed before the 1st of January 1978 in Germany under the name Hewekzem-Salbe. In the first registration the following active ingredients were listed (in 100 g ointment): <table border="1" data-bbox="430 512 1384 1251"> <thead> <tr> <th>Name of the compound</th><th>Amount</th><th>Dilution</th></tr> </thead> <tbody> <tr> <td>all-rac-alpha-Tocopherol-acetate (Ph.Eur.)</td><td>200 mg</td><td></td></tr> <tr> <td>Retinol-palmitate</td><td>200000 I.E.</td><td></td></tr> <tr> <td>Panthenol</td><td>2 g</td><td></td></tr> <tr> <td>Chamomile oil</td><td>1 g</td><td></td></tr> <tr> <td>Smilax (Pot.-Information)</td><td>2 g</td><td>D1</td></tr> <tr> <td>Aristolochic acid</td><td>1 mg</td><td></td></tr> <tr> <td>Conium maculatum (Pot.- Information)</td><td>2 g</td><td>D3</td></tr> <tr> <td>Echinacea purpurea (Pot.- Information)</td><td>2 g</td><td>UT</td></tr> <tr> <td>Psorinum-Nosode (Pot.- Information)</td><td>2 g</td><td>D12</td></tr> <tr> <td>Anthrarobin</td><td>100 mg</td><td></td></tr> </tbody> </table> In 24.03.1983 aristolochic acid was removed from the active ingredients. In 29.03.1988 Conium maculatum, Psorinum-Nosode and anthrarobin were removed from the active ingredients.	Name of the compound	Amount	Dilution	all-rac-alpha-Tocopherol-acetate (Ph.Eur.)	200 mg		Retinol-palmitate	200000 I.E.		Panthenol	2 g		Chamomile oil	1 g		Smilax (Pot.-Information)	2 g	D1	Aristolochic acid	1 mg		Conium maculatum (Pot.- Information)	2 g	D3	Echinacea purpurea (Pot.- Information)	2 g	UT	Psorinum-Nosode (Pot.- Information)	2 g	D12	Anthrarobin	100 mg		
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	In 31.01.2001 panthenol, retinol-palmitate, all-rac-alpha-tocopherol-acetate, Echinacea purpurea and Smilax were removed from the active ingredients. Since 10.05.2006 the ointment contains from the original active ingredients just panthenol, retinol-palmitate, all-rac-alpha-tocopherol-acetate as excipients. Additionally hydrophile ointment was also added to the excipient list. Only Chamomile oil remained as single active substance. Until 31.01.2001, from the originally named 10 active ingredients, 9 (all-rac-alpha-tocopherol-acetate, retinol-palmitate, panthenol, Smilax, aristolochic acid, Conium maculatum, Echinacea purpurea, Psorinum-Nosode and anthrarobin) were removed from the list of active ingredients. Only Chamomile oil remained as single active substance. Therefore the product can be considered as mono-preparation of chamomile oil in an application form as ointment with a history of more than 30 years of medicinal use in the European Union. The life cycle of this product clearly shows that Hewekzem novo Heilsalbe N can be considered as mono-preparation of chamomile oil in semi-solid dosage form (Hewekzem novo Heilsalbe 2014). The presence of this product (in semi-solid dosage form) on the German market fulfills the criteria of the traditional use as declared in the directive 2001/83/EC.	
Alpinia Institute	<u>Comment:</u> 4, Alpinia Institute recommends the extension of the Community Herbal Monograph on <i>Matricaria recutita</i> L., aetheroleum in the field of traditional use: Additional therapeutic indications in semi-solid dosage forms: treatment of chronic dermatosis, eczema, furunculosis, pyodermatitis, psoriasis and to use for the treatment of minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles).	The comment is not endorsed (see above, lack of tradition). Additionally suggested therapeutic indications in semi-solid dosage forms like treatment of chronic dermatosis, eczema, furunculosis, pyodermatitis, psoriasis are not suitable for traditional use due to excluded medical advice. The other indications are already covered.

Interested party	Comment and Rationale	Outcome
	<u>Rational:</u> Hewekzem novo Heilsalbe N (Marketing Authorization Holder: Hevert-Arzneimittel GmbH & Co. KG; Registration number [Eingangsnummer]: 0886191) was registered with the following applications: chronic dermatosis, eczema, furunculosis, pyodermitis and psoriasis by the German Federal Public Health Office (Bundesgesundheitsamt ([BGA]) in 1978. The name of the product was Hewekzem-Salbe at that time. (Bundesgesundheitsamt 1978). The presence of this product (in semi-solid dosage form) with the above mentioned indications on the German market fulfills the criteria of the traditional use as declared in the directive 2001/83/EC. <u>Information from textbook(s):</u> The main topical applications of chamomile flowers and chamomile oil are named together as: inflammatory condition of the skin and mucous membrane, irritation in mouth, throat, anal and genital areas; in the forms of ointment, cream, inhalation, compresses, and bath (Wagner, Vollmar, Bechthold, 2007). The Comment to the European Pharmacopoeia (Bracher et al., 2009), in the case of the application of chamomile oil refers to the application of chamomile flowers (Ph.Eur.) e.g. in semi-solid application forms (ointments and creams): maintenance therapy of the atopic eczema. In the book of Pharmazeutische Biologie: Drogen und ihre Inhaltsstoffe (Wagner, 1988), the applications of chamomile flowers and chamomile oil are named together as skin inflammation, rhagade, mastitis, burns and Ulcus cruris. Chamomile oil is often also part of ointments (Teuscher 1997). The Community herbal monograph on <i>Matricaria recutita</i> L., flos (EMA/HMPC/55843/2011, Adoption by Committee on Herbal Medicinal Products (HMPC) for release for consultation on 01. July 2014) proposes the traditional use of chamomile flowers to use for the treatment of minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles)	

Interested party	Comment and Rationale	Outcome
	(EMA/HMPC/55843/2011). Since textbooks on Pharmacognosy name the topical applications of chamomile oil the same as chamomile flowers, it is recommended to add to the indications of chamomile oil in the Community Herbal Monograph on <i>Matricaria recutita</i> L., aetheroleum, the traditional use indications of chamomile flowers (as it is proposed in the Community herbal monograph on <i>Matricaria recutita</i> L., flos, EMA/HMPC/55843/2011; see above). <u>Recent studies in animals:</u> The anti-inflammatory effect of topical (-)-α-bisabolol was shown in a mouse model for acute dermatitis induced by croton oil, arachidonic acid, phenol and capsaicin. Pretreatment of the animals ears with (-)-α-Bisabolol (0.7 and 1.4 mg/ear, 15 min. before application) inhibited the dermatitis induced by all noxious agents except capsaicin (Leite et al., 2011). In mice with atopic dermatitis induced by 2,4-dinitrochlorobenzene (1 %, 100 μl, 2x per week; challenged the following week with 0.2 %, 100 μl, 2x per week), the application of German chamomile (GC) oil on the dorsal skin of the animals (3 %, 1x per day, 6 x per week, 70 μl, for 4 weeks) resulted a significant reduction of blood IgE levels at the end of the study. The scratching frequency of the animals in the GC-oil group was also significantly lower than either control groups (saline or jojoba oil). The GC oil application for 4 weeks resulted in reduction in serum IgG1 level compared with that after 2-week application. The GC oil application group showed a significantly lower serum histamine level than the control group 2 weeks after oil application. These experimental data suggest that the application of GC oil on the skin of atopic dermatitis cases could alter production of IL-4 from Th2 cells and also alter IgE, IgG1 and histamine production, performing a series of immunoregulatory functions to alleviate the occurrence or progression of atopic dermatitis (Lee et al., 2010).	

Interested party	Comment and Rationale	Outcome
	<u>Older publication (not cutaneous application):</u> The antibacterial effects of chamomile oil (0.6 - 0.7 %, v/v) against gram positive bacteria (e.g. <i>S. aureus</i>, <i>B. subtilis</i>) were shown to be good and better than against gram negative bacteria (e.g. <i>E. coli</i>, <i>P. aeruginosa</i>). Chamomile oil (0.7 %, v/v) showed also good antifungal activity against <i>C. albicans</i>. The authors have suggested the incorporation of chamomile oil in topical preparations for staphylococcal infections (Aggag and Yoursef, 1972). Based on the presented, data Alpinia Institute recommends the extension of the Community herbal monograph on <i>Matricaria recutita</i> L., aetheroleum in the field of traditional medical use in semi-solid dosage forms (ointment) for cutaneous application with the following recommended traditional therapeutic indications: the treatment of the chronic dermatosis, eczema, furunculosis, pyodermatitis, psoriasis and the use for the treatment of minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles). <u>References:</u> Achterrath-Tuckermann U, Kunde R, Flaskamp E, Issac O, Thiemer K. (1980) Pharmacological investigations with compounds of chamomile. V. Investigations on the spasmolytic effect of compounds of chamomile and Kamillosan on the isolated guinea pig ileum. <i>Planta Med</i>; 39:38-50. Aggag ME, Yoursef RT. (1972) Study of antimicrobial activity of chamomile oil. <i>Planta Med</i>. 22:140-144. Bracher F., Heisig P., Langguth P., Mutschler E., Rücker G et al., (2009) Kommentar zum Europäischen Arzneibuch, (Kamillenöl; Part of Kamillenblüten); Bundesgesundheitsamt 1978; Community herbal monograph on <i>Matricaria recutita</i> L., flos (draft,	

Interested party	Comment and Rationale	Outcome
	EMA/HMPC/55843/2011); Hewekzem novo Heilsalbe (2014) Information on authorisation status in Germany. DIMDI: AMIS-Öffentlicher Teil (AJ29) and Beschiedene Änderungsanzeigen (AJ30).; Hitziger T, Höll P, Ramadan M, Dettmering D, Imming P. (2003) Die alte junge Kamille. Pharmazeutische Zeitung online. Isaac O. (1979) Pharmacological investigations with compounds of chamomile i. on the pharmacology of (-)-alpha-bisabolol and bisabolol oxides (review) (author's transl). Planta Med; 35:118-124. Isaac O, Thiemer K. (1975) Biochemical studies on camomile components/III. In vitro studies about the antipeptic activity of (-)-alpha-bisabolol (author's transl). Arzneimittelforschung; 25:1352-1354. Jakovlev V, Isaac O, Flaskamp E. (1983) Pharmacologic studies on chamomile compounds. VI. Studies on the antiphlogistic effect of chamazulene and matricine. Planta Med; 49:67-73. Lee SH, Heo Y, Kim YC. (2010) Effect of German chamomile oil application on alleviating atopic dermatitis-like immune alterations in mice. J. Vet. Sci.;11(1):35-41.; Leite Gde O., Leite LH., Sampaio Rde S., Araruna MK., de Menezes IR., da Costa JG et al., (2011) (-)-α-Bisabolol attenuates visceral nociception and inflammation in mice. Fitoterapia, 82(2):208-11. Opdyke DL. (1974) Chamomile oil German. Food Cosmet. Toxicol., 12:851-852. Szelenyi I, Isaac O, Thiemer K. (1979) Pharmacological experiments with compounds of chamomile. III. Experimental studies of the ulcerprotective effect of chamomile (author's transl). Planta Med; 35:218-227.	

Interested party	Comment and Rationale	Outcome
	Teuscher E, (1997) Biogene Arzneimittel (5 überarbeitete und erweiterte Auflage) Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 249-50. Wagner H, Vollmar A, Bechthold A. (2007) Pharmazeutische Biologie 2: Biogene Arzneistoffe und Grundlagen von Gentechnik und Immunologie, Auflage. Stuttgart: Wiss. Verl., page: 57. Wagner H, (1988) Pharmazeutische Biologie Drogen und ihre Inhaltsstoffe (4., neubearbeitete Auflage) Gustav Fischer Verlag, Stuttgart, New-York, 78-80.	
Herbresearch	The Draft monograph mentions the use of chamomile essential oil exclusively in the context of bath additives. The use in bath additives is backed by the assessment report, chapter 2.2 (Information on traditional/current indications and specified substances/preparations in European countries), section on Germany, item 16, where the use in bath additives is confirmed. Next to the use in bath additives, there is a documented use in topical preparations applied for inflammatory skin affections and wound healing through German-authorized medicinal products. For example, DIMDI lists the ointment "Hewekzem novo Heilsalbe N", where the history of the product demonstrates an unchanged content of one per cent chamomile essential oil throughout the history of the product. This history can be traced back to the entry into the German speciality register in 1978. Details are given below in the comments to Chapter 3 of the draft Community Herbal Monograph. We recommend that the use in topical preparations is added to the monograph.	The comment is not endorsed. (see above)
MEDA Pharm	No comment	All comments regarding monograph <i>Matricariae flos</i> and AR, if applicable, are considered in the relevant documents.

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
3. Pharmaceutical Form	Herbresearch	Chapter 3 on the “Pharmaceutical form” mentions herbal preparations in liquid dosage forms for use as a bath additive. The Assessment Report refers to bath additives as the only identified form of chamomile essential oil preparations, and exclusively from German products. There is, however, another form of chamomile oil preparations: the use in ointments applied against inflammatory skin disorders. The AMIS database has an entry on an ointment preparation (1), for which the general composition has changed over the years, but the content and quantity of chamomile essential oil was left unchanged since the first notification to the German Bundesgesundheitsamt and the entry into the pharmaceutical speciality register on Januar 1st, 1978. The ointment was originally registered as “Hewekzem Salbe” and had the following composition per 100 g of ointment: Aristocholic acid: 1 mg Anthrarobin: 100 mg Phanthenol: 2 g Vitamin A palmitate: 200,000 IU Vitamin E acetate: 200 mg Oleum Chamomillae: 1 g Conium D3: 2 g Echinacea mother tincture: 2 g	The comment is not endorsed. (see above)

Section number and heading	Interested party	Comment and Rationale	Outcome
		Psorinum D12: 2g Sarsaparilla D1: 2 g By variation of 24. March 1983 the composition was changed by removing aristolochic acid. By variation of 29. March 1988 the name was changed to "Hewekzem novo", and the composition was adjusted by removing the components anthrarobin, Conium D3 and Psorinum D12. Finally, another variation was made on 31. January 2001, changing the name to "Hewekzem novo Heilsalbe N" and removing all remaining constituents except chamomile oil, thus turning the product into a mono-preparation with 1 g chamomile oil per 100 g of ointment. Taking the possibility of minus variants in traditional herbal medicinal product registration into account (Article 16c of Directive 2001/83/EC as amended), this ointment exceeds the requirements of 30 years of medicinal use, even uninterrupted). The indication (see comments to Chapter 4.1 – Therapeutic indication) was left essentially unchanged throughout the history of the product. The same goes for the dosing recommendations (see comments to Chapter 4.2 – Posology and method of administration). We therefore recommend inserting the following text after the "use a bath additive": Herbal preparations in semisolid dosage forms for cutaneous use. Of note: A corresponding entry was made for chamomile extracts in the Draft Community Herbal Monograph on <i>Matricaria recutita</i> L., flos (EMA/HMPC/55843/2011).	

Section number and heading	Interested party	Comment and Rationale	Outcome
4.1. Therapeutic indications	Herbresearch	The draft Community Herbal Monograph indicates (by reference to the bath additives) the indication: “Traditional herbal medicinal product used for adjuvant therapy of irritations of skin and mucosae in the anal and genital region, after serious conditions have been excluded by a medical doctor”. The ointment described in the comments to Chapter 3 was originally registered with the indication “chronic dermatoses, eczema, furunculosis, pyodermias, psoriasis”. By variation of 29. March 1988, the therapeutic indication was changed to “Eczema, dermal fungi, pyoderma such as acne or furunculosis, psoriasis, chronic dermatoses”. This formulation is currently still used and essentially covers the original uses. With the ointment fulfilling the precondition of a 30-year use (see comments to Chapter 3) we recommend changing the text of Chapter 4.1 as follows (or similar): Use in bath additives: Traditional herbal medicinal product used for adjuvant therapy of irritations of the skin and mucosae in the anal and genital region, after serious conditions have been excluded by a medical doctor. Use in semisolid forms for cutaneous use: Traditional herbal medicinal product used for the treatment of chronic skin eruptions such as eczema, psoriasis diagnosed by a physician, dermatomycosis and bacterial or inflammatory skin affections like acne or furunculosis.	The comment is not endorsed. (see above)

Section number and heading	Interested party	Comment and Rationale	Outcome
		The product is a traditional... Of note: The Draft "Community Herbal Monograph on <i>Matricaria recutita</i> L., flos (EMA/HMPC/55843/2011) lists two corresponding uses: "Indication 4): Traditional herbal medicinal product used for adjuvant therapy of irritations of the skin and mucosae in the anal and genital region, after serious conditions have been excluded by a medical doctor" and "Indication 5): Traditional herbal medicinal product used for the treatment of minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles)." These uses explicitly refer to semi-solid pharmaceutical forms for cutaneous use, which confirms the plausibility in the intended applications (irritations and inflammations of the skin, furuncles). Correspondingly, the uses proposed above are in accordance with uses recognized as traditional for semisolid dose forms containing chamomile extracts – dose forms which contain the fraction of the essential oil and especially bisabolol, which is presented in the Assessment Report as one of the constituents possibly linked to the claimed effect.	
4.1. Therapeutic indications	Robugen	The following statement should be added: Examples might be added in accordance with the traditional long-standing use of the preparation in question.	The comment is not endorsed. There are no specific examples listed. The monograph is covering published data considering the regulatory framework. The wording of the therapeutic indication is consistent with European Union monographs addressing the same therapeutic area. Product specific data may be provided in an individual application.

Section number and heading	Interested party	Comment and Rationale	Outcome
4.2. Posology and method of administration	Herbresearch	The posology and method of administration for the ointment “Hewekzem” described in the comments to Chapter 3 and 4.1 is defined as “Apply on the affected skin areas several times daily”. The Draft Community Herbal monograph on <i>Matricaria recutita</i>, flos (EMA/HMPC/55843/2011) indicates for the semi-solid dosage forms for cutaneous use and the indications 4 and 5 cited in the comments to Chapter 4.1: “Single dose: Apply a thin layer on the affected area. Daily dose: several times” We therefore recommend adding the posology of the semi-solid dose forms: “Use in semi-solid dose forms for cutaneous use: Apply a thin layer on the affected area. Daily dose: several times.”	The comment is not endorsed. (see above)
4.2. Posology and method of administration	Robugen	As there have been no age restrictions in these indications during traditional use, the wording “Adolescents, adults and elderly” should be discarded.	The comment is not endorsed. The establishment of European Union monographs is based on public data. The assessment is taking into account special patient groups. There are no data regarding the use in children which are sufficient to consider use in children.
4.4. Special warnings and precautions for use	Robugen	The use should only be restricted in early infancy (under 1 year) due to lack of data. The preparation in question has been used traditionally without further age restrictions.	The comment is not endorsed. (see above)
4.6. Fertility, pregnancy and lactation	Robugen	Since there is no risk with the use of <i>matricaria</i> teas during pregnancy and lactation (as documented on Page 57, assessment report) and since <i>matricaria</i> tea contains the ingredients of <i>matricaria aetheroleum</i> beside other compounds the following text should be sufficient: The preparation should only be used after recommendation by a physician.	The comment is not endorsed. For traditional use an obligatory recommendation by a physician is excluded. There are no data regarding the use of the essential oil in pregnant women.

Section number and heading	Interested party	Comment and Rationale	Outcome
4.8. Undesirable effects	Robugen	There should be made a differentiation between the application of Matricaria tea and preparations with matricaria aetheroleum: In the mentioned case reports (see assessment report 4.7) Subiza et al. 1989, Pereira et al. 1997, Rycroft 2003, Thien 2001, Benner and Lee 1973 only matricaria tea has been reported in connection with severe allergic reactions, obviously due to the large amount of chamomile pollen in it according to Subiza et al. 1989 and 1990. Preparations with matricaria aetheroleum do not contain matricaria pollen and had not been involved in the above mentioned cases. The allergic reactions reported by Jensen-Jarolim et al. 1998 and Senff et al. 1989 resulted from a misuse of the matricaria extracts (enema and aerosol therapy) which should be excluded for all matricaria preparations. The wording of the first part in 4.8. should be changed to: Hypersensitivity reactions including severe allergic reactions (dyspnea, Quincke's disease, vascular collapse, anaphylactic shock) following mucosal contact with liquid chamomile preparations have been reported with the use of matricaria tea. The frequency is not known. Preparations with matricaria aetheroleum should not be used as enema or aerosol. No copies of the literature attached as it is mentioned in the list of references (EMA/HMPC/55810/2011).	The comment is not endorsed. There are no specific data available which contribute the allergic reactions to the pollen.