European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

London, 6 March 2008
Doc. Ref. EMEA/HMPC/590044/2007

OVERVIEW OF COMMENTS RECEIVED ON
'COMMUNITY HERBAL MONOGRAPH ON
***CALENDULA OFFICINALIS* L., FLOS'**
EMEA/HMPC/179281/2007

Table 1: Organisations that commented on the document as released for consultation in May 2007 until 15 August 2007

	Organisation
1.	Association of the European Self-Medication Industry (AESGP)
2.	European Scientific Cooperative on Phytotherapy (ESCOP)
3.	Pharmonta Dr. Fischer GmbH, Austria (Pharmonta)

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

General comments	Comment and rationale	Rapporteur's comments
1	We suggest to include a well-established use for topical application in indication a) into the monograph. Clinical data from three studies (references are given) are available supporting the efficacy of extracts from Calendula officinalis, flos, in burns and as anti-inflammatory agents in the prevention of acute dermatitis after radiotherapy.	Indication 'burns', reference Baranov 1999: Pilot study with a Calendula jelly containing 10% of a homoeopathic mother tincture in 30 patients with first- and second-degree burns. The lack of a control group makes the evaluation of the efficacy impossible. This study can only be used for support of the traditional use of Calendula for the treatment of minor inflammations of the skin because of the chemical similarity of homoeopathic mother tinctures and phytotherapeutic tinctures. Indication 'prevention of acute dermatitis after radiotherapy', references Lievre M et al (1992), Pommier P et al (2004): both trials have been conducted with a preparation called 'pommade au calendula par digestion' which is prepared from the complete aerial parts of Calendula officinalis. A bridging from these studies to preparations containing the ligulate flowers only is not allowed. Therefore well-established use cannot be included into this monograph. Such a preparation should be considered in a separate monograph.

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
2. Qualitative and quantitative composition	Addition of the liquid extract DER 1:2, extraction solvent ethanol 50% (v/v). This type of extract is produced in our company more than 30 years.	Endorsed
	Well-established use: With regard to the marketing authorisation application of Article 10a of Directive 2001/83/EC as amended *Calendula officinalis* L., flos Herbal substance *Calendula officinalis* L., flos (calendula flower) Herbal preparations A) Liquid extract (DER 1:1, ethanol 40-50% v/v) B) Tincture (DER 1:5, ethanol 70-90% v/v) C) Liquid extract (DER 1:10, fatty vegetable oil e.g. olive oil) D) Ointment (DER 1:5 – 1:25, hardened vegetable fat, petroleum jelly)	Well-established use not endorsed. See comments above.
3. Pharmaceutical form	Well-established use: Herbal preparation in semi-solid or liquid dosage forms for topical use.	Well-established use not endorsed. See comments above.
4.1 Therapeutic indication	Well-established use: Symptomatic treatment of minor inflammations of the skin; as an aid to the healing of minor wounds.	Well-established use not endorsed. See comments above.
4.2 Posology and method of administration	Well-established use: Herbal preparations: Adults: A) Liquid extract (DER 1:1, ethanol 40-50% v/v) In semi-solid dosage forms: amount equivalent to 2-10% herbal substance B) Tincture In compresses diluted at least 1:3 with freshly boiled water; in semi-solid dosage forms: amount equivalent to 2-10% herbal substance	Well-established use not endorsed. See comments above.

	C) Liquid extract (DER 1:10, fatty vegetable oil e.g. olive oil) In semi-solid dosage forms: amount equivalent to 2-8% herbal substance D) Ointment Equivalent to 4-20% herbal substance Children [4]: 0-1 years of age: preparations equivalent to1-2 g of the herbal substance more than 1 up to 4 years of age: 2-4 g of the herbal substance more than 4 years of age: preparations equivalent to 2-5 g of the herbal substance Topical application, two to four times daily	
	The liquid extract (DER 1:2) is mixed with excipients to a final DER of 1:20.	Endorsed
	Traditional use: Indication a) The external use of Calendulae flos preparations was permitted for cosmetic purposes in children by the Council of Europe 1989 (10% admixture at max.) For this reason we propose to delete the statement: ***"The use in children under 6 years of age is not recommended because there is no experience available."***	Cosmetic products are intended for an application on the intact skin, whereas herbal medicinal products containing herbal preparations from Calendula flowers are used for the treatment of inflamed skin or minor wounds, where the absorption of substances may be different. Since the evaluation of literature concerning the safe use of preparations containing Calendula in the paedriatic population did not reveal sufficient data, the use in children below 6 years of age cannot be recommended.
	Traditional use: The restrictions of use in children under 6 years of age in indication a) and under 12 years of age in indication b) in traditional use are not justified, especially when the route of administration, the long time of experience and available experimental data are taken into account.	See above
	Traditional use: The restriction for duration of the compress is not clear.	The restriction mentioned gives an advice to the duration of a single application. The limit of 1 week applies to all herbal preparations. The wording will be improved.
4.3 Contraindications	Well-established use: Hypersensitivity to members of the Asteraceae family (Compositae family).	Well-established use not endorsed. See comments above.

4.4 - Special warnings and precautions for use	Well-established use: If signs of skin infection are observed, medical advice should be sought.	Well-established use not endorsed. See comments above.
	Traditional use: Indication a) The external use of Calendulae flos preparations was permitted for cosmetic purposes in children by the Council of Europe 1989 (10% admixture at max.) For this reason we propose to delete the statement: ***"The use in children under 6 years of age is not recommended because there is no experience available."***	See above
	Traditional use: The restrictions of use in children under 6 years of age in indication a) and under 12 years of age in indication b) in traditional use are not justified, especially when the route of administration, the long time of experience and available experimental data are taken into account.	See above
4.5 Interactions	Well-established use: None reported.	Well-established use not endorsed. See comments above.
4.6 Pregnancy and lactation	Well-established use: No data available. However, there are no objections to external use during pregnancy and lactation.	Well-established use not endorsed. See comments above.
	Traditional use: No data available. However, there are no objections to external use during pregnancy and lactation.	Since no data on the safe medicinal use of Calendula flowers during pregnancy and lactation in the mentioned indications are available, the use during pregnancy and lactation cannot be recommended
	Traditional use: We propose the following wording: "Safety during pregnancy and lactation has not been established. **No adverse effects have been reported from the use of Calendulae flos as a medicinal product during pregnancy and lactation**. **As a precautionary measure,** the use during pregnancy and lactation is not recommended." This is in line with the ESCOP monograph.	See above

4.7 Effects on ability to drive and use machines	Well-established use: Not relevant.	Well-established use not endorsed. See comments above.
4.8 Undesirable effects	Well-established use: Skin sensitization. The frequency is not known. If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted.	Well-established use not endorsed. See comments above.
	Traditional use: The text reads: "Skin sensitisation. The frequency is not known. If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted." We propose: **Skin sensitisation was reported anecdotally.** Reason: There is no case report in the literature which proves a relationship between the external use of Calendulae flos preparations and skin sensitisation.	According to the guideline on the SPC statements like 'isolated/single cases/reports' should not be used. If for a specific ADR a frequency cannot be estimated or a frequency category not be chosen an additional category frequency 'not known' may be added. Change not endorsed.
4.9 Overdose	Well-established use: No case of overdose has been reported.	Well-established use not endorsed. See comments above.
5.1 Phyrmacodynamic properties	Well-established use: We refer to the ESCOP monograph and clinical studies [1,2,3]. The respective pharmacotherapeutic group and the ATC code for treatment of wounds should be added.	Well-established use not endorsed. See comments above.
5.2 Pharmacokinetic properties	Well-established use: No data available.	Well-established use not endorsed. See comments above.
5.3 Preclinical safety data	Well-established use: We refer to the ESCOP monograph: Aqueous, hydroethanolic and ethyleneglycol extacts have shown low toxicity in rodents during acute tests and no toxicity after administration of repeated doses over periods of 2 – 20 months. Neither genotoxicity nor carcinogenicity were observed *in vivo.*	Well-established use not endorsed. See comments above.