5 May 2015
EMA/HMPC/41015/2015
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Capsicum annuum* L. var. *minimum* (Miller) Heiser and small fruited varieties of *Capsicum frutescens* L., fructus (EMA/HMPC/674139/2013)

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Capsicum annuum* L. var. *minimum* (Miller) Heiser and small fruited varieties of *Capsicum frutescens* L., fructus as released for public consultation on 12 September 2014 until 15 December 2014.

	Organisations and/or individuals
1	Association of the European Self-medication Industry (AESGP)
2	Arkopharma Laboratoires Pharmaceutiques, France

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	AESGP welcomes the development of the above-mentioned Community herbal monograph which, by providing harmonised assessment criteria for Capsicum-containing products, should facilitate mutual recognition in Europe. We have the following specific comments.	

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
4.1 Therapeutic indications	ARKOPHARMA Laboratoires	The therapeutic indication is presently restricted to "*the relief of muscle pain such as lower back pain*" based on clinical data obtained with herbal preparations containing a soft extract (DER 4-7:1), standardised to 2.0–2.78% total capsaicinoids, extraction solvent ethanol 80% (V/V), i.e. herbal preparation a). As summarized in the draft assessment report EMA/HMPC/674138/2013, primary pharmacology of capsaicin is well-documented. Repeated application of capsaicin (and also of its congeners as a mixture of capsaicinoids) leads to neuronal substance P depletion and persisting desensitization to burning sensation and pain. The effects on sensory afferent nerves of the locally-acting isolated compound capsaicin and of capsaicinoids used as a mixture contained in Capsici fructus being of equivalent activity via the membrane vanilloid	Not endorsed. The HMPC monograph is based on clinical data generated with herbal medicinal products containing herbal preparations of Capsici fructus and not synthetic capsaicin. Medicinal products in the European Union containing herbal preparations of Capsici fructus have as indication only 'muscle pain' and not 'articular pain'. The clinical trials performed with herbal preparations included only patients

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		receptor TRPV1 (for details, see comments under "*4.2 Posology and method of administration*" below), results of clinical trials performed with capsaicin should support the therapeutic indications of Capcisi fructus herbal preparations. Elevation of pain perception threshold following topical application of capsaicin has been demonstrated via numerous clinical studies [draft assessment report EMA/HMPC/674138/2013] which also confirmed the efficacy in the treatment of: - disorders of the musculoskeletal system, such as degenerative joint disease (including osteoarthritis as well as rheumatoid arthritis and fibromyalgia); - neuropathy, particularly in diabetics and following herpes zoster and post-mastectomy pain syndrome; - diseases associated with pruritus of different etiology, such as prurigo nodularis or psoriasis. A systematic review, including 16 placebo-controlled studies (15 double-blind, one single-blind) corresponding to 1556 patients suffering from chronic pain due to either musculoskeletal disorders or neuropathic conditions, showed that capsaicin was significantly better than placebo for treatment of chronic pain [Mason, 2004]. Four randomized, double-blind and placebo controlled studies showed greater reduction in pain score or in articular tenderness in patients with osteoarthritis when treated with capsaicin in comparison to placebo, supporting efficacy in the relief of articular pain [McCleane, 2000, Deal, 1991, Altman, 1994, and Schnitzer, 1994] (for details of studies not included in the draft assessment report, see "ANNEX 1" below). A recent review of randomized controlled trials	matching the proposed indication. Results of clinical trials with isolated or synthetic capsaicin are included in the assessment report only as supportive data.

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		on the efficacy and tolerability in the case of osteoarthritis pain concluded that topical capsaicin treatment (from 0.025 % to 0.075%) four times daily is moderately effective in reducing pain intensity up to 20 weeks regardless of application site or dose in patients with at least moderate pain and clinical or radiologically defined osteoarthritis [1]. Conclusion: **Taking into account the beneficial effects of topical capsaicin and of capsicum preparations based on clinical trials in pain-related indications, it appears justified to include the other therapeutic indication related to disorders of the musculoskeletal system, i.e. treatment of pain from osteoarthritis and rheumatoid arthritis to feature alongside the relief of muscle pain such as lower back pain as stated in the ESCOP monograph CAPSICI FRUCTUS [ESCOP monograph, supplement 2009]. The therapeutic indication of a registered capsaicin cream in Ireland and the UK is "*for the symptomatic relief of pain associated with osteoarthritis*"** [2-4]. **It is proposed that the indication reads as follows**: *Herbal medicinal product for the relief of muscle pain such as lower back pain and of articular pain*.	
4.2. Posology and method of administration	AESGP	*[Note: in the following rationale, "capsaicin" will be used although the soft extract is meant since the monograph refers to "capsaicin" too]* The draft HMPC Assessment Report cites the study performed by *Simone & Ochoa* (1991*). In this study the authors evaluated the effects of a cream containing 0.075% capsaicin applied to an area as small as 4 cm^2 area of skin.	Not endorsed. The therapeutic activity depends on the size of the medicated plaster. The clinical efficacy has been demonstrated for the mentioned sizes only.

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		Even after application on such a small area the authors observed different effects such as mild burning (for further details see drafted HMPC Monograph). This observation is fully supported by several theoretical considerations and other *in vitro* and *in vivo* studies; a full elaborate report is available upon request, however, all studies and relevant data are already covered by the drafted Monograph. Capsaicin is a highly selective and potent (low nanomolar affinity) exogenous agonist for the TRPV1 - receptor, a trans-membrane receptor-ion channel complex which provides integrated responses to temperature, pH, and endogenous/exogenous agonists [1]. The majority of pharmacokinetic studies on capsaicin distribution are those performed after topical administration because of the important therapeutic implications of this route. Topical capsaicin in humans is rapidly and well absorbed through the skin [2]. There is no evidence that topical capsaicin works through a transdermal systemic delivery into tissues other than the skin. Indeed capsaicin is a very lipophilic, non-water-soluble compound which resists diffusion into aqueous solutions such as blood, and shows limited potential for transdermal delivery across human skin even if applied at higher concentrations as they are used e.g. in neuropathic pain [3]. Therefore application methods and doses used therapeutically produce only a local effect, avoiding systemic actions [4]. <u>Conclusion:</u> Due to the pharmacological mode of action and pharmacokinetic data of capsaicin, it is evident that capsaicin is acting locally on the afferent nerve endings without a noteworthy systemic availability. Therefore the term “dose”	Deviations in the size may be acceptable, but have to be fully justified by the applicant. In order to demonstrate therapeutic equivalence additional data from clinical trials might be necessary.

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		must be defined differently in comparison to systemic available drugs. Systemic available drugs are leading to a dose dependent plasma concentration and there is therefore a direct correlation between the total applied dose and the efficacy of a given drug. In case of topically applied and topically acting capsaicin, the dose directly applied to the painful area leads to a dose dependent alleviation of pain sensation in the area of application. Therefore the important parameter of the dose dependent efficacy is the concentration of the drug per cm^2. This means that it is not the total concentration of capsaicin administered with one plaster which is the determining factor for the efficacy in pain reduction but the concentration of capsaicin per cm^2. Therefore other plaster sizes are neither a reduction nor an increase of the dose because capsaicin content per cm^2 will be the same and therefore the efficacy of the products will remain unchanged. <u>Proposed changes:</u> **Medicated plaster** *Adolescents, adults, and elderly* 1 medicated plaster (e.g. 22 x 14 cm) containing […] 11 mg capsaicinoids expressed as capsaicin (= 35 µg /cm²). 1 medicated plaster (e.g. 12 x 18 cm) containing […] 4.8 mg capsaicinoids expressed as capsaicin (= 22 µg /cm²). Other sizes are possible. **Available at HMPC, therefore not submitted.*	

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4.2 Posology and method of administration	ARKOPHARMA Laboratoires	Proposal to include semi-solid dosage forms corresponding to 25 mg capsaicinoids / 100 g (0.025%): Four publications deal with clinical studies performed with semi-solid dosage forms containing isolated capsaicin at a dosage of 25 mg per 100 g (0.025%) in the treatment of musculoskeletal disorders. Two are described in the draft assessment report EMA/HMPC/674138/2013 [Deal, 1991 and McCleane, 2000]. Two other randomized, double-blind and placebo controlled studies based on 0.025% capsaicin local preparations also showed greater reduction in pain score or in articular tenderness in patients with osteoarthritis when treated with capsaicin in comparison to placebo (see details under "ANNEX 1" below) [5, 6]. Capsaicinoids present in Capsici fructus consist of a mixture of capsaicin (63-77%) and dihydrocapsaicin (20-32%) as major constituents with nordihydrocapsaicin (1-8%) and a very low content of other capsaicinoids [Blaschek, 2012]. They are all amide derivatives of vanillylamine and a fatty acid having eight to eleven carbon atoms. The peripheral pain stimulation followed by analgesia effect of capsaicinoids is mediated via the membrane vanilloid receptor TRPV1 (transient receptor potential vanilloid) also sensitive to elevated temperature and acids as described in the draft assessment report EMA/HMPC/674138/2013. The pungent feeling caused by capsaicin is also due to activation of the heat thermo- and chemosensitive TRP ion channel TRPV1 nociceptor which acts as molecular sensor for distinct pain, temperature, chemesthesis and test modalities [7, 8]. **Threshold pungency of capsaicinoids, determined by ASTA method 21.0 (Scoville heat test), showed an identical "hot" and "burning" sensation for capsaicin and dihydrocapsaicin (16.1 ± 0.6 x**	Acceptance of semi-solid dosage forms containing 0.025% of total capsaicinoids: not endorsed. The HMPC monograph is based on clinical data generated with herbal medicinal products containing herbal preparations of Capsici fructus and on medicinal products authorized in the member states. Clinical trials with isolated/synthetic capsaicin and medicinal products containing isolated/synthetic capsaicin are not considered. Combination of the posology / strength of semi-solid dosage forms in the monograph: endorsed

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		10^6) while the one for nordihydrocapsaicin is a little bit lower (9.3 ± 0.4 x 10^6) [9]. As the integrator of capsaicin stimuli peripheral sensory neurons is identical for locally-acting analgesic agent and for burn-like irritation of mucous membranes in the mouth and the stomach, it may be postulated that the antinociceptive effect of capsaicin and capsaicinoid mixture contained in Capsici fructus is equivalent, capsaicin and dihydrocapsaicin showing the same effect on taste receptors and accounting for ca. 95% capsaicinoids of Capsici fructus. Additionally, as mentioned in the draft assessment report EMA/HMPC/674138/2013, a medicinal cream containing an oleoresin of *Capsicum annum* L., equivalent to 25 mg capsaicin per 100 g is on the Spanish market since 1996. A MA for another identical finished product was granted in 1993 by Spanish authorities [10]. It also must be mentioned that a medicinal product was registered in France in 2005 containing a standardized Capsicum soft extract and a Devil's claw tincture. Presently, a simplified formulation is in the validation process based solely on the Capsicum soft extract (DER 4-7:1), standardized to 2.0-2.78% total capsaicinoids, extraction solvent, ethanol 80% (V/V), corresponding to 25 mg capsaicinoids per 100 g. A 0.025% capsaicin cream was granted a marketing authorization in Ireland (1999) and the UK (2003) for the treatment of osteoarthritis in Europe [2-4]. **Based on clinical efficacy of capsaicin at the dosage of 25 mg per 100 g and on the presence of products on the EU market for more than 10 years at a dosage of 25 mg capsaicinoids per 100 g, it seems appropriate to take into account this dosage for Capsicum fructus**	

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		preparations as recommended in the ESCOP monograph CAPSICI FRUCTUS [ESCOP monograph, supplement 2009]. Proposal to define a common dosage for all semi-solid dosage forms: According to the draft assessment report EMA/HMPC/674138/2013, "*Capsaicinoids are considered to be responsible for the clinical efficacy. Therefore finished products have to be standardized to a certain content of capsaicinoids. As for standardized herbal preparations the extraction solvent and the DER are of less importance*". Indeed, the established dosages of all community herbal monographs on herbal drugs corresponding to standardized herbal preparations, i.e. monographs on stimulant laxatives with hydroxyanthracene glycosides and the monograph on *Aesculus hippocastanum* L., are based on constituents with known therapeutic activity and include only a single dosage, independently of the herbal preparation (respectively, a maximum daily dose of 30 mg hydroxyanthracene glycosides and 50 mg triterpene glycosides, twice daily). Same approach looks appropriate for the monograph on Capsici fructus and is also supported by the fact that available clinical data are not sufficient to establish such distinctions between preparations as only one (preparation a)) has been the subject of a clinical study [Chrubasik, 2010]. **Accordingly, capsaicin and congeners being constituents with known therapeutic activity, it is recommended not to individualize capsaicinoid content per 100 g of semi-solid dosage form for each of the three soft extracts in the Capsici fructus monograph**.	

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		Conclusion: **In a similar fashion as aforementioned community herbal monographs on herbal drugs for standardized herbal preparations and taking into account equivalent therapeutic activity of capsaicin and capsaicinoids contained in Capsicum fructus, it is justified to include a single dosage for all semi-solid dosage forms corresponding to 25-53 mg capsaicinoids / 100 g.** **Proposed reading**: ***Semi-solid dosage forms*** *Herbal preparations a), b) and c)* *Adults and elderly* *Semi-solid dosage forms ~~containing 0.6-1.9 g soft extract~~ corresponding to ~~40~~25-53 mg capsaicinoids / 100 g.* *Apply 2-4 times daily. To be applied in a thin layer on the affected area.* *The use in children and adolescents under 18 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').* ~~*Herbal preparation b)*~~ ~~*Adults and elderly*~~ ~~*Semi-solid dosage forms containing 0.9-2.9 g soft extract corresponding to 50 mg capsaicinoids / 100 g.*~~ ~~*Apply 2-4 times daily. To be applied in a thin layer on the affected area.*~~	

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		~~*The use in children and adolescents under 18 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').*~~ ~~*Herbal preparation c)*~~ ~~*Adults and elderly*~~ ~~*Semi-solid dosage forms containing 0.24-1.02 g soft extract corresponding to 53 mg capsaicinoids / 100 g.*~~ ~~*Apply 2-4 times daily. To be applied in a thin layer on the affected area.*~~ ~~*The use in children and adolescents under 18 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').*~~ **ANNEX 1**: Altman et al. 1994 [5]: In a randomized, double-blind, placebo-controlled multicentre study 113 patients with osteoarthritic pain applied a thin film of capsaicin cream (Zostrix®, 0.025%; n=57) or placebo (n=56) 4 times daily over a period of 12 weeks. Improvement was assessed by physician's global evaluation in 83% of the patients treated with capsaicin compared to 63% treated with placebo at week 4 (p = 0.042) and at the end of the study (capsaicin: 81%; placebo: 54%; p = 0.026). Similar results were obtained by patients' global evaluation (week 4: p = 0.023, week 12: p = 0.028). Capsaicin-treated patients reported a 53 % reduction of pain on the visual analogue scale (VAS) compared with 27% in placebo-treated patients at week 12 (p = 0.02). Capsaicin-treated patients also had a greater reduction in pain on passive range of motion (=measurement for tenderness in target joint) by week 8 (p = 0.03) that was sustained until week 12 (p=0.03). Joint tenderness evaluated by palpation declined in capsaicin-treated patients at week 4 (p =	

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		0.03), week 8 (p = 0.01), and week 12 (p = 0.01). No significant differences were established between the groups in terms of the additional target criteria, namely morning stiffness and health questionnaire. Mild to moderate burning or stinging occurred at the application site in 46% of patients who received capsaicin but rapidly ameliorates with continuing use. Schnitzer et al., 1994 [6]: In a randomized, double-blind, placebo-controlled, parallel-group study, 59 patients (40 women and 19 men) with moderate to severe osteoarthritis of the hands applied a thin film of capsaicin cream (Zostrix®, 0.025%) or vehicle. For 3 weeks the affected hands were treated 4 times per day and in a second phase for 6 weeks twice daily. Forty-eight patients completed the 9-weeks study. Although capsaicin-treated patients showed an improvement in symptoms after 3 and 9 weeks of treatment superior to the placebo group (pain severity measured by Visual Analog Scale (VAS), categorial pain scale, joint swelling) but the results were not significant. Measured by a dolorimeter, a reduction of 26% in articular tenderness on active treatment could be shown after 3 weeks (placebo: 6%, p = 0.018) and of 22% after 9 weeks (placebo: 1.2%, p = 0.013). Grip strength increased after 3 weeks (capsaicin-treated = 30%, placebo = 16%) to a significant difference between groups after 9 weeks (capsaicin-treated = 32%, placebo = 3%; p = 0.046) in favour of the capsaicin cream. 12 capsaicin-treated patients (placebo: 4) reported mild burning or stinging at the application sites disappearing with continued use. In conclusion of this study, capsaicin cream 0.025% applied 4 times daily provided significant reduction in articular tenderness and clinically relevant reductions in pain severity. Once effective, a reduction after 3 weeks in application frequency to twice daily led to an effective maintenance therapy.	

AESGP references	[1] Alawi, 2010 [2] Hayman M, Kam PCA. Capsaicin: A review of its pharmacology and clinical applications. Current Anaesthesia and Critical Care 2008, 19: 338-343 [3] Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. British Journal of Anaesthesia 2011, 107 (4): 490–502 [4] O'Neill J, Brock C, Estrup Olesen A, Andresen T, Nilsson M, Dickenson AH. Unravelling the mystery of capsaicin: A tool to understand and treat pain. Pharmacol Rev 2012, 64(4): 939–971
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