7 July 2015
EMA/HMPC/706538/2014
Committee on Herbal Medicinal Products (HMPC)

# Overview of comments received on European Union herbal monograph on *Matricaria recutita* L., flos (EMA/HMPC/55843/2011)

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

| | Organisations and/or individuals |
|---|---|
| 1 | Robugen GmbH, Germany |
| 2 | Herbapol S.A., Poland |
| 3 | European Scientific Cooperative on Phytotherapy (ESCOP) |
| 6 | Phytopharm Klęka S.A., Poland |
| 7 | MEDA Pharma GmbH & Co. KG, Germany |

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Table 2: Discussion of comments

## General comments to draft document

| Interested party | Comment and Rationale | Outcome |
|---|---|---|
| AESGP | No comment regarding Matricaria flos | |
| MEDA | MEDA Pharma as MAH of various chamomile products appreciates the thorough and comprehensive analysis presented in the assessment report (AR) of 1 July 2014. MEDA Pharma and the predecessors Homburg/Degussa Pharma and ASTA Medica have accumulated broad experience with herbal medicinal products and, in particular, with chamomile, already registered in 1921 as chamomile concentrate. A large number of basic information addressing both preclinical and clinical results were retrieved on initiatives or sponsoring by MEDA Pharma and their predecessors. Consequently, MEDA Pharma would like to take the opportunity to comment on this draft AR. | The Assessment Report is summarizing the data which contribute to establishing a harmonized view in a Community Monograph. It is mentioned in the introduction for public consultation that the focus is not to comment on the assessment report. If suggestions for changes of the monographs are justified and substantiated with references, the suggestions are discussed and if finally endorsed the relevant documents will be amended.<br><br>With respect to the existing literature it is not the objective to include all publications. If appropriate specific references are added.<br><br>The overall conclusions raised from MEDA are not systematically specified for distinct herbal preparations and not specified for the monograph. The AR already summarized why a well-established use could not be assigned, the data provided in the comment to the AR did not change this opinion. (see below) |

## Specific comments on text

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| 2. Qualitative and quantitative composition | Herbapol S.A. | We suggest changing the description of the preparation “j)” in the following manner:<br><br>“Liquid extract (1:2), extraction solvent: ethanol 70% V/V”<br><br>The drug-extract ratio proposed in the monograph appears to be a typing mistake. This herbal preparation seems to be included in the monograph on the basis of traditional use status of Polish herbal medicinal product Azulan, which is monocomponent product with the above mentioned extract. Azulan has been marketed in Poland for more than 30 years.<br><br>In case the description of the preparation “j)” was in fact correct we suggest adding the above mentioned preparation to the monograph.<br><br>*References:*<br>Podlewski K, Podlewska-Chwalibogowska A. Leki wspolczesnej terapii [Modern Therapy Medicines]. 4th ed. Warsaw: Panstwowy Zakład Wydawnictw Lekarskich; 1962. p. 76<br><br>Ozarowski A, Lancucki J, Gasiorowska K. Leki roślinne: Informator [Herbal medicines: guidebook]. Warsaw: Zjednoczenie Przemyslu Zielarskiego Herbapol; 1978. p. 51-52<br><br>Ministry of Health and Social Welfare. Registration Certificate. Warsaw; November 1991.<br><br>Azulan. Summary of Product Characteristics. January 2008. | Endorsed.<br><br>The comment was checked with the NCA of Poland. The Polish market survey is consistent with the AR and monograph. The specification of the extracts i) and j) are fused and the posology broadened. |

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| 2. Qualitative and quantitative composition | Phytopharm Klęka S.A. | Draft monograph mentions preparation i) Liquid extract (0.5:1) extraction solvent: ethanol 96% V/V which corresponds to extract 13 of the section 2.2. of draft AR Information on preparations in European countries - Poland, while no product with such drug substance exist on Polish market. Whereas there are products with Chamomillae anthodii extractum fluidum (0.5:1, 70% V/V ethanol) as active substance which have traditional use according to Article 16d(1) of Directive 2001/83/EC (proven during harmonisation in 2011-2012). Products are mentioned in points 7 and 8 of official list of approved traditional herbal medicinal products available<br><br>http://bip.urpl.gov.pl/system/article_attachments/attachments/5780/original/Wykaz_Tradycyjnyh_Produkt_w_Leczniczych_Ro_linnych_2014-05-12.pdf?1399900545.<br><br>These products are also mentioned in the List of references supporting the assessment of Matricaria recutita L., flos: Ożarowski A, Łańcucki J, Gąsiorowska K, Azulan. Herbal medicines, Guidebook 1978.<br><br>We propose to correct preparation i) or include preparation Chamomillae anthodii extractum fluidum (0.5:1, 70% V/V ethanol). | Clarification given by Polish NCA. Both extracts i) and j) have the same specification, the posology is adapted and widened. A sufficient tradition of products with Chamomillae anthodia extractum fluidum (DER 0.5:1, 70% ethanol V/V was not confirmed. |
| 3. Pharmaceutical form | Robugen | The following preparation is lacking: Herbal preparation in liquid dosage forms for preparations of dilutions for oromucosal or cutaneous use. | Endorsed |
| 4.1 Therapeutic indications | Robugen | Indication 4): Examples of irritations of skin and mucosae in the anal and genital region might be added as it is in accordance with the traditional long-standing use of the preparation in question.<br><br>Indication 5): Other examples of minor inflammation of the skin and | 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 |

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| | | superficial wounds might be added as it is in accordance with the traditional long-standing use of the preparation in question. | European Union monographs addressing the same therapeutic area. Product specific data may be provided in an individual application. |
| 4.2 Posology and method of administration | Robugen | Preparation g):<br><br>Indication 1) should be changed to indication 1) and 3) according to the traditional long-standing use as documented by the assessors comment (see assessment report page 10, number of extract 5).<br><br>Indication 4) and 5): As there have been no age restrictions in these indications during traditional use, the wording “Adolescents, adults and elderly” should be discarded.<br><br>Preparation h):<br><br>Indication 4) should be changed to indication 4) and 5) according to the traditional long-standing use as documented by the assessors comment (see assessment report page 11, extract 7). As there had been no age restriction in these indications, the wording “Adolescents, adults and elderly” should be discarded. | Partially endorsed.<br><br>The indication of extract g) is modified according to page 10 AR, indication 2 (inhalation) and indication 3) are added.<br><br>There are no data regarding the local tolerance in children available, therefore the comment is not indorsed.<br><br>Comment partially endorsed, indication 5 is added.<br><br>The suggestion concerning the age groups 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 of use | Robugen | Preparation h):<br><br>Indication 1) and 2): Preparation h) should be discarded as there are stated specific dosages for children from 6 – 12 years in the section 4.2 Posology and method of administration. | Endorsed |

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| 4.6 Fertility, pregnancy and lactation | Robugen | Preparation g), h) and p): Since there is no risk with the use of matricaria teas during pregnancy and lactation (as documented on page 57, assessment report) and since the qualitative spectrum of ingredients in matricaria tea and alcoholic extracts is approximately the same (with the exception of pollen) the following text should be sufficient: Preparation g) should only be used after recommendation by a physician. | Not endorsed (see above) |
| 4.6 Fertility, pregnancy and lactation | ESCOP | We do not agree with the statement that preparation b) to p) cannot be used during pregnancy and lactation.<br><br>Preparation c), f), n), o) and p) are not indicated for oral use, therefore they can be used during pregnancy and lactation. | Not endorsed, since no data are available; for a different wording appropriate data must be provided. |
| 4.8. Undesirable effects | Robugen | There should be made a differentiation between the application of Matricaria tea and alcoholic matricaria extracts such as preparations g) and p): 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 matricaria pollen in it according to Subiza et al. 1989 and 1990. Preparations g) and p) are filtrated using a 0.45 µm filter which clearly holds back matricaria pollen (diameter 40 – 50 µm). No alcoholic extract such as preparation g) and p) had been involved in the above mentioned cases.<br><br>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.<br><br>The wording of the first part in 4.8. should be changed to: | Comment not endorsed, since there are no reliable data associating severe allergic reactions exclusively with occurrence of pollen. The last sentence of the proposal would be a precaution and is not to be included under 4.8 |

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| | | 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. Alcoholic extracts should not be used as enema or aerosol.<br><br>No copies of the literature attached as it is mentioned in the list of references (EMA/HMPC/55810/2011). | |
| 4.8. Undesirable effects | ESCOP | "Hypersensitivity reactions ….. The frequency is not known."<br><br>Most of the described allergic reactions to "chamomile" were not due to matricaria but to Anthemis cotula or related species, which contain high amounts of the contact allergen anthecotulide. Based on this and the fact that millions of people come into contact with matricaria daily, allergic reactions to matricaria can be considered as extremely rare.<br><br>*Reference:*<br>Chamomile, German (Matricaria recutita L. (syn. Chamomilla recutita [L.] Rauschert ; M. chamomilla L. ; M. suaveolens L.) Monograph, The ABC Clinical Guide to Herbs | Comment not endorsed, the wording is in accordance with the SPC Guideline |