5 June 2018
EMA/HMPC/772735/2015
Committee on Herbal Medicinal Products (HMPC)

# Overview of comments on second draftEuropean Union herbal monograph on *Silybum marianum* (L.) Gaertn., fructus (EMA/HMPC/294187/2013)

Final

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph as released for public consultation on 7 November 2016 until 15 February 2017

| | Organisation or individual |
|---|---|
| 1 | Association of the European Self-Medication Industry (AESGP) |

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Table 2: Discussion of comments

## General comments to draft document

| Interested party | Comment and Rationale | Outcome |
|---|---|---|
| AESGP | We appreciate the opportunity to comment on this draft. This revised draft is actually extremely disappointing; we make particular reference to the deletion of the well-established use. Our comments concern as well the revised draft assessment report and the draft of the HMPC reply on our comments submitted on the first draft, because these documents are closely linked to the monograph. | The HMPC appreciate the Interested party comments.<br><br>The outcome is explained in each Section below. |

## Specific comments on text

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| 4.1. Therapeutic indications<br><br>Well-established use | AESGP | In accordance with our comments submitted on the earlier draft, we propose to include an indication for the well-established use. It is not clear to us why an indication was proposed in an earlier HMPC draft monograph, and the new assessment lead to the conclusion that there is not sufficient coherent data available to justify a well-established use. From our point of view the statement *"The decision is a compromise taking into account the long-standing use of Silybum marianum fruit and the proven safety"* is not satisfactory.<br><br>As suggested earlier, we therefore propose to take the following indication into consideration: | **Not endorsed**<br><br>Documents and available data have been discussed at HMPC meetings and the final decision, according to the majority was to keep only Traditional Use.<br><br>While existing authorisations of one product in many Member States were acknowledged, there was no majority to support a recognised efficacy for the proposed indication related to liver disease based on available clinical evidence.<br><br>In conclusion, on the basis of the pharmacological and clinical data, HMPC concluded that due to lack of coherence of scientific data an well-established use indication cannot be established for theEuropean |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| | | ***"For the supportive treatment of chronic inflammatory liver diseases, hepatic cirrhosis and toxic liver damage".***<br><br>This is in accordance with products authorized by health authorities e.g. in Austria or Germany.<br><br>Moreover, well-established use indications would be in line with the existence of a Ph.Eur. monograph on a standardised extract.<br><br>The HMPC reply dated 20 September 2016 on the AESGP comments submitted earlier states **"The only herbal preparation the efficacy of which has been demonstrated by clinical trials is the dry extract (DER 36-44:1), (extraction solvent: ethyl acetate) standardised to contain 40-65 % silymarin, calculated as silibinin."**<br><br>Even in case these findings might not be extrapolated to other preparations (as explained in the draft HMPC reply), the mentioned extract should be included under "well-established use" with the above indication. We therefore do not agree upon the "compromise" quoted in the new draft assessment report. | Union herbal monograph on *Silybum marianum* (L.) Gaertn, fructus. |
| 4.1. Therapeutic indications | AESGP | As already done in our previous comments, we propose the following indication: "Traditional herbal medicinal product used to support digestive | **Not endorsed**<br><br>The proposed traditional indication in the *Silybum marianum* monograph is: *Traditional herbal medicinal* |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| Well-established use | | function by stimulation of the liver-bile-system."<br><br>For **preparation d)**, a registration was granted in Germany in 2014 with the indication „Traditionell angewendet zur Unterstützung der Verdauungsfunktion durch Anregung der Funktion des Leber-Galle-Systems.". The product contains 200 mg Milk Thistle dry extract (30-40:1), extraction solvent ethanol 96 % (V/V) and corresponds to preparation d) under "traditional use".<br><br>From our point of view the reply of the HMPC on our proposal submitted earlier is not satisfactory. It reads: "The HMPC decided that indications referring to the liver are not adequate for traditional use in European Union herbal monographs." From our point of view, the indication itself relates to the digestive function, whereas the mechanism to support this function is stimulation of the liver-bile-system.<br><br>As written in our previous comments, efficacy of milk thistle for the support of digestive function is plausible and can be deduced from the effects of the herbal drug. The choleretic effect has been proven by Crocenzi et al (2006). Thus the stimulating effect on the biliary system should be reflected in the wording of the indications. The | *product for the symptomatic relief of digestive disorders, sensation of fullness and indigestion and to support the liver function, after serious conditions have been excluded by a medical doctor Traditional herbal medicinal product for the relief of dyspepsia and digestive complaints of hepatic origin, after serious conditions have been excluded by a medical doctor*.<br><br>The decision takes into account the long-standing use of *Silybum marianum* fruit and the proven safety as it has to be a non-prescription medicines "intended and designed for use without the supervision of a medical practitioner".<br><br>In European Union herbal monographs, the reference 'after exclusion of serious conditions by a medical doctor' may be included to prevent treatment of more serious pathologies with traditional herbal medicinal products. In particular, liver diseases should need a careful medical evaluation and decisions will be taken on a case-by-case basis (Public statement on the interpretation of therapeutic indications appropriate to traditional herbal medicinal products in European Union herbal monographs, EMA/HMPC/473587/2011, 13 September 2011). |

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| | | mentioned product has been used in this therapeutic area for many years. | |
| 4.3 Contra-indications | AESGP | Besides a contra-indication in people with hypersensitivity to the active substance, a general contra-indication in people with any kind of hypersensitivity to plants of the Asteraceae (Compositae) family is included. The draft assessment report accompanying the draft monograph does not provide any rationale for this inclusion, scientific or otherwise. Section “5.5.2. Contraindications” of the assessment report provides the entry “not applicable” and no further reference to plants of the Asteraceae family other than Silybum is given in the monograph. For those medicinal products which are already on the market and listed in the assessment report, only hypersensitivity to the active substance itself was provided as contraindication, if contraindications were provided by the assessment report.<br><br>We therefore ask for a scientific rationale for including a general contra-indication to Asteraceae (Compositae) or to delete the statement. | **Not endorsed**<br><br>Wording in this section follows the same format as for all plants of Asteraceae family. |
| 4.2. Posology and method of administration | AESGP | We suggest to add the German standard marketing authorization (“Standardzulassung”)[1] to the assessment report as well as respective information on the posology. For the pharmaceutical form “Comminuted herbal substance as herbal tea for | **Partially endorsed**<br><br>The German product has been included in the AR<br><br>Nonetheless, it can’t be included in the monograph posology as the marketing authorisation does not |

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| | | oral use", it provides a slightly different posology than posology a) of the draft monograph: 3-4 times per day approx. 3,5 g of the comminuted herbal substance in 150 ml of boiling water. The maximum daily dose is slightly lower than the one provided in the monograph (14 g of herbal substance compared to a maximum of 15 g in the monograph), but it allows for a maximum of four daily single doses instead of three. Since this posology has relevance on the European market, we think it should also be listed in the monograph. | fulfil 30 years in the EU and so no enough data are available |
| 4.8. Undesirable effects | AESGP | The monograph lists "Mild gastrointestinal symptoms such as dry mouth, nausea, upset stomach, gastric irritation and diarrhoea may occur; headache; allergic reactions (dermatitis, urticaria, skin rash, pruritus, anaphylaxis, asthma)" as known undesirable effects. According to section "5.3. Adverse events, serious adverse events and deaths" of the assessment report, these undesirable effects have been observed in the clinical trials listed in section 4.2 of the assessment report, while "no adverse events, serious adverse events or deaths related to milk thistle have been reported" according to the pharmacovigilance database. The clinical trials in section 4.2 used various dry extracts of milk thistle, but not the (comminuted) herbal substance, for which no undesirable effects have been reported in the | **Not endorsed**<br><br>Undesirable effects have been reported for some preparations. The opinion of the HMPC is to keep this information available for the patients, while no frequency is reported. |

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| | | pharmacovigilance database. We think that, aside from hypersensitivity, which can occur with any form of preparation containing (glyco-)proteins, the monograph should differ between dry extracts and (comminuted) herbal substance as far as undesirable effects are concerned. | |

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# Overview of comments received on first draft European Union herbal monograph on *Silybum marianum* (L.) Gaertn., fructus (EMA/HMPC/294187/2013)

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph as released for public consultation on 22 July 2015 until 31 October 2015

| | **Organisations and/or individuals** |
|---|---|
| 1 | Association of the European Self-Medication Industry (AESGP) |

Table 2: Discussion of comments

## General comments to draft document

| Interested party | Comment and Rationale | Outcome |
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## Specific comments on text

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| 2. Qualitative and quantitative composition | AESGP | In the draft of the European Union herbal monograph on *Silybum marianum* (L.) Gaertn., fructus, only one specific herbal preparation is allocated to the well-established use. This specific preparation is a dry extract (DER 36-44:1), (extraction solvent ethyl acetate) standardised to contain 40-65% silymarin, calculated as silibinin. From our point of view it is not justified to restrict the well-established use to one specific herbal preparation for the following reasons:<br><br>The therapeutic active principle of milk thistle fruits is silymarin. Silymarin mainly consists of a series of the flavolignan-isomers silibinin A and B, Isosilibinin A and B, silidianin and silichristin. The inner composition and amount of silymarin contained in preparations for therapeutic use is defined in the monograph “Milk thistle dry extract, refined and standardised” of the Ph. Eur., volume 8.0. As shown in the following, the monograph also mentions a range of the extraction solvents to be used for the | **Not endorsed**<br>European Pharmacopoeia monograph refers to a quality parameter to assess the pharmaceutical quality of the product, but does not assure efficacy.<br>The only herbal preparation where the efficacy has been demonstrated by clinical trials is the dry extract (DER 36-44:1), extraction solvent: ethyl acetate, standardised to a content of 40-65% silymarin, expressed as silibinin.<br>For the other herbal preparations representing different dry extracts efficacy is not proven based on specific clinical trials. Moreover, comparability of the extracts has not been demonstrated and the contribution of other constituents than silymarin is not fully understood. Therefore, the positive outcomes from the clinical trials with |

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| | | production of dry extracts from milk thistle fruits:<br><br>"DEFINITION<br>Dry extract, refined and standardised, produced from *milk thistle fruit*.<br>Content: 90% to 110% of the nominal content of silymarin, expressed as silibinin ($C_{25}H_{22}O_{10}$; $M_r$ 482.4), stated on the label.<br>The nominal content of silymarin is within the range 30% m/m to 65% m/m (dried extract).<br>The content of silymarin corresponds to:<br>- sum of the contents of *silichristin* and *silidianin* (both $C_{25}H_{22}O_{10}$; $M_r$ 482.4): 20% to 45%, calculated with reference to total silymarin;<br>- sum of the contents of *silibinin A* and *silibinin B* (both $C_{25}H_{22}O_{10}$; $M_r$ 482.4): 40% to 65%, calculated with reference to total silymarin;<br>- sum of the contents of *isosilibinin A* and *isosilibinin B* (both $C_{25}H_{22}O_{10}$; $M_r$ 482.4): 10% to 20%, calculated with reference to total silymarin;<br><br>PRODUCTION<br>The extract is produced from the herbal drug by an appropriate procedure, using one or more of the following solvents:<br>- ethyl acetate;<br>- acetone or mixture of acetone and water;<br>- ethanol or mixture of ethanol and water;<br>- methanol or mixture of methanol and water."<br>Dry extracts from milk thistle fruits contained in preparations for | standardised extract cannot be extrapolated to the other herbal preparations, although previously marketed in different Member States. |

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| | | therapeutic use must comply with the Ph. Eur. monograph, must have a standardised content of silymarin with a specific inner composition and must be produced with defined extraction solvents. For this reason, in our opinion the results of clinical studies are applicable to any preparation standardised in relation to its active principle silymarin in compliance with the Ph. Eur. monograph.<br><br>In addition, a product-specific dissolution test has to be performed for standardised extracts according to the respective quality guidelines. Thus, reference to the Ph.Eur. monograph is considered sufficient and, as a consequence, all extracts complying with the Ph. Eur. should be included under well-established use. Allocation to the well-established use independent from DER and extraction solvent has also been performed within the HMPC monographs on Cassia senna, folium and fructus, respectively. The same should apply to milk thistle. The situation is comparable insofar because in both cases the herbal preparations are standardised to a defined amount of constituents with known therapeutic activity.<br><br>Therefore, we do not agree to the statement in the draft assessment report on *Silybum marianum* which claims that the results of the cited clinical trials would justify the treatment with only the one above mentioned specific standardised milk thistle extract. In our opinion, the statement that other preparations currently marketed in different EU Member States would not fulfil the well-established use criteria is not plausible. | |

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| | | Consequently and in order to achieve consistency between HMPC and Ph. Eur. monographs, all extracts complying with the Ph. Eur. monograph on milk thistle dry extract should be included under well-established use.<br><br>This is also reflected in the statement made in the commentary on the Ph. Eur., 8.0/1860 *Silybi mariani fructus.* It states that extract/active substance (silymarin-complex) of milk thistle fruits are used for supportive treatment or prophylaxis of toxic liver diseases, inflammatory or degenerative liver diseases (e.g. hepatitis, liver cirrhosis, fatty liver) and for the treatment of death cap fungus poisoning.<br><br>Furthermore, in case extracts authorised as “well-established use” are now allocated to the “traditional use”, we assume that some health authorities would no longer accept standardisation, which, however, is demanded by the Ph. Eur. monograph as shown above. | |
| 4.1 Therapeutic indications – **Well-established use** | AESGP | The draft of the European Union herbal monograph on *Silybum marianum* mentions the indication “Herbal medicinal product for supportive treatment of alcoholic liver disease” under “well-established use”.<br>In accordance with products authorised by health authorities e.g. in Austria or Germany, we propose the following wording:<br>***“For the supportive treatment of chronic inflammatory liver diseases, hepatic cirrhosis and toxic liver damage”.***<br>This indication has also been mentioned in the HMPC draft Assessment report. From our point of view there is no reason to restrict the therapeutic use of milk thistle preparations to cases of | **Not endorsed**<br><br>Based on the existing clinical data it is considered that the well-established use has only been adequately demonstrated for the indication of supportive treatment of alcoholic liver disease. |

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| | | alcoholic liver diseases. In contrast, our proposed indication is supported by a number of clinical studies which can be regarded as studies of good quality, demonstrating a positive effect on liver diseases of different etiology which are not limited to alcoholic liver diseases.<br><br>E.g., the double-blind, randomised and placebo-controlled study by El-Kamary *et al.* (2009) and in the observational study by Schuppan *et al.* (1998) clearly demonstrate a positive effect of silymarin in the treatment of liver diseases of different etiologies, not only in cases caused by alcohol. A significant improvement of non-alcoholic fatty liver disease after treatment with silymarin was demonstrated by Hashemi *et al.* (2009), Buturova *et al.* (2010) and Hajiaghamohammadi *et al.* (2012). Furthermore, it was shown that silymarin has a positive effect in patients with liver damage caused by chemicals or certain drugs (e.g. Allain *et al.*, 1999, Palasciano *et al.*, 1994, Szilard *et al.*, 1988, Boari *et al.*, 1981, Saba *et al.*, 1976). In the review by Rambaldi *et al.* (2005) thirteen randomised clinical trials were assessed in patients with alcoholic but also hepatitis B or C liver diseases. It is stated that in all trials liver-related mortality was significantly reduced by milk thistle.<br><br>The Assessment Report states that “Most of these studies demonstrate positive effects for indications including cirrhosis and alcoholic liver disease, hepatitis, and psychotropic drug-induced liver damage.” (4.4 Overall conclusions on clinical pharmacology and efficacy, page 76), showing that there is evidence for efficacy in the treatment of liver diseases other than that caused by | |

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| | | alcohol. Although the quality of some of these studies might not correspond to current standards, they nevertheless have to be considered for the well-established use since they reflect the scientific knowledge of that time.<br><br>There is also a number of clinical studies available performed with heterogeneous groups of patients suffering from liver disorders caused by different or multiple reasons or by other compounds than alcohol or fungal toxins which are not mentioned in the assessment report:<br><br>One of the first controlled clinical studies which gave evidence for the therapeutic effect of silymarin was published in 1969 by Schopen *et al.* 25 patients with toxic-metabolic liver damages, fatty livers and chronic hepatitis were treated with silymarin for four months. Subjective parameters like digestive trouble, tiredness etc. as well as objective parameters (albumin, gamma-globuline, GOT, GPT, cholinesterase etc.) were monitored. Patients with similar disorders who were treated with usual other preparations served as control. The result showed a clear improvement or normalisation, respectively, for some of the parameters.<br>In an open multicenter study, the efficacy and tolerance of silymarin was tested in 277 patients suffering from chronic-inflammatory hepatic disorders or hepatic disorders caused by intoxication (Held, 1992). The main parameter to monitor the status of the liver in this study was the concentration of prokollagen-III-peptide in the serum. The clinical symptoms were improved significantly after treatment with silymarin. Pathologic | |

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| | | clinical-chemical values as well as prokollagen-III-peptide levels were normalised significantly during the therapy.<br><br>Ladas *et al.* (2010) studied the effect of milk thistle (MT) for the treatment of hepatotoxicity in children with acute lymphoblastic leukaemia in a double-blind study. The authors demonstrated that the administration of milk thistle was associated with a trend toward significant reductions in liver toxicity whereas milk thistle did not antagonise the effects of chemotherapy agents used for the treatment of acute lymphoblastic leukaemia.<br><br>In summary, there is a number of randomised and controlled studies demonstrating a positive effect of silymarin in the treatment of liver disorders caused by other factors than alcohol, but a number of such studies. In our opinion, this large body of evidence sufficiently confirms the above mentioned therapeutic indications for the well-established use. It is even stated in the overall conclusions of the Assessment Report that “Silymarin treatment induces a statistically significantly and clinically relevant reduction of elevated serum parameters which are reflecting hepatocellular injury in patients with chronic liver disease of various etiologies and progression”.<br><br>Therefore, the proposed wording “For the supportive treatment of chronic inflammatory liver diseases, hepatic cirrhosis and toxic liver damage” adequately reflects the available scientific data. Furthermore, this indication is in accordance with the criteria for | |

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| | | well-established use since medicinal products containing milk thistle preparations have been in well-established medicinal use within the Community (with exactly these indications) for more than ten years, with recognised efficacy and an acceptable level of safety.<br><br>As explained under 2., all extracts complying with the Ph. Eur. Monograph should be included under well-established use. There is no explanation in the Assessment Report for the restriction of the indication to only one specified extract. | |
| 4.1 Therapeutic indications – **Traditional use** | AESGP | For **preparation d)** we propose the following indication: *"Traditional herbal medicinal product used to support digestive function by stimulation of the liver-bile-system."*<br><br>For this preparation, a registration was granted in Germany in 2014 with the indication "Traditionell angewendet zur Unterstützung der Verdauungsfunktion durch Anregung der Funktion des Leber-Galle-Systems.". The product contains 200 mg milk thistle dry extract (30-40:1), extraction solvent ethanol 96% (V/V) and corresponds to preparation d) under "traditional use". Efficacy of milk thistle for the support of digestive function is plausible and can be deduced from the effects of the herbal drug. The choleretic effect has been proven by Crocenzi et al (2006). Thus the stimulating effect on the biliary system should be reflected in the wording of the indications. The mentioned product has been used in this field for 39 years. The draft Assessment Reports (2.3 Overall assessment on medicinal use) as well refers to | **Not endorsed**<br><br>The HMPC decided that indications referring to the liver are not adequate for traditional use in European Union herbal monographs. |

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| | | the registered product “Mariendistel Kapsel” and mentions the indication “traditionally used to support digestive function”. | |
| 4.1 Therapeutic indications – **Traditional use** | AESGP | **Comments:**<br>The proposed therapeutic indication for the powdered milk thistle fruit, which only focuses on digestive disorders, is partly in line with the approved traditional indications registered in Spain and with a long-standing use of the product on the French market.<br>Besides the digestive disorders, the traditional use of the powdered milk thistle fruit in “digestive disorders with a hepatic origin and as a hepatoprotective” has also been recognised by the Spanish Authorities since 1991.<br>Also in France, the powdered milk thistle fruit has been marketed in hard capsules of 300 mg doses, as a hepatoprotective since 1983 according to the “*Résumé de Phytotherapie*” published in Nice, France.<br>**Proposed change:**<br><br>“Traditional herbal medicinal product for the symptomatic relief of digestive disorders of hepatic origin with a sensation of fullness, bloating and flatulence and as a hepatoprotective”. | **Not endorsed**<br>Please see above |
| 4.2. Posology | AESGP | In former times content of silymarin has been determined by spectrophotometry, which is nowadays no longer accepted by authorities; quantification by HPLC is required. The internationally agreed correct conversion factor UV --- HPLC is: **silymarin 140 mg (spectrophotometry) = 108.2 mg (HPLC)** | **Endorsed** |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| | | Therefore chapter 4.2. Posology<br>*Herbal preparation*<br>*c) Single dose: Dry extract corresponding to 120 mg silymarin, calculated as silibinin*<br>*Daily dose: 3 times daily, up to 360 mg, before meals*<br><br>should be corrected to:<br><br>*Herbal preparation*<br>*c) Single dose: Dry extract corresponding to **108.2 mg** silymarin, calculated as silibinin*<br>*Daily dose: 3 times daily, up to **324.6 mg**, before meals*<br><br>In the draft AR the products and posology of herbal preparation c) Dry extract (DER 20-70:1), extraction solvent acetone 95% (V/V)<br>are cited correctly, e.g.:<br><br>Draft AR, page 6:<br>Austrian WEU product Nr. 5:<br>*"Standardised dry extract, corresp. silymarin 140 mg (spectrophotometry), = 108.2 mg (HPLC). Extraction solvent acetone 95% V/V"*<br><br>Draft AR page 15:<br>German WEU products 45, 46, 47, 48) > 18 years:<br><br>*3 x daily 1 containing 177.4-240.4 mg dry extract* | |

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| | | *corresponding to 108.2 mg Silymarin calculated as Silibinin (HPLC)*<br><br>This should be corrected in the monograph as well. | |
| 4.8. Undesirable effects | AESGP | **Traditional use:**<br>In the draft assessment report is mentioned: “no data of adverse events are available for the traditional use part. The possible adverse events regarding the use of traditional products are the same than those reflected for the WEU part”.<br>The preparations included in the WEU part are exclusively dry extracts and not powered herbal substances.<br><br>The adverse effects described in the assessment report have been observed in clinical trials with only dry extracts milk thistle preparations, not with powdered herbal substance.<br><br>So according to it, the fact to refer to undesirable effects of the Well-established use preparations, in the case of all traditional use milk thistle preparations is questionable and not justified, considering that for the traditional use preparations corresponding to powdered herbal substance no data are available, there are only data just for dry extracts.<br>As is known dry extracts and powdered herbal substance preparations are very different preparations, with different content of constituents.<br><br>Also in absence of undesirable effects observed through the post-marketing surveillance system on the powdered milk thistle fruit since 1982 in France and Spain, it is proposed to reconsider the | **Partially endorsed**<br><br>In the Traditional Use side of the monograph , are several extracts included, that may cause the same adverse events.<br>These side effects are mild and include allergic reactions that refer to the herbal substance itself.<br><br>As the undesirable effects are associated with the WEU preparation, the wording “have been reported” is written for the well-established use and “may occur” is left to the traditional use. |

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| | | described possible undesirable effects in a more appropriate way.<br><br>**Proposed change:**<br>For extracts of *Silybum marianum L.*, the following effects have been reported:<br>Mild gastrointestinal symptoms such as dry mouth, nausea, upset stomach, gastric irritation and diarrhoea may occur; headache; allergic reactions (dermatitis, urticaria, skin rash, pruritus, anaphylaxis, asthma), have been reported. The frequency is not known.<br><br>For powdered herbal preparations of *Silybum marianum* L. no undesirable effects are known. | |
| Comment on the Assessment Report | AESGP | In the Assessment Report, page 6/chapter 2.1.1. the following extract is missing which has been authorised in Austria:<br><br>- Standardised dry extract, DER 20-35:1, corresp. silymarin 105 mg. Extraction solvent ethyl acetate<br>- Since when on the market: 2002<br>- Pharmaceutical form: Coated tablets<br>- Posology/ daily dosage: Adults and adolescents 2 x daily 1-2 coated tablets<br>- Indications: Toxic liver damage, supportive treatment of chronic inflammatory liver diseases and cirrhosis of the liver. | **Endorsed** |