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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Commiphora molmol* Engler*, gummi-resina

* In the Ph. Eur. monograph on Myrrh (Ph. Eur. ref.: 1349) the preferred botanical name of the plant is *Commiphora myrrha* (Nees) Engl. *Commiphora molmol* (Engl.) Engl. Ex Tschirch, is listed as a synonym.

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HMPC decision on review of monograph on *Commiphora molmol* Engler, gummi-resina, adopted on 12 July 2011	5 April 2016
Call for scientific data (start and end date)	From 15 July 2016 to 15 October 2016
Agreed by Working Party on European Union monographs and list (MLWP)	June 2018
Adoption by Committee on Herbal Medicinal Products (HMPC)	24 July 2018

Review of new data on *Commiphora molmol* Engler, gummi-resina

Periodic review (from 2011 to 2018)

Scientific data (e.g. non-clinical and clinical safety data, clinical efficacy data)

☒ Pharmacovigilance data (e.g. data from EudraVigilance, VigiBase, national databases): The EudraVigilance database was search on 2018-05-08 using the search term “myrrh” and “myrrh tincture”

☒ Scientific/Medical/Toxicological databases: PubMed (Using the Mesh term "Commiphora" from 2011 to present, Search date: 30 April 2018, 94 hits), Embase (Using the search terms "Commiphora" and “Myrrh” from 2011 to present, Search date: 30 April 2018, 439 hits and

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145 hits, respectively), ToxNet (Using the search terms “Commiphora” and “Myrrh” excluding PubMed records, Search date: 30 April 2018, 4 hits and 0 hits, respectively), National Toxicology Program (NTP) website (Using the search terms “Commiphora” and “Myrrh”, Search date: 30 April 2018, 2 hits but related to documents on Gum guggul, the oleoresin of the plant *Commiphora mukul*), Cochrane Database of Systematic Reviews (Using the search terms “Commiphora” and “Myrrh”, Search date: 30 April 2018, 0 hits)

☒ Other: CosIng 30 April 2018: No restriction on use of Commiphora Myrrha Resin in cosmetics (described as the resin obtained from *Commiphora myrrha*, Burseraceae)

Regulatory practice

☒ Old market overview in AR (i.e. products fulfilling 30/15 years on the market)

☒ New market overview

☒ Referral

☒ Ph.Eur. monograph

☐ Other

Consistency (e.g. scientific decisions taken by HMPC)

☒ Public statements or other decisions taken by HMPC

☒ Consistency with other monographs within the therapeutic area

☐ Other

Availability of new information (i.e. likely to lead to a relevant change of the monograph)

Scientific data	Yes	No
New non-clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New data introducing a possibility of a new list entry	☐	☒
New clinical data regarding the paediatric population or the use during pregnancy and lactation likely to lead to a relevant change of the monograph	☐	☒
New clinical studies introducing a possibility for new WEU indication/preparation	☐	☒
Other scientific data likely to lead to a relevant change of the monograph	☐	☒
Regulatory practice	Yes	No
New herbal substances/preparations with 30/15 years of TU	☐	☒
New herbal substances/preparations with 10 years of WEU	☐	☒
Other regulatory practices likely to lead to a relevant change of the monograph	☐	☒
Referrals likely to lead to a relevant change of the monograph	☐	☒
New Ph.Eur. monograph likely to lead to a relevant change of the monograph	☐	☒
Consistency	Yes	No
New or revised public statements or other HMPC decisions likely to lead to a relevant change of the monograph	☐	☒

Inconsistencies with other monographs within the therapeutic area likely to lead to a relevant change of the monograph	☐	☒
Other inconsistencies likely to lead to a relevant change of the monograph	☐	☒

Summary and conclusions on the review

During the review the following number of new references not yet available during the previous assessment were identified:94 new references in PubMed using the Mesh term "Commiphora"; 439 new references in Embase using the search term "Commiphora"; 145 new references in Embase using the search term “Myrrh”; 4 new references in ToxNet using the search term "Commiphora" and excluding PubMed records. There were some duplicates identified between the new references in PubMed and Embase.

No references were provided by Interested Parties during the Call for data.

Nine references were considered to be relevant for the assessment.

No references justify a revision of the monograph.

No revision is considered required because:

Scientific data

In the scientific literature there are only a few new studies on the plant species *Commiphora molmol*. Most of the studies report on non-clinical pharmacological activities, e.g. wound healing on mouse dermal fibroblast cells (Negahdari *et al*., 2017), effect on acetic acid-induced ulcerative colitis in rats (Fatani *et al*., 2016), effect on *Trichinella spiralis* infection in mice (Attia *et al*., 2015), antispasmodic effect in inflamed rat small intestinal preparations (Vissiennon *et al*., 2015) and analgesic activity in mice, anti-inflammatory activity in rats and anti-hyperlipidemic activity in rats (Shalaby and Hammouda, 2014).

Two studies report that orally co-administrated aqueous suspension of myrrh (oleo-gum resin of *Commiphora myrrha*) decreases the bioavailability of cyclosporine A in rats (380 mg/kg of myrrh and 60 mg/kg of cyclosporine A) (Al-Jenoobi, Ahad *et al*., 2015) and affect the metabolism and elimination when co-administered with theophylline in rabbits (176 mg/kg of myrrh and 16 mg/kg of theophylline) (Al-Jenoobi, Alam *et al.*, 2015). The authors conclude that the results indicate that the bioavailability of cyclosporine A was reduced by about 45% when co-administered with myrrh and that myrrh affects the metabolism and elimination of theophylline. The clinical relevance of these findings has not been confirmed.

Germano *et al*., (2017) studied the analgesic effects of a myrrh (*Commiphora myrrha*) extract in a clinical pilot study with 89 men and 95 women in Italy). The extract was provided as a yellowish powder produced from myrrh gum resins with a total furanodiene content > 40 mg/g. The study was double blinded, randomised and placebo controlled (an identical number of volunteers as in the verum group received placebo). The verum group received one tablet containing either 200 or 400 mg of myrrh extract for 20 days. The authors conclude that the results of this study indicate analgesic activities against pain symptoms, particularly headaches, muscle aches, joint pain, lower back pain, fever-dependent pain, and menstrual cramps. No side effects were reported by any of the volunteers.

The clinical efficacy and safety of a myrrh-based oral mucoadhesive gels (0.5% w/w) has been studied in 30 patients in Saudi Arabia in the management of minor recurrent aphthous stomatitis (Mansour *et*

al., 2014). The study was a randomised, double-blind, vehicle-controlled study (30 patients received plain mucoadhesive gel as placebo). Patients with fresh ulcers (<48-h duration) were instructed to apply the gel four times a day for a period of 5 days. Clinical efficacy was investigated in the form of changes in ulcer size, pain intensity, erythema, and exudation at days 4 and 6 of study entry. Participants were interviewed for the emergence of any side effects. The authors report that the myrrh gel resulted in ulcer size reduction, pain reduction, and reduction in erythema and exudation levels compared to placebo. No side effects were reported.

In a study in Egypt, the efficacy of an oleo-resin extract from *Commiphora molmol* (myrrh) against *Trichomoniasis vaginalis* infection was evaluated in 13 female patients resistant to the combined treatment with metronidazole and tinidazole (El-Sherbiny and El-Sherbiny, 2011). All 13 patients received capsules of 600 mg extract once daily for six to eight successive days. The authors report that 11 of the patients were cured by the oleo-resin extract from myrrh. There is no information available on a control group or if the study was blinded. There is no information available on side effects.

Assessor's comment:

There are no new safety concerns from non-clinical or clinical data. The clinical relevance of the interaction with cyclosporine A in rats and theophylline in rabbits has not been confirmed.

In the clinical study by Germano et al. (2017), the authors state that the randomization was concealed and the attending physicians, the outcome assessor, and the statistician were all blinded to the group allocations. However, in contrast to the verum group, the patients in the placebo group were asked to immediately report any symptoms and if symptoms were reported, the patients were asked to interrupt the placebo administration and use analgesics. Hence, the blinding of the study could be questioned. Importantly, the authors present the study as a pilot study and the number of men and women included in each pain symptom group was small (i.e. from 3 women with lower back pain to 3 women with headaches). The results for each pain symptom were presented for women and men separately. In addition, there is no information available that myrrh has been in medicinal use within the EU for at least ten years for the treatment of headaches, muscle aches, joint pain, lower back pain, fever-dependent pain, and menstrual cramps. Thus, this new clinical study does not introduce the possibility for the establishment of a well-establish use monograph.

The clinical study by Mansour et al.(2014), is also considered small i.e. 30 patients were treated with a myrrh gel (0.5% w/w) for the treatment of minor recurrent aphthous stomatitis. There is no information available that myrrh gels (0.5% w/w) have been in medicinal use within the EU for at least ten years for the treatment of minor recurrent aphthous stomatitis. Thus, this new clinical study does not introduce the possibility for the establishment of a well-establish use monograph.

In the clinical study by El-Sherbiny and El-Sherbiny (2011), 13 patients only were included and there is no information available on a control group or if the study was blinded. There is no information available that myrrh has been in medicinal use within the EU for at least ten years for the treatment of Trichomoniasis vaginalis infection. Thus, this new clinical study does not introduce the possibility for the establishment of a well-established use monograph.

Regulatory practice

No new medicinal products with myrrh as the single active substance have been reported from the MS.

In the market overview it was reported that Gummiresina myrrha has been a subject of Czechoslovak/Czech Pharmacopoeia since 1947. In the last version of the Czech Pharmacopoeia (2016): for local use single dose 5.0 g, daily dose 10.0 g. No information is available on an indication.

In the definition of the Ph. Eur. monograph on Myrrh (Ph. Eur. ref.: 1349) the preferred botanical name of the plant is *Commiphora myrrha* (Nees) Engl. and *Commiphora molmol* (Engl.) Engl. Ex Tschirch, is listed as a synonym.

The Ph. Eur. monograph on Myrrh Tincture (Ph. Eur. ref.: 1877) is included as herbal preparation in the first version of the assessment report on *Commiphora molmol*, gummi-resina. However, the reference to the Ph. Eur. monograph on Myrrh Tincture was not included as a footnote in the first version of the monograph.

Assessor's comment:

There is no need to revise the EU herbal monograph due to new regulatory practice. In particular, there is no need to revise the EU herbal monograph due to the use of another preferred botanical name of the plant in the Ph. Eur. monograph on Myrrh. The botanical name Commiphora molmol that is used in the title of the EU herbal monograph is included as a synonym in the Ph. Eur. monograph. Thus, there is no risk for misunderstanding about which plant that is referred to. However, to highlight this issue, a footnote has been introduced in the title of this review report.

Also, there is no need to revise the EU herbal monograph due to the missing footnote on Myrrh Tincture. If a herbal preparation used in medicinal products in EU is complying with a Ph. Eur. monograph, the Ph. Eur. monograph should be used.

References

a) References relevant for the assessment:

Al-Jenoobi FI, Ahad A, Raish M, Al-Mohizea AM, Alam MA. Investigating the Potential Effect of *Commiphora myrrha* on the Pharmacokinetics of Theophylline, a Narrow Therapeutic Index Drug. *Drug Res (Stuttg)*. 2015, 65(6):312-6.

Al-Jenoobi FI, Alam MA, Al-Mohizea AM, Ahad A, Raish M. Orally co-administrated oleo-gum resin of *Commiphora myrrha* decreases the bioavailability of cyclosporine A in rats. *Pharmazie* 2015 Aug, 70(8):549-52

El-Sherbiny GM, El-Sherbiny ET. The Effect of *Commiphora molmol* (Myrrh) in Treatment of *Trichomoniasis vaginalis* infection. *Iran Red Crescent Med J* 2011, 13(7):480-6

Fatani AJ, Alrojayee FS, Parmar MY, Abuohashish HM, Ahmed MM, Al-Rejaie SS. Myrrh attenuates oxidative and inflammatory processes in acetic acid-induced ulcerative colitis. *Exp Ther Med* 2016, 12(2):730-738

Germano A, Occhipinti A, Barbero F, Maffei ME. A Pilot Study on Bioactive Constituents and Analgesic Effects of MyrLiq®, a *Commiphora myrrha* Extract with a High Furanodiene Content. *Biomed Res Int* 2017, 3804356, 11pp. Doi 10.1155/2017/3804356

Mansour G, Ouda S, Shaker A, Abdallah HM. Clinical efficacy of new aloe vera- and myrrh-based oral mucoadhesive gels in the management of minor recurrent aphthous stomatitis: a randomized, double-blind, vehicle-controlled study. *J Oral Pathol Med* 2014, 43(6):405-9.

Negahdari S, Galehdari H, Kesmati M, Rezaie A, Shariati G. Wound Healing Activity of Extracts and Formulations of Aloe vera, Henna, Adiantum capillus-veneris, and Myrrh on Mouse Dermal Fibroblast Cells. *Int J Prev Med* 2017, 8:18.

Shalaby MA, Hammouda AA. Analgesic, anti-inflammatory and anti-hyperlipidemic activities of Commiphora molmol extract (Myrrh). *J Intercult Ethnopharmacol* 2014, 3(2):56-62.

Vissiennon C, Goos KH, Goos O, Nieber K. Antispasmodic effects of myrrh due to calcium antagonistic effects in inflamed rat small intestinal preparations. *Planta Med* 2015, 81(2):116-22.

b) References that justify the need for the revision of the monograph:

None

Rapporteur's proposal on revision

☐ Revision needed, i.e. new data of relevance for the content of the monograph

☒ No revision needed, i.e. no new data of relevance for the content of the monograph

HMPC decision on revision

☐ Revision needed, i.e. new data of relevance for the content of the monograph

☒ No revision needed, i.e. no new data of relevance for the content of the monograph

The HMPC agreed not to revise the monograph, assessment report and list of references on Myrrha (Commiphora molmol) by consensus.