20 July 2022
EMA/HMPC/166164/2022
Committee on Herbal Medicinal Products (HMPC)

# Addendum to Assessment report on *Curcuma xanthorrhiza* Roxb. (*C. xanthorrhiza* D. Dietrich), rhizoma

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| Rapporteur(s) | B. Kroes |
| Assessor(s) | H. Kuin |
| Peer-reviewer | E. Svedlund |

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| HMPC decision on review of monograph *Curcuma xanthorrhiza* Roxb. (*C. xanthorrhiza* D. Dietrich), rhizoma adopted on 28 January 2014 | 13 January 2021 |
| Call for scientific data (start and end date) | From 01 February 2021 to 30 April 2021 |
| Discussion in Committee on Herbal Medicinal Products (HMPC) | March 2022<br>May 2022<br>July 2022 |
| Adoption by Committee on Herbal Medicinal Products (HMPC) | 20 July 2022 |

## Review of new data on *Curcuma xanthorrhiza* Roxb. *(C. xanthorrhiza* D. Dietrich*)*, rhizoma

### Periodic review (from 2013 to 2022)

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

☒ Pharmacovigilance data (e.g. data from EudraVigilance, VigiBase, national databases)

☒ Scientific/Medical/Toxicological databases: PubMed was searched on 21 February 2022

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Regulatory practice

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

☒ New market overview (including pharmacovigilance actions taken in member states)

☐ 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

**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 / Updated 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 | ☐ | ☒ |
| Relevant inconsistencies with other monographs within the therapeutic area that require a change of the monograph | ☐ | ☒ |
| Other relevant inconsistencies that require a change of the monograph | ☐ | ☒ |

**Summary and conclusions on the review**

During the review, 43 new references not yet available during the first/previous assessment were identified. One reference indicated a potential interaction between *Curcuma xanthorrhiza* Roxb. (*C. xanthorrhiza* D. Dietrich), rhizoma and warfarin was considered to be relevant for the assessment and may be a reason for update of the monograph.

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

In 2015 the Ph. Eur. monograph was revised. There was a change in the name from *Curcuma xanthorrhiza* into *Curcuma zanthorhizza* and several method changes. This is not per se a reason for change of the EU herbal monograph.

There were no new products that entered the European market.

**Scientific data**

*Pharmacovigilance*

The Eudravigilance database was searched on 21 February 2022 for the preferred term (PT) *Curcuma xanthorrhiza* dry extract. There were only 3 side effects reported (malaise, dizziness and hyperhidrosis). The PT *Curcuma zanthorhiza* rhizoma did not have any results.

In the Vigibase database the PT *Curcuma xanthorrhiza* nor *Curcuma zanthorrhiza* were available. However, the synonym temoe lawak was present and produced only one reported side effect of oesophageal pain, search date 21 February 2022.

*Assessor's comment: Data from pharmacovigilance databases cannot be related directly to the use of Curcuma xanthorrhiza* Roxb. (*C. xanthorrhiza* D. Dietrich), rhizoma *and therefore do not trigger the change of the EU herbal monograph.*

*Ph. Eur. Monograph*

The Ph. Eur. monograph for *Curcuma xanthorrhiza* (1441) was updated in 2015. The name was changed from *Curcuma xanthorrhiza* into *Curcuma zanthorrhiza*. Furthermore, the microscopic examination was changed, as well as the thin layer chromatography method, the exclusion of *Curcuma longa* test and the assay method.

*Assessor's comment: These changes in the Ph. Eur. monograph are not per se a reason for changing the monograph.*

*Pubmed search*

A search was performed on PubMed with the search terms *Curcuma xanthorrhiza* OR temoe lawak in the timeframe from 2013 to 2022. Forty-three results were obtained. Most of these results were *in vitro* and *in vivo* animal studies that were considered not relevant for the monograph.

Furthermore, potential interaction with vitamin D (Wahono, 2017) and warfarin (Rusdiana, 2021) were studied. In the latter study it was shown that male Wistar rats (n=6 in each group) that were fed (oral administration) during 7 days with an unspecified *Curcuma xanthorrhiza* extract from Conimex (18 mg/kg bw and subsequently treated with a single dose of warfarin i.v. (1 mg/kg) showed a significant increase of serum warfarin compared to the control (AUC of serum R-warfarin 78 mg.h/L vs 35 mg.h/L and S-warfarin 316 mg.h/L vs 40 mg.h/L). A lower concentration of *Curcuma xanthorrhiza* (6 mg/kg bw) did not show a statistically significant result. One additional group of rats (n=6) were administrated 6 mg/kg of fluconazole as a positive control (AUC of R-warfarin 86 mg.h/L and S-

warfarin 172 mg.h/L). In the multiple-dose study, male Wistar rats (n=6 in each group) were treated with 0.2 mg/kg warfarin i.v. for 11 days. On the 7th to 9th day of the multiple dose study the rats were treated with 6 mg/kg or 18 mg/kg *Curcuma xanthorrhiza* extract. One additional group of rats (n=6) were administrated 6 mg/kg of fluconazole as a positive control. After the 8th day of observation almost all rats in the fluconazole group had major bleeding and died. In the high *dose Curcuma xanthorrhiza* extract, the increase in concentration level of warfarin was moderately higher, but no significant increase in the low dose *Curcuma xanthorrhiza* extract. According to the authors, the lower dose of the *Curcuma xanthorrhiza* extract in this experiment was calculated on the adult human daily dose of 60-120 mg.
An additional search with the search term *Curcuma zanthorrhiza* had 5 results in the same period. None of these studies were considered relevant for the review of the monograph.

*Assessor's comment: In the study by Rusadian et al., 2021, an increase in the serum concentration of warfarin were shown in rats administrated a high dose Curcuma xanthorrhiza extract. However, there are no data found on humans that could be related to a possible interaction between warfarin and Curcuma xanthorrhiza. Until further data is available, this single study on rats does not trigger a revision of the monograph*.

**New market overview**

No new products containing *Curcuma xanthorrhiza* as a single active substance have been reported from the Member States. Hungary reported that 2 combination products containing *Curcuma xanthorrhiza* are on their market.

*Assessor's comment: As the monograph only involves mono-component products, the products reported by Hungary are not a valid reason to revise the EU herbal monograph.*

**Consistency with other monographs within the therapeutic area**

The indication is in line with the EU herbal monograph for *Curcuma longa*.

**References**

a) References relevant for the assessment:

European Pharmacopoeia (Ph. Eur.). *Curcuma zanthorrhiza*. Council of Europe. 1441
Rusdiana T, *et al*. The influence of Javanese turmeric (*Curcuma xanthorrhiza*) on the pharmacokinetics of warfarin in rats with single and multiple-dose studies. *Pharmaceutical Biology* 2021, 59(1):639–646
Wahono CS, Setyorini CD, Kalim H, Nurdiana N, Handono K. Effect of *Curcuma xanthorrhiza* supplementation on systemic lupus erythematosus patients with hypovitamin D which were given vitamin D3 towards disease activity (SLEDAI), IL-6, and TGF-$\beta$1 Serum. *International Journal of Rheumatology* 2017, article ID 7687053, 8 pages

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

None

**Rapporteur's proposal on revision**

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

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

**HMPC decision on revision**

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

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