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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Curcuma longa* L., rhizoma

Rapporteur(s)	B. Kroes / H. Kuin
Peer-reviewer(s)	A. Assisi

HMPC decision on review of monograph *Curcuma longa* L., rhizoma adopted on 25 September 2018	31 January 2024
Call for scientific data (start and end date)	From 01 April 2024 to 30 June 2024
Discussion in Committee on Herbal Medicinal Products (HMPC)	November 2024 March 2025 May 2025 September 2025 November 2025
Adoption by HMPC	19 November 2025

Review of new data

Periodic review (from 2016 to 2024)

Sources checked for new information:

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

☒ Scientific/Medical/Toxicological databases

PubMed and EMBASE were searched in January 2025 using "Curcuma" AND "longa" OR "turmeric" as search terms and years 2016-2025 as limit resulting in 5096 and 7771 references, respectively. Another search in EMBASE with the same limits and "Curcuma" AND "Longa" OR "turmeric AND 'liver toxicity" as search terms resulted in 298 references and with "Curcuma" AND "Longa" OR "turmeric" AND "drug interaction" in 794 hits.

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
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☒ Pharmacovigilance databases

☒ data from EudraVigilance

☒ from other sources (e.g. data from VigiBase, national databases)

☐ Other

Regulatory practice

☒ Old market overview in AR (i.e. check products fulfilling 30/15 years of TU or 10 years of WEU on the market)

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

☒ PSUSA

☒ Feedback from experiences with the monograph during MRP/DCP procedures

☒ 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 that could trigger a revision of the monograph

Scientific data	Yes	No
New non-clinical safety data that could trigger a revision of the monograph	☐	☒
New clinical safety data that could trigger a revision 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 that could trigger a revision of the monograph	☐	☒
New clinical studies introducing a possibility for new WEU indication/preparation	☐	☒
Other scientific data that could trigger a revision 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	☐	☒
New recommendations from a finalised PSUSA	☐	☒
Feedback from experiences with the monograph during MRP/DCP procedures that could trigger a revision of the monograph	☐	☒

New/Updated Ph. Eur. monograph that could trigger a revision of the monograph	☐	☒
Other regulatory practices that could trigger a revision of the monograph	☐	☒
Consistency	Yes	No
New or revised public statements or other HMPC decisions that could trigger a revision of the monograph	☐	☒
Relevant inconsistencies with other monographs within the therapeutic area that could trigger a revision of the monograph	☐	☒
Other relevant inconsistencies that could trigger a revision of the monograph	☐	☒

Summary of new references

In the review, 7771 new references not yet available during the previous assessment were identified. Out of these new references, 298 references were related to liver toxicity and 794 to drug interaction. None of references triggers revision of the monograph.

A search in pharmacovigilance databases revealed no new safety issues that trigger revision of the monograph.

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

Assessment of new data

New scientific data that could trigger a revision of the monograph

Based on national risk assessments from Germany, France and Spain, the Head of food safety agencies working group on food supplements raised concerns regarding a potential risk to consumers linked to the consumption of products containing curcumin in *Curcuma spp.* preparations or curcuminoids due to hepatotoxicity in humans (at very high doses) and animals (Head of Food Safety Agencies, 2024). Concerns were also raised regarding possible drug interactions.

Using "Curcuma" AND "longa" OR "turmeric AND "liver toxicity" as search terms and publication years 2016-2025 as limit, 298 references were found.

Lombardi *et al*., 2020 reported 37 cases of liver injury following turmeric use. In all cases, hepatotoxicity was associated with *Curcuma longa* formulations with high bioavailability and/or high dosage of curcumin/curcuminoids. They identified 23 cases through a systematic review of literature databases. The majority of these patients were concomitantly exposed to at least one other medication.

Papke *et al*., 2025 identified via a retrospective pathology archive review, 11 patients with turmeric supplement-associated hepatitis. Their Roussel Uclaf causality assessment method (RUCAM) analysis estimated the likelihood of turmeric supplement-associated liver injury to be probable (eight cases) and possible (three). However, in the majority of the reported cases the preparation and the dose used were unknown. In those cases when this information was available patients had used high amounts of curcuminoids and/or turmeric combined with black pepper and in all cases, there was concomitant use of other supplements/ medicinal products.

Assessor's comment

Several case reports on liver injury after turmeric/curcumin intake are reported in literature. In all reported cases, there was concomitant use of other medicines and/or supplements. Also, details (e.g. type of preparation, dose) of the products used are not provided. In those cases where these details were provided, products often contain a pepper (extract) to increase the bioavailability of curcumin, and/or the daily intake of Curcuma longa and/curcumin was higher than the posology of the EU herbal monograph.

Due to the concomitant use in the reported cases, causality could not be established. However, the available data suggests that hepatotoxicity is a risk associated with turmeric formulations with high bioavailability and high dosage of curcumin/curcuminoids.

So far, no liver toxicity has been reported for the posologies listed in the EU herbal monograph. Therefore, revision of section 4.8 is not recommended. Change of section 4.9 is also not recommended because it is unknown at which (minimal) dose hepatoxicity can occur.

Using "Curcuma" AND "longa" OR "turmeric" AND "drug interaction" as search terms and publication years 2016-2025 as limit, 794 references were found. Curcumin was found to inhibit the P-gp and CYP3A4 activities *in vitro*, and to activate CYP3A4 and suppresses P-gp abilities *in vivo*. (Cheng *et al*., 2018). Drug interaction was observed in several clinical trials after co-administration of *Curcuma longa* or curcumin with talinolol, endoxifen, sulphasalazine and tamoxifen. However, the dose of curcumin (300 mg per day, 1200mg 3dd or 2 g per day) used in these studies is higher than the maximum daily dose of 4 g *Curcuma longa* (corresponding to a maximum of 209 mg curcuminoids) recommended in the monograph. (Chan *et al.*, 2023, Hussaarts *et al.*, 2019, Juan *et al*., 2007, Kusuhara *et al.*,2012). No change in tacrolimus plasma concentrations was observed after intake of 10g turmeric per day for 4 days (Boissiere *et al.*, 2023).

Not-clinically relevant changes in the pharmacokinetic parameters of paclitaxel were observed after intake of 2 g per day turmeric. The authors of the study conclude that 2 g turmeric per day can be combined safely with paclitaxel (Kalluru *et al.*, 2022)

Assessor's comment

Drug interactions of curcumin and turmeric have been reported in several clinical trials. The dose used in these studies are higher than the intake recommended by the EU herbal monograph.

No drug interaction has been reported with the posologies listed in the EU herbal monograph. Therefore, revision of section 4.5 is not recommended.

EudraVigilance data

The EudraVigilance database was searched in November 2024 for reports on the active substances "C*urcuma longa"* or "*Turmeric*". There are 22 reports on (possible) drug interaction and 9 for jaundice.

VigiLyze reports for "Curcuma longa" or "Turmeric"

From the WHO VigiBase 26 reports of drug interaction for products containing *Curcuma longa* were retrieved.

Assessor's comment

None of the reported cases triggers a revision of the EU herbal monograph because there was concomitant use of other drugs/supplements and/or details of the preparations used were missing (e.g. dose/type of extract is not included in the case reports.)

The Ph. Eur. monograph includes only a limit for the minimum curcumin content: 2% w/w.

In literature it is reported that curcumin content of *Curcuma longa* varies between 3 and 9% w/w. (e.g. El-Saadony *et al*., 2023, Priyadarsini, 2014). However, the sources that mention a curcumin content of 5% and higher do not contain analytical data. They refer to other publications but also these sources do not contain analytical data on the curcumin content of *Curcuma longa*.

In publications with analytical data, the curcumin content is around 3%. Hayakawa *et al.,* 2011 reported a content of curcumin between 2.3 – 3.2% analysing curcuma from 5 sources; Tayyem *et al.,* 2006 and Nie *et al.,* 2011 reported a content of curcumin of 3.14% and 3.43%, respectively.

The average curcuminoids content of 21 batches analysed by European Directorate for the Quality of Medicines & HealthCare (EDQM) was 2.34% m/m and varied between 1.15 and 5.15 % m/m.

According to batch data provided by competent authorities, the daily curcumin intake via herbal medicinal products is 192 mg or 60 mg.

Using the batch data of the EQDM the maximum curcumin intake corresponding to the posologies listed in the monograph was calculated:

Preparation	Dose	Frequency daily	Maximum daily dose Curcuma (g)	Maximum daily dose Curcumin (mg)	Maximum daily dose Curcumin mg/kg BW [1] based the <u>average</u> content	Maximum daily dose Curcumin mg/kg BW [1)] based the <u>maximum</u> content
Powdered herbal substance	0.5-1g	2-3	3	35-155	1.40	3.1
Herbal tea	0.5-1g	2-3	3	35-155	1.40	3.1
Tincture (1:10)	0.5-1 ml	3	0.3	3,5-15.5	0.140	0.31
Dry extract (DER 13-25:1)	90-162mg		4.05	47-209	1.90	4.18
Dry extract (DER 5.5-6.5:1)	100-200mg	2	2.6	30-134	1.22	2.68
Tincture (1:5)	5 ml	3	3	35-155	1.40	3.1

[1)] Using 50 kg as weight for an adult

The European Food Safety Authority (EFSA) recommends an acceptable daily intake (ADI) of 3 mg curcumin/kg body weight per day.

Assessor's comment

With the average content of the batches tested by the EDQM, the curcumin intake corresponding to the posologies listed in the EU herbal monograph is in the range of the ADI recommended by EFSA. However, when the herbal substance contains more that 5 % m/m curcumin (i.e. 1 of the 19 batches tested) the curcumin intake will be higher than the ADI.

To date, no drug interaction has been reported for posologies listed in the EU herbal monograph or for a curcumine intake corresponding to the ADI. Therefore, revision of section 4.5 is not recommended.

New regulatory practice that could trigger a revision of the monograph

No new herbal substances/preparations with 30/15 years of TU or 10 years of WEU was declared from the EU member countries in the review period.

Inconsistency that could trigger a revision of the monograph

Not applicable.

Other issues that could trigger a revision of the monograph

Not applicable.

New information not considered to trigger a revision at present but that could be relevant for the next review

Inclusion of a warning in section 4.5 for drug interactions in case of concomitant use of curcumin bioavailability enhancers should be explored in the next review.

References

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Rapporteur's proposal on revision

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

☐ Revision likely to have an impact on the corresponding list entry (if applicable)

☒ 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