03 March 2021
EMA/HMPC/601683/2020
Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Cinnamomum verum* J.S. Presl, cortex

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HMPC decision on review of monograph *Cinnamomum verum* J.S. Presl, cortex adopted on 10 May 2011	15 January 2020
Call for scientific data (start and end date)	From 1 March to 31 May 2020
Adoption by Committee on Herbal Medicinal Products (HMPC)	03 March 2021

Review of new data on *Cinnamomum verum* J.S. Presl, cortex

Periodic review (from 2011 to 2020)

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

- ☒ Pharmacovigilance data (EudraVigilance)
- ☒ Scientific/Medical/Toxicological databases: Embase, Medline. Search terms: cinnamon, *Cinnamomum, zeylanicum, cortex.*
- ☐ Other

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

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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 / 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	☐	☒

Market overview

No new products on the market.

Pharmacovigilance

A search in the EudraVigilance database was done from 1995 until 2020. It resulted in 231 hits on '*Cinnamomum*': 49 related to *Cinnamomum* (without other precision), 109 related to *Cinnamomum* cortex, 14 to *Cinnamomum zeylanicum*, 48 to *Cinnamomum* oil, 2 to *Cinnamomum* flavour and 9 related to another species of *Cinnamomum* (*Cinnamomum* cassia, *Cinnamomum camphora* and Chinese *Cinnamomum*). *Cinnamomum* was never solely mentioned. Sometimes, only one product is mentioned but it always contents several constituents (herbal parts or essential oils). The

pharmacovigilance information obtained does not reveal any need to revise the monograph on *Cinnamomum* cortex for safety reasons.

Summary and conclusions on the review

During the review 2675 new references not yet available during the first/previous assessment were identified. Clinical references were selected on diabetes (n=71), diverse therapeutic applications (n=44), safety issues (n=43), obesity (n=4) and gastro-intestinal use (n=1).

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

12 references were considered to be relevant for the assessment.

Reference 1: Davis *et al*. (2011): cinnamon and diabetes

The authors made a meta-analysis of clinical studies of the effect of cinnamon intake on people with type 2 diabetes and/or prediabetes. Eight clinical studies were taken into consideration after a literature search (Pub Med and Biosis through May 2010). It were randomized, placebo-controlled trials reporting data on cinnamon and/or cinnamon extract and fasting blood glucose. A meta-analysis was performed on the identified data for both cinnamon bark powder and cinnamon extract intake using a random-effects model that determined the standardized mean difference (= mean change control – mean change cinnamon / pooled SD of post scores). Cinnamon intake results in a statistically significant lowering in fasting blood glucose of -0.49 ± 0.2 mmol/L; P = 0.025; 8 studies). Intake of cinnamon extracts only lowered the fasting blood glucose -0.48 ± 0.17 mmol/L; P = 0.008; 5 studies). The authors conclude that cinnamon and/or cinnamon extracts lower fasting blood glucose significantly in diabetes and prediabetes patients.

Assessor's comment

This meta-analysis is not useful for evaluation and changing of the monograph for several reasons.

Reason one: the patients. In one study healthy subjects were included. In the other 7 selected clinical trials, patients with an impaired fasting blood glucose, metabolic syndrome or type-2 diabetes were studied. Patients were poorly documented on the medication they used. Apparently, at least a part of the patients were already treated with antidiabetic medicines. It was mentioned that the population was gender mixed, but the percentage man and women and their age are not specified. No adjustments or corrections for population differences were mentioned. The number of patients is low in each study, varying from 20 to 136. In total 186 patients were treated with cinnamon, which is a too limited number to come to conclusions.

Reason two: the intervention. The species used was Cinnamomum cassia Blume in seven studies and not specified in one study. Although this species is comparable to Cinnamomum zeylanicum Presl it is not taken into consideration in the actual monograph. The duration was variable: 4 to 16 weeks. The DER of the extracts and the chemical composition were not specified. If mentioned it seemed like water extracts were used. Posology of the powder was 1 to 6 g per day.

Reason three: the outcome. Controlling fasting blood glucose is not yet taken into consideration in the accepted therapeutic indications. There are no authorised products on the market with this indication.

Although the authors suggest that the results are consistent, they base their conclusions on standard mean differences. It is not clear how individual patients reacted, and what the clinical importance of the lowering might be. For how many patients was the glucose level lowered to normal values? An odds ratio would have been better to make a quantitative estimation of the number of patients for whom a clinically relevant result was obtained as compared to the controls. Finally one study accounted for about 30% of all patients.

Reference 2: Deyno *et al*. (2019): cinnamon and diabetes

Sixteen randomized controlled studies with diabetes Type-2 and prediabetes patients were included in the meta-analysis. Cinnamon significantly reduced fasting blood glucose and insulin resistance compared to placebo. There was no significant change in weighted mean difference of glycosylated hemoglobin A1C (HbA1c) % and lipid profiles (mmol/L). In only 3 studies *Cinnamomum zeylanicum / verum* (most probably bark powder) was used in a daily dose from 1 to 3 g and 214 patients completed a study period of 2 weeks to 3 months. Patients took cinnamon in monotherapy or as an adjuvant to existing therapy. The authors warn for a high degree of heterogeneity between the studies.

Assessor's comment

Apart from the reasons already mentioned in the former meta-analysis by Davis et al. (2011), the therapeutic outcomes are limited. Cinnamon did not influence HbA1c and lipid profiles. This meta-analysis does not justify a change of the monograph.

Reference 3: Ranasinghe *et al. (*2013): pharmacological activities

A literature search identified 70 articles in PubMed, Web of Science, SciVerse Scopus and in the reference lists of the selected references on *Cinnamomum zeylanicum*. The articles dealt with experimental *in vitro* and *in vivo* beneficial health effects: a) anti-microbial and anti-parasitic activity; b) lowering of blood glucose, blood pressure and serum cholesterol; c) anti-oxidant and free-radical scavenging properties; d) inhibition of tau aggregation and filament formation (hallmarks of Alzheimer's disease); e) inhibitory effects on osteoclastogenesis; f) anti-secretagogue and anti-gastric ulcer effects; g) anti-nociceptive and anti-inflammatory activity; h) wound healing properties and i) hepato-protective effects. The studies reported minimal toxicity.

Assessor's comment

Most of the effects are already in the preclinical part of the assessment report. There is no need to change the monograph, based on the results of the systematic review.

Reference 4: Bracheau *et al*. (2015): case report hepatitis

A 73-year-old woman was seen in the Emergency Department complaining of abdominal pain associated with vomiting and diarrhoea after she started taking cinnamon supplements for about 1 week. The patient's pain was epigastric, radiating into her right upper quadrant and also into her chest. It was reported to be worse with palpation and deep inspiration, and was quite different from her angina pain, which necessitated her to have 2 stents placed approximately 8 months before this admission. The patient had hypertension, diabetes, depression, hyperlipidaemia, gastroesophageal

reflux, and chronic back pain. She also had a history of cholecystectomy, hysterectomy, and exploratory laparotomy for recurrent abdominal pain. She was a social alcohol drinker and current tobacco abuser. She was taking rosuvastatin 40 mg orally once a day for coronary artery disease. Her other medications included paroxetine, amlodipine, aspirin, clopidogrel, insulin, losartan, metoprolol, and pantoprazole. She had started taking a cinnamon supplement to treat her diabetes. Blood analysis showed strongly enhanced transaminases, alkaline phosphatase and gamma-glutamyl transferase. Tests for hepatitis A, B and C were negative. The Naranjo scale gave a sore of 6, which means a probable relationship. Rosuvastatin and cinnamon were stopped. Her hospital course progressed and her abdominal pain slowly resolved. After discharge and restarting the statin therapy no elevated liver enzymes or abdominal pain occurred. The authors warn against combining statins and cinnamon.

Assessor's comment

This case reporting suffers from poor information on the cinnamon species used, the composition of the preparation and the doses. Confirming by other cases seems justified.

Reference 5: Gonçalves *et al*. (2019): human health risk related to contamination

The authors found significant differences in Zn, Fe, Al, and Cl concentrations between different cinnamon powder products marketed in Portugal, with bulk products exhibiting higher concentrations of Fe and Al than all other products. Estimated values for hazard quotient and hazard index (HI) were lower than 1, indicating that the estimated dietary intake of Cu, Zn, Fe, Al, Cl, Mn, and Sr from daily consumption of 6 g of the investigated cinnamon samples does not present potential non-carcinogenic risks to consumers' health. Given the estimated HI value of 0.660, and the exposure to these metals by other routes, potential toxicological risks exist.

Assessor's comment

The paper focuses on quality issues of cinnamon samples, including Cinnamomum verum / zeylanicum. Possible consequences for quality control arise, but are out of scope with regard to the content of the monograph.

Reference 6: Hajimonfardnejad *et al*. (2019): adverse events

The authors undertook a comprehensive literature search in March 2016 using electronic databases, using the search terms "cinnamon" or "cinnamomum". Apart from literature references, spontaneous reports about adverse effects of cinnamon were requested from vigilance databases. Twenty case reports and seven case series, as well as, spontaneous reports including 160 adverse events were included. Topical exposure to cinnamon oil was reported in six cases, mostly as a bath additive. Use of cinnamon oil pills was only mentioned once with acute exacerbation of rosacea as a consequence. One case of swelling and mild erythema about the lips was mentioned after using chewing gum with cinnamon oil. The authors conclude that the available data suggest that cinnamon is safe to be used in routine diet as spice and/or flavouring agent. It is well tolerated in controlled clinical settings. However, its use for medicinal purposes, in large doses or long durations, may lead to some adverse effects and it should be clinically monitored.

Assessor's comment

The authors provide little information on adverse events with the cortex. Mostly flavouring or local exposure is discussed. Attention has to be given to posology and duration. No hepatotoxicity is mentioned.

Reference 7: Haroun *et al*. (2011): allergic contact stomatitis

The authors present the case of a 26-year-old woman who suffered an intense itching in jugal mucosa, soft palate and oropharynx after eating a cinnamon gum accompanied by pharyngeal occupation sense without respiratory distress. The same happened after eating rice pudding with cinnamon, but with less intensity. Her medical history did not contribute and she was not taking any medications regularly. Skin prick test with powder cinnamon was positive with erythema and intense itching. Epicutaneous test with cinnamon gum and powder cinnamon were positive after 24 h, with the withdrawal of them because of intense itching.

Assessor's comment

This is a case of contact allergy, which can occur when taking cinnamon by mouth. It is not communicated which species of cinnamon is involved. Hypersensitivity remains a contraindication in the monograph.

Reference 8: Iwata *et al*. (2016): hepatotoxicity and coumarins

The authors started from the coumarin content of Kampo medicines derived from cinnamon bark. They evaluated the risk for hepatotoxicity in clinical practices, knowing that many of the patients had a coumarin intake exceeding the tolerable daily intake (TDI) .When comparing patients with an intake lower (n=31) and higher (n=98) than the TDI, they did not observe cases of abnormal liver function caused by cinnamon bark in the higher patients group. These results suggest that ingestion of the coumarin contained in Kampo medicines that exceeds the TDI is not associated with hepatotoxicity. Kampo medicines may be used safely in clinical practice, without concern for exceeding the TDI.

Assessor's comment

There is no evidence for hepatoxicity due to coumarin in cinnamon.

Reference 9: Mertens *et al*. (2017): allergic reaction by cinnamon tea

This publication describes a 26-year-old atopic female student presented at the emergency department with a widespread and itchy maculopapular skin eruption that had been present for 1 week. The lesions had started on the abdomen, and had spread to the arms, chest, legs, and thighs. The patient did not have any prior illness, and had not taken any medication. The day before she had drunk multiple cups of a specific herbal tea, containing 27.1% *Cinnamomum zeylanicum* cortex. The patient got the advice to avoid fragrance cosmetics and cinnamon containing food. There was no recurrence after a follow-up of 6 years.

Assessor's comment

This is a serious case of generalized allergy that quickly solved after refraining from intake or contact with cinnamon. This is a case of serious hypersensitivity covered by the contraindication of the

monograph.

Reference 10: Neto *et al*. (2019): cinnamon intake during lactation (experimental setup)

Intake of an aqueous extract of cinnamon by female Wistar rats induced long-term molecular, metabolic, and hormonal changes in the adult progeny, including visceral obesity, higher lipid accumulation, and lower glycogen content. The male adult offspring were evaluated at 180 days old.

Assessor's comment

The daily doses administered, corresponding to 3 to 5 g cinnamon cortex, were started immediately after delivering and continued for 20 days. Most probably, Cinnamomum zeylanicum cortex was used. It is difficult to extrapolate from rats to humans. Although interesting for the preclinical part of the assessment report, these findings will not change the monograph that already gives the warning: "Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended".

Reference 11: Ranasinghe *et al*. (2017): phase I trial

The authors enrolled 28 subjects in a 3 months follow up phase I trial. Mean age was 38.8 ± 10.4 years, 50% female. The subjects took daily 85 mg (1st month), 250 mg (2nd month) and 500 mg (3rd month) of refined *Cinnamomum zeylanicum* (corresponding to 1, 3 ad 5 g cortex respectively; refining process not specified). Compliance level situated between 85 and 95%. Both systolic and diastolic blood pressure lowered significantly during the 1st month and this lowering remained until the end of the study. A significant reduction in total cholesterol ($p < 0.05$) and LDL-c ($p < 0.001$) was noted after 3 months. There were no serious adverse effects (including hypersensitivity). Two patients dropped out because of dyspepsia.

Assessor's comment

Although these findings are interesting, they will not lead to a change of the monograph. The study is done with healthy subjects. The preparation is not on the EU market with the appropriate therapeutic indications. Although the mean systolic and diastolic blood pressure sunk significantly, the clinical relevance is poor. There is a considerable spread on the mean total cholesterol and LDL-c, pointing to considerable individual differences.

Reference 12: Shiga *et al*. (2014): generalized erythema

A 70-year-old man presented himself with a complaint of edematous erythema over the entire body. He had taken a Japanese medicine against common cold. The medicine contained among others Chinese cinnamon bark (Latin name not specified). The next morning, he developed a generalized erythema that worsened the days after. Laboratory data showed mild liver dysfunction, impaired renal function and enhanced C-reactive protein. Patch testing was only positive with concentrations of 20%, not with 5% and not with 30% of the crude medicine.

Assessor's comment

The patient reacted only to high concentrations of cinnamon. Apparently, the medicine, which also contained Kudzu, Ephedra and Jujube, caused the erythema. The role of cinnamon is not clear. Moreover, the species of cinnamon is not unambiguously identified and cinnamon is used in a non-

Western tradition.

No reference justify a revision of the monograph

No revision is considered required because:

- There are no new safety concerns, no new therapeutic indications or clinical data on special populations and no new scientific data leading to change of the monograph.
- The market overview did not reveal the authorisation of new herbal substances and the monograph remains in line with the monograph of the European Pharmacopoeia.
- There are no inconsistencies creating the need for revision.

References

a) References relevant for the assessment:

Brancheau D, Patel B, Zughaib M. Do Cinnamon Supplements Cause Acute Hepatitis? *Am J Case Rep*, 2015, 16: 250-254

Davis PA, Yokoyama W. Cinnamon Intake Lowers Fasting Blood Glucose: Meta-Analysis. *J Med Food* 2011, 14 (9): 884–889

Deyno S, Eneyew K, Seyfe S. *et al*. Efficacy and safety of cinnamon in type 2 diabetes mellitus and pre-diabetes patients: A meta-analysis and meta-regression. *Diabetes research and clinical practice* 2019, 156: 1-14

Gonçalves LL, Fernandes T, Bernardo MA, Brito JA. Assessment of Human Health Risk of Toxic Elements Due to Cinnamon Ingestion in the Diet. *Biological Trace Element Research* 2019, 189: 313–324

Hajimonfarednejad M, Ostovar M, Raee MJ, Hashempur MH, Mayer JG, Heydari M. Cinnamon: A systematic review of adverse events. *Clinical Nutrition* 2019, 38: 594-602

Haroun E, Perez N, Uriarte S, Hernandez E, Sastre J. Allergic contact stomatitis due to cinnamon. *Allergy* 2011, 66 Suppl. 94: 286 (abstract)

Iwata N, Kainuma M, Kobayashi D, *et al*. The Relation between Hepatotoxicity and the Total Coumarin Intake from Traditional Japanese Medicines Containing Cinnamon Bark. *Frontiers in Pharmacology* 2016, 7: article 174 doi: 10.3389/fphar.2016.00174

Mertens M, Gilissen L, Goossens A, Lambert J, Vermander E, Aerts O. Generalized systemic allergic dermatitis caused by *Cinnamomum zeylanicum* in a herbal tea. *Contact Dermatitis* 2017, 77: 250–267

Neto JGO, Bernardes TB, Pazos-Moura CC, Oliveira KJ. Maternal cinnamon intake during lactation led to visceral obesity and hepatic metabolic dysfunction in the adult male offspring. *Endocrine* 2019, 63: 520–530

Ranasinghe P, Jayawardena R, Pigera S, *et al*. Evaluation of pharmacodynamic properties and safety of *Cinnamomum zeylanicum* (Ceylon cinnamon) in healthy adults: a phase I clinical trial. BMC *Complementary and Alternative Medicine* 2017, 17: 550 DOI 10.1186/s12906-017-2067-7

Ranasinghe P, Pigera S, Premakumara S, Galappaththy P, Constantine GR, Katulanda P. Medicinal

properties of 'true' cinnamon (*Cinnamomum zeylanicum*): a systematic review. *Complementary and Alternative Medicine* 2013, 13: 275 Available at: http://www.biomedcentral.com/1472-6882/13/275

Shiga T, Matsushima T, Sano S. A case of erythema multiforme caused by cinnamon included in Japanese herbal medicine, Kakkonto. *Journal of Dermatology* 2014, 41 (Suppl. 1): 71

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

The HMPC agreed not to revise the monograph, assessment report and list of references on *Cinnamomum verum* J.S. Presl, cortex, by consensus.