



03 March 2021  
EMA/HMPC/601695/2020  
Committee on Herbal Medicinal Products (HMPC)

## Addendum to Assessment report on *Cinnamomum verum* J.S. Presl, corticis aetheroleum

Rapporteur(s)	G Laekeman
Assessor(s)	P Bodart
Peer-reviewer	S Mamoucha

HMPC decision on review of monograph <i>Cinnamomum verum</i> J.S. Presl, corticis aetheroleum 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, corticis aetheroleum

#### Periodic review (from 2011 to 2020)

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

- Pharmacovigilance data (data from EudraVigilance)
- Scientific/Medical/Toxicological databases: Embase, Medline. Search terms: cinnamon, *Cinnamomum*, *zeylanicum*, aetheroleum, oil, cinnamaldehyde.
- 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



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)**

<i>Scientific data</i>	Yes	No
New non-clinical safety data likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New clinical safety data likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New data introducing a possibility of a new list entry	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New clinical data regarding the paediatric population or the use during pregnancy and lactation likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New clinical studies introducing a possibility for new WEU indication/preparation	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Other scientific data likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Regulatory practice</i>	Yes	No
New herbal substances/preparations with 30/15 years of TU	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New herbal substances/preparations with 10 years of WEU	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Other regulatory practices likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Referrals likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
New / Updated Ph. Eur. monograph likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<i>Consistency</i>	Yes	No
New or revised public statements or other HMPC decisions likely to lead to a relevant change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Relevant inconsistencies with other monographs within the therapeutic area that require a change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Other relevant inconsistencies that require a change of the monograph	<input type="checkbox"/>	<input checked="" type="checkbox"/>

**Market overview**

No new single products on the European 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*.

*Cinnamomum* was never solely mentioned. The pharmacovigilance information obtained does not reveal any need to revise the monograph on *Cinnamomum aetheroleum* for safety reasons.

### **Summary and conclusions on the review**

During the review 2675 new references not yet available during the first 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.

2 references only among the studied ones were considered relevant for the assessment.

#### Reference 1: Hagvall *et al.* (2018)

Hagvall *et al.* (2018) investigated the clinical relevance of contact allergy to epoxycinnamyl alcohol (concentrations of cinnamylacetate in the essential oil of cinnamon bark vary between 0.3 - 10.6%) and epoxy-cinnamaldehyde (concentrations of cinnamaldehyde in the essential oil of cinnamon bark vary between 55 - 76%). Cinnamyl alcohol is considered to be a prohaptens and prehapten with cinnamal as the main metabolite. However, many individuals who are allergic to cinnamyl alcohol do not react to cinnamal. Sensitizing epoxides of cinnamyl alcohol and cinnamal have been identified as metabolites and autoxidation products of cinnamyl alcohol. The purity of chemicals used was 98.7% for cinnamyl alcohol and 99.3% for cinnamal. The irritative effects of both epoxides were patch tested in nearly 800 patients. Cinnamyl alcohol and cinnamal were patch tested in more than 1200 patients. Both epoxides were irritants, but no more positive reactions were detected than when testing was performed with cinnamyl alcohol and cinnamal. Late allergic reactions to epoxycinnamyl alcohol were observed. In general, patients with late reactions (= after the regular reading time of 7 days) showed doubtful or positive reactions to cinnamal. The authors conclude that the investigated epoxides were no important haptens in contact allergy to cinnamon flavour and fragrance. No additional cases of cinnamon fragrance allergy were shown by patch testing with the epoxides within a regular reading time. However, late allergic reactions were seen, which implies that the epoxides might cause weak reactions after a prolonged reading.

#### **Assessor's comment**

*The actual monograph on the essential oil of cinnamon is already including a warning against hypersensitivity and irritation. According to the results, there is no reason for adding a special warning related to epoxycinnamyl alcohol or epoxycinnamaldehyde.*

#### Reference 2: Hajimonfarednejad *et al.* (2019)

The authors undertook a comprehensive literature search in March 2016 - in 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 on the lips was mentioned after using chewing gum with cinnamon

oil. The authors concluded 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 monograph of the essential oil of cinnamon allows a posology of 50 to 200 mg daily, in 2 to 3 doses. This is a well-defined posology with therapeutic duration of use limited to two weeks. The monograph fulfils the criteria for a safe oral use. Most undesirable effects were mentioned after topical exposure. Topical use is not included in the actual monograph and there are no authorised products on the EU market for topical application.*

No reference justify a revision of the monograph.

No revision is considered required because:

- Some references dealt with constituents of the essential oil, but no new therapeutic indications activities were evidenced. No new information related to the traditional therapeutic indication in the monograph was found.
- No new non-clinical or clinical safety data related to the essential oil were retrieved.
- No new scientific data justify a revision of the actual monograph.
- No new market information about the essential oil was found.
- No consistency issues exist.

### **References**

a) References relevant for the assessment:

Hagvall L, Niklasson IB, Luthman K, Karlberg A-T. Can the epoxides of cinnamyl alcohol and cinnamal show new cases of contact allergy? *Contact Derm* 2018, 78: 399-405

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

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, corticis aetheroleum, by consensus.