

12 May 2023 EMA/HMPC/883123/2022 Committee on Herbal Medicinal Products (HMPC)

# Addendum to Assessment report on *Ricinus communis* L., oleum

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HMPC decision on review of monograph <i>Ricinus communis</i> L., oleum adopted on 02 February 2016	26 January 2022
Call for scientific data (start and end date)	From 15 April 2022 to 14 July 2022
Discussion in Committee on Herbal Medicinal Products (HMPC)	March 2023
	May 2023
Adoption by Committee on Herbal Medicinal Products (HMPC)	12 May 2023

# **Review of new data**

# Periodic review (from 2016 to 2022)

# Sources checked for new information:

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

Scientific/Medical/Toxicological databases: PubMed was searched on 2022-06-21;

period covered: April 2014-July 2022

Pharmacovigilance databases

🖾 data from EudraVigilance

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

🗌 Other

Regulatory practice

 $\boxtimes$  Old market overview in AR (i.e. check products fulfilling 30/15 years of TU or 10

years of WEU on the market)

 $\boxtimes$  New market overview (including pharmacovigilance actions taken in member states)



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🛛 PSUSA

 $\boxtimes$  Feedback from experiences with the monograph during MRP/DCP procedures

Ph. Eur. monograph

🗌 Other

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

- $\boxtimes$  Public statements or other decisions taken by HMPC
- $\boxtimes$  Consistency with other monographs within the therapeutic area
- 🗌 Other

# Availability of new information that could trigger a revision of the monograph

Scientific data		No
New non-clinical safety data that could trigger a revision of the monograph		$\boxtimes$
New clinical safety data that could trigger a revision of the monograph		
New data introducing a possibility of a new list entry		$\boxtimes$
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		$\boxtimes$
Regulatory practice		No
New herbal substances/preparations with 30/15 years of TU		$\boxtimes$
New herbal substances/preparations with 10 years of WEU		$\boxtimes$
New recommendations from a finalised PSUSA		$\boxtimes$
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		$\boxtimes$
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		$\square$

# Summary of new references

During the review, 1147 new references not yet available during the first/previous assessment were identified. Out of these new references 6 references were considered to be relevant for the monograph and none could 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

#### Clinical safety data

EudraVigilance was searched by the Pharmacovigilance Department of NAMDMR for adverse reactions on 5-07-2022, using the keywords "castor oil" and "*Ricini oleum*"; cases related with cutaneous use or concomitant administration with other drugs were excluded.

Sixteen ICSRs were found for the reference period (adverse reactions list: headache, diarrhoea, nausea, abdominal pain, anorectal discomfort). The causality between exposure to castor oil and adverse reactions reported was confirmed in the descriptive part of ICSRs.

Assessor's comment: These adverse reactions are already listed in EU monograph, in section 4.8 Undesirable effects. The frequency is unknown. Therefore, these data do not trigger a revision of the monograph.

#### New regulatory practice that could trigger a revision of the monograph

New herbal substances/preparations with 30/15 years of TU or 10 years of WEU

Not applicable.

Updated Ph. Eur. monographs

Both Castor oil, refined (ref.:2367) and Castor oil, virgin( ref.: 0051) monographs were updated in Ph.Eur edition 10. The fatty acid fraction of the oil was updated, by adding limits for oleic acid and isomer (2.5%- 6.0%) and any other fatty acid (max.1.0%).

Assessor's comment: No revision is considered required. Reference to the updated pharmacopoeia monographs should be adapted in the HMPC monograph and supporting documents when there is a need to revise the monograph.

#### 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

There are some clinical trials that investigated the efficacy of castor oil as as bowel preparation for colon capsule endoscopy (CCE).

Tian *et al.*, 2019 investigated the efficacy and safety of castor oil on bowel preparation for colonoscopy in addition to polyethylene glycol (PEG). Two hundred and forty-six patients were allocated randomly to ingest 2 L PEG with 30 mL castor oil, 1 L PEG with 30 mL castor oil plus 5 g ascorbic acid, or 3 L PEG. The authors used Boston Bowel Preparation Scale (BBPS) to evaluate bowel preparation efficacy and to determined other outcomes such as procedure time, polyp or adenoma detection rate, and adverse events (AEs). Of 282 patients recruited, 36 were excluded. Patient's satisfaction was higher in 2 L PEG- castor oil and 1 L PEG-castor oil-ascorbic acid groups. Patient's compliance was 67.5, 71.4, and 80.5% in 3 L PEG, 2 L PEG-castor oil, and 1 L PEG- castor oil-ascorbic acid groups. Adequate bowel preparation rate was 75, 78.57, and 53.66% in 3 L PEG, 2 L PEG-castor oil, and 1 L castor oil-ascorbic acid. The authors concluded that despite an increase in patient's satisfaction and compliance, 1 L PEG- castor oil-ascorbic

acid significantly decreased adequate bowel preparation rate. However, 2 L PEG-castor oil improved the patient's satisfaction and compliance and increased adequate bowel preparation rate.

Ohmiya *et al.*, 2018 assessed retrospectively the effectiveness of 30 mL castor oil as bowel preparation for colon capsule endoscopy in 319 patients from 4 Japanese hospitals. Of 319 examinees who underwent colon capsule endoscopy, 152 and 167 examinees took regimens with castor oil and without castor oil, respectively. Capsule excretion rates within its battery life in the groups with and without castor oil were 97% and 81%, respectively. Small bowel transit time was shorter and total volume of lavage and fluid intake was lower with castor oil than without (p = 0.0154 and 0.0013, respectively). Overall adequate cleansing level ratios with and without castor oil was effective for improving capsule excretion rate and reducing liquid loading.

Semenov *et al.*, 2021 investigated effect of castor oil as a booster in colon capsule endoscopy in completion rates and polyp detection. All 186 patients received split bowel preparation (MP) [polyethylene glycol (PEG)-3350, sodium sulphate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid for oral solution]. Control booster regimen included MP with 750 mL of water (booster 1) on reaching the small bowel. A further dose of MP with 250 mL of water was given 3 h later and a 10 mg bisacodyl suppository after 8 h, if the capsule was not excreted. In addition to our standard booster regimen, cases received an additional 15 mL of castor oil given at the time of booster 1. Overall, CCE completion was 77%, image quality was adequate/diagnostic in 91%, mean colonic transit time was 3.5 h, and the polyp detection rate was 57%. Completion rates were significantly higher with castor oil, 87% cases *vs* 73% controls. The number needed to treat with castor oil to result in an additional complete CCE study was 7, absolute risk reduction = 14.52%, 95% confidence interval (CI): 3.06- 25.97. This effect of castor oil on excretion rates was more significant in the over 60's and in females. Colonic transit times were similar, 3.2 h and 3.8 h, respectively.

Comparable results were obtained by Takashima et al. (2021) in a prospective cohort study including 20 patients that underwent CCE. The primary outcome was the capsule excretion rate within the battery life, as evaluated by the total large bowel observation rate, large bowel transit time, and bowel creasing level using a five-grade scale in different colorectal segments. The secondary outcomes were complications, colorectal lesion detection rates, and patient's tolerability. The castor oil-based regimen (20 mL) was implemented in 17 patients. Three patients cancelled CCE because they could tolerate castor oil, but not liquid laxatives. The capsule excretion rate within the battery life was 88%. The mean large bowel transit time was 236 min. Approximately 70% of patients had satisfactory colon cleansing levels. CCE detected colon polyps (82%) and colonic diverticulum (33%). The sensitivity, specificity, and diagnostic accuracy rates for detecting colorectal polyps (size  $\geq$  6 mm) were 76.9%, 75.0%, and 76.4%, respectively. The sensitivity, specificity, and diagnostic accuracy rates for detection of diverticulum were 100% each. Twelve patients (71%) rated CCE as more than "good", confirming the new regimen's tolerability. No serious adverse events occurred during this study. The authors concluded that the castor oil-based regimen could reduce bowel preparation dose and improve CCE tolerability.

Assessor's comment: Parameters such as posology, the presence of enema treatment, sample sizes are heterogeneous, therefore the clinical data are not sufficient to support this indication. As there are no products on the market for more than 10 years in the EU with this indication, the data will not trigger a revision of the EU herbal monograph in order to include a new well-

established use indication. The findings from the clinical trials can be supportive for the clinical safety of castor oil.

# References

European Pharmacopoeia 10<sup>th</sup> ed. Castor oil, virgin. Council of Europe. 7/2021: 0051; Castor oil, refined Council of Europe. 07/2021:2367

Ohmiya N, Hotta N, Mitsufuji S, Nakamura M, Omori T, Maeda K, *et al*. Multicenter feasibility study of bowel preparation with castor oil for colon capsule endoscopy. *Digestive Endoscopy* 2019 Mar, 31(2):164-172. in press, doi: 10.1111/den.13259

Semenov S, Ismail MS, O'Hara F, Sihag S, Ryan B, O'Connor A, *et al*. Addition of castor oil as a booster in colon capsule regimens significantly improves completion rates and polyp detection. *World Journal of Gastrointestinal Pharmacology and Therapeutics* 2021 Nov 5, 12(6):103-112. in press, doi: 10.4292/wjgpt.v12.i6.103

Takashima K, Komeda Y, Sakurai T, Masaki S, Nagai T, Matsui S, *et al*. Castor oil as booster for colon capsule endoscopy preparation reduction: A prospective pilot study and patient questionnaire. *World Journal of Gastrointestinal Pharmacology and Therapeutics* 2021 Jul 5, 12(4):79-89. in press, doi: 10.4292/wjgpt.v12.i4.79

Tian X, Shi B, Liu XL, Chen H, Chen WQ. A Randomized Trial of Split Dose 3 L Polyethylene Glycol Lavage Solution, 2 L Polyethylene Glycol Lavage Combined With Castor Oil, and 1 L of Polyethylene Glycol Lavage Solution Combined With Castor Oil and Ascorbic Acid for Preparation for Colonoscopy. *Frontiers in Medicine* (Lausanne) 2019 Jul 5, 6:158. in press, doi: 10.3389/fmed.2019.00158

# 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 *Ricinus communis* L., oleum, by consensus.