



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

07 May 2025
EMA/HMPC/524702/2024
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Zingiber officinale* Roscoe, rhizoma (EMA/HMPC/885789/2022)

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Zingiber officinale* Roscoe, rhizoma as released for public consultation on 15 June until 15 September 2024.

	Organisations and/or individuals
1	AESGP

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

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	<u>Comment on the draft monograph (EMA/HMPC/885789/2022) about 4.1. Therapeutic indications: Traditional use</u> The use of ginger in pregnancy induced nausea and vomiting has been widely studied and evidenced and this should be reflected in the well-established use part of the monograph. The literature and guidelines from USA, Canada, UK, Belgium and France recommend the use of Ginger for mild nausea and vomiting during pregnancy. 21 clinical studies attests the efficacy of ginger root in pregnancy induced nausea and vomiting. A Comprehensive Systematic Review of 109 Randomized Controlled Trials provide a comprehensive discussion in terms of the clinical effects of ginger in all reported areas [Anh, 2022]. In Nausea and Vomiting of Pregnancy (NVP), ginger showed a promising effect on NVP. All 8 RCTs on NVP concluded that ginger is as effective as other antiemetic medications such as pyridoxine, metoclopramide or dimenhydrinate or more effective than the placebo at least in some aspects with a dosage less than 1.5 g. An observation study from Portnoi et al. reported that a group of pregnant women showed no statistical differences in teratogenicity when compared to a group receiving nonteratogenic drugs [Portnoi, 2003]. A large population-based cohort from the Norwegian Mother and Child Cohort study correspondingly reported that ginger did not affect the risk of teratogenicity and abnormalities in birth [Heitmann, 2013]. Moreover, a review from Stanisiere et al. found that there were no severe side effects with ginger consumption in controlled, uncontrolled, and pre-clinical studies, with a significant reduction in nausea and vomiting [Stanisiere, 2018]. These results support the idea that ginger may be an alternative approach for antiemetic	Not endorsed. The conclusion on efficacy of ginger in nausea and vomiting in pregnancy (NVP) presented in the draft AR remains. The 21 clinical efficacy studies included in Annex 1 were provided already in 2019 during the request for a new WEU indication i.e. "for the relief of pregnancy-induced nausea and vomiting" triggering an unscheduled review. All references have been carefully assessed and concluded upon before the publication of the draft AR. Also the safety studies Portnoi <i>et al.</i> 2003, Heitmann <i>et al.</i> 2013, Viljoen <i>et al.</i> 2014 and Stanisiere <i>et al.</i> 2018, were all already assessed and included in the draft AR. The new references submitted are acknowledged e.g. the systematic review by Anh, 2022. However, the 8 RCTs on NVP included in the review are not new and already assessed and included in the published draft AR. The umbrella review by Crichton <i>et al.</i> 2022, included four systematic reviews on ginger in NVP i.e. Anh <i>et al.</i> 2020, Khorasani <i>et al.</i> 2020, Hu <i>et al.</i> 2020, and Ozgoli <i>et al.</i> 2018. The authors state that the reviews Anh <i>et al.</i> 2020, Khorasani <i>et al.</i> 2020, and Hu <i>et al.</i>

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	therapy in women during the gestation period of pregnancy. Given the number of high-quality and recent RCT, this qualifies the use of ginger in pregnancy induced nausea and vomiting for WEU Umbrella review [Crichton, 2022]. This umbrella review identified a convincing body of evidence that, in humans, ginger conferred analgesic, metabolic, and gastrointestinal therapeutic effects on a range of health conditions. The strongest evidence for therapeutic effects, with high certainty of the evidence (GRADE level: high) and very large effect size, was found for the antiemetic effects of ginger in pregnant women (1.0–2.5 g/d for 4–21 d) [Crichton, 2022]. This year, an overview of systematic reviews and meta-analyses evaluates the reporting and methodological qualities of meta-analyses on ginger for nausea and vomiting, and summarises the available evidence on the efficacy and safety [Li, 2024]. Reporting quality was assessed using the PRISMA 2009 statement. Ginger shows promise in alleviating pregnancy-related nausea and vomiting symptoms. The pooled evidence suggests ginger as a safe botanical option for managing nausea and vomiting, but it is important to improve the scientific quality of published meta-analyses in the future [Li, 2024]. Preclinical data suggest a clinically relevant mechanism for the treatment of nausea and vomiting which is a serotonin 5-HT₃ receptors antagonism of the central nervous system. Moreover, cholinergic/muscarinic (M3), vanilloid receptors and TRPA1 channels could be also involved in the antinausea activity. At the level of various guidelines (from professional health associations or national agencies), the use of ginger is also regularly supported. This list is not exhaustive: • College of French Gynecologists and Obstetricians, Management of nausea and vomiting of pregnancy and hyperemesis gravidarum [Deruelle, 2022]: If the PUQE (Pregnancy Unique Quantification of Emesis and nausea) score is < 6, ginger (as well as vitamin B6 and	2020 were rated as low quality and Ozgoli <i>et al.</i> 2018, as critically low quality. Importantly, there are no new studies reported. Li <i>et al.</i> 2024, is an overview of systematic reviews and meta-analyses including four meta-analyses on the effect of ginger on NVP i.e. Thomson <i>et al.</i> 2014, Viljoen <i>et al.</i> 2014, Hu <i>et al.</i> 2022 and Gaur <i>et al.</i> 2022. The overall conclusions by the authors are that they have underscored several challenges related to the reporting and methodological quality of meta-analyses. Thus, the authors suggest that future studies concentrate on enhancing the methodological and reporting quality of meta-analyses. Importantly, there are no new studies reported. In addition, AESGP refers to various guidelines (from professional health associations or national agencies) on the use of ginger in NVP. It must be emphasised that this kind of guidelines are not developed in the same process as assessing B/R for a therapeutic indication of a well establish use monograph (<i>reference to HMPC clinical guideline</i>). These guidelines could recommend use although the level of proof of efficacy has not been established. This is for example stated in Deruelle <i>et al.</i> 2022, i.e., ginger (as well as vitamin B6 and other methods) can be used, even in the absence of proof of benefit. Regarding the comment to change the number of pregnancy outcomes in the monograph section 4.6,

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	other methods) can be used, even in the absence of proof of benefit. • <u>The French national agency ANSES</u>, has recently published an opinion assessing the relevance of applying the warnings and recommendations expressed in the EMA's herbal monographs to food supplements containing these same plants [ANSES, 2023]: For all the plants, the Plants Working Group has adopted the EMA's recommendations, with the exception of ginger, where additional data on safety in pregnant women have been taken into account. Indeed, they conclude: "it appears that a warning for pregnant women is not necessary in the current state of knowledge for food supplements containing ginger, under traditional conditions of use, i.e., over short periods (one week), for the usual preparations." • <u>The Flemish Society for Obstetrics and Gynaecology</u> [VVOG, 2024]: "In mild NVP with a PUQE score ≤ 6, non-drug advice and alternative therapy may provide improvement. In addition, ginger preparations are recommended." • <u>The National Institute for Health and Care Excellence (UK), and the Royal College of Obstetricians and Gynaecologists</u> [NICE, 2021]: Guideline for antenatal care. The advice for the medical specialist is the following: "1.4.3 For pregnant women with mild-to-moderate nausea and vomiting who prefer a non-pharmacological option, suggest that they try ginger." • <u>The American College of Obstetricians and Gynecologists</u> [ACOG, 2018]: Practice Bulletins Number 189, January 2018 "Clinical Management Guidelines for Obstetrician–Gynecologists". Ginger capsules are included in the First Line Therapy. • <u>The Society of Obstetricians and Gynaecologists of Canada</u> [Campbell, SOGC, 2016]: Clinical practice guidelines for The Management of Nausea and Vomiting of Pregnancy; they notably conclude that "ginger may be beneficial in ameliorating the	the references cited in Appendix "Clinical trials with pregnancy outcomes" (see below) have already been included in the published draft AR. From HMPC point of view, the references with a herbal preparation corresponding to the preparation in the monograph and with the number of pregnancy outcomes studied and reported on remains unchanged.

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	symptoms of nausea and vomiting of pregnancy. There is evidence obtained from at least one properly randomized controlled trial + there is good evidence to recommend the clinical preventive action." • <u>WHO recommendations on antenatal care for a positive pregnancy experience</u> [WHO, 2016]: Ginger, like other plants or vitamins, is recommended. Additionally, usual allopathic treatments (doxylamine, metoclopramide) should be reserved for pregnant women who are not relieved by other means. • <u>Belgian Advisory Commission for Plant Preparations: A ginger preparation</u> (notified as a food supplement for over 10 years) was authorized in 2019 for use during pregnancy. The nutravigilance data collected for this product are favorable; no harmful effects have been reported in pregnant women. • <u>ESCOP: For nausea and vomiting of pregnancy, dried ginger powder can be administered</u> at doses ranging from 0.075 g to 2 g daily (in divided doses) for 1 to 5 days. This treatment should be taken under medical supervision [ESCOP, 2009]. • <u>UK Teratology Information Service (UKTIS)</u> mentions that ginger, one of the most commonly used non-medicinal remedies for pregnancy-related nausea, particularly during the first trimester, seems not to harm the baby [Wiesner & Knöss, 2017]. • <u>Embryotox database: Ginger can be used in all phases of pregnancy in commonly used dosages</u>. • <u>British Herbal Compendium lists ginger as a remedy for vomiting of pregnancy</u> along with other indications [Keating, 2002]. • <u>Pharmacopoeia of the People's Republic of China: There is no contraindication to ginger during pregnancy</u> [Keating, 2002]. Taking all this information into consideration, ginger shows to be more effective than placebo and as effective as antiemetic medications for	

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	Nausea and Vomiting during pregnancy. It is also recommended by a large number of independent bodies and healthcare professionals. <u>Comment on the draft monograph (EMA/HMPC/885789/2022) about 4.6. Fertility, pregnancy and lactation</u> It is indicated in the assessment report, in its current draft form, that a moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or feto/neonatal toxicity of ginger root. We have found more than 1000 pregnancy outcomes in the literature (see table in appendix). Ginger is undoubtedly the most analyzed herbal remedy used in pregnancy. According to the EMA Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling, at least 1,000 documented positive pregnancy outcomes after exposure during the first trimester are necessary to consider the use of a medicine safe by pregnant women [EMA/CHMP/203927/2005]. Indeed, the number of exposed pregnancies (before 20th weeks of gestation) with known outcome has reached a value of 1,231. The total number of pregnancies exposed to ginger with known outcome has reached a value of 1,794. Within this population, the overall number of malformations is 3% (cfr table in the appendix). As stated in EMA/CHMP/203927/2005, the overall incidence of malformations generally detected at birth is approximately 3% of all live births. Therefore, the use of ginger during pregnancy doesn't raise the risk of malformations.	

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	From literature review, it appears that ginger is safe for human embryo and foetus development: • No higher incidence of birth defects or deformities was observed than in the general population [Willetts et al., 2003; Smith et al., 2004]. • The prospective, interventional, open and real-life pilot trial conducted by Laekeman did not reveal serious malformations in the newborn after first trimester maternal exposure to standardized ginger dry-extract. A lower incidence of stillbirth, a higher number of prematurity and consequently a lower birth weight, more cases of hip dysplasia in the baby and more maternal hypertension were observed in comparison with a general population (epidemiological data from the Studiecentrum voor Perinatale). However, more women got their baby when older than 34 years in the study population as compared to the epidemiological data, therefore the studied population was not representative for the general population in Flanders [Laekeman et al., 2021]. • There was no statistical difference in the outcomes (live births, spontaneous abortions, stillbirths, therapeutic abortions, birth weight or gestational age) between the ginger group and the comparison group with the exception of more infants weighing less than 2500 g in the comparison group (12 vs. 3; $P \leq 0.001$) [Portnoi et al., 2003]. • The use of ginger during pregnancy was not associated with any increased risk of congenital malformations. No increased risk for stillbirth/perinatal death, preterm birth, low birth weight, or low Apgar score was detected for the women exposed to ginger during pregnancy compared to women who had not been exposed [Heitmann et al., 2013]. According to the systematic review and meta-analysis performed by Viljoen (12 RCTs, 1278 pregnant women included; 574 used ginger), ginger did not pose a significant risk for spontaneous abortion compared to placebo (RR 3.14, 95% CI	

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	0.65-15.11, $p = 0.15$; $I^2 = 0\%$), or to vitamin B6 (RR 0.49, 95% CI 0.17-1.42, $p = 0.19$, $I^2 = 40\%$) [Viljoen et al., 2014]. Kennedy et al. [2016] evaluated and classified herbal medicines according to their safety in pregnancy based on current literature and determine the proportion of women using herbals in each of the safety categories. A second objective was to investigate risk factors associated with the use of potentially hazardous herbal medicines during pregnancy. Herbal medicines were categorized into one of four safety categories; safe, caution, contraindicated or unknown based on a summary of the literature, reference textbooks and monographs. The most frequently used herbal medicines classified as safe were <i>Zingiber officinale</i> (ginger) (56.7 %), <i>Vaccinium oxycoccus/macrocarpon</i> (cranberry) (55.0 %), and <i>Mentha x piperita</i> (peppermint) (15.9 %). The most studied herbal medicine is <i>Zingiber officinale</i> (ginger) with 10 individual studies [Kennedy, 2016]. Based on the evidence obtained from clinical trials, it appears that maternal exposure to ginger is not associated with spontaneous abortions, increased risks of adverse fetal/neonatal outcomes and of pregnancy complications and delivery by caesarian section. Moreover, some clinical trials described the side effects sensed by the pregnant women (table below and table in the Appendix). These are all minor sides effects. Some trials specify that no side effects were experienced by the pregnant women. It has to be noted that some of the adverse effects attributed to ginger may be related to pregnancy, such as heartburn.	

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	<table border="1"> <thead> <tr> <th>References</th><th>Ginger population (n)</th><th>Side effects on pregnant women using ginger</th></tr> </thead> <tbody> <tr> <td>Chittumma, 2007</td><td>61</td><td>Heart burn (8/61), arrhythmia (7/61), headache (0/61) and sedation (7/61). The occurrence of side effects from ginger was reported to be minor during the four-day period of treatment.</td></tr> <tr> <td>Javadi, 2013</td><td>47</td><td>No side effects</td></tr> <tr> <td>Ozgoli, 2009</td><td>32</td><td>No side effects</td></tr> <tr> <td>Pongrojapaw, 2007</td><td>77</td><td>Minor side effects: 5 drowsiness, 13 heartburns</td></tr> <tr> <td>Saberi, 2013</td><td>51</td><td>Minor side effects: 1 heartburn</td></tr> <tr> <td>Saberi, 2014</td><td>36</td><td>Minor side effects: 1 heartburn</td></tr> <tr> <td>Sripamote 2003</td><td>64</td><td>Minor side effects: 17 drowsinesses, 6 heartburns</td></tr> <tr> <td>Firouzbakht, 2014</td><td>24</td><td>Severity of nausea and vomiting in placebo group in some cases led to medicines discontinuation and the use of other treatment methods. Stomachache, heartburn and increased nausea were also reported in 10.2% of ginger recipients.</td></tr> </tbody> </table> Finally, in its review, Stanisiere et al. summarizes the effectiveness and safety of ginger. He explains that for 1 g of fresh ginger root per day for four days, results show a significant decrease in nausea and vomiting and no risk for the mother or her future baby. The available evidence suggests that ginger is a safe and effective treatment for NVP. However, beyond the ginger quantity needed to be effective, ginger quality is important from the perspective of safety. [Stanisiere, 2018]. In the assessment report, we note that it is stated that « the information on products used (i.e., quality of ginger), dosage, and administration are in most of the studies not available or very limited. » However, we would like to emphasize that most of the studies involved ginger powder, and ginger extract was also described in several studies [Willets, 2003; Biswass, 2011; Keating, 2002; Laekman, 2021]. Finally, in its review, Stanisiere et al. summarizes the effectiveness and safety of ginger. He explains that for 1 g of fresh ginger root per day for four days, results show a significant decrease in nausea and vomiting and no risk for the	References	Ginger population (n)	Side effects on pregnant women using ginger	Chittumma, 2007	61	Heart burn (8/61), arrhythmia (7/61), headache (0/61) and sedation (7/61). The occurrence of side effects from ginger was reported to be minor during the four-day period of treatment.	Javadi, 2013	47	No side effects	Ozgoli, 2009	32	No side effects	Pongrojapaw, 2007	77	Minor side effects: 5 drowsiness, 13 heartburns	Saberi, 2013	51	Minor side effects: 1 heartburn	Saberi, 2014	36	Minor side effects: 1 heartburn	Sripamote 2003	64	Minor side effects: 17 drowsinesses, 6 heartburns	Firouzbakht, 2014	24	Severity of nausea and vomiting in placebo group in some cases led to medicines discontinuation and the use of other treatment methods. Stomachache, heartburn and increased nausea were also reported in 10.2% of ginger recipients.	
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Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
Section 4.1	AESGP	Comment: there is no mention of the use of ginger as a first-line treatment of mild to moderate pregnancy associated nausea and emesis. Proposed change: as demonstrated previously, with all data showing both efficacy and safety of ginger in pregnancy induced nausea and vomiting, the use of ginger as first-line treatment of mild to moderate pregnancy associated nausea and emesis should be added in <u>well-established use</u> column, according to the guideline EMA/HMPC/104613/2005 – Rev. 1.	Not endorsed. Please justification above.
Section 4.2	AESGP	Comment: according to new indication proposed in 4.1, the posology and duration of use should also be added. Proposed change: - Posology: powdered herbal substance: 1 – 2 g daily (and dried extracts corresponding to the powdered herbal substance) - Duration of use: If the symptoms persist more than one week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.	Not endorsed. Please justification above.
Section 4.6	AESGP	Comment: it is stated "As a precautionary measure it is preferable to avoid the use during pregnancy"	Not endorsed. Please justification above.

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		Proposed change: given the evidence provided above, the removal of the warning.	

APPENDIX. Clinical trials with pregnancy outcomes. NM=not mentioned.

Reference	Ginger population (n)	Adverse events	Spontaneous abortions	Preterm birth	congenital malformations	Still birth	Low Apgar score	Found in Table 8 (HMPC)
Basirat, 2009	32	Minor side effects only: 1 dizziness, 1 hearburn	0	NM	0	0	NM	Yes
Biswas, 2011	34	No side effects	0	NM	0	0	NM	
Choi, 2015	159	Spontaneous abortions 17/306 (5.5%) in control. No differences were identified when comparing birth weight and length; head circumference at birth. In the case group, there were 2.7% stillbirths and 4.7% of babies that required attention at the neonatal intensive care unit. These rates were marginally greater than the 0.3% and 1.7% observed in the control group, respectively. In relation to the incidence of major malformations, no difference was observed between the two study groups.	7	NM	5	4	NM	
Ensiyeh, 2009	35	/	2	4	0	0		
Fischer-Rasmussen, 1990	27	No side effects	1	NM	0	0	NM	Yes
Heitman, 2013	1020	466 exposure to ginger during first trimester, 19 malformations (4.1%). The control gp has 4.7% malformations	/	38	41	6	11	
Keating, 2002	12	First trimester pregnant women	0	NM	0	0	NM	
Laekeman, 2021	44	Concerning the newborns, body weight, Apgar scores, and pH-values did not reveal an abnormal situation in the cohort	1	3	4	0	0	
Portnoi, 2003	187	There were no statistically significant differences between the two groups in terms of live births, spontaneous abortions, stillbirths, therapeutic abortions, birth weight, or gestational age, with the exception of more infants who weighed less than 2500 g in the comparison group.	3		3	2		

Smith, 2004	146	Women taking ginger reported belching (9%) more frequently compared with women taking vitamin B6.	3	5	3	0	NM	Yes
Trabace, 2015	9	Chamomile, fennel and ginger were taken regularly for the entire period of the pregnancy. No side effects were reported for these plants.	0	NM	0	0	NM	
Vutyavanich 2001	32	Minor side effects: 1 abdominal discomfort, 1 heartburn, 1 diarrhea.	1	0	0	0	0	Yes
Willetts 2003	57	Minor side effects: 4 heartburn/reflux, 1 dehydration. 1 allergic reaction. The rates of birth defects were similar to the general population and were all minor.	3	1	0	1	0	Yes
TOTAL	1794	1231 exposure to ginger before 20 th weeks of gestation	21	47	56	13	11	
% in ginger population			1.17%	2.62%	3.12%	0.72%	0.61%	