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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Zingiber officinale* Roscoe, rhizoma

Final – Revision 1

Based on Article 10a of Directive 2001/83/EC (well-established use)

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC (traditional use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)		*Zingiber officinale* Roscoe, rhizoma
Herbal preparation(s)		a) Powdered herbal substance b) Tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent ethanol 90% V/V c) Tincture (ratio of herbal substance to extraction solvent 1:2), extraction solvent ethanol 90% V/V
Pharmaceutical form(s)		Herbal preparations in solid or liquid dosage forms for oral use.
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1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

Ginger (Zingiberis rhizoma) consists of the whole or cut rhizome of *Zingiber officinale* Roscoe (Zingiberaceae), with the cork removed, either completely or from the wide, flat surfaces only (European Pharmacopoeia, 2011).

Constituents: Volatile oil 1-4 % (minimum 15 ml/kg essential oil (anhydrous drug) according to the Ph. Eur.). More than 100 compounds are identified, most of them terpenoids mainly sesquiterpenoids (α-zingiberene, β-sesquiphellandrene, β-bisabolene, α-farnesene, *ar*-curcumene (zingiberol) and smaller amounts of monoterpenoids (camphene, β-phellandrene, cineole, geraniol, curcumene, citral, terpineol, borneol). The composition of the oil depends on the origin of the material (Afzal *et al.* 2001; Ahmad *et al.* 2008; Ali *et al.* 2008; Chen and Ho 1988; Connell 1970; Erler *et al.* 1988; Lawrence 1984).

The pungent principles, the gingerols (4-7.5%) are a homologous series of phenols. The principal one of these is 6-gingerol. Gingerols with other chain-lengths, *e.g.* 8-gingerol and 10-gingerol, are present in smaller amounts. During drying and storage, gingerols are partly dehydrated to the corresponding shogaols which may undergo further reduction to form paradols, also present in stored ginger (Afzal *et al.* 2001; Bradley 1992; Connell 1970; Farthing and O'Neill 1990; Jolad *et al.* 2005; Steinegger and Stucki 1982). Other constituents are starch, up to 50%, lipids 6-8%, proteins, and inorganic compounds (Awang 1992; ESCOP 2009).

- Herbal preparation(s)
  a) Powdered herbal substance
  b) Tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent ethanol 90%
  c) Tincture (ratio of herbal substance to extraction solvent 1:2), extraction solvent ethanol 90%
- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable.

1.2. Search and assessment methodology

Revision 1:

On 14 March 2019, 136 references were provided by Interested Party regarding a request for a new WEU indication, i.e. "for the relief of pregnancy-induced nausea and vomiting", triggering an unscheduled review. Sixty-four new references not included in the first assessment report were identified. In January 2020, the HMPC decided to include the substance under 'Periodic reviews to be started'. During the periodic review 736 new references in the PubMed database, not yet available during the first/previous assessment, were identified. PubMed was searched on 2020-10-18 using the Mesh term 'Ginger' and the filters 'humans' and 'other animals' from year 2012. In addition, the Mesh terms 'Carcinogenicity Test' and 'Mutagenicity Test' were combined with 'Ginger'.

On 9 December 2021, Embase was search using the search terms 'ginger'/de or 'ginger extract'/de or (ginger* or shogaol* or zingerone* or zingiber* or zintona):ti,ab,kw and publication year 2010-2022, filtered to include nausea, vomit, emesis, motion sickness, osteoarthritis, rheumatism, diabetes, obesity, dysmenorrhea, menorrhagia, migraine, inflammatory bowel disease, colitis, pain, anticoagulant, blood pressure, pregnancy, lactation, childbirth, newborn, interaction, safety+bleeding (combined), toxicology, toxicity, safety, clinical trial, in ti,ab,kw.

On 9 December 2021, Cochrane Library was search using the search terms MeSH descriptor: (Ginger) explode all trees or (ginger* or shogaol* or zingerone* or zingiber* or zintona):ti,ab,kw and publication year 2011-2021, filtered to include nausea, vomit, emesis, motion sickness, osteoarthritis, rheumatism, diabetes, obesity, dysmenorrhea, menorrhagia, migraine, inflammatory bowel disease, colitis, pain, anticoagulant, blood pressure, pregnancy, lactation, childbirth, newborn, interaction, safety+bleeding (combined), toxicology, toxicity, safety, clinical trial, in ti,ab,kw.

References in English, German, Swedish, Norwegian, and Danish.

In some new references, additional cited references were considered relevant.

EudraVigilance was searched on 2020-10-08 using the search terms 'ginger', 'zingiber', 'zingiberis', and 'ingwer'.

1.3. Main changes introduced in the first revision

During the first revision new information on medicinal use from products on the market and herbal preparations, indications and posologies fulfilling traditional use have been introduced in chapter 2. 'Data on medicinal use'.

Regarding chapter 3. 'Non-Clinical Data', additional non-clinical pharmacology studies have been published since the first version of the monograph. However, no substantial new findings were identified during the first revision and only a few new references were added. In addition, some references were considered not relevant during the first revision and were deleted.

In chapters 4. 'Clinical Data' and 5. 'Clinical Safety/Pharmacovigilance' additional studies have been introduced. In particular, new pharmacokinetic data and data related to the use in nausea and vomiting in pregnancy have been included. Some references were considered not relevant during the first revision and were deleted for example, the scope of the assessment in chapter 4. 'Clinical Data' has been reduced to studies related to products that have been in medicinal use for more than 10 years in EU.

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	**Indication**	**Pharmaceutical form** **Strength (where relevant)** **Posology** **Duration of use**	**Regulatory status (date, Member State)**
Zingiberis rhizoma pulvis, Ph. Eur.	Prevention of symptoms of motion sickness (kinetosis), *e.g.* dizziness, nausea and vomiting.	250 mg/capsule Adults and children from 6 years: 2 capsules half an hour before the start of the travel, then 2 capsules every 4 hours.	Austria MA since 1987
Comminuted herbal substance	THMP for the supportive treatment of rheumatic complaints (like pain in muscle or joints)	250 mg powder per hard capsule; adults: 2-3 x daily 2 capsules; 4 weeks	Austria TUR since 2017
Comminuted herbal substance	Herbal medicinal product for prevention of symptoms of travel sickness; symptomatic treatment of mild forms of vomiting and nausea in early pregnancy (up to week 16)	250 mg powder per hard capsule Travel sickness: adults, adolescents and children above 6 years of age: 2 capsules half an hour before start of travel, 2 capsules every 4 hours, max. 6 capsules daily; Nausea and vomiting in pregnancy: 2 capsules in the morning, in case of recurrent symptoms 2 additional capsules, max. 4 capsules daily. Duration of use: if symptoms worsen or no improvement after 2-3 days a doctor should be consulted.	Austria WEU MA since 1987 (indication vomiting in pregnancy authorised 2010)
Zingiberis rhizoma powder	Prevention of symptoms of the travel sickness (kinetosis) like dizziness, nausea and vomiting.	250 mg per hard capsule for oral use in adults and children > 6 y 2 capsules ½ h before travelling then 2 capsules every 4 h not more than 10 capsules per day	Germany MA since 1992
Each hard capsule contains 250 mg of *Zingiber officinale* Roscoe, rhizoma (ginger) powder.	A traditional herbal medicinal product for use in specified indications exclusively based on long-term use only, indicated for the relief the symptoms of motion sickness.	250 mg hard capsules <u>Dosage</u> Adolescents, adults and the elderly: 3 capsules (750 mg) half an hour before travelling. *Pediatric population* Children aged 6-12 years: 1-2 capsules	Lithuania TUR since 2003

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory status (date, Member State)
		(250-500 mg) half an hour before travelling. The use in children under 6 years of age is not recommended (see section 4.4 "Special warnings and precautions for use"). *Elderly patients* No dose adjustment is required.	
Zingiber officinale Roscoe, rhizoma	THMP for relief of symptoms of travelling illness, for relief of mild mild digestive complaints including bloating and flatulence	Hard capsule, 250 mg/capsule Digestive complaints: 1 capsule, 3 times daily Duration: if symptoms remain or increase after more than 14 days of use, medical supervision should be sought Travelling illness: 3 capsules approx. ½ - 1 hour before start of the trip Duration: if symptoms remain or increase after more than 5 days of use, medical supervision should be sought Digestive complaints: Use in children under 18 years is not recommended Travelling illness: Children 12-18 Years 3 capsules approx. ½ - 1 hour before start of the trip Children 6-12 Years 1 or 2 capsules approx. ½ -1 hour before start of the trip Use in children under 6 years is not recommended	Netherlands TUR since 2014
Zingiber officinale Roscoe, rhizome, powdered herbal substance	Symptoms of motion sickness	Capsules, hard, 250mg Children 6 – 12 y: 1 – 2 capsules take half an hour before the trip.	Poland National registration since 2000

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory status (date, Member State)
		Adolescents, adults: 3 capsules taken half an hour before the trip. Duration of use: The product is intended for temporary use.	
Powdered herbal substance for oral use (dried root powder)	a) Dyspepsia, as an aid to digestion b) For motion sickness (to avoid nausea and vomiting)	280 mg/capsule a) 2 capsules x 3 times daily b) 4 capsules 25 minutes before travelling	Spain Registration since 1991
Ginger 250 mg	An herbal remedy for the symptomatic relief of travel sickness.	Adults and the elderly: 3 tablets to be taken with water half an hour before commencing journey. Children aged 6-12 years: 1-2 tablets to be taken with water half an hour before commencing journey.	UK Licensed medicine since 1970s
Pulverised ginger 180 mg	A traditional herbal remedy used as a carminative.	Adults*:* 1 tablet, three times daily as necessary. Children: Not recommended for children.	UK Licensed medicine since 1970s
Ginger rhizome (*Zingiber officinale* Roscoe)	Traditional herbal medicinal product used to relieve symptoms of travel sickness	Capsules, 250 mg Adults, the elderly and children over 12 years: 500 mg approximately 30 minutes to one hour before travelling. Do not take more than 2 g per day.	UK TUR since 2011
Ginger rhizome (*Zingiber officinale* Roscoe)	Traditional herbal medicinal product used to relieve the symptoms of minor digestive complaints such as indigestion, dyspepsia, feeling of fullness, flatulence and temporary loss of appetite	Capsules, 250 mg Adults, the elderly and children over 12 years: 250 mg to be taken three times a day at mealtimes.	UK TUR since 2011
Zingiber officinale Roscoe	A traditional herbal medicinal product used for the relief of rheumatic or muscular pain, and general aches and pains in the muscles and joints based on traditional use only.	Adults and elderly: 500 mg, 2-3 times daily. Do not take more than 1.5 g per day.	UK TUR since 2019

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

Information on relevant combination medicinal products marketed in the EU/EEA

Not applicable.

Information on other products marketed in the EU/EEA (where relevant)

Stanisiere *et al*. (2018) report that for around 10 years, ginger imports in Europe have increased significantly, and many foods and food supplements have appeared on the market.

2.1.2. Information on products on the market outside the EU/EEA

Not applicable.

2.2. Information on documented medicinal use and historical data from literature

Ginger for dyspepsia and for the prevention of motion sickness in daily doses of 2-4 g is described in Commission E monograph on Zingiberis rhizoma from 1990 (Blumenthal *et al*. 1998).

The medicinal use of ginger described includes prophylaxis of nausea and vomiting associated with motion sickness, postoperative nausea, pernicious vomiting in pregnancy, and seasickness. In addition, the use of ginger in dyspepsia, flatulence, colic, vomiting, diarrhoea, spasms, and other stomach complaints have been described in pharmacopoeias and in traditional systems of medicine. Powdered ginger is further employed in the treatment of colds and flu, to stimulate the appetite, as a narcotic antagonist, and as an anti-inflammatory agent in the treatment of migraine headache and rheumatic and muscular disorders (WHO, 1999).

In Western traditions ginger has been used particularly for congestive chest problems, dyspepsia, flatulent colic, gastritis and diarrhoea associated with depletion (Bone and Mills, 2013).

In Ayurvedic medicine, the ginger rhizome is used as a carminative, promoter of digestion, anti-colic and as treatment for piles. It has also been recommended for chronic skin diseases, obesity, abnormal bleeding after childbirth and filariasis (Dev 2006; Kapoor 1990). Monographs of ginger are included in the Ayurvedic Pharmacopoeia of India (2009), Indian Herbal Pharmacopoeia (2002) and Indian Pharmacopoeia (2007). In the Indian Herbal Pharmacopoeia (2002) ginger is described as a carminative, anti-emetic, anti-inflammatory substance. The posology used in Ayurvedic medicine is for powdered dry drug: 1-2 g (Ayurvedic Pharmacopoeia of India 2009; Indian Herbal Pharmacopoeia 2002; Kapoor 1990).

In traditional Chinese medicine, fresh ginger is used for abdominal distension, coughing, vomiting, and for promoting sweating and reducing the poisonous effect of other herbs. The steamed and dried rhizome is used to treat abdominal pain, lumbago and diarrhoea, and also for the treatment of cholera, haemorrhage, rheumatism and toothache (Awang 1992; Bone 1997; Mills 2002). Monographs of ginger rhizome, dry and fresh, are included in the Pharmacopoeia of the People's Republic of China (2005) for epigastric pain with cold feeling, vomiting and diarrhoea accompanied with cold extremities and faint pulse and for dyspnoea and cough with copious frothy expectoration. The posology used in Chinese medicine is for the powdered drug or fresh drug: 3-9 g.

Further information on medicinal use and posology from literature is presented in table 2.

Table 2: Overview of historical data.

Herbal preparation	**Documented Use / Traditional Use**	**Pharmaceutical form** **Strength (where relevant)** **Posology** **Duration of use**	**Reference**
Dried powdered rhizome tincture (1:10, 90% ethanol, weak ginger tincture) tincture (1:2, 90% ethanol, strong ginger tincture)	Atonic dyspepsia, colic, prophylaxis of travel sickness, vomiting of pregnancy, anorexia, bronchitis, rheumatic complaints	As an antiemetic 1-2 g single dose. For other indications 0.25-1 g three times daily; tincture (1:10, 90% ethanol) 1.5-3 ml, tincture (1:2, 90% ethanol) 0.25-0.5 ml	Bradley, 1992

2.3. Overall conclusions on medicinal use

Table 3: Overview of evidence on period of medicinal use.

Herbal preparation **Pharmaceutical form**	**Indication**	**Strength** **Posology**	**Period of medicinal use**
Prevention/relief of motion sickness			
Comminuted (powdered) herbal substance	For prevention of symptoms of travel sickness	Adults, adolescents and children above 6 years of age: 500 mg half an hour before start of travel, 500 mg every 4 hours, not more than 2500 mg daily	MA since 1987 Austria and 1992 Germany
Powdered herbal substance for oral use (dried root powder)	For motion sickness (to avoid nausea and vomiting)	1120 mg 25 minutes before travelling	Registration since 1991 Spain
Dried powdered rhizome	Prophylaxis of travel sickness	1-2 g single dose	Bradley, 1992
Zingiber officinale Roscoe, rhizome, powdered herbal substance	For symptoms of motion/travel sickness	Adults and the elderly: 750 mg to be taken with water half an hour before commencing journey. Children aged 6-12 years: 250-500 mg to be taken with water half an hour before commencing journey.	Licensed medicine since 1970s, UK National registration since 2000 Poland TUR since 2003 Lithuania
Symptomatic treatment of mild, spasmodic gastrointestinal complaints including bloating and flatulence			
Powdered herbal substance for oral use (dried root powder)	Dyspepsia, as an aid to digestion	560 mg x 3 times daily	Registration since 1991 Spain
Pulverised ginger 180 mg	A traditional herbal remedy used as a carminative.	Adults*:* 180 mg, three times daily as necessary. Children: Not recommended for children.	Licensed medicine since 1970s, UK

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
Dried powdered rhizome	Atonic dyspepsia, colic	0.25-1 g three times daily	Bradley, 1992
Tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent ethanol 90%	Atonic dyspepsia, colic	1.5-3 ml three times daily	Bradley, 1992
Tincture (ratio of herbal substance to extraction solvent 1:2), extraction solvent ethanol 90%	Atonic dyspepsia, colic	0.25-0.5 ml three times daily	Bradley, 1992
Prevention/relief vomiting and nausea in pregnancy			
Comminuted herbal substance	Herbal medicinal product for symptomatic treatment of mild forms of vomiting and nausea in early pregnancy (up to week 16)	500 mg in the morning, in case of recurrent symptoms additional 500 mg, max. 1 g daily. Duration of use: if symptoms worsen or no improvement after 2-3 days a doctor should be consulted.	WEU MA since 2010 Austria
Dried powdered rhizome	Vomiting of pregnancy	1-2 g single dose	Bradley, 1992
Temporary loss of appetite			
Dried powdered rhizome	Anorexia	0.25-1 g three times daily	Bradley, 1992
Tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent ethanol 90%	Anorexia	1.5-3 ml three times daily	Bradley, 1992
Tincture (ratio of herbal substance to extraction solvent 1:2), extraction solvent ethanol 90%	Anorexia	0.25-0.5 ml three times daily	Bradley, 1992
Relief of minor articular pain			
Dried powdered rhizome	Rheumatic complaints	0.25-1 g three times daily	Bradley, 1992
Tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent ethanol 90%	Rheumatic complaints	1.5-3 ml three times daily	Bradley, 1992
Tincture (ratio of herbal substance to extraction solvent 1:2), extraction solvent ethanol 90%	Rheumatic complaints	0.25-0.5 ml three times daily	Bradley, 1992
Relief of symptoms of common cold			
Dried powdered rhizome	Bronchitis	0.25-1 g three times daily	Bradley, 1992
Tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent ethanol 90%	Bronchitis	1.5-3 ml three times daily	Bradley, 1992

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
Tincture (ratio of herbal substance to extraction solvent 1:2), extraction solvent ethanol 90%	Bronchitis	0.25-0.5 ml three times daily	Bradley, 1992

Well established use monograph

The WEU indication "Herbal medicinal product for the prevention of nausea and vomiting in motion sickness" was included in the first version of the monograph. The posology in the first version of the monograph was for adults and elderly 1 - 2 g 1 hour before start of travel. The clinical efficacy and safety based on Article 10a of Directive 2001/83/EC (well-established use), is evaluated in chapter 4 'Clinical data' and chapter 5 'Clinical Safety/Pharmacovigilance'.

Traditional use monograph

The traditional use indications "Traditional herbal medicinal product for the symptomatic relief of motion sickness" and "Traditional herbal medicinal product symptomatic treatment of mild, spasmodic gastrointestinal complaints including bloating and flatulence" were included in the first version of the monograph. In relation to the posology of 1-2 g for the well-established use indication "Herbal medicinal product for the prevention of nausea and vomiting in motion sickness" from 18 years of age, the traditional use posology for the indication "Traditional herbal medicinal product for the symptomatic relief of motion sickness" from 12 years of age was limited to 750 mg in the first version of the monograph.

For the three additional traditional use indications, the wording of the indication in the monograph is harmonised with other traditional use monographs in the same therapeutic area, to include indications to be considered safe for the user without the supervision of a medical practitioner for diagnostic purposes or prescription or monitoring of treatment. Using the same approach as in previous monographs established by the HMPC, anorexia will be temporary loss of appetite in the monograph, rheumatic complaints will be relief of minor articular pain in the monograph, and bronchitis will be relief of symptoms of common cold in the monograph.

Due to the conclusion on the use during pregnancy included already in the first version of the monograph section 4.6, i.e. "As a precautionary measure it is preferable to avoid the use during pregnancy.", a traditional use indication in pregnant women is considered not appropriate, see also sections 3.3.5. 'Reproductive and development toxicity' and 5.5.5. 'Fertility, pregnancy and lactation'.

Clinical safety is further evaluated in chapter 5 'Clinical Safety/Pharmacovigilance'. Preparations and posologies that are included in the TU monograph is summaries in chapter 6 'Overall conclusion'.

3. Non-Clinical Data

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Many non-clinical pharmacological studies have reported that ginger, preparations thereof and its constituents display many (often interconnected) properties *in vivo* and *in vitro*. A systematic review of all these studies will not be attempted here, rather a selection of studies with emphasis on studies with relevance for the indications in the monograph is reviewed.

3.1.1. Primary pharmacodynamics

Gastrointestinal motility and antiemetic studies

Experiments with rats have demonstrated a dose-dependent reversal of pyrogallol-induced (a free radical generator) delay in gastric emptying of oral ginger acetone extract (100, 250 and 500 mg/kg); however, ginger extract did not change gastric emptying in animals that were not pre-treated with pyrogallol (Gupta and Sharma 2001), and a study by the same group showed a partial reversal of the inhibitory effect of cis-platin on gastric emptying in rats by ginger acetone or ethanol extracts (in doses of 200 and 500 mg/kg orally) or ginger juice (2 and 4 ml/kg) (Sharma and Gupta 1998). In the musk shrew, oral administration of acetone extract of ginger (150 mg/kg), 6-gingerol (25 mg/kg and 50 mg/kg) and metoclopramide (25 mg/kg) administered 60 minutes prior to cyclophosphamide provided complete protection from emetic episodes (Yamahara *et al.* 1989a). Dried ginger (1 gram) stimulated contractile activity primarily in the gastric antrum in conscious dogs (Shibata *et al.* 1999) while an aqueous ginger extract administered over 6 days had no inhibitory activity on gastric emptying in mice in terms of the test meal weight in the stomach assessed at 20 minutes after giving the test meal (Chen *et al.* 2002).

One *in vitro* study showed that ginger acetone extract as well as 6-, 8- and 10-gingerol were able to inhibit serotonin-induced contractions of the isolated guinea pig ileum and hypothesised that they all act by blocking 5-hydroxytryptamin 3 (5-HT_3) receptors (Yamahara *et al.* 1989b). Furthermore, *in vitro* studies have demonstrated that ginger hexane extract and some of its active principles (6-gingerol, 8-gingerol, 10-gingerol and 6-shogaol) are able to inhibit 5-HT_3 receptor function (Abdel-Aziz *et al.* 2005; Abdel-Aziz *et al.* 2006). Ghayur and Gilani (2005a) showed that a methanolic ginger extract produced a dose-dependent (dose range 0.01-5.0 mg/ml) stimulant and then a spasmolytic effect in atropinized rat and mouse stomach fundus, and a dose-dependent (0.1-3.0 mg/ml) spasmolytic effect on rabbit jejunum, and rat, mouse and guinea pig ileum. Other *in vitro* studies have shown that ginger extract inhibited rat ileum smooth muscle activity provoked by electrical stimulation (Heimes *et al.* 2009), which was reduced by a vanilloid receptor antagonist suggesting pre-junctional vanilloid receptor involvement (Borelli *et al.* 2004).

In rats with postoperative ileus, a single dosage of processed ginger root (150 mg/kg orally) did not affect the delayed gastrointestinal tract transit (Tokita *et al.* 2007).

In mice an acetone extract of ginger at 75 mg/kg, 6-shogaol at 2.5 mg/kg and 6-, 8- and 10-gingerol at dosages of 5 mg/kg significantly enhanced the transport of a charcoal meal (Yamahara *et al.* 1990). In mice an aqueous ginger extract in an oral dosage of 150 mg/kg inhibited the accelerated small intestinal transit induced by carbacholin, an effect that was ascribed to shogaol (Hashimoto *et al.* 2002). A methanolic ginger extract enhanced a charcoal meal travel (that was completely blocked by atropine pre-treatment) through the small intestine in mice in a dose-dependent (30 and 100 mg/kg) fashion (Ghayur and Gilani 2005a).

An hydroalcoholic ginger extract provided significant protection against 2 GY gamma-radiation induced conditioned taste aversion (which is considered as an equivalent to emesis) in male and female rats in a dose-dependent manner up to 200-250 mg/kg intraperitoneally (Sharma *et al.* 2005), an effect that was better in comparison with ondansetron and comparable to that of dexamethasone (Haksar *et al.* 2006).

Table 4: Overview of the gastrointestinal motility and antiemetic non-clinical data/conclusions

Herbal preparation tested	**Strength Dosage Route of administration**	**Experimental model** ***In vivo/ In vitro***	**Reference** **Year of publication**	**Main outcome(s) according to the authors**
Ginger rhizome				
dried	70 mg/kg, oral	*In vivo,* dogs	Shibata *et al.* 1999	Induced phasic contractions in the gastric antrum
dried	150 mg/kg, oral	*In vivo,* rats with postoperative ileus	Tokita *et al.* 2007	No effect on delayed gastrointestinal tract transit
Other preparations				
acetone extract	250 mg/kg oral	*In vivo,* rats	Gupta and Sharma 2001	Reversal of pyogallo-induced delay in gastric emptying
acetone extract, ginger juice	200 mg/kg, 2 ml/kg, oral	*In vivo,* rats	Sharma and Gupta 1998	Reversal of cisplatin-induced delay in gastric emptying
acetone extract	150 mg/kg, oral	*In vivo,* musk shrews	Yamahara *et al.* 1989a	Inhibition of cyclophosphamide induced emetic
methanolic extract	0.01-5.0 mg/ml, oral	*In vivo,* rats, mice, guinea pigs, rabbits	Ghayur and Gilani 2005a	Spasmolytic effect
acetone extract	75 mg/kg, oral	*In vivo,* mice	Yamahara *et al.* 1990	Gastrointestinal motility enhanced
aqueous extract	150 mg/kg, oral	*In vivo,* mice	Hashimoto *et al.* 2002	Inhibited small intestinal transit induced by carbacholin, an effect that was ascribed to shogaol
ethanolic extract	200 mg/kg, intraperitoneal	*In vivo,* rats	Sharma *et al.* 2005	Protection against induced taste aversion
ethanolic extract	200 mg/kg, intraperitoneal	*In vivo,* rats	Haksar *et al.* 2006	Protection against induced taste aversion

Anti-inflammatory studies

Inhibition of lipopolysaccharide (LPS) induced prostaglandin E (PGE_2) has been demonstrated in *in vitro* test systems for ginger extract (Lantz *et al.* 2007), and for many gingerols and shogaols (Dugasani *et al.* 2010; Jolad *et al.* 2004; Jolad *et al.* 2005; Pan *et al.* 2008). Studies in animals (rat) have shown reduced blood concentrations of PGE_2 with daily oral or intraperitoneal administration (50 and 500 mg/kg doses) of an aqueous extract of ginger (Thomson *et al.* 2002). Gingerols and shogaols are also potent *in vitro* inhibitors of lipoxygenase (Flynn *et al.* 1986). An increased activity of cyclooxygenase (COX-2) by oxidative stress was completely abolished by oral pre-treatment of rats with 100 mg/kg dose of an ethanolic ginger extract (El-Sharaky *et al.* 2009), and topical administration of 6-gingerol

(30 µM) prior to UV-radiation of hairless mice inhibited the induction of COX-2 mRNA and activation of nuclear factor-kappaB (NF-κB); the key transcriptional factor for synthesis of pro-inflammatory mediators, including inducible nitric oxide synthase (iNOS), COX-2 and tumour necrosis factor alpha (TNF-α) (Kim *et al.* 2007).

Ginger root may inhibit the induction of genes encoding cytokines and chemokines that are synthesised and secreted at sites of inflammation. *In vitro* standardised extracts of ginger were reported to inhibit amyloid Aß peptide induced cytokine and chemokine expression in cultured THP-1 monocytes (a cell culture model of human microglial cells) (Grzanna *et al.* 2005). In a murine macrophage cell line alcoholic ginger extract at a concentration of 100 µg/ml induced macrophage inducible nitric oxide synthase mRNA expression and nitrogen oxide (NO) production (Imanishi *et al.* 2004), while in murine microglial cells ginger extract inhibited the LPS induced excessive production of NO (by down-regulating iNOS) and pro-inflammatory cytokines associated with suppression of NF-κB and mitogen activated protein kinase (Jung *et al.* 2009), and in human synoviocytes ginger extract suppressed cytokine production (associated with suppression of NF-κB and IκB-α activation) (Frondoza *et al.* 2004) and chemokine expression (Phan *et al.* 2005). Treatment with processed ginger inhibited the upregulation of cytokine induced neutrophil chemoattractant in monocrotaline induced sinusoidal obstruction syndrome in rat liver (Narita *et al.* 2009). *In vitro* studies showed that fresh ginger in a dose-dependent fashion suppressed mitogen and alloantigen mediated lymphocyte proliferation (Wilasrusmee *et al.* 2002a) and interleukin-2 production from mixed lymphocyte culture (Wilasrusmee *et al.* 2002b), and a study by Tripathi *et al.* (2008) suggested that the mechanism behind the inhibition of T-cell proliferation by ginger was suppression of the antigen presenting cell function of macrophages by down-regulating MHC class II molecule expression.

In vitro studies with cultured human airway epithelial cells (Tjendraputra *et al.* 2001) and human histiocytes (Lantz *et al.* 2007) have shown that many gingerols and shogaols express anti-inflammatory activity. 6-gingerol seems to be able selectively to inhibit the production of pro-inflammatory cytokines from macrophages, but unlike whole ginger, 6-gingerol had no effect on the up-regulation of either MHC class II, co-stimulatory molecules or macrophage antigen presentation (Tripathi *et al.* 2007). Other *in vitro* studies showed that especially 6-shogaol inhibited arachidonic acid release and NO synthesis (Sang *et al.* 2009) and was responsible for down-regulating inflammatory iNOS activity and COX-2 gene expression by inhibiting transcriptional activity of NF-κB in LPS stimulated mouse macrophages (Pan *et al.* 2008).

Furthermore, in experimentally induced inflammation in several animal models ginger extracts exhibit anti-inflammatory properties. In rats, intraperitoneal injections of alcoholic ginger rhizome extract in single doses from 50 to 800 mg/kg inhibited albumin (Ojewole 2006) and carrageenan induced (Penna *et al.* 2003) paw oedema, an effect that seemed to be elicited by 6-gingerol (Young *et al.* 2005). Aimbire *et al.* (2007) found that an ethanolic extract of ginger (186 mg/kg administered intraperitoneally 30 minutes after LPS) reduced LPS induced rat trachea hyper-reactivity and lung inflammation, reduced the serum and lung parenchyma levels of PGE_2 and thromboxane A_2 (TXA_2), and reduced myeloperoxidase activity and cell number in bronchoalveolar gavage. In a mouse model of pulmonary inflammation induced by T-helper lymphocytes (airway challenge after sensitisation with ovalbumin) intraperitoneal injection of a methanolic extract of ginger (45-720 mg/kg on the day of challenge) resulted in a dose-dependent marked decrease in the recruitment of eosinophils to the lungs accompanied by a decreased level of cytokines, and allergen-specific antibodies, an effect that was ascribed to 6-gingerol (Ahui *et al.* 2008). In an acetic acid-induced ulcerative colitis model in rats, the ingestion of ethanolic ginger extract (100-400 mg/kg) for 3 consecutive days before disease induction, mucosal injury was reduced concomitantly with reduced colonic contents of cytokines, PGE_2 and myeloperoxidase (El-Abhar *et al.* 2008). Sharma *et al.* (1994) demonstrated that ginger oil (33 mg/kg) given orally for 26 days suppressed mycobacterial adjuvant inflammation in the paw and

knee joint in rats. Fouda and Berika (2009) showed that intraperitoneal injections of ethanolic ginger extract (100 mg/kg/day for 25 days) in rats with type II collagen induced arthritis (a model of human rheumatoid arthritis) lowered the incidence of arthritis, and improved clinical and histopathological arthritis scoring, and lowered pro-inflammatory cytokines and autoantibodies, compared with vehicle-treated rats. Orally administered acetone extract at 1000 mg/kg, and zingeribene and 6-gingerol at 100 mg/kg, significantly inhibited HCl/ethanol induced gastric lesions in rats (Yamahara *et al.* 1988), and a study by Nanjundaiah *et al.* (2009) showed that oral administration of an aqueous ginger extract in daily dosages at 200 mg/kg for 2 weeks effectively reduced stress and ethanol induced gastric ulcers in rats. Oral administration of 6-gingerol and 6-shogaol at dosages of 140 mg/kg was shown to have antipyretic effect in rats (Suekawa *et al.* 1984) and intraperitoneal injections of 6-gingerol dose-dependently (2.5-25 mg/kg) decreased resting body temperature and metabolic rate in normal rats (Ueki *et al.* 2008).

In a model of necrotic enterocolitis in newborn rats Cakir *et al.* (2018) observed antioxidant, anti-inflammatory, anti-apoptotic or immunomodulatory effects of an aqueous ginger extract administered orally at high doses (1000 mg/kg).

Ezzat *et al*. (2018) studied anti-inflammatory activity of aqueous ginger extracts in carrageenan-induced rat paw edema. A dose-dependent effect was observed after oral dosing of 25-200 mg/kg, with reduction in paw volume, decrease in pro-inflammatory cytokines and chemokines as well as replenishment the total antioxidant capacity.

The anti-inflammatory effects of ginger were also studied by Hsiang *et al.* (2013) in mice with 2,4,6-trinitrobenzene sulphonic acid (TNBS)-induced colitis. An ethanolic ginger extract administered orally (1-100 mg/kg), dose-dependently ameliorated TNBS-induced colonic injury as assessed by colonic weight/length ratio, macroscopic lesion, and histological examination. *Ex vivo* imaging and immunohistochemical staining showed that the ginger extract given intrarectally suppressed TNBS-induced NF-jB activation and IL-1b protein levels in the colon. In addition, the same group studied the effect of ginger in lipopolysaccharide (LPS)-induced acute systemic inflammation in mice via nuclear factor-κB (NF-κB) bioluminescent imaging (Hsiang *et al.*, 2015). In this model the ethanolic ginger extract (100 mg/kg) given orally significantly reduced the whole body LPS-induced luminescent intensity by 27±14% and decreased LPS-induced IL-1β and TNF-α production in sera by 74±23% and 64±18%, respectively.

The immunosuppressive activity of ginger was investigated by using a mouse model of ovalbumin-induced allergic asthma (Khan *et al.*, 2015). After treatment with ethanol extract (500 mg/kg, i.p.) and aqueous extract (720 mg/kg, i.p.) of ginger rhizomes, significant reductions were observed in goblet cell hyperplasia, infiltration of inflammatory cells in airways, oedema with vascular congestion, total and differential count of eosinophils and neutrophils in the bronchoalveolar lavage fluid (BALF), eosinophil count in blood, mRNA expression and protein levels of IL-4 and IL-5 in BALF and total serum IgE levels.

Yocum *et al.* (2020) demonstrated that chronic administration of whole ginger CO_2-extract (40 mg/kg, twice daily p.o.) mitigates in vivo house dust mite (HDM) antigen-mediated lung inflammation in mice. Significantly decreased bronchoalveolar lavage (BAL) eosinophil and lymphocyte cell counts compared to vehicle treatment were observed. In vitro studies also demonstrate that 6-shogaol augments cAMP concentrations in CD4 cells exposed to PGE2 and limits the induction of nuclear factor-κB signalling and the production of proinflammatory cytokines in activated CD4 cells.

Cifici *et al.* studied the effect of a ginger extract in newborn rat pups exposed to hyperoxia and lipopolysaccharide. The extract, standardized to 5% gingerols and 5% shogaols, given orally in high doses (1000 mg/kg) reduced lung damage. Tissue antioxidant status levels were protected and total

oxidant status, malondialdehyde, myeloperoxidase, TNF-α, IL-1β, and IL-6 concentrations were significantly decreased in the ginger-treated group.

Table 5: Overview of the main anti-inflammatory non-clinical data/conclusions

Herbal preparation tested	**Strength Dosage Route of administration**	**Experimental model** ***In vivo/ In vitro***	**Reference** **Year of publication**	**Main outcome(s) according to the authors**
aqueous extract	50 mg/kg, oral or intraperitoneal	*In vivo,* rats	Thomson *et al.* 2002	Reduced blood PGE_2
ethanolic extract	100 mg/kg, oral	*In vivo,* rats	El-Sharaky *et al.* 2009	Inhibited increased COX-2 by oxidative stress
ethanolic extract	100 mg/kg, oral	*In vivo,* rats	El-Abhar *et al.* 2008	Reduced colonic PGE_2 and myeloperoxidase in acetic acid-induced ulcerative colitis
aqueous extract	200 mg/kg, oral	*In vivo,* rats	Nanjundaiah *et al*. 2009	Reduced stress and ethanol induced gastric ulcers
aqueous extract	100-200 mg/kg, oral	*In vivo,* rats	Ezzat *et al*. 2018	Anti-inflammatory by inhibition of macrophage and neutrophils activation and monocyte and leukocyte migration. Reduction in PGE2, TNF-α, IL-6, MCP-1, MPO in induced paw oedema.
ethanolic extract	100 mg/kg, oral	*In vivo,* mice	Hsiang *et al*. 2015	Suppressed NF-κB activities in LPS-induced acute systemic inflammation. Decreased IL-1β and TNF-α in sera
ethanolic extract	100 mg/kg, oral/intrarectal	*In vivo,* mice	Hsiang *et al*. 2013	Improved TNBS-induced colitis in mice and suppressed NF-κB activity and IL-1β productions in the colon of the mice.
CO2-extract (1:15 of dried)	40 mg/kg (2/day), oral	*In vivo,* mice	Yocum *et al*. 2020	Mitigates lung inflammation in a murine asthma model, decreased BAL eosinophil and lymphocyte cell counts

Analgesic studies

Dried ginger rhizome ethanolic extract administered intraperitoneally in doses of 50 mg/kg to 800 mg/kg produced a dose-dependent delay in reaction time using the hot plate analgesic test method and inhibited acetic acid induced writhes in mice suggesting a central as well as a peripheral analgesic effect (Ojewole 2006). Animal experiments have suggested analgesic properties for both 6-shogaol and 6-gingerol (Suekawa *et al.* 1984; Young *et al.* 2005). Gingerols are potent vanilloid receptor (VR1) agonists which may in part explain ginger's analgesic effects (Dedov *et al.* 2002).

3.1.2. Secondary pharmacodynamics

Blood lipids and blood glucose studies

Ethanolic extract of ginger root (200 mg/kg) has been shown to reduce plasma lipids and severity of aortic atherosclerosis in cholesterol-fed hyperlipidaemic rabbits (Bhandari *et al.* 1998), and in streptozotocin (STZ) induced diabetic rats (Bhandari *et al.* 2005), and was also found to inhibit LDL oxidation in apolipoprotein deficient atherosclerotic mice (Fuhrman *et al.* 2000). Besides, the aqueous extract of ginger root has also been shown to reduce serum cholesterol, LDL-cholesterol, VLDL-cholesterol and triglycerides and to raise HDL-cholesterol in normal rats (Thomson *et al.* 2002). The mechanism of action is uncertain; however, it may be caused by an up-regulation of liver LDL receptor expression (an indication of increased cholesterol elimination) and down-regulation of liver 3-hydroxy-3-methylglutaryl coenzyme A expression (an indication of decreased cholesterol biosynthesis) in rats on a high fat diet (Nammi *et al.* 2010).

Blood glucose lowering and insulin increasing effect of ginger juice was observed in STZ induced diabetic rats and in 5-hydroxytryptamine induced hyperglycaemic normal rats (Akhani *et al.* 2004). The oily extracts of ginger root have also been shown to lower blood glucose and increase insulin in normal rabbits and rats (Heimes *et al.* 2009; Ojewole 2006), and in alloxan (Kar *et al.* 2003) and STZ induced (Bhandari *et al.* 2005; Ojewole 2006) diabetic rats. The ethanolic extract of ginger has been shown to protect rats from the metabolic disturbances induced by a high fat diet (Nammi *et al.* 2009). This effect may partially be mediated through 6-gingerol and 6-shogaol (Isa *et al.* 2008).

The anti-atherogenic effects of ginger in hypercholesterolaemia has been studied on rabbits on atherogenic diet. Orally administered methanolic ginger extract powder, 50 mg/kg bodyweight, exerted effects on plasma lipids, reverse cholesterol transport, cholesterol synthesis and inflammatory status (Elseweidy *et al*. 2015). Reduced plasma levels of total and LDL-cholesterol as well as triglycerides were observed through inhibition of arginase activity in preventing hypercholesterolemia in rats that received a high-cholesterol diet and 2% fresh ginger rhizome (Akinyemi *et al*. 2016). A study on hamsters administered 800 µg/kg 6-gingerol in a high cholesterol diet, showed that 6-gingerol restored the apoA-I levels in plasma, functional HDL production, and promotes cholesterol efflux even under hyperlipidaemic conditions (Barbalata *et al*. 2019).

Cardiovascular studies

In anaesthetized rats methanolic extracts of fresh ginger injected intravenously induced a dose-dependent (0.3-3 mg/kg) fall in blood pressure, and in guinea pig atria the extract caused an inhibitory effect on the spontaneous force and beating rate of atrial contractions similar to verapamil, a standard calcium antagonist, and an endothelium independent vasodilator effect in rabbit and rat aorta (Ghayur and Gilani 2005b). Vasodilator effects may be caused by gingerols and shogaols (Ghayur *et al.* 2005; Suekawa *et al.* 1984). However, another study demonstrated no significant changes in systolic blood pressure or heart rate when rats were administered oral dosages of 50 and 100 mg/kg EV.EXT33, an ethanol extract of dry rhizomes (Weidner and Sigwart 2000).

Ginger extract (ethanolic), 3 µg/ml, induced relaxation of KCl-induced contraction in ex vivo porcine coronary arteries in an endothelium-dependent manner (Wu *et al*. 2018). Several gingerol and shogaol analogues extracted from ginger exhibited vasorelaxant effects on chemically induced contraction of ex vivo rat aorta, at around 30 µM and above (Liao *et al*. 2012).

Antithrombotic studies

In vitro investigations have repeatedly shown that an aqueous ginger extract inhibited the formation of thomboxane B_2 (TXB) and platelet aggregation induced by several aggregating agents, an inhibition that has been explained by an inhibitory effect of ginger on platelet COX enzyme (leading to a reduced amount of the pro-aggregatory TXB) (Nurtjahja-Tjendraputra *et al.* 2003; Srivastava 1984; Srivastava 1986). The gingerols (Guh *et al.* 1995), primarily 8-gingerol and 8-paradol, may be the major active principles that inhibit platelet activation (Koo *et al.* 2001; Nie *et al*. 2008; Nurtjahja-Tjendraputra *et al.* 2003).

Further constituents of ginger may contribute to antithrombotic activity. Zingerone has shown antithrombotic and anticoagulant effects in a mouse model of arterial and pulmonary thrombosis. Antithrombotic effects were observed from i.v. injections representing approx. 10 µg/kg bodyweight of zingerone, on male C57BL/6 mice in groups of 20, when acute thrombosis is induced 1 h later by collagen/epinephrine injection. The effect was repeated in five separate experiments (Lee *et al*. 2017).

Furthermore, several gingerol and shogaol analogues extracted from ginger exhibited anti-platelet aggregation properties using *in vitro* experiments on rabbit platelets. (6)-gingerol and (6)-shogaol exhibit complete inhibition of arachidonic acid-induced aggregation at 3-4 µM (Liao *et al*. 2012).

Antineoplastic studies

Mice, orally fed methanolic ginger extract powder 250 mg/kg daily, exhibited growth-inhibitory effects in human prostate tumour xenografts (Gundala *et al*. 2014).

Ginger root and some of its constituents have also been reported to have tumour preventive effects (Shukla and Singh 2007). Non-clinical *in vivo* studies have revealed that topical application of the ethanol extract of ginger prior to 12-O-tetradecanoylphorbol-13-acetate protected against mouse tumour promotion initiated by 7,12-dimethyl-benz(a)anthracene (Katiyar *et al.* 1996), an effect that was attributed to 6-gingerol (Bode *et al.* 2001; Park *et al.* 1998). 6-gingerol significantly induced apoptosis and inhibited prostate enlargement in testosterone treated mice (Shukla *et al.* 2007).

Antiparasitic studies

One plasmodium inoculated mice study showed a significant 33% reduction of plasmodial burden trough orally administered powdered ginger at 1 g/kg bodyweight (Biruksew *et al*. 2018).

3.1.3. Safety pharmacology

No studies available.

3.1.4. Pharmacodynamic interactions

A ginger ethanolic extract, EV.EXT33, administered orally in a dose of 100 mg/kg to rats had no effect on warfarin induced changes in prothrombin time and activated partial thromboplastin time (Weidner and Sigwart 2000).

Shehab *et al*. (2018) evaluated the synergistic or antagonistic interaction between oral dabigitran etexilate and some foods. Aqueous extracts of various foods, among them ginger were prepared and lyophilized, and total phenolic acids and flavonoid contents evaluated. The residues of the aqueous

extracts were given daily to the rats (500 mg/kg dose, oral) 1 h after administration of dabigatran (1.83 mg/kg dose) for 14 days. Bleeding time, International Normalized Ratio (INR), prothrombin time (PT) as well as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) in blood were measured. Oral administration of ginger with dabigatran increased bleeding time (from 26.0 ±1.4 min to 86.5 ±6.4 min), INR (from 2.75 ±0.07 to 6.75 ±0.35) and PT (from 37.4 ±1.8 min to 97.8 ±3.3 min). Elevation in ALP level was observed after aqueous extract of ginger was administered with dabigatran.

3.1.5. Conclusions

Many non-clinical pharmacological studies have reported that ginger, preparations thereof and its constituents display many properties *in vivo* and *in vitro*. However, results from relevant non-clinical pharmacodynamic studies on preparations included in the monograph are limited.

One study report that dried ginger stimulated contractile activity primarily in the gastric antrum in dogs. However, the pathophysiology of nausea and vomiting is not entirely known. Several peripheral and central stimuli may provoke nausea and vomiting, which may occur independently. Hence, the mechanism of action for prevention or relief of motion sickness from these non-clinical gastrointestinal motility studies are considered not known.

In some non-clinical mechanistic studies effects on specific pathways associated with antithrombotic activity have been shown. One *in vivo* study suggested an interaction with dabigatran, while another *in vivo* study did not show an interaction with warfarin. The risk of bleeding events and interactions with anticoagulants are further assessed in chapter 5 "Clinical safety".

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Under *in vitro* acidic condition, similar to that in the stomach, 6-gingerol and 6-shogaol have been shown to display reversible dehydration and hydration reactions to form an equilibrium mixture of 6-shogaol and 6-gingerol, respectively (Bhattarai *et al*. 2007); however, in simulated intestinal fluid, both 6-gingerol and 6-shogaol demonstrated insignificant inter-conversion between one another. Mostly 6-shogaol was converted into 6-paradol, which could be explained by the action of microbial reductive enzymes.

Jiang *et al*. (2008) studied the plasma pharmacokinetics and the tissue distribution profile of 6-gingerol in rats after oral administration. Fasting rats were administered a single dose of 240 mg/kg of a ginger extract containing 53% (w/w) 6-gingerol. They demonstrated a rapid absorption into the plasma of 6-gingerol. The absorption rate constant was 12.2 h^{-1}. The maximal concentration (C_{max}) was 4.23 µg/ml and was reached 10 minutes post-dosing. The plasma concentration then decreased with time in a bi-exponential pattern. At 2 hours post-dosing, the plasma concentration dropped below detection level. A 2-compartment model was adequate to describe the plasma pharmacokinetics of 6-gingerol. The apparent total body clearance of 6-gingerol was 40.8 l/h and the apparent volume of distribution was 18.4 l. The elimination half-time was 1.77 hours. In the tissue distribution study, it was shown that 6-gingerol was distributed to all the examined tissues (brain, heart, lung, spleen, liver, kidney, stomach and small intestine), with the highest concentrations found in the gastrointestinal tract. Maximal concentrations were reached in most tissues at 0.5-hour post-dosing, and concentrations were higher in the tissues than in plasma 15 minutes post-dosing.

In rats fed with ginger incorporated diet (0.1, 1 and 5% powdered ginger) for 1 month the drug metabolising enzyme glutathione-S-transferase (GST) activity was stimulated in the liver at all dosage levels, and in lungs, kidney and intestine increased GST activity was seen at 1 and 5% diet levels

(Nirmala *et al*. 2010). There was some increase in the activity of uridine diphosphoglucuronyl transferase in liver, lung, kidney and intestines in rats fed with ginger though not statistically significant. Significantly elevated quinone reductase enzyme levels were also noted in 1 and 5% ginger fed groups; however activities of aryl hydrocarbon hydroxylase were unaffected in all rat tissues.

Gundala *et al*. (2014) studied the PK profile of four ginger extract (GE) components 6-gingerol (6G), 6-shogaol (6S), 8-gingerol (8G), 10-gingerol (10G) in male mice (fasted 3h) upon oral administration of 250 mg/kg of methanolic GE. The resulting maximal concentration (C_{max}) was 306±92 ng/ml for 6G, 72±32 ng/ml for 8G, 327±40 ng/ml for 10G and 5.7±0.2 ng/ml for 6S. There were multiple C_{max} peaks observed for the gingerols after the first at 10 min, associated with recirculation of compounds from intestine to systemic circulation after getting eliminated through bile. The β-glucuronidase hydrolysis of both plasma and faeces samples obtained post-IV administration of pure ginger biophenolics are considered to confirm that the gingerols re-enter the liver via hepatic portal vein from the intestine for reabsorption into the systemic circulation.

In a study by Mukkavilli *et al*. (2017) GE phenolics showed low to moderate solubility in various pH buffers but were stable in simulated gastric and intestinal fluids, indicating their suitability for oral administration. All GE phenolics (6G, 8G, 10G and 6S) were metabolically unstable and showed high intrinsic clearance in mouse, rat, dog, and human liver microsomes. In male mice (fed ad lib), upon oral administration of 250 mg/kg GE, sub-therapeutic plasma concentrations of GE phenolics were observed. Treatment of plasma samples with β-glucuronidase increased the exposure of all GE phenolics by 10 to 700-fold. Phase II metabolism seems to be the predominant clearance pathway for GE phenolics. The first-pass metabolism, particularly glucuronide conjugation of GE phenolics, underlies low systemic exposure.

In a follow up study Mukkavilli *et al*. (2018), compared the plasma concentration-time profiles of ginger phenolics (GPs; 6G, 8G, 10G and 6S) on day 1 and day 7 following repeated daily oral administration of ginger extract (GE) at 250 mg/kg to mice (fed ad lib). The GE contained, per 1mg, 30.03 µg of 6G, 6.86 µg of 8G, 7.77 µg of 10G and 5.96 µg of 6S. While the plasma exposure (AUC_{last}) of 10G (1244±98 ng*h/mL) was twice that of 6G (615±196 ng*h/mL), plasma exposure of 8G (117±34 ng*h/mL) was 5 times lower than 6G. Notably, the plasma exposure of 6S was lowest at (AUC_{last}) 47±15 ng*h/mL, indicating its low bioavailability compared to other GPs. Exposure (AUC_{last}) of GPs was similar on day 7 compared to day 1 suggesting no induction or inhibition of their clearance pathways. Furthermore, the presence of multiple peaks was evident on day 1 for all GPs indicating enterohepatic recirculation.

Li *et al*. (2019) examined the concentrations of 6-gingerol, 6-shogaol, 8-gingerol, 8-shogaol, 10-gingerol, 10-shogaol, zingerone and 6-isodehydrogingenone in plasma and organ samples after oral administration of ginger extract (75% ethanol) to rats (fasted 12h) at a dose of 400 mg/kg. Results showed that all analytes were quickly absorbed into the circulatory system with different concentrations; gingerols have similar drug–time curves to shogaols with a corresponding carbon chain length due to structural similarity. The T_{max} of 6-, 8-, and 10-gingerols/shogaols (T_{max} 0.7 – 1.5h) showed that shogaols were absorbed faster than gingerols with a corresponding carbon chain length. Additionally, the increase in the alkyl side chain length weakened the entry capacity in blood of gingerols and shogaols. The $T_{1/2}$ of shogaols (2.5-3.9 h) were longer than gingerols (2.6-2.7h). 6-gingerol is the most abundant GP in ginger, but the detected plasma concentration was not very high (the C_{max} of 6-gingerol was 255.4 ± 45 µg/L), probably due to the major existing form of 6-gingerol in plasma is its glucuronide metabolites. The plasma exposure of 10S was lowest of the gingerols/shogaols at C_{max} of 32.5 ± 6.2 µg/L. 6- and 8-gingerols/shogaols had double absorption peaks at about 3 h in the concentration–time profile after administration. Tissue distribution was determined in various tissues of rats, including the liver, heart, spleen, lung, kidney, stomach,

intestine, and brain. Maximal concentrations were reached in most tissues at 0.5-1.5 hours post-dosing. The ingredients could be detected in the studied organs except for 10-shogaol and 6-isodehydro-gingenone. The highest concentrations were found in the gastrointestinal tract. 6-shogaol and zingerone were able to penetrate the blood–brain barrier and enter the brain.

Assessor's comment:
The different ginger phenolics (GPs) studied display similar pharmacokinetic profiles in mice and rats. The absorption appears quick, although with high variation, possibly influenced by food intake. Several plasma concentration peaks have been observed, indicating enterohepatic recirculation. The GPs appear to be extensively metabolised with a high degree of conjugation. GE constituents distribute in all studied tissues, although to a lesser extent in brain.

3.2.1. Pharmacokinetic interactions

In vivo studies

A small study in rabbits in which the effect of ingested water extracted ginger preparation, 1 ml/kg, on the pharmacokinetics of metronidazole showed that the ginger extract significantly increased the maximum absorption (C_{max}: 16.5 vs. 4.2 µg/ml; ginger vs. no ginger), absorption rate (T_{max}: 4.0 vs. 2.0 hours) and plasma half-time (t½: 12.7 vs. 8.6 hours), and decreased the elimination rate constant Kel 0.054 vs. 0.079 h-1) and clearance (CL: 0.558 vs. 1.648 ml/kg x hour) of metronidazole (Okonta *et al*. 2008).

Chiang *et al*. (2006) investigated the effect of ginger juice on the pharmacokinetics of cyclosporine in rats. Rats were orally administered cyclosporine alone and in combination with ginger juice concomitantly, as well as 2 hours after the ginger juice, respectively, in crossover designs. In addition, rats were intravenously administered cyclosporine with and without an oral dose of ginger juice. The content of (6)-gingerol in ginger juice was 522.5 µg/ml. The results indicated that concomitant intake of ginger juice (5 ml/kg) significantly decreased Cmax and AUC0–t of oral cyclosporine by 70.9% and 63.1%, respectively. The intake of ginger 2 hours before cyclosporine significantly decreased Cmax and AUC0–t by 51.4% and 40.3%, respectively. In contrast, the pharmacokinetics of intravenous cyclosporine not altered by orally in combination with ginger juice. In conclusion, ginger significantly decreased the oral bioavailability of cyclosporine, and the interaction should occur at the absorption phase.

Egashira *et al*. (2012) studied the effect of ginger and other foods on the pharmacokinetics of tacrolimus in rat. Tacrolimus which has a narrow therapeutic range is a substrate of CYP3A4. Its absorption is further limited due to involvement of P-glycoprotein. It was found that the exposure, AUC0-120min for intraduodenally administered tacrolimus increased from approximately 20 ng*h/ml to 38 ng*h/ml after oral administration of fresh grated and filtered ginger juice.

Nduka *et al*. (2013) studied the effects of *Zingiber officinale* on the plasma pharmacokinetics and lung penetrations of ciprofloxacin and isoniazid. Albino rats of both genders (5 rats per group) received oral ciprofloxacin (20 mg/kg) or isoniazid (15 mg/kg). Other groups were fed with ginger extract (90% methanol) at 5 mg/kg for 10 days followed by the drug administration on the 11th day. Treatment with ginger extract increased the area under the concentration-time curve (AUC) of ciprofloxacin (205.7 ± 0.7 vs 119.0 ± 4.9 µg*h/ml), whereas Cl was decreased (0.16 ± 0.01 vs 0.09 ± 0.002 mL/kg/h). Ginger decreased the AUC of isoniazid (151.6 ± 13.8 vs 491.8 ± 56.8 µg*h/ml), whereas Vz and Cl were increased (Vz: 0.88 ± 0.13 vs 0.40 ± 0.01 mL/kg; Cl: 0.09 ± 0.01 vs 0.02 ± 0.007 mL/kg/h).

Al-Mohizea *et al*. (2015) investigated the effect of commonly used dietary ingredient like ginger on the pharmacokinetic of theophylline (metabolised by CYP1A2) in rabbits. In the experimental groups,

theophylline (16 mg/kg) was given orally to the rabbits. Where aqueous saline suspension of dry powdered ginger (264 mg/kg, p.o.), was given to the rabbits and the blood samples were withdrawn at different time intervals from marginal ear vein after dosing and theophylline in plasma was analysed by HPLC method. The coadministration of ginger increased the Cmax and AUC0–t of theophylline; the change was observed by 12.21 and 11.8% ($p < 0.05$), respectively, and 12.48% decrease in the CL/F.

Kotwal *et al*. (2020) investigated the possible role of phytochemicals on *in vivo* oral bedaquiline pharmacokinetics in rats. Bedaquiline (TMC-207) is the substrate for both P-gp and CYP3A4. The Cmax of bedaquiline (10 mg/kg) was notably elevated upon coadministration with 10 mg/kg of 6-gingerol from 315 ± 77 ng/mL to 509 ± 47 ng/mL and the AUC0–10 was significantly raised from 1813 ± 372 ng*h/mL to 3431 ± 391 ng*h/mL.

Ahad *et al*. (2020) studied the pharmacokinetics of *Zingiber officinale* and losartan in N-Nitro-l-arginine methyl ester (L-NAME) induced hypertensive rats. Rats (n=5) were treated with methanol extract of dried root of Z. officinale (75 mg/kg) orally for 2 weeks. On day 15, the rats were treated with a single oral dose of losartan (10 mg/kg). The Cmax and AUC0-t of losartan increased by 0.7, 1.99 and 1.51, 3.00-fold, respectively.

In vitro studies with ginger preparations

Kimura *et al*. (2010) investigated effects of 55 spices on human microsomal CYP3A4 and CYP2C9 activity based on testosterone 6β-hydroxylation and diclofenac 4'-hydroxylation reactions. Powdered ginger inhibited CYP3A4 or CYP2C9 enzymes with IC50 values of 5.1 and 10 µg/ml respectively.

Kim *et al*. (2012) studied the effect of an aqueous-ethanolic (30%) extract of ginger (containing 5.2% 6-gingerol and 2.1% 6-shogaol) on incubations of CYP450-specific substrates with human liver microsomes fortified with an NADPH-generating system. The ginger extract inhibited CYP2C19-mediated drug metabolism of mephenytoin in a concentration-dependent manner with an IC50 value of 3.8 microg/mL. The inhibitory effect on other CYP isozymes was negligible. When the ginger extract was pre-incubated and assessed, the inhibition pattern did not change, indicating that the inhibition of CYP2C19 was competitive rather than mechanism based.

Gorman *et al*. (2013) investigated the impact of commercially available herbal supplements on the metabolic activation of tamoxifen and irinotecan in human liver microsomes. The data suggest that ginger root alcohol-free fluid extract inhibited biotransformation of tamoxifen and irinotecan to their active metabolites, with IC_{50} of 8.3 mg/ml and 25.5 mg/ml respectively.

Langhammer and Nilsen (2014) investigated ginger for their *in vitro* CYP1A2, 2D6, and 3A4 inhibitory potential. An ethanolic extract (60%) was made from commercially available ginger capsules and incubations were performed with recombinant cDNA-expressed human CYP enzymes in the presence of positive inhibitory controls. Metabolite formation was determined by validated LCMS/MS or HPLC methodologies. IC_{50} inhibition constants were estimated from CYP activity inhibition plots using non-linear regression and were estimated to for CYP1A2: 320 ± 41, for CYP2D6: 445 ± 35 and for CYP3A4: 565 ± 16 µg/ml. The authors state that reports on ginger's CYP inhibitory potential are inconsistent.

Foster *et al*. (2003) reported that a 25 mg/ml aqueous ginger extract inhibited cDNA-expressed human CYP2D6 and 3A4 by 70 and 88%, respectively.

Kim *et al*. (2012) tested CYP inhibitory potentials of 5 µg/ml ethanolic ginger extracts with negligible effects on human microsome CYP1A2, 2D6, and 3A4 activities.

Kimura *et al*. (2010) found an IC_{50} constant as low as 5.1 µg/ml for CYP3A4 in human microsomes. In the present study, the IC_{50} constants were for CYP1A2: 320 ± 41, for CYP2D6: 445 ± 35 and for CYP3A4: 565 ± 16 µg/ml, i.e for CYP3A4.

Mukkavilli *et al*. (2014) reported that individual gingerols are potent inhibitors of CYP isozymes, whereas methanolic ginger extract (GE) exhibits a much higher half-maximal inhibition value, indicating no possible herb-drug interactions. However, GE's inhibition of CYP1A2 and CYP2C8 reflects additive interactions among the constituents. In addition, studies performed to evaluate transporter-mediated intestinal efflux using Caco-2 cells revealed that GE and its phenolics are not substrates of P-glycoprotein (Pgp).

In vitro studies with constituents

The effects on P-glycoprotein function were investigated using human multidrug-resistant carcinoma KB-C2 cells and the fluorescent P-glycoprotein substrates daunorubicin and rhodamine 123. The accumulation of daunorubicin in KB-C2 cells increased in the presence of [6]-gingerol, in a concentration-dependent manner. The accumulation of rhodamine 123 in KB-C2 cells was also increased, and the efflux of rhodamine 123 from KB-C2 cells was decreased. The authors conclude that [6]-gingerol is suggested to have inhibitory effect on P-glycoprotein (Nabekura *et al*. 2005).

The effects of eight components from six commonly consumed spices on P-glycoprotein (P-gp) transport and CYP3A4 metabolism were evaluated *in vitro*. 6-gingerol at 100 to 500 μM were observed to inhibit P-gp-mediated [3H] digoxin transport in L-MDR1 and Caco-2 cells. In addition, CYP3A4-mediated 4-hydroxylation of midazolam was inhibited by 6-gingerol at 60, 100, and 500 μM (71, 68, and 38%) (Zhang and Lim 2008).

6-gingerol, 8-gingerol and 10-gingerol inhibited CYP2C9 activity, exerted moderate inhibition on human CYP2C19 and CYP3A4, and weak inhibion on CYP2D6. 8-Gingerol was the most potent in inhibition with IC50 values of 6.8, 12.5, 8.7, and 42.7 μmol/L for CYP2C9, CYP2C19, CYP3A4, and CYP2D6, respectively. By comparing the effects of gingerols on CYP3A4 with three different fluorescent substrate probes, it was demonstrated that the inhibition of gingerols on CYP3A4 had no substrate-dependence. In HepG2 cells, 8-gingerol and 10-gingerol inhibited, but 6-gingerol induced mRNA expression of CYP3A4 (Li *et al*. 2013).

Paradols are unsaturated ketones produced by biotransformation of shogaols in gingers. 6-Paradol showed concentration-dependent inhibitory effects on CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 isozymes, with IC50 values ranging from 3.8 to 21.4 mM in recombinant human CYP isozymes. The inhibition was not potentiated following pre-incubation, indicating that 6-paradol is not a mechanism-based inhibitor. Previously published data from eight studies on the inhibition properties of ginger biophenols were also summarized. The reviewed studies show that gingerols and shogaols, generally exhibit inhibitory effects on CYP1A2 (IC50 3-19 μM), CYP2B6 (IC50 4-41 μM), CYP2C8 (IC50 2-22 μM), CYP2C9 (IC50 3-28 μM), CYP2C19 (IC50 4-19 μM), and CYP3A4 (with testosterone as substrate, IC50 7-37 μM) (Kim *et al*. 2017).

The human doxorubicin resistant uterine sarcoma cells (MES-SA/Dx5) that overexpress Pgp, were treated with antiemetic alone (1, 10 and 20 μM) or in combination with different doxorubicin concentrations (2, 4, and 8 μM). The authors measured the intracellular accumulation and cytotoxicity of doxorubicin (MTT assay), the cellular GSH content (GSH assay) and ROS production (DFC-DA assay), in comparison with verapamil, a specific inhibitor for Pgp, used as reference molecule. The authors found that exposure of doxorubicin concentrations in the presence (6)-gingerol enhanced significantly doxorubicin accumulation (up to 44%) and cytotoxicity (2.9-fold) on resistant MES-SA/Dx5 cells when compared with doxorubicin alone (Angelini *et al*. 2013).

Assessor's comment:
The results from non-clinical studies (in vitro and in vivo) indicate that ginger and its constituents may inhibit CYP450 enzymes 1A2, 2C9, 2C19 and 3A4 and P-glycoprotein mediated transport. The clinical relevance of the results from these non-clinical studies is not known and further studies are needed.

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

3.3.1. Single dose toxicity

Dried ginger rhizome

No studies found.

Extracts

Intraperitoneal administration of graded doses of ginger dried rhizomes ethanol extract in mice gave an LD_{50} value of 1551 ±75 mg/kg (Ojewole 2006). Jagetia *et al.* (2004) could show that a hydroalcoholic extract of ginger root was non-toxic up to a dose of 1500 mg/kg body weight in mice (the highest dose that was tested for acute toxicity).

In a study with either ethanolic or aqueous extracts of *Z. officinale* roots in male and female mice no toxic symptoms or mortalities were reported following administration of the extracts in doses up to 5 g/kg bw (Shalaby and Hamonwieh 2010).

Acute oral toxicity of steamed and dried ginger (*Zingiber officinale*) aqueous extract was determined in male and female Sprague-Dawley rats at doses of 0 and 5000 mg/kg body weight. After a single oral dose no changes in body weight, clinical signs, or necropsy and histopathological changes were detected (Kim and Choi 2017).

A dried ethanolic extract was tested in healthy Sprague Dawley rats. The results showed no evidence of toxicity and death in the acute toxicity testing with the maximum tolerated dose (MTD) of 5000 mg/kg body weight (Plengsuriyakarn and Na-Bangchang 2020).

Acute toxicity tests were performed in a total of sixty hamsters (5 males and 5 females for each group) which were fed (via gastric gavage) with three dose levels of ethanolic extract of ginger, i.e. 1000, 3000, and 5000 mg/ kg body weight. Only stomach irritation was observed in all animals immediately after feeding them with the extract. The animals however, recovered from the symptom within one hour of dosing (Plengsuriyakarn *et al*. 2012).

In a study by Benny *et al*. (2021), dry ginger rhizome was extracted with ethyl acetate, and gingerol content was enriched by liquid-liquid extraction. Acute toxicity was studied by feeding ginger extract at 2000 mg/kg body weight to overnight fasted female rats. The animals were observed daily for clinical signs of abnormality/mortality. In the acute toxicity study, no mortality or clinical signs of toxicity were observed at a maximum recommended dose level of 2000 mg/kg.

Constituents

In mice, acute toxicity tests LD_{50} values for intravenous (i.v.), intraperitoneal and oral administrations of 6-shogaol were respectively 50.9 (38.9-66.6; 95% confidence interval CI), 109.2 (96.3-123.8) and 687.0 (528.1-893.7) mg/kg; the respective values for 6-gingerol were 25.5 (23.4-27.7), 58.1 (47.1-71.6) and 250.0 (215.2-290.4) mg/kg (Suekawa *et al.* 1984).

3.3.2. Repeat dose toxicity

Dried ginger rhizome

No studies found.

Extracts

The effects of oral and intraperitoneal administration for 28 days of an aqueous extract of fresh ginger root were investigated in female rats at dose levels of 50 mg/kg and 500 mg/kg for haematological parameters (haemoglobin, haematocrit), serum enzymes (fractionated lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, protein) and systemic toxicity (liver lactate dehydrogenase and acid phosphatase, protein, histopathological examinations of lung and liver tissues) (Alnaqeeb *et al.* 2003). The study demonstrated that ginger at 500 mg/kg administered intraperitoneally is slightly toxic. At this dosage level consistent lower serum haemoglobin, increased serum cardiac LDH isoenzymes and slightly decreased liver proteins were observed. Histopathological examinations of the lungs and liver also suggested that ginger at 500 mg/kg intraperitoneally caused abnormalities (thickened alveolar walls in lungs, and granular cytoplasm and large intercellular spaces in liver). The low doses of ginger did not demonstrate toxic effects on the tested parameters.

Adanlawo and Dairo (2007) administered 1 ml daily for 1 month of an ethanolic (90% V/V) ginger extract dried and diluted to concentrations of 100, 200, 300, 400 and 500 mg/ml, respectively, to rats. Enzyme activities – alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and acid phosphatase in brain, kidney, heart and serum – were examined and compared to control animals. Although there were some significant changes in enzyme activities in the tissues tested, they did not follow a credible pattern (*e.g.* dose response), and the few changes observed were probably caused by mass significance.

In a study to investigate the toxicological profile (acute, sub-acute, chronic) and also the potential anti-CCA (cholangiocarcinoma) effect of a dried extract (extraction solvent 95% ethanol,) test were performed in healthy Sprague Dawley rats. The rats (five per group) orally received the ginger dried extract in doses of 500, 1000 or 2000 mg/kg. The results showed no evidence of toxicity (changes in body weight, behaviour, histopathology and laboratory parameters) or mortality in the subacute toxicity testing (28-days repeat dose) with the maximum tolerated dose (MTD) of 2000 mg/kg body weight. However, effects on hematological parameters (increase in hemoglobin, total white blood cells, neutrophils and lymphocytes) and biochemistry parameters (decrease in cholesterol and triglyceride) were observed. Chronic toxicity (12-moths repeat dose) revealed MTD and No-Observed-Adverse-Effect level (NOAEL) of 1000 mg/kg body weight (Plengsuriyakarn and Na-Bangchang 2020).

In the study by Benny *et al*. (2021), dry ginger rhizome was extracted with ethyl acetate, and gingerol content was enriched by liquid-liquid extraction. Sub-acute toxicity of ginger extract was studied by feeding the extract at 100, 500, and 1000 mg/kg daily to rats.The repeated administration of ginger extract for 28 days in rats at the maximum dose level of 1000 mg/kg did not induce any observable toxic effects when compared to its corresponding control animals. The hematology and biochemistry profile of treated rats was similar to control animals. The histopathology of major organs of all the control and treated animals was normal. In this study, the NOAEL (No Observed Adverse Effect Level) was calculated as 1000 mg/kg daily for rats.

An ethanolic extract of ginger powder administered intraperitoneally to mice in dosages of 10, 20 and 40 mg/kg every 48 hours for 20 days resulted in reduced blood urea nitrogen at all dosage levels, however, did not affect serum creatinine compared to control animals (Mehrdad *et al.* 2007). The study is difficult to interpret since it did not present pre-treatment concentrations.

Sixty hamsters (5 males and 5 females for each group) were fed (via gastric gavage) with three dose levels of ethanolic (95%) extract of ginger, i.e. 1000, 3000, and 5000 mg/ kg body weight for 30 days. Body weight, and food and water consumption were recorded daily. Animals were also closely observed for awareness, status of mood, motor activity, CNS excitation, posture, muscle tone, reflexes, and autonomic signs during the first 30 minutes, periodically during the first 24 hours, and then daily for 30 days. Only stomach irritation was observed in all animals immediately after feeding them with the extract. The animals however, recovered from the symptom within one hour of dosing. The average

daily intake of water and food, including the average body weight of animals were comparable in all groups. No abnormal histopathology was observed in any vital organ at autopsy (Plengsuriyakarn *et al*. 2012).

Assessor's comment:
Results from oral repeat dose toxicity studies of ethanolic ginger extracts, not well described or not corresponding to the preparations included in the monograph, indicate that doses required to induce potentially toxic effects, are rather high. A chronic toxicity study (12-months) in rats revealed NOAEL at a dose of 1000 mg/kg body weight daily, higher than what would normally be administered to humans.

3.3.3. Genotoxicity

Dried ginger rhizome

No data found.

Extracts

In *Salmonella typhimurium* strains TA 100 and TA 1535, an 70% ethanol extract of ginger was tested at concentrations of 25 and 50 mg/plate. Sodium azide and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) were used as positive controls and untreated plates were considered as negative controls. The mutagenicity of ginger was higher than negative controls but was much lower than the positive controls (Soudamini *et al.* 1995).

An ethanolic ginger extract was tested in *Salmonella typhimurium* strains TA 100, TA 98, TA 1535 and TA 1538 in the presence and in absence of S9 mix at concentrations between 10 and 200 µg/plate. It was observed that ginger extract was mutagenic on metabolic activation in strains TA 100 and TA 1535 (Nagabhushan *et al.* 1987).

In a study of the mutagenic potential of different extracts of *Zingiber officinale* (methanol, chloroform or water) in an Ames assay using bacterial strains TA 98 and TA 100 with or without metabolic activation with S9 only the water extract demonstrated mutagenic potential and only with the TA100 strain and metabolic activation (Abudayyak *et al*. 2015).

The aim of the study made by Bidinotto *et al*. (2006), was to study the chemoprotective effects of ginger on the DNA damage and the development of bladder cancer induced by N-butyl-N-(4-hydroxibutyl) nitrosamine (BBN)/N-methyl-N-nitrosourea (MNU) in male Swiss mice. Male swiss mice were fed with 1 or 2 % of a lyophilized extract of rhizome ginger (hydroalcoholic extraction by a spray dryer system) containing approximately 2.54% gingerol. After 1, 3, 10 or 18 weeks, peripheral blood was collected, and Comet assay was performed on leucocytes and micronucleus assay was performed on reticulocytes. Ginger itself was not genotoxic and did not alter the DNA damage induced by nitrosamine or nitrosurea.

Ratanavalachai *et al*. (2015) aimed to investigate the genotoxic and cytotoxic potentials of 95% ethanolic extract of *Zingiber officinale* rhizome (EEZOR) alone and EEZOR pre-treatments followed by 0.1 µg/ ml DXR, a genotoxic chemotherapeutic agent, in human lymphocytes by sister chromatid exchange (SCE) assay *in vitro*. Human lymphocytes were treated with EEZOR alone at 25-500 µg/ml and EEZOR pre-treated at 12.5-200 µg/ml followed by 0.1 µg/ml DXR. SCE levels and cell cycle kinetics were evaluated. EEZOR significantly induced biphasic SCE at 50 and 400 µg/ml ($p<0.05$). However, cytotoxicity manifested at 500 µg/ml. All EEZOR pre-treatments at 12.5, 25, 50, and 100 µg/ml, except at 200 µg/ml, prior to DXR, moderately enhanced DXR-induced genotoxicity by 1.3 times ($p<0.05$). Both EEZOR alone and EEZOR prior to DXR at certain concentrations delayed cell

cycle. The authors concluded that the ethanolic ginger extract could induce genotoxicity at certain doses and in pre-treatments could moderately enhance DXR-induced genotoxicity and delay cell cycle.

An essential oil from ginger demonstrated mutagenic activity in *Salmonella typhimurium* strains TA 100 and TA 1535 at concentrations of 5-10 mg/plate (Sivaswami *et al.* 1991).

Constituents

Nakamura and Yamamoto (1982) found that the juice of ginger rhizome contained both mutagen and anti-mutagen, and that 6-gingerol in particular was mutagenic. The group could also demonstrate that 6-shogaol was much less mutagenic (strain Hs30 of *Escherichia coli*) than 6-gingerol, and that the active part of 6-gingerol was the hydroxylated aliphatic side chain moiety (Nakamura and Yamamoto 1983). Capsaicin, the alkaloid present in chili, is structurally related to gingerol and shogaol, and is also found to be mutagenic (Nagabhushan and Bhide 1985).

Gingerol, shogaol and zingerone were tested in Salmonella typhimurium strains TA 100, TA 98, TA 1535 and TA 1538 in the presence and in absence of S9 mix. Gingerol and shogaol were mutagenic in strains TA 100 and TA 1535 with metabolic activation by rat liver S9 fraction, while zingerone did not display mutagenic effects in all the four strains with or without S9 mix (Nagabhushan *et al.* 1987).

In a study by Yang *et al*. (2010), the genotoxic effect of 6-gingerol, was studied using human hepatoma G2 (HepG2) cells. At higher concentrations 6-gingerol induced DNA strand breaks in Hep2G cells in Comet assay *in vitro* (20, 40, 80 µM, but not 10 µM). There was also a statistically significant increase of micronuclei frequencies at higher concentrations (20, 40, but not 5 or 10 µM). These results indicate that 6-gingerol caused DNA strand breaks and chromosome damage at high concentrations. Furthermore, Yang and co-workers reported that lysosomal membrane stability was reduced after treatment by 6-gingerol (20–80 µM) for 40 min, mitochondrial membrane potential decreased after treatment for 50 min, GSH and ROS levels were significantly increased after treatment for 60 min, suggesting that 6-gingerol caused DNA strand breaks and chromosome damage induced by oxidative stress.

Assessor's comment:
Available data from non-guideline compliant studies suggests that ginger extracts and its constituents have mutagenic properties in microbial test systems and in Comet assays. A possible dose-dependent genotoxic effect of an ethanolic ginger extract was also seen in a sister chromatid exchange assay, although results from this study are difficult to interpret since the extract alone exhibited biphasic genotoxicity at a low dose and at a high dose.

3.3.4. Carcinogenicity

Not available.

3.3.5. Reproductive and developmental toxicity

Female fertility and embryo-fœtal development

Ginger rhizome (in vivo)

In a study by Dissabandara and Chandrasekara (2007) pregnant rats were administered dried powder of ginger dissolved in water orally (gavage) at doses of 500 or 1000 mg/kg daily during gestation days 5 to 15. Compared to a control group of rats, food and water intake and weight gain were significantly lower in the ginger treated group during the exposure period. Duration of pregnancy, litter size, number of implantation sites and live birth index were not altered by ginger, however a statistically

significant higher number of embryo resorption was observed in both test groups. No external congenital abnormalities were found either in the ginger fed groups or the controls and physical maturation (eruption of incisors, opening of the eyes, opening of the vagina, separation of prepuce) was unaffected by treatment with ginger.

Habeeb *et al*. (2019) conducted a study on the effect of ginger and curcumin addition to the diet of rabbits exposed to severe heat stress conditions for the possible improvement of the productive and reproductive traits of female rabbits during pregnancy and lactation periods. The study included 45 healthy mature New Zealand white (NZW) virgin female rabbits. Before 1 week from mating, animals were divided into three groups, 15 animals in each. The 1st group was fed the basal ration and kept as control group while the 2nd and 3rd groups were fed the same commercial pelleted diet but supplemented with 250 mg daily from roots crushed of ginger or curcumin per animal, respectively. The supplementation lasted 2 months during summer season (July and August 2017) including pregnancy and lactation periods. Results showed that the physiological thermoregulatory parameters were lower in rabbits received ginger or curcumin than control rabbits and that water intake values were lower while body weight and feed intake values were higher in rabbits received ginger or curcumin compared to rabbits that did not receive any supplement. Furthermore, conception rate, litter size and litter weight at both birthing and weaning improved significantly with addition of ginger or curcumin in the diet of female rabbits. The authors concluded that supplementation with ginger or curcumin in the diet improved the productive and reproductive performance of female rabbits under heat stress condition.

Extracts (in vivo)

EV.EXT33, an ethanol extract of dry ginger rhizomes was administered by oral gavage in concentrations of 100, 333, and 1000 mg/kg to 3 groups of pregnant female rats from days 6 to 15 of gestation (Weidner and Sigwart 2001). For comparison, a fourth group received the vehicle, sesame oil. Body weight and food and water intake were recorded during the treatment period. The rats were killed on day 21 of gestation and examined for standard parameters of reproductive performance. The foetuses were examined for signs of teratogenic and toxic effects. No deaths or treatment-related adverse events were observed. Weight gain and food consumption were similar in all groups during gestation. Reproductive performance was not affected by treatment with ginger. The examination of foetuses for external, visceral and skeletal damages showed no embryotoxic or teratogenic effects of ginger. No differences were seen in foetal body weight or gender ratio. It was concluded that EV.EXT33 when administered to pregnant rats during the brief period of organogenesis caused neither maternal nor developmental toxicity at daily doses of up to 1000 mg/kg body weight.

Wilkinson (2000) examined reproductive and developmental toxicity in pregnant rats administered 20 g/l or 50 g/l ginger tea via their drinking water from gestation day 6 to day 15. Ginger teas were made by placing the required quantity of grated ginger in boiling water; final concentrations were either 20 or 50 g/l. The ginger was allowed to infuse for 10 min followed by straining to remove the pieces of ginger. The solution was then allowed to cool prior to being added to the animals' water bottles. Fresh ginger tea was provided each day. Group A (20 g/l) drank 22.3 ml corresponding to 446 mg ginger and group B (50 g/l) drank 21.0 ml corresponding to 1050 mg ginger. No maternal toxicity was observed, however embryonic loss in the treatment groups was double that of the controls ($P<0.05$) without an effect on overall number of live foetuses. No gross malformations were seen in the treated foetuses. Foetuses exposed to ginger tea were found to be significantly heavier than controls (about 4 to 6%). Treated foetuses also had more advanced skeletal development as determined by measurement of sternal and metacarpal ossification centres. The effects seen were greater in foetuses exposed to 20 g/l ginger compared with those exposed to 50 g/l.

ElMazoudy and Attia (2018), evaluated the impact of ginger aqueous extract on the oestrous cycle and implantation in female mice. Cleaned rhizomes were peeled, chopped, and dried under the sunlight and then ground into fine powder. 200 g of the powder was soaked in one litre of distilled water for 24 h at room temperature. The aqueous extract was filtered by double gauze and concentrated into the final concentrations (250 mg/ml) under reduced pressure. One experimental episode considered the main study of outcomes and lasted 90 days; one lasted 35 days and considered the oestrous cycle; while the third and fourth intended antifertility and abortifacient and continued 20 days for each. Mice dosed ginger orally at 0, 250, 500, 1000 or 2000 mg/kg/day (GNC, GN1, GN2, GN3, GN4, respectively). Doses of 1000 and 2000 mg/kg bw/day resulted in maternal toxicity, with increased mortality and significant decreases in maternal weight gain. Also, histopathological damage was observed in the GN4 group after 90 days, i.e. histopathological damage of follicles and granulosa cells prevalent in ovarian tissue. Furthermore, doses of 2000 mg/kg bw/day significantly reduced the number of live foetuses, increased foetal death and resorption and displayed significant decreases in implantation sites. Ginger at 2000 mg/kg/day prolonged the length of oestrous cycle with a significant decrease in the duration of dioestrous-metestrus (luteal) phase, prolonged proestrus-oestrus (ovulatory) phase and reduced the number of cycles as well. The authors report that despite there were signs of fetotoxicity recorded in GN4 group, no evidence of foetal malformations was observed. The gross developmental toxicity was evident with growth retardation, reduced pup weight, and delayed in the crown-rump length. No significant adverse effects were noticed in the 250 and 500 mg/kg/day dose group.

Constituents (in vitro)

Mohammed *et al*. (2016) studied the potential embryotoxicity of 6-gingerol using chick embryonic heart micromass (MM) and Mouse D3 embryonic stem cells (ESD3). Although both these systems are potentially predictive of effects on cardiac cells, they may not directly predict a cardiac malformation. At low to moderate concentrations (0.75–6 μM) 6-gingerol treated primary embryonic chick cardiomyocytes showed no significant changes in; contractile activity, cellular activity or changes in total protein content in comparison to the control ($p>0.05$). At higher 6-gingerol concentrations of 12.5–100 μM, inhibition in contractile activity was observed ($p < 0.05$) at 48 (except for 100 μM) and 144 h of cell culture. All high 6-gingerol concentrations, 12.5–100 μM, tested in MM, significantly altered ($p<0.05$) both the cellular activity and protein content in a dose-dependent manner. The same concentrations (0.75 μM –100 μM) of 6-gingerol were used to treat the ESD3, which showed a significant ($p<0.05$) decrease in cardiomyocyte differentiation for all tested concentrations except 0.75 μM, i.e 1.5 μM and higher. Furthermore, the cellular activity and protein content of stem cell-derived cardiomyocytes followed the same pattern of significant ($p<0.05$) decrease with increased 6-gingerol concentration exposure. The authors conclude that 6-gingerol has the ability to prevent myofibroblast differentiation and may be considered as a cytotoxic teratogen for growing foetal cardiomyocytes at high levels and for stem cell differentiation at any level.

Male fertility

Several studies have been conducted into the effects of ginger on testosterone levels and sperm quality. Results from studies on the effects of ginger on testosterone have been reviewed by Banihani (2018). Most of these studies were conducted on diabetic rat models and showed a positive effect on testosterone production. Banihani also reviewed the effect of ginger on semen quality and draw the conclusion that ginger enhances semen quality and improves the main sperm parameters such as concentration, viability, motility and morphology (Banihani 2019).

Ginger rhizome (in vivo)

In a study in which rats were administered ginger rhizome powder in daily dosages of 50 and 100 mg/kg for 20 days did not demonstrate any changes in morphology or weight of testes compared

to control rats; however, serum testosterone levels increased in the experimental group that received 100 mg ginger/kg/day (Khaki *et al.* 2009). Besides, the percentage of sperm viability and motility in both test groups significantly increased in comparison to the control group, whereas, LH, FSH, and sperm concentration in both experimental and control group were similar.

Extracts (in vivo)

To examine possible androgenic effects an aqueous extract of ginger root was administered orally for 8 consecutive days in a daily dosage of 600 mg/kg to male Wistar rats (Kamtchouing *et al.* 2002). The rhizome was shade dried at room temperature and crushed to powder. The powder (125 g) was macerated in 200 ml of distilled water for 12 h at room temperature and then filtered to obtain the final aqueous extract (concentration: 120 mg/ml) for use in the experiment. The treated group was gavage 2 ml of the plant extract (corresponding to 600 mg/kg). Compared to control rats ginger root extract caused a significant increase in testicular weight, and increased levels of testosterone and cholesterol in the testicles and α-glucosidase in the epididymis.

Assessor's comment:
Findings of advanced skeletal development have been reported in one study in rats (Wilkinson 2000) and increased embryo resorption in another study rats (Dissabandara and Chandrasekara 2007). In the absence of any maternal toxicity or gross foetal toxicity or defects, the studies are difficult to interpret.
From the study by ElMazoudy and Attia on an aqueous ginger extract, no adverse effects were shown on oestrous cycle and implantation in mice at doses up to 500 mg/kg daily for 35 and 20 days, respectively. At high doses of 2000 mg/kg daily, maternal toxicity was observed as well as a reduced number of live foetuses, increased foetal death and resorption and decreases in implantation sites. By using allometric factors in line with the "Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products" (EMEA/CHMP/SWP/28367/07 Rev. 1), a human equivalent dose (HED) in mg/kg can be calculated when using factors derived from the "Guideline for Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (FDA, 2005). To convert the dose in mice the factor 0.081 is recommended resulting in a HED of 162 mg/kg. For an adult human (50 kg) this would correspond to 8100 mg of the aqueous ginger extract.
One repeated dose toxicity study in rats (Kamtchouing et al. 2002), 600 mg/kg per day of an aqueous extract of ginger root demonstrated increased testicular weight and increased levels of testosterone in the testes. Another study (Khaki et al. 2009), in which rats were administered ginger rhizome powder in daily dosages of 50 and 100 mg/kg for 20 days, did not demonstrate any changes in morphology or weight of testes compared to control rats. On the other hand, the studies reported by Banihani (2018; 2019) and Habeeb et al. (2019) reported improvements on fertility in diabetic male rats and heat affected female rabbits upon receiving ginger extracts.

3.3.6. Local tolerance

Not available.

3.3.7. Other special studies

Not available.

3.3.8. Conclusions

Results from acute toxicity and repeat dose toxicity studies are not consistent and show that doses required to induce potentially toxic effects are rather high, normally higher than what would be administred to humans.

Tests on genotoxicity for the herbal preparations included in the monograph are missing. There are no guideline compliant genotoxicity studies on dried ginger rhizome or preparations from ginger rhizome.

Available non-guideline compliant reproductive toxicity studies are inconclusive. While in some rodent studies, effects (mainly embryo resorption and advanced skeletal development, no further malformation) with and without maternal toxicity were found, one rat study show no adverse effects. Different preparations, animal species and experimental settings were used in these studies.

Overall, with the limited data available it is difficult to draw any firm conclusions especially regarding genotoxicity (and therefore carcinogenicity) and reproductive and developmental toxicity.

3.4. Overall conclusions on non-clinical data

Many non-clinical pharmacological studies have reported that ginger, preparations thereof and its constituents display many properties *in vivo* and *in vitro*. However, results from relevant non-clinical pharmacodynamic studies on preparations included in the monograph are limited. Several of the studies have been performed using extracts not included in the monograph. Hence, the clinical relevance of these non-clinical studies is considered not known.

In some non-clinical mechanistic studies effects on specific pathways associated with antithrombotic activity have been shown. One *in vivo* study suggested an interaction with dabigatran, while another *in vivo* study did not show an interaction with warfarin. The risk of bleeding events and interactions with anticoagulants are further assessed in chapter 5 "Clinical safety".

The results from non-clinical studies (*in vitro* and *in vivo*) indicate that ginger and its constituents may inhibit CYP450 enzymes 1A2, 2C9, 2C19 and 3A4 and P-glycoprotein mediated transport. The clinical relevance of the results from these non-clinical studies is not known and further studies are needed.

Results from repeat dose toxicity studies are not consistent and show that doses required to induce potentially toxic effects are rather high, normally far higher than what would be administered to humans.

Tests on genotoxicity for the herbal preparations included in the monograph are missing. There are no guideline compliant genotoxicity studies on dried ginger rhizome.

Available, non-guideline compliant reproductive toxicity studies are inconclusive. While, in some rodent studies, effects (mainly embryo resorption and advanced skeletal development, no further malformation) with and without maternal toxicity were found, one rat study show no adverse effects. Different preparations, animal species and experimental settings were used.

Overall, toxicity studies (non-guideline compliant) of ginger rhizome regarding genotoxicity, carcinogenicity and reproductive and developmental toxicity have not been performed. With the limited guideline compliant data available it is difficult to draw any firm conclusions especially regarding genotoxicity and reproductive and developmental toxicity. The following text is included in the monograph section 5.3:

"Adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

Studies in mice and rats showed inconsistent results.

Repeat dose studies in pregnant rodents showed increased embryo resorption after dosing of ginger powder or aqueous extracts. The doses used are comparable to a range from slightly above to a few times higher than human therapeutic dosage. At higher doses, advanced skeletal development, maternal toxicity, a reduced number of live foetuses and implantation sites was observed. Another study in rats dosed with an ethanolic extract of ginger showed no adverse effects.

In male rats, increases in testicular weight and levels of testosterone were observed after 8 days treatment with an aqueous ginger extract at doses comparable to roughly twice human therapeutic doses."

4. Clinical Data

4.1. Clinical pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Nausea and vomiting

In a placebo-controlled, double-blind, cross-over study in 12 male volunteers, Micklefield *et al*. (1999) reported that inter-digestive antral motility of the stomach during phase III of the migrating motor complex and the motor response to a test meal in the corpus measured by stationary manometry were stimulated by ginger (200 mg of ginger rhizome extract) in both the fasting and postprandial states. However, a randomised, placebo-controlled, cross-over study by Phillips *et al*. (1993) did not observe an impact on gastric emptying rate in 16 healthy volunteers using the oral paracetamol absorption technique (without an accompanying nutrient load) after 1 g of powdered ginger, suggesting that ginger, although increasing motility, may not affect the gastric emptying rate.

A total of 28 volunteers participated in a non-blinded study by Stewart *et al*. (1991) designed to evaluate the anti-motion sickness activity of ginger root and to characterise the effects of ginger on gastric function. Subjects made timed head movements in a rotating chair (blind-folded and for some subjects in a drum with alternating black and white stripes = combined) until they reached an endpoint of motion sickness short of vomiting (malaise III (MIII) on the Graybiel scale of motion sickness symptoms). In the first study, 8 subjects received 500 mg or 1000 mg of dried ginger root, 0.6 mg of scopolamine or lactose on separate days. All tests were conducted at weekly intervals. Eight additional subjects were evaluated for motion sickness after taking a capsule with 1000 mg of ground fresh ginger or lactose. Neither powdered ginger nor fresh ginger increased the number of head movements to reach the MIII compared to lactose. In contrast, subjects administered scopolamine tolerated significantly more head movements than subjects on placebo. In a third test, ground ginger (940 mg) was tested using combined (visual and vestibular) emetic stimuli. Gastric emptying was measured using nuclear medicine techniques, and electrogastrography (EGG) was measured by cutaneous electrodes positioned over the abdominal area in 8 subjects. When tested 15 minutes after MIII gastric emptying was slowed compared to under non-motion sick conditions, but did not differ for ginger and control treatments. During motion sickness, ginger inhibited the increased EGG frequency (tachygastria) which occurred after MIII; however, ginger did enhance the EGG amplitude in motion sick subjects.

Lien *et al*. (2003) studied the effect of ginger on gastric dysrhythmias (that are involved in the pathogenesis of motion sickness) and nausea in 13 volunteers with a history of motion sickness who underwent circular vection in a cross-over design, double-blind, placebo-controlled study. Cutaneous EGG was recorded for 15 minutes before vection. Subjects ingested 1000 or 2000 mg ginger capsules

or a placebo of identical appearance 1 hour before circular vection studies were initiated. At least 3 days separated the 3 vection episodes. At 30 minutes post-prandially the subject was seated in the centre of a drum, the interior of which was painted with alternating black and white stripes. After a basal 15 minutes EGG-recording the drum was rotated for 15 minutes or until the subject reported severe nausea. After cessation of drum rotation, the subject remained in the drum for another 15 minutes during which EGG was recorded. Tachygastric activity increased during vection, however ginger reduced tachygastric activity compared to placebo and ginger reduced the duration of tachygastria compared to placebo.

Wu *et al*. (2008) conducted a randomised double-blind, placebo-controlled, cross-over study to examine the effect of ginger on gastric emptying and motility in 24 healthy volunteers. Ultrasonic measurements of antral area, proximal gastric dimensions and antral contractions were performed, and the gastric half-emptying time was calculated from the change in antral area. Following a fast for 8 hours, volunteers took 3 capsules (total 1200 mg) of powdered ginger or 3 identical placebo capsules containing starch. One hour later volunteers consumed 500 ml chicken and corn soup. Gastric ultrasonic measurements were performed before study and at frequent intervals for 90 minutes after meal ingestion. The authors report that ginger markedly accelerated the gastric emptying of the soup meal (half-emptying time with ginger vs. placebo was 13.1±1.1 min vs. 26.7±3.1 min; $P<0.01$). Ginger also reduced post-prandial antral area and stimulated antral contractions when compared with placebo. Fundus dimensions were not affected by ginger.

The effect of the intake of 1 g of dried ginger powder suspended in 100 ml of water on lower oesophageal sphincter pressure and oesophageal peristalsis by manometry was studied in 14 healthy young men in a randomised, controlled study (Lohsiriwat *et al*. 2010). Subjects drank 100 ml of water as a control, then performed 5 wet swallowings at 30 minutes after the drink, followed by drinking the ginger suspension and performed 5 wet swallowings every 30 minutes thereafter for 180 minutes. The study showed that the lower oesophageal sphincter pressure remained unchanged; however, the percent relaxation at swallowing was increased throughout the 180 minutes. The amplitude and duration of oesophageal contractions were not changed, while the velocity of contraction waves was decreased at 30, 120, 150 and 180 minutes suggesting a greater likelihood of gastric gas expel or anti-flatulent effect.

Hyperglycaemia delays gastric emptying and induces slow wave dysrhythmias. A double-blind, placebo-controlled study in 22 healthy volunteers showed that oral intake of 1 g of ginger root powder effectively prevented the induction of slow wave dysrhythmias induced by hyperglycaemic clamping (Gonlachanvit *et al*. 2003). Ginger had no effect on slow wave rhythm disruptions elicited by the prostaglandin E1 inhibitor misoprostol, suggesting that ginger acts to blunt production of endogenous prostaglandins rather than inhibit their action.

A placebo-controlled, cross-over (with a wash-out period of 48 hours), double-blind study including 8 healthy volunteers investigated the effect of powdered ginger root upon nystagmus following caloric stimulation of the vestibular system (Grøntved and Hentzer 1986). Ginger, 1 g, and placebo (lactose), 1 g, was administered one hour prior to irrigating the ear with 44°C warm water 3 times at 20 minutes intervals and the provoked nystagmus was recorded with electronystagmography. Ginger root did not have any effect on the duration of nystagmus and the maximum slow phase velocity, and thus did not seem to affect the vestibular system. The degree of vertigo was also examined, by using a Likert scale (1-5), after irrigation. The authors report that the study showed that ginger root reduced vertigo better than placebo.

In a placebo-controlled, cross-over, double-blind study, the effect of ginger and dimenhydrinate was studied for their effects on experimentally induced nystagmus in 38 subjects (Holtmann *et al*. 1989). The dosages were: powdered ginger root, 1000 mg, and dimenhydrinate, 100 mg, administered 90

minutes before commencing the stimuli: an optokinetic test (optokinetic nystagmus); a caloric test (vestibular nystagmus); and a rotatory test (combined optokinetic and vestibular nystagmus). The wash-out period between study days was 2 weeks. The authors conclude that the results demonstrated that powdered ginger did not affect nystagmus responses compared to placebo, while expectedly dimenhydrinate reduced nystagmus responses compared to placebo and ginger.

To evaluate the effects of ginger on gastric motility and emptying, abdominal symptoms, and hormones that influence motility in dyspepsia, eleven patients with functional dyspepsia were studied twice (two afternoons separated by at least 7 days) in a randomized double-blind manner. After an 8-h fast, the patients ingested three capsules that contained 400 mg ginger root powder (total 1.2 g) or placebo, followed after 1 h by 500 mL low-nutrient soup. Antral area, fundus area and diameter, and the frequency of antral contractions were measured using ultrasound at frequent intervals, and the gastric half-emptying time was calculated from the change in antral area. Gastrointestinal sensations and appetite were scored using visual analogue questionnaires, and blood was taken for measurement of plasma glucagon-like peptide-1 (GLP-1), motilin and ghrelin concentrations, at intervals throughout the study. The authors report that gastric emptying was more rapid after ginger than placebo (median (range) half-emptying time 12.3 (8.5-17.0) min after ginger, 16.1 (8.3-22.6) min after placebo, $P \leq 0.05$). Fundus dimensions and gastrointestinal symptoms did not differ, nor did serum concentrations of GLP-1, motilin and ghrelin (Hu *et al*. 2011).

Mowrey and Clayson (1982) performed a study of experimental motion sickness when they induced motion sickness by placing 36 susceptible undergraduate students blindfolded in a tilted rotating chair. The subjects were unaware of the purpose of the experiment. The subjects were randomly assigned to each of 3 groups: 2 gelatine capsules (940 mg) of powdered ginger, 100 mg dimenhydrinate or 2 capsules of powdered chickweed herb (placebo). The time between swallowing the pills and the rotating chair experiment was 20-25 minutes. The subjects were asked to tell the investigators by using numbers how intense the feelings in their stomach were. The experiment was stopped if the subject vomited, or if he requested it to be stopped, or if there was a 3-fold increase in the magnitude estimation on 3 consecutive occasions or after 6 minutes. The mean magnitude estimations (gastrointestinal sensations) increased most rapidly in the placebo group, followed by those in the dimenhydrinate group, while the ginger group rose only slowly. The authors conclude that the results showed that differences between the mean magnitude estimations of the 3 groups were significantly different as were the mean times in the tilted rotating chair in favour of ginger.

Wood *et al.* (1988) used the rotating chair in combination with timed head movements to provoke experimental nausea in healthy subjects. Three dosages of ginger were administered: 500 mg of powdered ginger, 1000 mg of powdered ginger and 1000 mg of fresh ginger. The powdered ginger was given 2 hours prior to testing; however, the minced fresh ginger was tested 30 minutes after ingestion. Seven groups of 8 subjects were tested, and each subject received 3 test medications (several other drugs and drug combinations were tested) and a placebo. The motion sickness endpoint was determined using the Graybiel scale of motion sickness symptoms. According to the authors, the results showed that the 3 ginger doses were not significantly different from placebo.

Assessor's comment:
The pathophysiology of nausea and vomiting is not entirely known. Several peripheral and central stimuli may provoke nausea and vomiting, which may occur independently, however both involve a central nervous system response using the same neural pathways to and from the area postrema and chemoreceptor trigger zone in the medulla oblongata. Once activated, regardless of the trigger, a gastrointestinal response, with ejection of the stomach and small intestine contents often follows. In pharmacodynamic studies powdered ginger seems to modify gastro-intestinal motility.

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Zick *et al*. (2008) recruited 27 healthy volunteers to perform a single dose pharmacokinetic escalation study of the ginger constituents 6-gingerol, 8-gingerol, 10-gingerol and 6-shogaol. Two-hundred-and-fifty mg of the dry extract of ginger root used in the study was standardised to 15 mg of total gingerols, with 5.38 mg 6-gingerol, 1.28 mg 8-gingerol, 4.19 mg 10-gingerol, and 0.92 mg 6-shogaol. Dose levels were 100 mg, 250 mg, 500 mg, 1.0 g, 1.5 g and 2.0 g, and 3 participants were assigned to each dose level except for the 1.0 g (n = 6) and 2.0 g (n = 9) dose level. Blood samples were taken at 15, 30, and 45 minutes as well as 1, 2, 4, 6, 10, 24, 48 and 72 hours after intake of ginger. The results showed that no free 6-gingerol, 8-gingerol, 10-gingerol, or 6-shogaol was detected in the blood. With the exception of 6-gingerol, the analytes were not well absorbed, with no detectable conjugate metabolites below the 1.0 g ginger extract dose. All 4 analytes were, however, quickly absorbed and could be detected as glucuronide and sulfate conjugates, with the majority being glucuronide conjugates. Ginger conjugates began to appear 30 minutes after intake, reaching their T_{max} between 45 minutes and 120 minutes with elimination half-lives ranging from 75 minutes to 120 minutes at the 2 g dose. The maximum blood concentrations were reached at either the 1.5 g or 2.0 g dose and were 1.69 µg/ml for 6-gingerol, 0.23 µg/ml for 8-gingerol, 0.53 µg/ml for 10-gingerol, and 0.15 µg/ml for 6-shogaol. Because of the low levels of absorption, the participants receiving the highest dose did not have adequate detectable concentrations after C_{max} to reliably calculate the elimination half-life. Consequently, no pharmacokinetic model was able to be constructed, and the pharmacokinetic parameters were based on non-compartment analysis with an elimination half-life only presented for the 2.0 g dose.

Yu *et al*. 2011, studied the pharmacokinetics of 6-, 8-, and 10-gingerols and 6-shogaol and their glucuronide and sulfate metabolites in nine healthy volunteers after a 2-g oral dose of ginger extract (250-mg dry extract of ginger root contained 6.60 mg (2.64%) 6-gingerol, 1.58 mg (0.63%) 8-gingerol, 3.05 mg (1.22%) 10-gingerol, and 5.63 mg (2.25%) 6-shogaol). Blood was drawn from the participants at baseline, 0.25, 0.5, 0.75, 1, 2, 4, 6, 10, 24, 48, and 72 h after ingestion of the ginger extracts. Free 10-gingerol and 6-shogaol were detected in plasma with peak concentrations 9.5 and 13.6 ng/mL, respectively at 1 h after oral administration, but no free 6-gingerol and 8-gingerol were detected in plasma. The terminal half-lives of 10-gingerol and 6-shogaol were 2.1 and 1.3 h, respectively. The peak concentrations of glucuronide metabolites of 6-, 8-, and 10-gingerols and 6-shogaol were 0.47, 0.17, 0.37, and 0.73 µg/mL at 1 h, respectively and of the sulphate metabolites 0.28, 0.027, 0.018, and 0.047 µg/mL at 1 h, respectively. Pharmacokinetic analysis showed that half-lives of these four analytes and their metabolites were 1–3 h in human plasma. No accumulation was observed for 6-, 8-, and 10-gingerols and 6-shogaol and their metabolites in both plasma and colon tissues after multiple daily dosing.

Assessor's comment:
The pharmacokinetics of 6-, 8-, and 10-gingerols and 6-shogaol and their metabolites has been studied in healthy volunteers after oral administration of a dry extract of ginger root. At a dose of 2 g dry extract, free 6-gingerol and 8-gingerol could not be detected in plasma and free 10-gingerol and 6-shogaol only at very low nanomolar-concentrations with Tmax at 1 h after administration. Glucuronide- and sulfate-conjugates of the ginger phenolics (GPs) are rapidly formed, reaching Tmax between 45 minutes and 120 minutes. The maximal blood concentration (Cmax) of conjugates of the different GPs ranged from 0.2 to 1.7 µg/mL, with the highest levels of 6-gingerol conjugates. The elimination half-lives (T½) of the four GPs and their metabolites were 1–3 h in human plasma. Since the active constituents of ginger have not been established, the clinical relevance of pharmacokinetic data of gingerols and shogaol is not known and will not be included in the monograph.

4.2. Clinical efficacy

There are numerous clinical studies performed with ginger. In accordance with the guideline 'Assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products' (EMA/HMPC/104613/2005 – Rev. 1), the assessment of well-establish use should also include if the products reported for more than 10 years in the market overview can be considered as similar to the product studied in relevant clinical studies found in the literature (see chapter 2.1.1. 'Information about products on the market in the EU/EEA Member States'). Therefore, the scope of the assessment in this section is prevention/relief of nausea and vomiting in motion sickness, mild forms of vomiting and nausea in early pregnancy (up to week 16), and mild spasmodic gastrointestinal complaints. Only studies related to these indications are included below.

Beside these investigations, ginger preparations have been tested for clinical efficacy for instance in postoperative nausea and vomiting, chemotherapy-induced nausea and vomiting, rheumatic pain, osteoarthritis, dysmenorrhoea, diabetes, obesity, hypertension, and migraine. There is no information available that dried ginger root products have been in medicinal use for more than 10 years in EU in these indications (see chapter 2.1.1. 'Information about products on the market in the EU/EEA Member States'). Thus, these studies will not be considered for a well-establish use monograph.

4.2.1. Dose response studies

In the study by Lien *et al*. (2003), 13 volunteers with a history of motion sickness who underwent circular vection (study design already presented in chapter 4.1.1) ingested 1000 or 2000 mg ginger capsules or a placebo of identical appearance 1 hour before circular vection studies were initiated. Subjects were asked to report the first sensation of nausea and to describe the severity of nausea on a 4-point Likert scale. The time to first perception of mild nausea after vector initiation and the duration of nausea after vector cessation were recorded. The subjects were also asked to evaluate the severity of nausea at different time-points after vection on a 100 mm Visual Analogue Scale (VAS). The authors report that the maximal nausea score in the control study was 2.5±0.2 and that ginger pre-treatment of 1 or 2 g reduced the maximal nausea score to 1.7±0.3 and 1.8±0.2, respectively ($P<0.05$). In addition, the authors report that ginger prolonged latency before nausea onset, and it took subjects longer time to overcome nausea during placebo than during ginger.

4.2.2. Clinical studies (case studies and clinical trials)

Motion sickness

In a randomised, double-blind, placebo-controlled trial in Denmark, Grøntved *et al.* (1988) examined the effect of ginger on seasickness in 80 naval cadets, unaccustomed to sailing in heavy seas. A few days after the cruise had started when the ship met heavy seas for the first time, the study was carried out. Half of the cadets received 1 g of powdered ginger and the other half 1 g of lactose. Every hour for the next 4 hours the cadets noted the following symptoms of seasickness: nausea (score 0-3), vertigo (score 0 - 2), vomiting (score 0-2) and cold sweating (score 0-1). One cadet dropped out. A total of 48 cadets (61%) noted symptoms of seasickness: 16 in the ginger group and 15 in the placebo group reported no symptoms of seasickness. In a distribution made according to the severity of symptoms, ginger showed to be statistically significantly better than placebo in reducing the frequency of vomiting and cold sweating. The severity of nausea and vertigo showed no statistically significant difference between the treatments.

The objective of a study by Schmid *et al.* (1994) was to compare the efficacy of seven drugs frequently used for the prevention of seasickness: cinnarizine, cinnarizine with domperidone, cyclizine, dimenhydrinate with caffeine, meclozine with caffeine, scopolamine and ginger root. The study was double-blind with a partial double dummy method, so that subjects were treated with an active drug and a placebo of one other active substance. No placebo-only group was included. The study was performed in tourists aged 16-65 years participating in a whale safari in Norway. Among 2963 men and women participating in the whale safari, 1741 were recruited and 1475 were fully evaluated. 203 subjects took 500 mg ginger 2 hours before leaving port, and if necessary 4 hours later. The tours lasted approximately 6 hours. Vomiting and retching were used as endpoints and reported as none, slight/moderate, sever/vomiting and vomiting. Symptoms of seasickness were evaluated by a questionnaire using standard Graybiel criteria to be completed after the whale safari. In the various treatment groups 18.2%-26.8% reported at least slight seasickness and 4.1%-10.2% severe symptoms with no significant difference between groups. The authors compare the result with a historical seasickness rate reported to be 80%, without prophylaxis. The authors conclude that ginger showed similar result compared to the other substances included in this study.

Assessor's comment:
The WEU indication "Herbal medicinal product for the prevention of nausea and vomiting in motion sickness" was included in the first version of the monograph published in 2010. The posology in the first version of the monograph was for adults and elderly 1-2 g 1 hour before start of travel. During the first revision of the monograph in 2024 (~15 years later), no new clinical studies to substantiate efficacy in motion sickness were found. However, the quality of available studies in motion sickness included in the first version of the assessment report and the clinical relevance of the results from these studies to substantiate efficacy in motion sickness are considered low in relation to current requirements ('Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products' (EMA/HMPC/104613/2005–Rev. 1). For example, in the two old studies by Grøntved et al. (1988) and Schmid et al. (1994) motion sickness was not an inclusion criteria and subjects with no motion sickness could have been included. Furthermore, there is no information available if the tools used to measure motion sickness had been validated and there is no specification of which group difference should be classified as clinically relevant and thus no calculation of the sample size derived from this. This makes the interpretation of the results of the studies difficult. Furthermore, the posologies are not in compliance with the posologies in the monograph.

Nausea and vomiting in pregnancy (NVP)

Nausea and vomiting in pregnancy (NVP) affect up to 85% of all women during pregnancy which typically begins by the fourth week and disappears by the 16th week of pregnancy. For the majority self-management suffices, but for the remainder, symptoms are more severe and the most severe form of NVP, hyperemesis gravidarum (HG), affects 0.3–1.0% of pregnant women. There is no widely accepted point at which NVP becomes HG. There are medicinal and non-medicinal treatments for nausea and vomiting. Changes in diet or lifestyle are often the first treatments women might try (O'Donnell *et al*. 2016).

For a potential WEU indication, at least 10 years of medicinal use in the EU is a prerequisite for the establishment of a WEU monograph. There is one medicinal product in the EU with comminuted ginger rhizome in mild forms of vomiting and nausea in early pregnancy (up to week 16) since 2010. Therefore, studies in mild forms of vomiting and nausea in early pregnancy (up to week 16) are considered relevant and studies including patients with hyperemesis gravidarum have been excluded. Since the assessment of well-establish use includes if the products reported for more than 10 years in the market overview can be considered as similar to the product studied in relevant clinical studies

found in the literature. Therefore, studies with unknown quality of the active substance have been excluded.

Furthermore, studies with a cross-over design of a study are not usually appropriate when symptoms may not be stable over time and such studies have also been excluded. Also, blinding and placebo comparator may be particularly relevant where the main outcome is subjective, self-reported symptoms.

Overall, there is no pivotal study available to support a WEU MO in mild forms of vomiting and nausea in early pregnancy (up to week 16). In the public domain, five randomised double-blind placebo-controlled studies that have evaluated the efficacy of powdered ginger in mild to moderate NVP in non-EU countries were found i.e. Vutyavanich et al. (2001), Basirat et al. (2009), Saberi et al. (2014), Firouzbakht et al. (2014), and Sharifzadeh et al. (2018). All five studies have methodological problems and are considered of low quality. For example, in Basirat et al. the taste of ginger in a biscuit makes true blinding difficult, in Saberi et al. the baseline data is missing, in Firouzbakht et al. there is a high drop-out rate, in particular in the ginger group, and in Sharifzadeh et al. (2018) the number of included patients at the start of the study is not presented.
In the study by Fischer-Rasmussen et al. (1990), with a cross-over design, patients were diagnosed with hyperemesis gravidarum.

Meta-analyses

Borelli *et al.* (2005) included 6 double-blind randomised studies with oral administration of ginger for the treatment of pregnancy-induced nausea and vomiting (morning sickness and hyperemesis gravidarum). In 4 of the 6 randomised trials, ginger was compared to placebo; the remaining 2 trials ginger was compared to vitamin B_6. The authors conclude that a meta-analysis was deemed impossible due to the different measures used to assess outcome and to the different control groups (placebo and reference drug) in the studies.

Thomson *et al*. 2014 considered six studies fulfilled their main criteria (1) randomized placebo-controlled design; (2) use of ginger or *Zingiberis officinale*; and (3) extractable data on improvement in symptoms. The authors report heterogeneity among the clinical studies and the following limitations of the meta-analysis: there is variability in the dosage and formulation of ginger; the durations of intervention also differed; variation in the combined sample size in the studies; variability of scores used to qualify and quantify outcome measures.

In Viljoen *et al*. (2014), randomised trials at any stage of pregnancy and published in English were included despite lack of blinding or placebo treatment. Any form of orally administered ginger intervention (fresh root, dried root, powder, tablets, capsules, liquid extract, and tea) compared with an inert (placebo) or active ingredient, were included. According to the authors, all studies had high or moderate risk of bias and results from two studies only could be included in a meta-analysis. The authors suggest potential benefits of ginger in reducing nausea symptoms in pregnancy but not the number of vomiting episodes, bearing in mind the limited number of studies, the small sample sizes, difference in dosage and duration, variable outcome reporting and low quality of evidence.

In Matthews *et al*. (2015), the objective of the study was to assess the effectiveness and safety of all interventions (i.e. not only ginger) for symptomatic relief of nausea, vomiting and retching in early pregnancy, up to 20 weeks' gestation. Trials of interventions for hyperemesis gravidarum was excluded. Cross-over trials were also excluded; such design is not usually appropriate during pregnancy when symptoms may not be stable over time. For many women symptoms are likely to resolve over time, particular as the pregnancy progresses beyond the first trimester and therefore, the outcomes were assessed at approx. 3 days after the start of treatment. The use of ginger (prepared as syrup, capsules or powder within biscuits) to relieve nausea was examined in 13 studies. The authors

conclude that the use of ginger products may be helpful to women, but the evidence of effectiveness was limited and not consistent.

O'Donnell *et al*. (2016), in a study aimed to determine the relative clinical effectiveness and cost-effectiveness of treatments for nausea and vomiting in pregnancy and hyperemesis gravidarum, concluded that ginger still looked promising in reducing symptoms, but the findings are not conclusive. Use of ginger was explored in 16 RCTs. Given the differences between trials in patient populations, settings, interventions and, in particular, the heterogeneous nature of the reported outcomes across trials, the authors did not attempt to perform meta-analyses and thus reported a narrative summary only for each intervention and comparator set. The authors report that the overall quality of the evidence was low or very low for all treatment comparisons due to clinical differences between studies, poor and incomplete reporting of outcomes and concerns regarding risk of bias.

Assessor's comment:
Available meta-analyses included a wide variety of ginger preparations and studies with methodological issues.

4.3. Clinical studies in special populations (e.g. elderly and children)

Motion sickness

A double-blind, randomised, parallel-group study compared the anti-motion sickness efficacy of ginger *vs.* dimenhydrinate in 28 children aged 4-8 years with a history of motion sickness (Careddu 1999). Standardised dried ginger root, 250 mg, or identical looking dimenhydrinate, 25 mg, were given. Children 5 years and younger took 1 capsule of ginger or ½ capsule of dimenhydrinate 30 minutes before the start of the trip, then, if necessary 1 or ½ capsule, respectively every 4 hours. Children 6 years and older took 2 capsules of ginger or 1 capsule of dimenhydrinate 30 minutes before the start of the trip, then, if necessary, 2 capsules or 1 capsule, respectively, every 4 hours. Treatment was administered for 2 days during travel with any form of transport (car, boat and airplane). Treatment – and safety – was physician-recorded based on the occurrence of subjective (vertigo, body temperature, headache, increased salivation, stomach ache, nausea and dryness of the mouth) and objective (pallor, cold sweat) symptoms. The authors report that the effect of ginger was found to be better and faster than dimenhydrinate.

Assessor's comment:
This small study has several methodological problems, e.g. the maintenance of double-blindness despite the different dosages employed in the 2 groups, the lack of information on total dosages during day 1 and 2, and the non-validated physician-rated symptom-description after termination of travel.

4.4. Overall conclusions on clinical pharmacology and efficacy

In pharmacodynamic studies powdered ginger seems to modify gastro-intestinal motility. However, results from relevant experimental studies to support the indication in the WEU monograph are limited. Therefore, relevant information on clinical pharmacology to be included in the monograph section 5.1 is missing.

Motion sickness

The WEU indication "Herbal medicinal product for the prevention of nausea and vomiting in motion sickness" was included in the first version of the monograph published in 2010. The posology in the first version of the monograph was for adults and elderly 1-2 g 1 hour before start of travel. During the first revision of the monograph in 2024 (~15 years later), no new clinical studies to substantiate

efficacy in motion sickness were found. However, the quality of available studies in motion sickness included in the first version of the assessment report and the clinical relevance of the results from these studies to substantiate efficacy in motion sickness are considered low in relation to current requirements ('Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products' (EMA/HMPC/104613/2005–Rev. 1). For example, in the two old studies by Grøntved *et al*. (1988) and Schmid *et al*. (1994) motion sickness was not an inclusion criteria and subjects with no motion sickness could have been included. Furthermore, there is no information available if the tools used to measure motion sickness had been validated and there is no specification of which group difference should be classified as clinically relevant and thus no calculation of the sample size derived from this. This makes the interpretation of the results of the studies difficult. Also, there are insufficient data to support the posology in the monograph. However, for regulatory consistency, the preparation and posology are retained in the revision of the WEU monograph. The small study in children aged 4-8 years with a history of motion sickness by Careddu (1999) has several methodological problems, e.g. the maintenance of double-blindness despite the different dosages employed in the 2 groups, the lack of information on total dosages during day 1 and 2, and the non-validated physician-rated symptom-description after termination of travel. Therefore, the efficacy in children has not been substantiated.

Nausea and vomiting in pregnancy (NVP)

There is no published pivotal study available to support a WEU MO in mild forms of vomiting and nausea in early pregnancy (up to week 16).

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

In the table below, references that have studied and reported adverse events following the exposure to dried powdered ginger root and ethanolic extracts have been included. Studies on chemotherapy-induced nausea and vomiting (CINV) have been excluded due to the concomitant use of chemotherapy.

Safety information included in the SmPC of products on the market

Austria

4.5 Drug interactions and other forms of interaction

- A possible prolongation of the bleeding with the simultaneous intake of is controversially discussed for Coumarin-type anticoagulants such as warfarin

4.8 Undesirable effects

- Hypersensitivity reactions (dermal and respiratory tract)

Germany

4.4 Special Warnings and precautions for use

- In case of gallstone disease, contact your doctor before using the medicinal product.
- Increased bleeding tendency. Stop taking this medicinal product, if a surgery is planned. Talk to your doctor to plan the further procedure.
- Increased effect of anticoagulants in case of concomitant use (Shalansky *et al*. 2007). Therefore, talk to your doctor before taking Zingiberis rhizome, because the dosage of the

anticoagulants may be adapted. Close monitoring of the coagulation parameters for up to 14 days after stopping the use of Zingiberis rhizome should be carried out. Bleeding tendency can be increased.

- Zingiberis rhizome can increase the absorption of sulphaguanidine. Therefore these medicinal products must not be used concomitantly.

4.5 Drug interactions and other forms of interaction

- Increased effect of anticoagulants and increased absorption of sulphaguanidine are possible.

Netherlands

4.5 Drug interactions and other forms of interaction

- Ginger may increase bleeding risk if concomittantly used with medicines influencing blood coagulation and have tendency to bleeding as aspirin, anticoagulantia as vitamin K antagonists, heparin, bloodplatelet inhibitors, as clopidogrel, and non-steroid inflammatory inhibitors as aspirin, ibuprofen and naproxen.

4.8 Undesirable effects

- blood/lymfe system: not known, 1 case report concerning inhibiton of platelet aggregation after consumption of large amounts of ginger marmalade

Table 6: Clinical safety data from clinical trials.

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, gender, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Adverse events (AE)**	**Comments on clinical relevance of results**
Studies in mild to moderate nausea and vomiting in pregnancy (NVP)						
To study efficacy of powdered ginger root in hyperemesis gravidarum Fischer-Rasmussen *et al*. 1990 Denmark	Double-blind, randomised, placebo-controlled, cross-over study	Capsules of powdered ginger or placebo 250 mg x 4 for 4 days 2 days wash-out period	30 3 drop outs, 2 did not take the capsules according to the study protocol and 1 ha a gallstone diagnosed.	Women admitted for hyperemesis gravidarum before the 20th week of gestation. Other antiemetic medication was withdrawn, but parenteral fluids (dextrose, dextrose-saline) were allowed.	No side effects were observed during the study. Pregnancy outcome: 1 patient had spontaneous abortion week 12 and 1 patient had a legal abortion. Mean birth weight: 3585 g (2450-5150 g); mean gestational length: 39.9 weeks (36-41 weeks). All infants were without deformities and all had Apgar scores of 9-10 after 5 min.	There are no safety issues detected from the reported pregnancy outcomes. In the monograph, as a precautionary measure it is preferable to avoid the use during pregnancy.
To determine the effectiveness	Randomised, double-blind,	Powdered ginger made from fresh root, baked at 60°C	70 randomised Ginger n=32	Patients with NVP before week 17	Ginger: Headache, n=6 (19 %)	Headache was the only adverse event reported in the ginger group with a

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of ginger for NVP Vutyavanich *et al*. 2001 Thailand	placebo-controlled	for 24 h and then ground or placebo 250 mg x 4 for 4 days	Placebo n=38 3 drop outs in the placebo group		Placebo: Headache, n=5 (14 %); Abdominal discomfort, n=1; Heartburn, n=1; Diarrhoea, n=1 Pregnancy outcome: Ginger: Spontaneous abortion, n=1 (3.1 %); Term delivery, n=31 (91.4 %); Caesarean deliveries, n=6 (18.8 %). Placebo: Spontaneous abortion, n=3 (8.6 %); Term delivery, n=32 (96.9 %); Caesarean deliveries, n=4 (11.4 %). No infants had congenital malformations.	similar frequency as in the placebo group. Study with unknown quality of ginger from a non-EU country. There are no safety issues detected from the reported pregnancy outcomes. In the monograph, as a precautionary measure it is preferable to avoid the use during pregnancy.
To investigate the effect of ginger extract on the symptoms of	Randomised, double-blind, placebo-	Commercial ginger extract (EV.EXT35) or placebo	120 randomised Ginger n=60 Placebo n=60	Patients less than 20 weeks pregnant with morning sickness daily for at least a week and	Exclusions due to AE: Ginger: Spontaneous abortion, n=3; Intolerance to	3 spontaneous abortion was reported in the ginger group vs. 1 in the placebo group.

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morning sickness Willetts *et al*. 2003 Australia	controlled study	125 mg x 4 (125 mg = 1.5 g of dried ginger) for 4 days	21 drop outs due to adverse events (n=12) and non-compliance (n= 9) Analysed: Ginger n=48 Placebo n=51	failed to respond to dietary measures Average gestation period 9 weeks	treatment, n=4; Worsening of symptoms, n=3; allergic reactions, n=1. Placebo: Spontaneous abortion, n=1; Worsening of symptoms, n=2. Pregnancy outcome, n=81: Rates of birth defects were similar to the general population and were all minor.	Study with ginger extract from a non-EU country. There are no safety issues detected from the reported pregnancy outcomes. In the monograph, as a precautionary measure it is preferable to avoid the use during pregnancy.
To estimate whether the use of ginger to treat nausea or vomiting in pregnancy is equivalent to pyridoxine hydrochloride (vitamin B6)	Randomised, controlled study	Ginger (no further information available) 350 mg x 3 or vitamin B6 25 mg x 3 for 21 days	291 randomised Ginger group n=146 Day 21 n=120 i.e. 26 drop outs Vitamin B6 n=145 Day 21 n=115 i.e. 30 drop outs	Patients with nausea or vomiting between 8 and 16 weeks pregnant Patients could continue to use any existing medication or other measures other than ginger or vitamin B6 during the trial. 75 (25%) reported using	Ginger: Retching, 52 %; Vomiting, 2 %; Burning sensation, 2 %; Belching, 9 %. Placebo: Retching, 56 %; Vomiting, 1 %; Burning sensation, 2 %; Belching, 0 %. Significant difference for belching.	Gastrointestinal disorders are included in the monograph. Study with unknown quality of ginger from a non-EU country. There are no safety issues detected from

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, gender, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Adverse events (AE)	Comments on clinical relevance of results
Smith *et al*. 2004 Australia				an antiemetic; these included metoclopramide (78%), prochlorperazine (12%), promethazine theoclate (5%), and ondansetron (4%). There were no differences in the use of medication between groups, and no data were available on the dosage used.	Pregnancy outcome: Ginger: Spontaneous abortion, n=3; Stillbirth, n=0; Neonatal death, n=0; Preterm birth, n=5. Congenital abnormalities: Cardiovascular, n=0; Gastrointestinal, n=1; Urogenital, n=2. Placebo: Spontaneous abortion, n=9; Stillbirth, n=3; Neonatal death, n=0; Preterm birth, n=3. Congenital abnormalities: Cardiovascular, n=1; Gastrointestinal, n=1; Urogenital, n=4. No difference in congenital abnormalities reported.	the reported pregnancy outcomes. In the monograph, as a precautionary measure it is preferable to avoid the use during pregnancy.

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, gender, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Adverse events (AE)	Comments on clinical relevance of results
					No difference in overall risk of pregnancy complications reported.	
To compare the effectiveness of ginger and vitamin B6 for treatment of nausea and vomiting in pregnancy. Chittumma *et al*. 2007 Thailand	Randomised, double-blind, controlled study.	Powdered ginger made from fresh root, dried and ground 650 mg x 3 or vitamin B6 25 mg x 3 for 4 days	126 randomised Ginger group n=63 Vitamin B6 n=63 3 drop outs, 2 in the ginger group, 1 in the vitamin B6 group	Patients with a gestational age of < 16 weeks who had nausea and vomiting, required anti-emetics, had no medical complication, and were not hospitalized	Ginger: Total AE, n=16 (25.4 %); Heartburn, n=8 (12.7 %); Sedation, n=7 (11.1 %); Arrhythmia, n=1 (1.6 %). Placebo: Total AE: n=15 (23.8 %); Heartburn, n=2 (3.2 %); Sedation, n=11 (17.5 %); Headache, n=2 (3.1 %).	Heartburn was more frequently reported in the ginger group. Gastrointestinal disorders are included in the monograph. One case of arrhythmia is reported in the ginger group. Study with unknown quality of ginger from a non-EU country.
To study the efficacy of ginger and dimenhydrinate in the treatment of	Randomised, double-blind, parallel-group, controlled study	Ginger powder 500 mg x 2 or dimenhydrinate 50 mg x 2 for 7 days	170 randomised Ginger group n=85 Dimenhydrinate group n=85	Patients less than 16 weeks of gestation attending an antenatal clinic with symptoms of nausea and vomiting	Ginger: Drowsiness, n=5 (6 %); Heartburn, n=13 (16 %). Dimenhydrinate: Drowsiness, n=66 (78	Heartburn was reported in both groups with the frequency: common (≥1/100 and <1/10). Gastrointestinal

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nausea and vomiting in pregnancy Pongrojpaw *et al*. 2007 Thailand			19 drop outs, 8 in the ginger group and 11 in the		%); Heartburn, n=9 (11 %). Significant difference for drowsiness No other adverse effect was observed in both groups during the one-week follow up.	disorders are included in the monograph. Study with unknown quality of ginger from a non-EU country.
To determine the effectiveness of ginger in biscuit form for the treatment of NVP Basirat *et al*. 2009 Iran	Randomised, double-blind, placebo-controlled	Powdered ginger incorporated in biscuit 500 mg x 5 or placebo for 4 days Time of consumption was based on patient's demand, especially when they experienced nausea.	65 randomised Ginger n=35 Placebo n=30 3 drop-outs in the ginger group due to its hot spicy taste	Patients with nausea and vomiting of pregnancy being between 7 and 17 weeks of gestation. No subjects in this trial took any other medications for nausea or vomiting as rescue dose.	No side effects in the placebo group whereas in ginger group one patient (3.12%) complained from dizziness and one (3.12%) from heartburn due to ginger biscuit, which were mild and did not result in stopping consumption. No abnormal pregnancy and delivery outcome occurred and no infants had any	Heartburn and dizziness reported in the ginger group. Gastrointestinal disorders are included in the monograph. Study with unknown quality of ginger from a non-EU country. There are no safety issues detected from the reported pregnancy outcomes. In the monograph,

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, gender, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Adverse events (AE)	Comments on clinical relevance of results
					congenital abnormalities recognized and all were discharged in good condition.	as a precautionary measure it is preferable to avoid the use during pregnancy.
To compare the effectiveness of ginger compared to acupressure in the treatment of NVP Saberi *et al*. 2013 Iran	Randomised, open, controlled 3-armed study.	The first 3 days, no interventions. The following 4 days: Ginger 250 mg x 3 (Zintoma, Goldaroo manufacturing Pharmaceutical Company) or acupressure wristband or control group no intervention	159 randomised Ginger group n=53 3 drop outs 50 analysed Acupressure group n=53 5 drop outs 48 analysed Control n=53 8 drop outs 45 analysed	Pregnant women with symptoms of mild to moderate nausea and/or vomiting before 16 weeks gestational age	One patient reported heartburn when she took the ginger capsules.	One patient in the ginger group dropped out due to heartburn. No other information on adverse events is included in the reference. Gastrointestinal disorders are included in the monograph. Study with unknown quality of ginger from a non-EU country.
To assess the effectiveness of ginger in the treatment of nausea and	Randomised, controlled, 3-armed study	The first 3 days, no interventions. The following 4 days: Ginger 250 mg x 3 (Zintoma, Goldaroo	120 randomised Ginger group n=40 Drop outs 3	Pregnant women with symptoms of mild to moderate nausea and vomiting before 16 weeks gestation.	One patient reported heartburn when she took the ginger capsules.	One patient in the ginger group dropped out due to heartburn. No other information on adverse events is

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, gender, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Adverse events (AE)	Comments on clinical relevance of results
vomiting in pregnancy. Saberi *et al*. 2014 Iran	No information on blinding.	manufacturing Pharmaceutical Company) or placebo or control group with no intervention for 4 days	Assessed n=37 Placebo group n=40 Drop outs 4 Assessed n=36 Control group n=40 Drop outs 7 Assessed n=33			included in the reference. Gastrointestinal disorders are included in the monograph. Study with unknown quality of ginger from a non-EU country.
To investigate the effect of ginger in nausea and vomiting during pregnancy in comparison with vitamin B6 and placebo. Firouzbakht *et al*. 2014 Iran	Randomised, double blind, placebo controlled, 3-armed study	Ginger 250 mg x 4 (Zintoma, dry powder Zingiber rhizome) Vitamin B6 40mg x 4 Placebo for 4 days	120 randomised 23 drop outs Ginger group n=40 Drop outs 16 Assessed n=24 Vitamin B6 group n=40 Drop outs 5 Assessed n=35 Placebo group n=40	Subjects of age 18–35 years, gestational age <20 weeks and experiencing nausea with or without vomiting.	46% of placebo recipients versus 16% of B6 and 27.6% of ginger recipients developed problems such sever nausea and vomiting, stomachache and heartburn during the treatment. Stomachache, heartburn and increased nausea were also reported in 10.2% of ginger recipients.	Stomachache, heartburn and increased nausea were reported in all groups. Gastrointestinal disorders are included in the monograph. Study with unknown quality of ginger from a non-EU country.

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, gender, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Adverse events (AE)	Comments on clinical relevance of results
			Drop outs 12 Assessed n=28			
Studies in postoperative nausea and vomiting (PONV)						
To study the efficacy of ginger for the prevention of PONV was studied in ASA 1 or 2 patients undergoing gynaecological laparoscopic surgery under general anaesthesia. Arfeen *et al*. 1995 Australia	Randomised, double-blind, placebo controlled trial	Powdered ginger BP 1988 One dosage Regimen 1: Ginger, 500 mg Regimen 2: Ginger, 1000 mg Regimen 3: Placebo All patients received diazepam 10 mg as oral pre-medication. Pre-medication and test drugs were administered 1 hour before induction of anaesthesia with thiopentone followed by vecuronium. Postoperative pain was treated by	108 randomised Regimen 1: Ginger, 500 mg; n=36 Regimen 2: Ginger, 1000 mg; n=36 Regimen 3: Placebo; n=36	ASA 1 or 2 women undergoing gynaecological laparoscopic surgery under general anaesthesia.	Regimen 1: Flatulence (n=1); Heartburn (n=1) Regimen 2: Burping (n=1); Heartburn (n=1); Nausea (n=1) Regimen 3: Flatulence (n=1)	Heartburn, burping and nausea were reported in the ginger groups. Flatulence was reported in all groups. Gastrointestinal disorders are included in the monograph. Study with unknown quality of ginger from a non-EU country.

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		administering small intravenous doses of morphine (1-2 mg) as required.				
To study the effectiveness of ginger for prevention of nausea and vomiting after gynecological laparoscopy Apariman *et al*. 2006 Thailand		No information on the quality of ginger. One dosage Regimen 1: Ginger, 1500 mg; n=30 Regimen 2: Placebo; n=30 Ginger or placebo was taken 1 hour before starting the operation. Similar anaesthetic technique and agents were used. Postoperative analgesics were given according to patients' requirements and metoclopramide was given if more than 2	60 randomised Regimen 1: Ginger, 1500 mg; n=30 Regimen 2: Placebo; n=30	Women undergoing gynaecological laparoscopic surgery under general anaesthesia.	Abdominal discomfort, flu-like symptoms, insomnia (NS between groups): Regimen 1: 16.7 % at 2 h and 6.7 % at 6 h postoperatively Regimen 2: 23.3 % at 2 h and 13.3 % at 6 h postoperatively	No difference in adverse events reported between ginger and placebo groups. Study with unknown quality of ginger from a non-EU country.

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		episodes of vomiting occurred.				
Studies in osteoarthritis						
To examine the effect of ginger extract on osteoarthritis. Bliddal *et al*. 2000 Denmark	Randomised, double-blind, controlled study.	Ginger extract (Eurovita Extract 33) Regimen 1: Ginger, 510 mg Regimen 2: Ibuprofen, 1200 mg Regimen 3: Placebo Cross-over study, n=65 For 3 weeks As a rescue drug for pain during wash-out and throughout the rest of the study, acetaminophen was delivered to the patients by the investigators and used in a maximum dosage of 3 grams daily	65 randomised Regimen 1: Ginger, 510 mg Regimen 2: Ibuprofen, 1200 mg Regimen 3: Placebo	Out-patients over 18 years of age with clinical dysfunction and pain due to osteoarthritis and radiologically verified.	A total of 47 AE were reported in 34 patients. AE mainly gastrointestinal Regimen 1 (ginger): Bad taste, n=5; Dyspepsia, n=1; Changes in stool/intestinal trouble, n=1; Nausea, n=1; Conjunctivitis, n=1. Regimen 2 (ibuprofen): Dyspepsia, n=7; Changes in stool/intestinal trouble, n=4; Nausea, n=3; Periorbital oedema, n=1. Regimen 3 (placebo): Dyspepsia, n=1; Changes in	Gastrointestinal AEs were reported. Gastrointestinal disorders are included in the monograph. One case of conjunctivitis was reported in the ginger group.

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, gender, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Adverse events (AE)	Comments on clinical relevance of results
					stool/intestinal trouble, n=6; Nausea, n=1; Skin allergy, n=1. No change in blood haemoglobin.	
Studies in diabetes						
Objective was to assess the effect of ginger consumption on glycemic status, lipid profile and some inflammatory markers in patients with type 2 diabetes mellitus Arablou *et al*. 2014 Iran	A double-blinded, placebo-controlled clinical trial, duration 12 weeks	Dried rhizomes of Z. officinale (from local market) were ground into fine particles and capsules containing 800 mg of powdered ginger were prepared. Dosage per day were 1600 mg of powdered rhizome of ginger (800 mg before lunch and 800 mg before dinner). The intervention lasted for 12 weeks	Seventy patients 30–70 years old, two patients in ginger group and five patients in placebo group were excluded from the study.	type 2 diabetes patients, BMI between 20 and 35 kg/m2, treated with oral hypoglycemic agents, HbA1C between 7% and 10%, no use of tobacco or alcohol, any renal, liver, thyroid and parathyroid disorders, cancer, infection, inflammation, and fever.	One patient in the ginger group was excluded from the study due to heartburn	Heartburn reported in one patient. No further information on adverse events in the reference. Gastrointestinal disorders are included in the monograph. Study with unknown quality of ginger from a non-EU country.

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, gender, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Adverse events (AE)	Comments on clinical relevance of results
The study aimed to evaluate the effects of *Zingiber officinale* on some biochemical parameters in type 2 diabetic (DM2) patients. Mahluji *et al*. 2013 Iran	A randomized double-blind placebo controlled trial duration 2 months	Fresh rhizomes of Z. officinale (from local market) were dried and ground into fine particles. The powder was prepared into tablets containing 1 g ginger in each. Subjects orally received 2 grams of ginger supplementation per day for 2 months.	64 patients with DM2 were assigned to ginger or placebo groups (receiving 2 g/d of each) 4 drop out in the ginger group, 28 patients completed the ginger treatment.	Type 2 diabetic patients	Two patients in the ginger group reported slight heartburn in the beginning of the intervention	Heartburn was reported in the ginger group. Gastrointestinal disorders are included in the monograph. Study with unknown quality of ginger from a non-EU country.
Studies in migraine						
Aim to evaluate the potential of ginger to improve acute migraine as an add-on strategy to standard treatment.	A double-blind placebo-controlled randomized clinical trial.	400 mg of ginger extract divided into two capsules (containing 5% gingerols) in addition to an intravenous drug (100 mg of ketoprofen).	60 patients 30 ginger and ketoprofen Age:32.7±8.8 Female: 26 Male: 4	Patients who sought medical care at the time of migraine attack. Only adults with episodic migraine (one to six migraine attacks per month) with or without aura were included.	Three patients who received ginger extract reported dyspepsia 0.5 h after the medication. One of these patients still had this symptom 2 h after medication. One participant that received placebo reported dizziness 1 h after medication and	Dyspepsia was reported in the ginger group. Gastrointestinal disorders are included in the monograph. Study with unknown quality of ginger

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Martins *et al*. 2019 Brasil			30 placebo and keoprofen Age:34.3±9.1 Female: 26 Male: 4		two patients complained of nausea 1.5 h and 2 h after medication.	from a non-EU country.
Aims to evaluate the efficacy of ginger in the ablation of common migraine attack in comparison to sumatriptan therapy. Maghbooli *et al*. 2014 Iran	Double-blinded randomized clinical trial	Five capsulets (sumatriptan or ginger powder) was delivered to each subject. Subjects were instructed to take only one capsulet upon headache onset. Each ginger capsulet contained 250 mg powder of ginger rhizome. Duration of study 1 month	100 patients with acute migraine without aura. 50 patients in the ginger group (GG) Age (GG): 33.9±8.3 years Female: 37 Male: 13	Confirmed diagnosis of migraine without aura by a neurologist, based on IHS criteria, aged ≥18 years, headache frequency between 2 and 10 days/month	The only reported clinical adverse effect of ginger was dyspepsia. Side effects from sumatriptan included dizziness, a sedative effect, vertigo and heartburn.	Dyspepsia was reported in the ginger group. Gastrointestinal disorders are included in the monograph. Study with unknown quality of ginger from a non-EU country.
UC/IBS						
Aims to investigate	Prospective, randomized,	Ginger powder was made by drying and	64 patients entered the study, 32	All patients' diagnosis of UC was previously	Adverse events of treatment were	Heartburn was reported in the

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the effect of ginger as a well-known antioxidant agent on the quality of life, disease activity index andoxidative stress in patients with UC. Nikkhah-Bodaghi *et al*. 2019 Iran	double-blind, placebo-controlled trial	milling fresh edible ginger. Patients were recommended to have 2000 mg ginger or placebo during a day along with their meals (1000 mg with breakfast, and 1000 mg with dinner) for 12 weeks.	control, 32 ginger (GG). 10 drop-out from the GG, due to heartburn (1), bloody diarrhoea (2), refused to continue (7). Drop-out from control were 8: bloody diarrhoea (1), constipation (1), refused to continue (6). Rendering control n=24, GG n= 22. Age (GG): 41.41±11.4 years Female: 7 Male: 15	confirmed by gastro-enterologist. Patients more than 18 years old, free of cancer or other inflammatory, autoimmune, infectious and intestinal diseases were included.	monitored during visits as well as follow up phone calls at third and ninth weeks. Reported adverse effects were heartburn (among some patients who took ginger capsules on an empty stomach) and some participants reported a severe smell of ginger in their digestive system.	ginger group. Gastrointestinal disorders are included in the monograph. Study with unknown quality of ginger from a non-EU country.
The goal of this pilot study was to test the	The study employed a randomized, controlled,	The ginger contained 2.29 mg/g of gingerols and 6-shogaols. The	15 subjects were randomly assigned	Patients aged 18 and older with a physician diagnosis of irritable bowel syndrome (IBS)	Patients were contacted within 24 h of ingesting first capsule, and biweekly	Gastrointestinal AEs were reported in patients with IBS. Gastrointestinal

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effects of ginger on IBS symptoms through a randomized placebo and dose dependent controlled trial. van Tilburg *et al*. 2014 US	parallel group design with 15 subjects in each arm.	placebo contained brown sugar Dosage was: placebo, 1 g ginger daily, or 2 g ginger daily. Treatment duration was 28 days. Treatment compliance was: 97.3%in the placebo group, 98.5% in the 1 g ginger group, and 85.2% in the 2 g ginger group.	to each of three arms: placebo (1 drop-out), 1 g ginger daily, or 2 g ginger daily. No differences between the 3 treatment arms were found in gender, age and IBS-SS scores at baseline.	verified by Rome III criteria. Participants needed to have symp-toms at least once a week severe enough to interfere with daily activities and report being on a stable dose of current medications for IBS for at least 4 weeks.	thereafter to check for compliance and side effects. Side effects were reported by 35.7% in the placebo and 16.7% in the ginger groups. Except for two subjects who reported headaches and tiredness, all side effects were gastrointestinal symp-toms including heart-burn, nausea, difficulty passing stool, more frequent stools, loose stools, bloating and hunger suppression. The placebo group reported twice as many side effects as the ginger group.	disorders are included in the monograph. Study with unknown quality of ginger from a non-EU country.
Heavy menstrual bleeding (HMB)						
To evaluate the effect of frankincense (Boswellia	Randomized, placebo-	All patients received ibuprofen (200 mg) and either frankincense (300	n = 102 All patients received ibuprofen	Gynecology outpatient	Side effects with ginger were constipation, abdominal pain,	Gastrointestinal AE were reported. Gastrointestinal disorders are

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, gender, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Adverse events (AE)	Comments on clinical relevance of results
serrata, oleoresin) and ginger (*Zingiber officinale*, rhizoma) as complementary treatments for heavy menstrual bleeding (HMB) among women of reproductive age Eshaghian *et al*. 2019 Iran	controlled, clinical trial single center Isfahan city, Iran,	mg, n=34), ginger (300 mg, n=34), or a placebo (n=34) three times a day for seven days of the menstrual cycle, starting from the first bleeding day and this was repeated for two consecutive menstrual cycles	(200 mg) and either frankincense (300 mg, n=34), ginger (300 mg, n=34), or a placebo (n=34) In the ginger group 20 completed the study and 21 in the placebo group.		dyspepsia, and headache (2.9%). One patient (2.9%) also had an allergic reaction to ginger. In the placebo group, side effects were diarrhea, abdominal pain, dyspepsia (2.9%), and headache (5.8%). Frequency of side effects was not different among the study groups (P>0.05)	included in the monograph. Allergic reaction was reported in the ginger group (1/20), but no further information on this case is available in the reference. Headache was reported in one patient in the ginger group and in two patients in the placebo group. Study with unknown quality of ginger from a non-EU country.

5.2. Patient exposure

Aside from data from studies, there are no concrete data concerning patient exposure.

5.3. Adverse events, serious adverse events and deaths

Adverse events in patients taking anticoagulant concomitantly are described in section 5.5.4. 'Drug interactions and other forms of interaction'.

In table 6 in section 5.1, references that have studied and reported adverse events following the exposure to ginger are included. The adverse events reported in clinical studies were mainly related to the SOC gastrointestinal disorders.

In addition, a few cases of headache (Vutyavanich *et al*. 2001; Eshagian *et al*. 2019), one case of arrythmia (Chittumma *et al*. 2007), one case of dizziness (Basirat *et al*. 2009) and one case of conjunctivitis (Bliddal *et al*. 2000) have been reported. However, the causality with ginger exposure is considered not sufficiently established.

Allergic reaction was reported for one patient taking ginger in the study by Eshaghian *et al*. (2019), but no further information on this case is available in the reference. In addition, a case of occupational IgE-mediated allergy (asthma) to ginger in a patient working with spices in the food industry has been described (van Toorenbergen and Dieges 1985). Schmidt *et al*. (2015) also present a case report of occupational allergic rhinoconjunctivitis after exposure to dust from ginger-containing herbal medicine. The likelihood of an aetiological connection between exposure and the patient's symptoms was supported by a temporal association, positive specific IgE, positive histamine release test, positive prick test, and positive acoustic rhinometry test. Occupational allergy to ginger has rarely been reported. The authors suggest that work-related IgE-mediated allergy is associated with exposure to dry aerosols/dust.

Okuhira *et al*. (2020) report a case of anaphylaxis to ginger induced by taking herbal medicine in a 59-year-old Japanese woman with a history of rheumatoid arthritis, hypertension, cedar pollen allergy, and skin eruptions induced by infliximab, pyrazolone drugs, iodine, lidocaine, vitamin preparations, and dairy products. Additionally, she has felt sick after taking cold remedies or raw eggs. In 2013, she took a dose of combination product containing powdered zedoary, powdered ginger, powdered turmeric, powdered Japanese kelp for motion sickness in a plane flying to Korea. Although she had taken this medication several times without any trouble more than twenty years previously, this time she felt pruritus throughout her whole body soon after taking it. On arriving in Korea, she lost consciousness and was taken into the emergency room of a university hospital. She was diagnosed with anaphylactic shock and put on an artificial ventilator breathing system. After accompanying lung embolism and digestive bleeding were recovered. The following year, she again developed dyspnea and itchy rash on her whole body, after taking another combination product containing taka-diastase N1, lipase AP12, bacillus coagulans, species of lactic acid-forming bacillus bacteria (butyric acid), Japanese mallotus essencel, powdered glycyrrhiza, magnesium aluminosilicate, hydrotalcite, magnesium hydroxide, powdered phellodendron bark, powdered cinnamon bark, powdered fennel, powdered clove and powdered ginger for digestive complaints. She was initially seen by a local doctor following her rheumatoid arthritis and was hospitalized due to hypoxemia. She recovered after an infusion of corticosteroid for treatment of anaphylaxis. She had been taken the product several times over the previous seventeen months. The authors report that the only component common to these two combination medicines is ginger. To determine the components responsible for anaphylaxis in this case, a SPT was performed for all components. Fifteen minutes after each of the sequential pricks, only zedoary, turmeric and ginger contained in the first product and ginger in second product induced itchy

rashes with central wheals. As diameters of the wheals were all longer than a half of that induced by 1% histamine, they were all determined as positive. Notably, itchy pale red flare with scattered dark red spots covered both of her palms soon after finishing all pricks and lasted for around half an hour. She had noticed similar itchy palm rash after drinking ginger ale, eating curry or ginger pork, but it was unclear when it had onset and why it had never developed anaphylaxis. No other apparent delayed responses were observed. From these findings, the patient was diagnosed with the immediate-type allergy to zedoary/turmeric/ginger-containing drugs and foods. The authors highlight that zedoary, turmeric and ginger are all derived from rhizomes of perennials belonging to the Zingiberaceae family. The authors were not able to identify a common antigenic component with western blotting. Therefore, the authors conclude that the mechanism of developing ginger allergy in the current case is still unclear and remains to be further investigated.

In the EudraVigilance search a few relevant case reports were related to hypersensitivity and the use of ginger (combination products with ginger excluded).

- A case report from Germany in 2011: A 58-year-old female patient started to receive celecoxib at 200 mg/day for arthritis years prior to this report. Approximately 45 minutes after she drank a fruit tea with fresh ginger tuber later, she developed an anaphylactic shock. The patient also developed urticaria.
- A case report from Germany in 2017. An 81-year-old female patient started therapy with oral edoxaban tosilate 60 mg once daily. While concomitantly drinking ginger tea, the patient experienced skin rash. Intake of ginger tea was stopped and the event resolved.

In a case report from Turkey, the authors report that a 59-year-old woman was admitted to the emergency department because of sudden loss of consciousness. She also had an episode of nausea. On admission, the patient was hypotensive (baseline blood pressure was 80/50 mm Hg), and resting 12-lead electrocardiogram revealed sinus bradycardia (45 beats/min) and first-degree atrioventricular block. The patient was on antihypertensive medication (telmisartan plus hydrochlorothiazide of 80/12.5 mg) and had no previous history of coronary artery disease. She had no signs of dehydration (e.g. dry mucus membranes and poor capillary refill). Baseline laboratory levels, that is, electrolytes and complete blood cell count, were within normal values. To rule out cardiac ischemic event, cardiac enzymes (creatinine phosphokinase MB fraction and troponin I) were obtained and showed normal limits. The patient also used a cup (150 mg) of ginger 3 times daily for 5 days because of flu (influenza-like illness). She got the ginger from a local grower. Because of symptomatic bradycardia, she was followed in coronary care unit and hydrated. After hydration therapy, normal sinus rhythm with 75 beats/min was restored and blood pressure normalized. Also, because the patient was hemodynamic, a transient pacemaker implantation was not requested. Bedside echocardiography showed normal ventricular contraction (ejection fraction of 65%) without any valve diseases. To exclude sinus node pathology, 24-hour Holter monitor was recorded and revealed normal sinus rhythm of 107 beats/min without signs of sinus node dysfunction. The patient was discharged 2 days after admission to the clinic. The authors summarise that there are no data showing bradycardic and hypotensive effects of ginger in humans but conclude that this case presenting hypotension and symptomatic bradycardia was due to ginger therapy (Gul *et al*. 2012).

Assessor's comment:
The reported adverse events of ginger are mainly gastrointestinal disorders. Particularly, upset stomach, eructation, dyspepsia, heartburn and nausea have been reported.
Reports on hypersensitivity reactions have also been found. Hypersensitivity reactions (dermal and respiratory tract) are also listed in SmPC section 4.8 of the WEU-product on the market in AT.
From available published case reports and clinical studies, the following information is added to the

monograph section 4.8 'Undesirable effects':

Gastrointestinal disorders: Stomach upset, eructation, dyspepsia, heartburn and nausea. Frequency: common (≥1/100 to <1/10).
Immune system disorders/Skin and subcutaneous tissue disorders: Hypersensitivity. Frequency not known.

5.4. Laboratory findings

Three randomised studies report laboratory results i.e. Wigler *et al*. 2003 (normal blood counts, liver test and creatinine), Bliddal *et al*. 2000 (no change in blood haemoglobin) and Zick *et al*. 2009 (no laboratory abnormalities).

Blood clotting

The first report that ginger might inhibit platelet aggregation in humans was that of Dorso *et al*. (1980) in which a subject was found to have platelets unresponsive to arachidonic acid following the consumption of large quantities of marmalade containing ginger. A non-randomised poorly controlled small study involving 7 healthy women could demonstrate a 37% (non-significant; P<0.1) reduction in *ex vivo* platelet thromboxane B2 production after ingestion of 5 g fresh ginger daily for 1 week (Srivastava 1989). In a randomised placebo-controlled, cross-over study in which 18 healthy subjects consumed vanilla custard containing 15 g of raw ginger root, 40 g of cooked stem ginger or no ginger daily for 2 weeks (length of wash-out period not available), no effect on maximum ex vivo platelet thromboxane B2 production was observed (Janssen *et al*. 1996).

Verma *et al*. (1993) gave 20 healthy male volunteers 50 g of butter twice daily for 7 consecutive days in addition to their daily diet, and then for the next 7 days supplemented the diet with either 5 g of powdered ginger rhizome (N = 10) or placebo (N = 10). *In vitro* platelet aggregation induced by adenosine phosphate and epinephrine was examined before start of the diet, 7 days after the fatty diet and at the end of the study. The daily administration of 100 g of butter increased platelet aggregation significantly. The addition of ginger along with the fatty meal significantly decreased aggregation compared to initial values and compared to placebo.

Verma and Bordia (2001) studied the effect on fibrinolysis after oral intake of 5 g of powdered ginger rhizome vs. placebo taken together with 50 g of butter in 30 adult healthy volunteers. Fibrinolysis was determined by the clot lysis time before (fasting) and after the fatty meal, and with ginger and placebo on 2 consecutive days. They could demonstrate that ginger not only neutralised the lowered fibrinolytic activity induced by fat, but also increased it significantly over the fasting level. The study lack description of the design and statistics.

A randomised double-blind, placebo-controlled, cross-over study (wash-out period: at least 2 weeks) performed in 8 healthy volunteers showed that a single 2 g dose of dried ginger did not change bleeding time, platelet count, thromboelastography and whole blood impedance platelet aggregometry at 3 and 24 hours after intake (Lumb 1994).

In a controlled study in patients with prior coronary heart disease (CHD) by Bordia *et al*. (1997) after oral intake of powdered ginger, 4 g daily, or placebo for 3 months, no effect was found on ADP and epinephrine induced platelet aggregation measured at 1.5 and 3 months. However, a single dose of 10 g of ginger after 4 hours produced a significant reduction in platelet aggregation in 10 CHD patients. The presented results do not include between-group statistical calculations.

No significant effect on platelet aggregation and coagulation could be demonstrated in a randomised open label study in healthy human subjects who received a daily dose of 3.6 g extract from powdered ginger root for 5 days (Jiang *et al*. 2005).

Powdered ginger (in a daily dosage of 1 g for 7 days) has been shown to potentate anti-platelet aggregation in healthy volunteers and hypertensive when co-administered with nifedipine (Young *et al*. 2006), however clinically significant pharmacodynamic interactions with nifedipine or other platelet aggregation inhibitors, such as non-steroidal anti-inflammatory drugs, have not been observed.

In an open label, two armed, parallel RCT, the primary end point of the study was the change in platelet aggregation from baseline and after five days of receiving ginger four gram once daily vs. ginger four gram twice daily. Secondary outcomes included change in the platelet count and platelet morphology. Healthy subjects between 18-60 years in Saudi Arabia were required to have normal platelet count and platelet function at baseline. Subjects with history of intake of warfarin, aspirin, clopidogrel, non-steroid anti-inflammatory drugs (NSAIDs), contraceptive pills, herbal treatment or ethanol ingestion within last two weeks prior to enrollment were excluded. Pregnant or lactating women were also excluded. The enrolled subjects refrained from smoking, taking aspirin, clopidogrel, contraceptive pills, or ingesting ethanol, wine, and beer during the study period. The pure ginger powder from Mehran (Pakistan) without any additives, commonly available in grocery stores was obtained to prepare the ginger tea. Group I (n=19) received powdered ginger four gram dissolved in 150 ml of boiling hot water given once daily orally in the morning for five consecutive days. Group II (n=20) received powdered ginger four gram dissolved in 150 ml of boiling hot water, twice daily once in the morning and second dose after six hours for five consecutive days. The authors conclude that the result of the study indicates that platelet count and platelet morphology stayed normal at baseline vs. at day 5 post ginger tea intake. The dose increment to 4 g twice daily did not show any change in platelet aggregation. However, the authors state that there are different varieties of ginger, with differences in bioactive concentration. The analysis of gingerols composition and molecular mechanism is beyond the scope of the study. Thus, one of the study limitations is that the results cannot be generalized due to the use of the commercial ginger powder. Furthermore, the authors state that the current sample size would be considered small for the observed effect size (AlAskar *et al*. 2020).

Assessor's comment:
Studies on blood clotting parameters are generally few, small and of inferior methodology. Studies have differed in effect variables, dosage and formulation of ginger root, and have produced different results, from no effect to decreased ex vivo thromboxane formation and platelet aggregation. For the moment, the data available is considered not sufficient to include a warning in the monograph that ginger increases the risk of haemorrhage.

Lipids, lipoproteins and glucose

In a controlled study with the oral intake of powdered ginger 4 g daily or placebo for 3 months, ginger did not affect blood lipids (triglycerides, total cholesterol and HDL-cholesterol) and blood sugar in patients with prior CHD (Bordia *et al*. 1997).

Alizadeh-Navaei *et al*. (2007) performed a double-blind, placebo-controlled study in 85 patients with hypercholesterolaemia or hypertriglyceridaemia. Patients were randomised to receive ginger capsules 6 g per day (6 capsules) or lactose capsules 6 g per day (6 capsules) for 45 days. Blood was drawn at the beginning of study and at the end. The mean decreases in total cholesterol and triglyceride (from before trial start to trial end) were significantly larger in the ginger group compared to the placebo group. No differences in the change in LDL-cholesterol, HDL-cholesterol, lipoprotein (a) and homocysteine were observed. The study did not control for diet and physical activity.

Assessor's comment:
There is not sufficient evidence of an effect of ginger on blood lipids and blood sugar to include a warning in the monograph.

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

There is sufficient evidence on the traditional use in children between 6 and 12 years of age for the symptomatic relief of motion sickness when taking 250 to 500 mg powdered herbal substance half an hour before travelling and for adolescents taking 500 to 750 mg half an hour before travelling. If the travel will continue for more than 4 hours, an additional dose may be taken every 4th hour, if needed, up to a daily dose of 1.5 g for children between 6 and 12 years of age and up to a daily dose of 2.5 g for adolescents. For all other indications and posologies the use in children and adolescents under 18 years of age has not been established due to lack of adequate data and is not recommended.

5.5.2. Contraindications

Hypersensitivity to ginger and preparations thereof is a contraindication in the monograph.

5.5.3. Special Warnings and precautions for use

For the traditional use indication symptomatic relief of motion sickness, the use in children under 6 years of age has not been established due to lack of adequate data and is not recommended. For all other indications and posologies the use in children and adolescents under 18 years of age has not been established due to lack of adequate data and is not recommended. This information is included as a warning in the monograph section 4.4.

Also the standard statement that if the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted, has been included in the monograph section 4.4.

In harmonisation with other monographs with the traditional use indication relief of minor articular pain, the following warning should be included in the monograph section 4.4: *"Articular pain accompanied by swelling of joints, redness or fever should be examined by a doctor."*

For tinctures containing ethanol, the appropriate labelling for ethanol, taken from the 'Guideline on excipients in the label and package leaflet of medicinal products for human use', should be included.

5.5.4. Drug interactions and other forms of interaction

Anticoagulants

One case report in Germany described a 76-year old woman on long-term phenprocoumon therapy for atrial fibrillation who was admitted with an elevated INR up to 10 and epistaxis (Krüth *et al*. 2004). It was revealed that the patient had a regular ginger intake (pieces of dried ginger, tea from ginger) during several weeks before the bleeding occurred. She was told to refrain from ginger, and subsequently the INR was maintained within the therapeutic interval with the same dose of phenprocoumon as before the incident.

Another study from US describes a 76-year old woman who was admitted because of epistaxis while taking warfarin for atrial fibrillation (Lesho *et al*. 2004). Her INR was 10 and after a detailed

questioning it was discovered that she had recently begun eating pieces of ginger root and drinking tea made from ginger powder. The patient was advised to stop all ginger consumption and her INR was maintained in the therapeutic interval with the same dose of warfarin as before the incident. None of the studies performed a provocation with ginger.

A randomised open-label, three-way, cross-over study with at least 14 days' wash-out between study periods was conducted in 12 healthy volunteers in Australia (Jiang *et al*. 2005). A single 25 mg dose of rac-warfarin was administered to each volunteer with and without pre-treatment of ginger rhizome powder at a dose of 0.4 g 3 times daily for 1 week. The quality of the ginger preparation was not established. Dosing of ginger was continued for a further 1 week after warfarin administration. Blood sample times in relation to warfarin dosing was: -48, -24, 0, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours. There were no significant differences in warfarin pharmacokinetics (C_{max}, t_{max}, elimination half-life, AUC, apparent clearance and apparent volume of distribution) after treatment with ginger. Also, urinary excretion rates of S-7-hydroxywarfarin, plasma protein binding, prothrombin time, (INR) and platelet aggregation were similar with and without ginger.

Shalansky *et al*. (2007) did a prospective longitudinal study over 16 weeks on 171 adults taking warfarin in Canada. They were asked weekly to record their use of complementary and alternative medicine. In a fully adjusted multivariate model, the use of ginger (Odds Ratio OR: 3.20; 95% CI: 2.42-4.24) was shown to be a statistically significant independent risk factor for bleeding (based on self-assessment); however, ginger use was not an independent risk factor for supra-therapeutic INR (defined as at least 0.5 units above target range).

In a published case report from Kuwait, Maaradarani *et al*. (2019), present an 80-year-old patient on dabigatran. The patient had a known history of NV-AF presented with a 1-day history of haematemesis and black stool which began 3 days after he had started taking 200 ml of a boiled mixture of ginger and cinnamon twice daily for 3 days before presentation to hospital. The patient was hypotensive and treated as a case of gastrointestinal bleeding and haemorrhagic shock. Despite continuous aggressive resuscitation measures including administration of a reversal agent for dabigatran, the patient died within 24 hours. The authors conclude that interaction of ginger and cinnamon with dabigatran led to fatal bleeding. On presentation, the patient had a haemoglobin (Hb) of 8 g/dl (normal 13.5–17 g/dl), haematocrit (Hct) of 24% (normal 45–52%) microcytic hypochromic anaemia, reticulocyte index >2, platelet count of 600,000 (normal range 150,000–450,000/l), International Normalized Ratio (INR) of 1.9 (normal INR 1.1 or less), and activated partial thromboplastin time (aPTT) of 45 sec (normal 30–40 sec). The history and clinical picture were suggestive of gastrointestinal bleeding with an element of haemorrhagic shock. The authors also refer to a publication by Verma *et al*. (1993) that showed that 5 g of ginger in two divided doses consumed with a fatty meal significantly inhibited platelet aggregation in healthy males. Furthermore, the authors refer to a publication by Buhner *et al*. (2012) that suggests that ginger is a P-glycoprotein (P-gp) inhibitor and has been reported to reduce the P-gp-mediated efflux of dabigatran.

Rubin *et al*. (2019) report that a 70-year-old patient in US on long-term warfarin therapy with a past medical history significant for obstructive sleep apnea, osteopenia, restless leg syndrome, deep venous thrombosis, and cerebral vascular accident came to the clinic for an international normalized ratio (INR) check after having a therapeutic INR of 2.7 one month prior. The warfarin was dosed at 7.5 mg daily except 10 mg on Wednesdays. The medication list included clonazepam 1 mg, metoprolol succinate 25 mg, paroxetine 10 mg, phenytoin 30 mg, rosuvastatin 20 mg, warfarin 7.5 mg, and warfarin 10 mg, none of which had been altered during the preceding month. During the visit the INR was 8.0, but the patient did not endorse bright red blood per rectum or melena, bleeding of her gums, hematuria, or epistaxis, and chest pain or shortness of breath. Since the last visit, one month prior, the patient had began taking "Ginger Rescue," a daily oral, chewable, 48 mg ginger supplement that

had no other herbal or active ingredients. The patient did not report any other dietary changes in the previous month nor introducing any other supplements, outside of ginger. Since a drug-drug interaction with rosuvastatin and warfarin is possible, it was confirmed consistent compliance, as well as no dosing changes for both medications. The patient was advised on holding 3 doses of the warfarin and stopping the ginger supplement. The patient returned 1 week later for an INR recheck. At this time, the INR returned to 2.6 and was subsequently advised to begin taking warfarin 7.5 mg daily.

In a published case report from Austria (Gressenberger *et al*. 2019), the authors report that a 36-year-old patient under stable rivaroxaban therapy for 18 months was admitted to the emergency room with sudden onset of hemoptysis appearing for the first time. Anticoagulant therapy was given after recurrent spontaneous deep vein thrombosis (DVT) and a heterozygous Factor-V-Leiden mutation was present. There was no co-medication reported, however, the patient reported a constant intake of 2-3 litres of home-brewed ginger tea per day in the last month. Laboratory testing showed no abnormalities, renal function was within reference range. The HAS-BLED Score was 0 points, Chest-X-ray was normal, a CT scan of the thorax was also unsuspicious, and ECG was found normal. The Ear Nose Throat (ENT)-specialist excluded a possible bleeding source in the Naso-oro-pharyngeal region. Platelet function testing (PFT) was performed 3 days after hospitalization and the value for the ADP test can be interpreted as a relevant antiplatelet effect caused by ginger, which is almost comparable to the effect of clopidogrel on the platelet function. The patient was advised to significantly reduce ginger consumption because of its obvious additional antiplatelet effect when used in such high concentrations. The patient was discharged after 4 days in a good general condition, rivaroxaban was re-started, however in a reduced maintenance dose.

In EudraVigilance some additional relevant case reports related to interaction with anticoagulantia and the use of ginger were found. Case reports already cited in text above, case reports on combination products with ginger or concomitant use of other herbal products and case reports with patients on other medications that already are known to interact with anticoagulants have been excluded.

- A case report from Germany in 2010: prolonged prothrombine time was reported in a male patient on phenprocoumon after consumption of large quantities of homemade ginger tea over 4 weeks. After stopping the tea, normal values again with constant phenprocoumon dosage.
- A consumer report in Germany 2018: in a female patient that took phenprocoumon and ate more ginger every day than usual, the INR value increased.
- A report from a pharmacist in Germany in 2019: severe diarrhea with external bleeding in a 79-year-old male patient. Not clear whether intestinal bleeding or just external. The patient took ginger extract capsules for osteoarthritis pain and phenprocoumon. Concomitant medicinal products spironolactone, bisoprolol, torasemid and candesartan cilexetil.
- A consumer report in Germany 2020: Conjunctival haemorrhage for one week was reported in a 91-year-old female patient who received rivaroxaban 10 mg and ginger tea taken for a couple of days at an unspecified dose and frequency.

Assessor's comment:
Case reports suggesting interaction between ginger and anticoagulants are few and un-convincing. One randomised study in healthy volunteers did not demonstrate interaction. It should, however, be stressed that results on interactions with warfarin and ginger performed in healthy volunteers may not be applicable to patients seen in clinical practice where warfarin is usually taken by patients who will display increased variability in warfarin pharmacokinetics and pharmacodynamics. For the moment there is not sufficient data to conclude in the monograph that ginger increases the risk of haemorrhage due to interaction with anticoagulants.

Other

In a French case report by Revol *et al*. (2020), a 48-year-old woman was treated with crizotinib 250 mg twice a day since November 2016 after a first line of chemotherapy with cisplatin and pemetrexed, for a lung adenocarcinoma. At the time of crizotinib initiation, acetylsalicylic acid 160 mg daily was also prescribed for a transient ischaemic attack in June 2015. While transaminases levels were normal until December 5, 2017 (aspartate aminotransferase, AST , 33 UI/L; alanine aminotransferase, ALT, 41 UI/L), a severe hepatic cytolysis (alanine aminotransferase ALT > 20 × ULN) was discovered in January 2018. The abdominal ultrasound was subnormal with fatty liver and other laboratory tests were negative. Liver biopsy showed histological lesions in favour of acute drug induced hepatitis and liver function gradually improved after discontinuation of crizotinib. Crizotinib plasma trough concentration was 384 µg/L 2 days after crizotinib discontinuation, against 205 µg/L in November 2017. The patient consumed an increasing amount of a drink made from grated ginger, honey, lemon juice, and hot water since November 2017, up to more than 1 L/day, for nonmedical purposes. Crizotinib is mainly metabolized by CYP3A4, and *in vitro* studies also suggested that crizotinib is a substrate for P-glycoprotein (P-gp) and the authors suggest a possible interaction with ginger that caused accumulation of crizotinib, which induced hepatotoxicity.

Assessor's comment:
For the moment there is insufficient evidence to include in the monograph that ginger has a clinically relevant effect on CYP-450 isoenzymes or P-glycoprotein.

5.5.5. Fertility, pregnancy and lactation

Fertility

No data available.

Pregnancy

In table 6 in section 5.1, clinical studies that have studied and reported on the pregnancy outcome following the exposure to ginger have been summarised.

A prospective comparative study examined the safety of ginger during pregnancy (Portnoi *et al*. 2003). The study group included first trimester pregnant women who called a counselling service requesting information about the safety of ginger. Various types of ginger were used; almost half used ginger capsules (other preparations were ginger tea, fresh ginger, pickled ginger, ginger cookies, ginger candy, inhaled powdered ginger, ginger crystals and sugared ginger). The comparison group was collected in the same fashion as the exposed group, but who had been exposed to non-teratogenic drugs that were not antiemetics. A total of 187 pregnancies exposed to ginger and 187 pregnancy controls were included. There were 181 live births, 2 stillbirths, 3 spontaneous abortions, and 1 therapeutic abortion in the ginger group. Three major malformations (baseline rate 1-3%) were ascertained in the ginger group (ventricular septal defect, lung abnormality and kidney abnormality) and none in the control group. One child in the ginger group was diagnosed with idiopathic precocious puberty at age 2 years. There were 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≤0.001). There were 8 sets of twins in the ginger group and none in the comparison group.

Five of the 6 randomised studies in the systematic review by Borelli *et al*. (2005) specifically evaluated safety in pregnancy (Fischer-Rasmussen *et al*. 1991, Vutyavanich *et al*. 2001, Sripramote *et al*. 2003, Willetts *et al*. 2003, Smith *et al*. 2004) and 4 studies (including 1 cross-over trial) investigated ginger-induced adverse effects on pregnancy outcome collected after delivery. There were no differences in

the occurrence of spontaneous abortions, stillbirths, term deliveries and caesarean deliveries, neonatal deaths, gestational age, and congenital abnormalities between women exposed to ginger and women exposed to placebo or vitamin B6. Similar results were found when the effect of ginger on pregnancy outcomes was compared with the general population. Adverse effects on pregnancies were observed in 4 studies. These included headache, diarrhoea and abdominal discomfort, drowsiness, reflux and heartburn, however with no significant differences between groups.

In the study by Ensiyeh and Sakineh (2009) the data presented for pregnancy outcome include 2 spontaneous abortions in the ginger group and 1 spontaneous abortion in the vitamin B6 group, and no infants had congenital malformations.

In addition, the clinical studies by Basirat *et al*. (2009) and Biswas *et al*. (2011), also reported pregnancy outcome safety data. In the study by Biswas *et al*. 34 pregnant women in India were exposed to a ginger extract (150 mg/tablet) three times daily (no further information on the extract is available). The authors report that all participants had normal pregnancy outcomes without any stillbirths, congenital malformations of the foetus or neonatal complications. In Basirat *et al*. 32 pregnant women in Iran were exposed to 500 mg powdered ginger root incorporated in a biscuit five times daily. The authors report that no abnormal pregnancy and delivery outcome occurred and no infants had any congenital abnormalities recognized and all were discharged in good condition.

In a study by Cuzzolin *et al*. (2010) aimed to explore the use of herbal products among a sample of Italian pregnant women and the possible influence of herbal consumption on pregnancy outcome, 392 interviews were considered. The study was conducted over a 10-month period (2 days a week, from January to October 2009) at the Maternity wards of two general hospitals in the northeast of Italy where 400 women were interviewed within 3 days after childbirth. 20 questions were designed to elicit information regarding: the type of herbal product consumed during pregnancy (a list was given, including products commonly sold in Italy); details on use (dosage, formulation, route of administration, frequency); timing of administration (1st, 2nd, 3rd trimester); symptom/disease and other reasons for consumption; place of purchase; relationship/communication with healthcare providers; general product knowledge in relation to quality, kind of use and risks; source of information; level of satisfaction; adverse reactions observed. In a second session, data about pregnancy history (primiparity, smoking and alcohol habits, chronic diseases, morbidities during pregnancy, medication use) and newborn (gestational age, birth weight, Apgar score, problems at birth, treatments) were both collected through the interview and abstracted from medical records by the same interviewer. The authors report on one case where a regular consumption of ginger (twice daily throughout pregnancy) could be related to maternal problems observed at 4th month (hypercontractility, placenta previa) and to the preterm birth at 36 weeks' gestation.

Heitmann *et al*. (2013) examined the safety of ginger use during pregnancy on congenital malformations and selected pregnancy outcomes in a population-based cohort study. The population consisted of 68,522 women in Norway. Data on ginger use and socio-demographic factors were retrieved from three self-administered questionnaires completed by the women during weeks 17 and 30 of the pregnancy and when their child was 6 months old. The data was collected between 1999-2009. Data on pregnancy outcomes were provided by the Medical Birth Registry of Norway. The following confounder set was used when estimating the risk for malformations and preterm birth: maternal age, parity, pre-pregnancy BMI, level of education, maternal smoking at the end of pregnancy, any maternal folic acid use, nausea and vomiting during first and second part of pregnancy, previous miscarriages or stillbirths, year of delivery, and infant gender. The same confounder set was used to estimate the risk for the remaining selected pregnancy outcomes, with the addition of the length of gestation. Among the 68,522 women in the study, 1,020 (1.5 %) women reported using ginger during pregnancy. Of the women who reported ginger use in relation to timing,

we found that 466 women (45.7 %) used ginger during the first trimester. Pregnancy induced nausea and vomiting (NVP) was the most frequently reported indication for the use of ginger (655 of 1,020, 63.8 %). 40 women (3.9 %) reported the use of ginger against other indications (influenza/cold (n=18), pelvic distortion due to pregnancy (n=5), reflux (n=9), other non-specified illness (n=8)). Among women who used ginger during pregnancy, a higher percentage experienced vaginal bleeding after week 17 compared to controls (7.8 % vs. 5.8 %, p=0.007). The association remained significant when adjusting for maternal age, parity, pre-pregnancy BMI, maternal smoking, maternal folic acid use, NVP during both the first and second part of pregnancy, previous miscarriages or stillbirths, and physical activity (adjusted OR 1.4, 95 % CI 1.0–1.7, p=0.02). However, when the analyses were restricted to vaginal bleeding more than spotting, neither crude nor adjusted ORs revealed a significant association (crude OR 1.1, 95 % CI 0.8–1.7; adjusted OR 1.2, 95 % CI 0.8–1.9). The authors conclude that the small increased risk of vaginal bleeding among the women who used ginger during pregnancy may be due to chance, the underlying ailment or due to use of ginger. As ginger has been reported to may inhibit thromboxane synthetase, an increased risk of bleeding is theoretically plausible and the risk of bleeding during pregnancy is something that should be investigated in depth with respect to dosage. 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. However, information on product used (quality of ginger), dosage and administration were not available and the timing of exposure could only be recorded when ginger was used for the specific given indications.

Choi *et al*. (2015) investigated if exposure to dried ginger during pregnancy would increase the risk of adverse foetal and neonatal outcomes. Participants consisted of 159 singleton pregnant women who received dried ginger as a herbal medication. Eligible participants consisted of participants with a history of treatment with dried ginger prescribed by a naturopathic doctor for a health disorder, who continue treatment during pregnancy, and who were referred to the Korean Motherrisk Program for prenatal risk counselling. The control group consisted of 306 pregnant women who had not been exposed to any herbal medication or any known teratogen. The study outcomes were the incidence of stillbirths, gestational age at birth (weeks), birth weight (g) and length (cm), head circumference (cm), 1-min and 5-min postnatal Apgar score and incidence of transient tachypnoea of the newborn, gross malformations and neonatal jaundice. The authors report that no increased risk of major malformations was detected in exposed women (OR = 4.9; 95% CI 0.9–25.5; p = 0.051). The incidence of stillbirths in the exposed group was marginally higher than in the controls (OR = 7.8; 95% CI 0.9–70.3; p = 0.05). The risk was more evident when the exposed group was compared with the general population in the Republic of Korea (OR = 7.9; 95% CI 2.9–21.4; p = 0.0001). Other foetal and neonatal study outcomes investigated in the exposed group were similar (p = 0.05) to the controls. The authors conclude that dried ginger does not appear to be a major teratogen. However, due to the limitations of the study, e.g. the large variability in the dose of dried ginger in the exposed group, as well as the concomitant exposure to other herbal medications, the increased incidence of stillbirths requires confirmation in larger cohort studies (Choi *et al*. 2015).

Furthermore, Laekeman *et al*. (2021) report from a pilot safety study on a concentrated dry extract of ginger (extraction solvent: 96% ethanol, DER 10:1, containing 10% gingerol derivatives) in Belgium. The target population consisted of pregnant women willing to use the product for digestive discomfort and fewer than 3 months pregnancy at inclusion. The authors report that 44 out of 51 included pregnant women completed the study. Participants could freely use the ginger tablets with a maximum of two tablets of 50 mg extract each (corresponding to 500 mg ginger root powder) daily during the first trimester in case of gastrointestinal discomfort (in average 12.4 tablets, minimum 1 tablet and maximum 55 tablets). One patient that had used two tablets daily had a spontaneous abortion after 17

weeks of pregnancy. From the limited data obtained, the authors conclude that no major safety concerns arise. The number of complications was compared with the rate in a Flemish population delivering during the same period. As compared to a general population, there was a lower incidence of stillbirth, a higher number of prematurity and consequently a lower birthweight, more cases of hip dysplasia in the baby and more maternal hypertension. Among the participants, the percentage of women older than 34 years were higher compared to the epidemiological data (27% vs. 14%). The authors concluded that the studied population was not representative for the general population in Flanders.

According to Wiesner and Knöss, 2017, Embryotox (the information webpage of the Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy of the Charité University Berlin, Germany), summaries that ginger can be used in all phases of pregnancy in commonly used dosages but it is to keep in mind that undesirable effects were seen frequently. Also, the UK teratology information service (UKTIS) summaries that even though that the available studies involve small numbers of exposed pregnant women, there is no evidence to suggest that use of ginger-containing products during pregnancy will harm the baby (Wiesner and Knöss, 2017).

Lactation

In a systematic review, Dilokthornsakul *et al*. (2022) the authours summarize the efficacy and safety of ginger on human milk volume. Ginger is widely used in various forms as a supplement for enhancing human milk volume in Thailand and some countries in Southeast Asia. For the primary outcome 24-h human milk volume, the authors found two studies in Thailand with ginger as a single intervention. The authors conclude that the studies showed conflicting evidence of the efficacy of ginger alone regarding human milk volume and that there is currently no strong evidence to suggest the efficacy of ginger for the enhancement of human milk volume. No adverse effect directly related to ginger was reported, but there is no conclusion on the long-term use of ginger in lactating mothers and infants.

Assessor's comment:
In the first version of the monograph it was concluded that prospective studies have not found a higher incidence of adverse pregnancy outcomes but as a precautionary measure it is preferable to avoid the use during pregnancy.
Additional safety data on pregnant women using ginger has been published since the first version of the monograph. Heitmann et al. (2013) report on the outcomes from 1020 pregnant women in Norway exposed to ginger and Choi et al. (2015) report on the outcomes from 159 pregnant women in Korea exposed to ginger. In both studies, the authors conclude that further studies are needed to evaluate the safety of using ginger during pregnancy. Importantly, both Heitmann et al. and Choi et al. concluded that information on products used (i.e. quality of ginger), dosage and administration are in most of the studies not available or very limited.
Only one small study with specified dosages and administration of powdered ginger root with reported pregnancy outcome safety data has been found during the first revision, i.e. Basirat et al. (2009). In Basirat et al. 32 pregnant women in Iran were exposed to 500 mg powdered ginger root incorporated in a biscuit five times daily for 4 days.
The risks of using ginger during pregnancy have been evaluated by several institutes and authorities. However, for the moment, the conclusions are not consistent. In the first version of the monograph section 4.6 it was recommended that as a precautionary measure it is preferable to avoid the use during pregnancy. For the moment, the data available is not sufficient to change this conclusion. The following text is included in the monograph section 4.6:

"A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or feto/neonatal toxicity of ginger root. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3 'Preclinical safety data').

As a precautionary measure it is preferable to avoid the use during pregnancy.

Safety during lactation has not been established. In the absence of sufficient data, the use during lactation is not recommended.

No fertility data available."

5.5.6. Overdose

No case of overdose has been reported.

5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability

No studies on the effect on the ability to drive and use machines have been performed.

Assessor's comment:

Based on the pharmacodynamic properties and reported adverse reactions, it is concluded that the herbal preparations in the monograph have no or negligible influence on the ability to drive and use machines.

5.5.8. Safety in other special situations

Not applicable.

5.6. Overall conclusions on clinical safety

The reported adverse events of ginger are mainly gastrointestinal disorders. Particularly, upset stomach, eructation, dyspepsia, heartburn and nausea have been reported. Reports on hypersensitivity reactions have also been found.

For the traditional use indication symptomatic relief of motion sickness, the use in children under 6 years of age has not been established due to lack of adequate data and is not recommended. For all other indications and posologies the use in children and adolescents under 18 years of age has not been established due to lack of adequate data and is not recommended.

In the first version of the monograph it was recommended that as a precautionary measure it is preferable to avoid the use during pregnancy. For the moment, the data available today is not sufficient to change this conclusion. Additional data will be needed to demonstrate the safe use of medicinal products containing ginger as the active substance in addition to normal use in food during pregnancy.

Studies on blood clotting parameters are generally few, small and of inferior methodology. Studies have differed in effect variables, dosage and formulation of ginger, and have produced different results. In addition, reports suggesting interaction between ginger and anticoagulants are few and un-convincing. There is insufficient evidence that ginger has a clinical relevant effect on CYP-450 isoenzymes or P-glycoprotein. For the moment, the data available is considered not sufficient to include a warning in the monograph that ginger increases the risk of haemorrhage or increases the risk of haemorrhage due to interaction with anticoagulants.

6. Overall conclusions

Well-established use monograph

Medicinal products with dried powdered ginger for the prevention of nausea and vomiting in motion sickness has been on the EU market for more than 10 years. The clinical efficacy of ginger root has been examined in studies in motion sickness. The WEU indication "Herbal medicinal product for the prevention of nausea and vomiting in motion sickness" was included in the first version of the monograph. The posology in the first version of the monograph was for adults and elderly 1 - 2 g 1 hour before start of travel. In the first revision of the monograph, no new clinical studies to substantiate efficacy in motion sickness were found. The quality of available studies in motion sickness included in the first version of the assessment report and clinical relevance of the results from these studies to substantiate efficacy in motion sickness are considered weak in relation to the current requirements ('Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products' (EMA/HMPC/104613/2005–Rev. 1). Also, there are insufficient data to support the posology in the monograph. There is one medicinal product on the EU market with the posology >1g. However, for regulatory consistency and since there are no new safety issues, the preparation and posology are retained in the revision of the WEU monograph.

In the first version of the monograph it was recommended that as a precautionary measure it is preferable to avoid the use during pregnancy. Animal studies are insufficient with respect to reproductive toxicity. For the moment, the data available today is not sufficient to change this conclusion. Additional data will be needed to demonstrate the safe use of medicinal products containing ginger as the active substance in addition to normal use in food during pregnancy. In the absence of sufficient data, the use during lactation is not recommended.

The reported adverse events of ginger are mainly gastrointestinal disorders. Particularly, upset stomach, eructation, dyspepsia, heartburn and nausea have been reported. Reports on hypersensitivity reactions have also been found.

Case reports suggesting interaction between ginger and anticoagulants are few and unconvincing. Studies on blood clotting parameters are generally few, small and of inferior methodology. Studies have differed in effect variables, dosage and formulation of ginger, and have produced different results. There is insufficient evidence to suggest induction or inhibition of CYP-enzymes or P-glycoprotein by ginger and its constituents.

Overall, for regulatory consistency and since there are no new safety issues, the preparation and posology included in the first version of the WEU monograph are retained in the first revision of the WEU monograph:

Indication	**Herbal preparation**	**Posology (oral use)**	**Duration of use**
Herbal medicinal product for the prevention of nausea and vomiting in motion sickness	Powdered herbal substance	*Adults and Elderly* 1-2 g 1 hour before start of travel	Single use before travel.

Pharmacotherapeutic group: Other antiemetics

ATC code: A04AD

Traditional use monograph

A traditional medicinal use of ginger has been found from the presence of medicinal products in the EU reported from Member States. In addition, traditional medicinal use of ginger has been found in several scientific references. The basic requirements that ginger is not harmful under normal conditions of use and has an efficacy that is plausible on the basis of long-standing use is considered fulfilled in the following indications considered appropriate for self-medication:

- Traditional herbal medicinal product for the symptomatic relief of motion sickness
- Traditional herbal medicinal product symptomatic treatment of mild, spasmodic gastrointestinal complaints including bloating and flatulence
- Traditional herbal medicinal product used for temporary loss of appetite.
- Traditional herbal medicinal product used for relief of minor articular pain.
- Traditional herbal medicinal product used for the relief of symptoms of common cold.

The herbal preparations, posologies and method of administration are presented in the table below. In relation to the posology of 1-2 g for the well-established use indication "Herbal medicinal product for the prevention of nausea and vomiting in motion sickness" from 18 years of age, the traditional use posology for the indication "Traditional herbal medicinal product for the symptomatic relief of motion sickness" from 12 years of age was limited to 750 mg in the first version of the monograph.

For the traditional use indication symptomatic relief of motion sickness, the use in children under 6 years of age has not been established due to lack of adequate data and is not recommended. For all other indications the use in children and adolescents under 18 years of age has not been established due to lack of adequate data and is not recommended.

In the first version of the monograph it was recommended that as a precautionary measure it is preferable to avoid the use during pregnancy. Animal studies are insufficient with respect to reproductive toxicity. For the moment, the data available today is not sufficient to change this conclusion. Additional data will be needed to demonstrate the safe use of medicinal products containing ginger as the active substance in addition to normal use in food during pregnancy. In the absence of sufficient data, the use during lactation is not recommended.

The reported adverse events of ginger are mainly gastrointestinal disorders. Particularly, upset stomach, eructation, dyspepsia, heartburn and nausea have been reported. Reports on hypersensitivity reactions have also been found. In the absence of sufficient data, the use during lactation is not recommended.

Case reports suggesting interaction between ginger and anticoagulants are few and unconvincing. Studies on blood clotting parameters are generally few, small and of inferior methodology. Studies have differed in effect variables, dosage and formulation of ginger, and have produced different results. There is insufficient evidence to suggest induction or inhibition of CYP-enzymes or P-glycoprotein by ginger and its constituents.

Adequate tests genotoxicity and carcinogenicity have not been performed. A European Union list entry is not supported due to lack of adequate data on genotoxicity.

Overall, the criteria for traditional medicinal use throughout a period of at least 30 years, including at least 15 years within the EU/EEA is considered fulfilled for the following ginger preparations, indications and posologies (oral use):

Indication	Herbal preparation	Posology (oral use)	Duration of use*
Traditional herbal medicinal product for the symptomatic relief of motion sickness	Powdered herbal substance	*Adolescents, Adults and Elderly* 500-750 mg half an hour before travelling. *Children between 6 and 12 years of age* 250-500 mg half an hour before travelling	Single use before travel. If the travel will continue for more than 4 hours, an additional dose may be taken every 4th hour, if needed, up to a daily dose of 2.5 g. For children not more than 1.5 g.
Traditional herbal medicinal product symptomatic treatment of mild, spasmodic gastrointestinal complaints including bloating and flatulence	Powdered herbal substance	*Adults and Elderly* 180 mg three times daily as necessary	If the symptoms persist longer than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.
	Powdered herbal substance	*Adults and Elderly* 0.25-1 g three times daily	
	Tincture 1:10, 90% ethanol V/V	*Adults and Elderly* 1.5-3 ml three times daily	
	Tincture 1:2, 90% ethanol V/V	*Adults and Elderly* 0.25-0.5 ml three times daily	
Traditional herbal medicinal product used for temporary loss of appetite.	Powdered herbal substance	*Adults and Elderly* 0.25-1 g three times daily	If the symptoms persist longer than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.
	Tincture 1:10, 90% ethanol V/V	*Adults and Elderly* 1.5-3 ml three times daily	
	Tincture 1:2, 90% ethanol V/V	*Adults and Elderly* 0.25-0.5 ml three times daily	
Traditional herbal medicinal product used for relief of minor articular pain.	Powdered herbal substance	*Adults and Elderly* 0.25-1 g three times daily	If the symptoms persist longer than 4 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.
	Tincture 1:10, 90% ethanol V/V	*Adults and Elderly* 1.5-3 ml three times daily	
	Tincture 1:2, 90% ethanol V/V	*Adults and Elderly* 0.25-0.5 ml three times daily	
Traditional herbal medicinal product used for the relief of symptoms of common cold.	Powdered herbal substance	*Adults and Elderly* 0.25-1 g three times daily	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.
	Tincture 1:10, 90% ethanol V/V	*Adults and Elderly* 1.5-3 ml three times daily	
	Tincture 1:2, 90% ethanol V/V	*Adults and Elderly* 0.25-0.5 ml three times daily	

*Duration of use is harmonised with other monographs with the same indications.

Therapeutic area indications 1 and 2: Gastrointestinal disorders

Therapeutic area indication 3: Loss of appetite

Therapeutic area indication 4: Pain and inflammation

Therapeutic area indication 5: Cough and cold

Annex

List of references