EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Zingiber officinale* Roscoe, rhizoma

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

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

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Not applicable.
Herbal preparation(s)	Powdered herbal substance.
Pharmaceutical forms	Herbal preparation ins solid dosage forms for oral use.

Note: This draft Assessment Report is published to support the release for public consultation of the draft Community herbal monograph on *Zingiber officinale* Roscoe, rhizoma. It should be noted that this document is a working document, not yet fully edited, and which shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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1. Introduction

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

- Herbal substance(s)

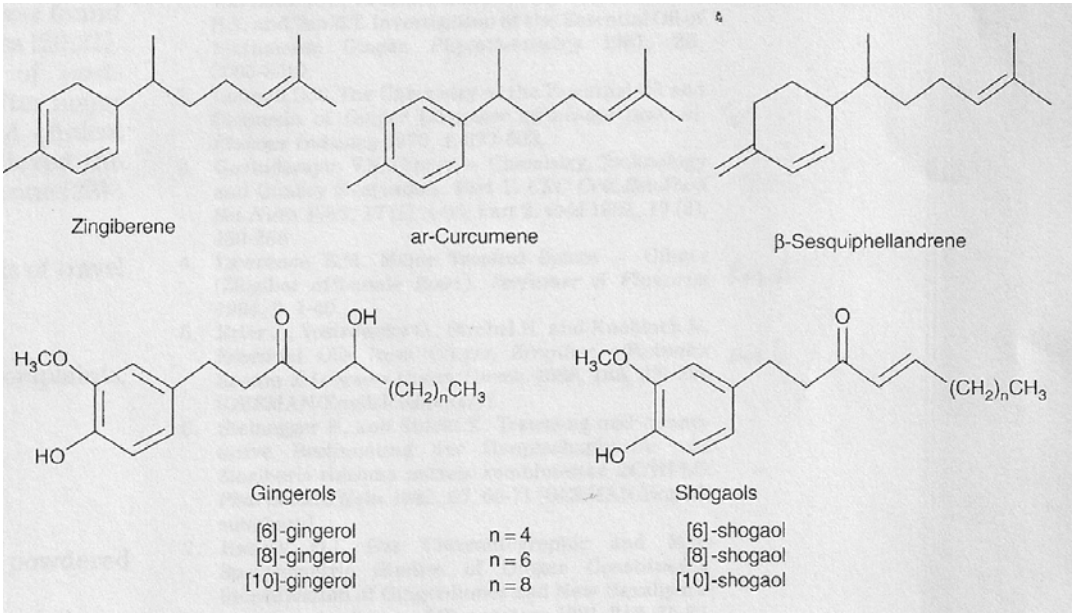
Ginger (Zingiberis rhizoma) consists of the whole or cut rhizome of *Zingiber officinale* Roscoe (*Zingiberaceae*), with the cork removed, either completely or from the wide flat surfaces only. Ginger plants have been extremely popular – for cooking as spice and to treat a host of ailments – throughout Asia, especially in India and China, for over 5000 years.

The species *Zingiber officinale* originates from Southeast Asia. It is not known to occur wild [Teuscher 2006; Langner *et al.* 1998; Germer *et al.* 1997]. It is a perennial herb, up to 1.5 metre in height, with asymmetric flowers. Due to the long period of breeding in different continents, different types of the species have developed. The herbal drug ginger , that complies with the monograph of the European Pharmacopoeia, originates from the West Indian type (Jamaica-ginger) with the cork removed or from Indian types (Bengal-ginger, Cochin-ginger) peeled on the flattened sides only.

Constituents: Volatile oil 1-4 % (Ph. Eur. Min 15 ml/l). 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 & 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 & O'Neill 1990; Jolad *et al.* 2005; Kim *et al.* 2008; Steinegger & Stucki 1982]. Other constituents are starch, up to 50 %, lipids 6-8 %, proteins, and inorganic compounds [Awang 1992; ESCOP 2009].

The requirements of the US Pharmacopoeia for ginger are: gingerols and gingerdiones not less than 0.8 %, volatile oil not less than 1.8 ml per 100 g, starch not less than 42 % and shogaols not *more* than 0.18 % [Bradley 1992; USP 2009].



- Herbal preparation(s)

Aromatic cardamom tincture. Strong ginger tincture. Weak ginger tincture [BP 2008]. Ginger tincture [USP 2009].

Proprietary preparations with powdered ginger or ginger preparations. Ginger as part of multi-ingredient preparations [Martindale 2009].

- 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. Information about products on the market in the Member States

Products on the market

Name of the product	**Active substance**	**Indication**	**Posology**	**Legal status**
Spain: "capsules"	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	Registration since 1991
Austria Zintona – Kapseln	Zingiberis rhizoma pulvis, Ph. Eur. 250 mg/capsule	Prevention of symptoms of motion sickness (kinetosis), *e.g.* dizziness, nausea and vomiting.	Adults and children from 6 years: 2 capsules half an hour before the start of the travel,	Marketing authorisation since 1987

Name of the product	Active substance	Indication	Posology	Legal status
			then 2 capsules every 4 hours.	
UK	1) 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. Adults: 1 tablet, three times daily as necessary. Children: Not recommended for children.	The product has been on the market for 42 years as a licensed medicine, during which time no adverse reactions have been reported.
	2) Pulverised ginger 180 mg	A traditional herbal remedy used as a carminative		

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Details in scheme
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	One product authorised 10 years ago; food supplements marketed.
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	2 combination products; monoproducts as food supplements
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products marketed
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	2 powder products with MA since 1992
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

Member State	Regulatory Status				Comments
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify: Food supplements	No medicinal products marketed
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	Details in scheme
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products
United Kingdom	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	2 products licensed since 42 years (indication: carminative and symptomatic relief of travel sickness)

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
Other: If known, it should be specified or otherwise add 'Not Known'
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

Clinical studies were searched with the use of MEDLINE using the PubMed interface to identify eligible articles. The search included all randomised studies indexed by PubMed that were published through June 2010. Unqualified key words were used, which are searched as text words in the title, abstract, and full journal article. The unqualified terms were also matched against a MeSH (Medical Subject Headings) Translation Table, a Journals Translation, a Phrase list, and an Author Index. The search strategy included the terms for ginger, and terms for the specific diseases or conditions derived from its traditional use and current indications, supplemented with those expected from non-clinical studies with ginger. In addition to the PubMed literature search, bibliographies of review articles and eligible articles were examined in an effort to identify all available literature that may not have been identified by the database research. The search was limited to English and German language papers. Only studies, in which the root of *Zingiber officinalis*, either fresh or in its many processed forms was used, are included. Randomised studies that used combination products with ginger as one of its ingredients are not included.

2. Historical data on medicinal use

Ginger has been cultivated and used for medicinal purposes since ancient times, as described in the old Chinese and Indian texts. It was an important ingredient in herbal medicines for catarrh, rheumatism, constipation, vomiting and other digestion disorders.

The species *Zingiber officinale* is not known to occur in the wild state. It is assumed that it originated in south-east Asia [Afzal *et al.* 2001; Teuscher 2006].

In ayurvedic medicine described in the Sanskrit texts dating back to 2000 BC, 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 child birth and filariasis [Dev 2006, Kapoor 1990]. A paste of ginger was used as a local stimulant and rubefacient in headache and toothache [Kapoor 1990].

Monographs of ginger are still included in the Ayurvedic Pharmacopoeia of India [2009], Indian Herbal Pharmacopoeia [2002], and Indian Pharmacopoeia [2007].

In traditional Chinese medicine ginger is classified as a warming remedy releasing exterior conditions. 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 Pharmacopoeioa of the People's Republic of China [2005].

2.1. Information on period of medicinal use in the Community

In Europe ginger was mentioned in the 1st century by the Greek physician Dioscorides to have digestive properties, for stimulating the gut and as profitable for the stomach [Langner *et al.* 1998]. It was used in all European countries from about 1100 [Afzal *et al.* 2001].

In the early European herbals, written by Harpestreng ca.1200, Lonicerus 1564, Matthiolus 1626, Bentley and Trimen 1880, ginger is described as useful for increasing appetite and digestion, for gout and for infection in the mouth and gingiva [Harpestreng 1200; Madaus 1938]. Monographs of ginger have been and are still a part of most of the European pharmacopoeias [Imbesi 1964; Ph. Dan. 1772].

Monographs of ginger have been and are still included in several non-European pharmacopoeias [Imbesi 1964; Pharmacopoeia of the People's Replublic of China 2005; The ayurvedic pharmacopoeia of India; Indian Pharmacopoeia 2007; Ph. Eur. 2010].

2.2. Information on traditional/current indications and specified substances/preparations

Prophylaxis of motion sickness [Barnes *et al.* 2007; Blumenthal *et al.* 1998; Bradley 1992; ESCOP 2009; Indian Herbal Pharmacopoeia 2002; Martindale 2009; WHO 1999].

Nausea and vomiting in pregnancy [Bradley 1992; ESCOP 2009; Martindale 2009; WHO 1999].

Postoperative nausea [ESCOP 2009; WHO 1999].

Digestive disorders [Barnes *et al.* 2007; Blumenthal *et al.* 1998; Bradley 1992; WHO 1999].

Rheumatic complaints [Barnes *et al.* 2007; Bradley 1992; WHO 1999].

In ayurvedic medicine: as carminative, promoter of digestion, anti-colic, and curative of piles and haemorrhoids as well as for treatment of chronic skin diseases, obesity and abnormal bleeding after child birth [Dev 2006].

Carminative, anti-emetic, anti-inflammatory [Indian Herbal Pharmacopoeia 2002].

In Chinese medicine dried ginger is used to treat abdominal pain, lumbago and diarrhoea, also for cholera, haemorrhage, rheumatism and toothache. Fresh ginger is used for abdominal distension, coughing, vomiting, and to promote sweating and reduce the poisonous effect of other herbs [Awang 1992; Bone 1997].

For epigastric pain with cold feeling, vomiting and diarrhoea accompanied with cold extremities and faint pulse. For dyspnoea and cough with copious frothy expectoration [Pharmacopoeia of the People's Republic of China 2005].

2.3. Specified strength / posology / route of administration / duration of use for relevant preparations and indications

2-4 g powdered rhizome daily [WHO 1999].

For prophylaxis of travel sickness: adults and children over 6 years: 1-2 g powdered rhizome (single dose) 30 minutes before travel [Barnes *et al.* 2007; Bradley 1992; Indian Herbal Pharmacopoeia 2002].

2-4 g powdered rhizome daily [Blumenthal *et al.* 1998].

0.5-2 g powdered rhizome 30 minutes before travel [ESCOP 2009].

Nausea of pregnancy: powdered rhizome, 500 mg 2-4 times daily [Mills & Bone 2000]; 750 mg-2 g daily in divided doses for 1-5 days [ESCOP 2009].

Postoperative nausea and drug induced nausea: powdered rhizome 0.5-1 g one hour before surgery [ESCOP 2009; Langner *et al.* 1998].

Digestive complaints: powdered rhizome 0.25-1 g three times daily, tincture (1:10, 90 % ethanol, weak ginger tincture) 1.5-3 ml, tincture (1:2, 90% ethanol, strong ginger tincture) 0.25-0.5 ml [Bradley 1992].

Ayurvedic medicine: Powdered dry drug: 1-2 g [Ayurvedic Pharmacopoeia of India 2009; Indian Herbal Pharmacopoeia 2002; Kapoor 1990]. Infusion: 28-56 ml every hour for ingestion and want of appetite [Kapoor 1990].

Powdered drug or fresh drug: 3-9 g [Pharmacopoeia of the People's Republic of China 2005].

3. Non-Clinical Data

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

Many pharmacological studies have demonstrated that ginger extracts 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 clinical efficacy will be reviewed (for a more extensive review, see Ali *et al.* [2008] and Chrubasik *et al.* [2005]).

3.1.1. Antiemetic properties

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 & 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 & 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 extract (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* trial 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]. Further, *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 & Gilani [2005a] showed that 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 dose-dependent (30 and 100 mg/kg) fashion [Ghayur & Gilani 2005a].

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 dexamethasone [Haksar *et al.* 2006].

Assessor's comment

Most studies in animals have demonstrated that ginger root extracts increase gastric emptying and gastrointestinal transit. Animal emesis models likewise have shown reduced emesis with the administration of ginger. Gingerols and shogaols seem to be active components. Nausea and vomiting are complex responses involving various neural pathways and motor responses to sensory stimuli; however, ginger and its constituents seem to function peripherally, by blocking 5-HT_3 receptors – and

most likely have an effect on other (cholinergic, vanilloid) peripheral receptors involved in smooth muscle contraction in the gastrointestinal tract.

3.1.2. Anti-inflammatory properties

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], and 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 pre-treatment of rats with 100 mg/kg dose of ethanolic ginger extract [El-Sharaki *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.* 2004]. In a murine macrophage cell line alcoholic ginger extract at a concentration of 100 µg/ml induced macrophage inducible nitric acid 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 up-regulation 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 [Wilarusmee *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) intra-peritoneal 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. More recently Fouda & 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 [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].

Assessor's comments

These, and many other in vitro and experimental animal studies, demonstrate that fresh ginger root and ginger root extracts have anti-inflammatory effects. These effects are at least partly derived from an inhibition of arachidonic acid metabolism via the COX-2 *(prostaglandins, thromboxanes) and lipoxygenase products (leukotrienes) pathways. However, a direct inhibitory action on genes encoding for pro-inflammatory substances (e.g., cytokines) may also play a role. Gingerols and shogaols seem to be active anti-inflammatory components.*

3.1.3. Antioxidant properties

Several authors have shown that ginger root is endowed with strong *in vitro* antioxidant and free radical scavenging properties [Jitoe *et al.* 1992; Nanjundaiah *et al.* 2009; Reddy & Lokesh 1992; Siddaraju & Dharmesh 2007; Singh *et al.* 2008].

Studies in experimental animals exposed to oxidative stress have confirmed the antioxidant action of fresh ginger [Ahmed *et al.* 2000; Ahmed *et al.* 2008; El-Sharaky *et al.* 2009; Mallikarjuna *et al.* 2008]. For instance, animal experiments have shown that ginger ethanolic extracts given as single doses or for several days can protect against nephrotoxicity from doxorubicin [Ajith *et al.* 2008] and cis-platin [Ajith *et al.* 2007a], hepatotoxicity from acetominophen [Ajith *et al.* 2007b] and bromobenzene [El-Sharaky *et al.* 2009], and testicular toxicity from cis-platin [Amin *et al.* 2008]. Xenobiotics that are considered to cause organ damage due to their strong oxidative properties. 6-gingerol and 6-shogaol are the main antioxidants of ginger [Aeschbach *et al.* 1994; Dugasani *et al.* 2010; Ippoushi *et al.* 2003; Kim *et al.* 2007; Masuda *et al.* 2004].

Assessor's comments

Fresh ginger root and alcoholic extracts of ginger have established antioxidative capacities in vitro and in whole animals. The main pungent constituents, 6-gingerol and 6-shogaol, appears to be the main antioxidants.

3.1.4. Antithrombotic properties

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 at al. 2008; Nurtjahja-Tjendraputra *et al.* 2003].

Assessor's comment

In vitro inhibition of thromboxane formation in platelets has repeatedly been shown with the addition of ginger extract

3.1.5. Hypolipidaemic and hypoglycaemic properties

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 streptozoticin (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.* 2009a].

From low to moderate, but significant 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 mechanism of action is uncertain. Interestingly, the ethanolic extract of ginger has been shown to protect rats from the metabolic disturbances induced by a high fat diet [Nammi *et al.* 2009b]. This effect may partially be mediated through 6-gingerol and 6-shogaol [Isa *et al.* 2008].

Assessor's comment

Most studies have shown a reduced plasma concentration of lipids, glucose and insulin in experimentally induced hyperlipidaemic and hyperglycaemic intact animals. The precise mechanism and the active constituents are not known.

3.1.6. Cardiovascular properties

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 & 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 [Weidner & Sigwart 2000].

Assessor's comment

There is presently not sufficient scientific evidence to suggest a cardiotonic or hypotensive effect of ginger root.

3.1.7. Antineoplastic properties

Several *in vitro* (using human cell line cultures) and *in vivo* (using tumour bearing animals) studies have demonstrated that ginger root and many of its phenolic components exhibit anti-neoplastic activity, however little is known regarding the precise mechanisms [Brown *et al.* 2009; Ishiguro *et al.* 2007; Jeong *et al.* 2009; Kim *et al.* 2005; Lee *et al.* 2008b; Lee & Surh 1998; Rhode *et al.* 2007; Sang *et al.* 2009; Suzuki *et al.* 1997; Unnikrishnan & Kuttan 1988; Yagihashi *et al.* 2008].

Ginger root and some of its constituents have also been reported to have tumour preventive effects. Preclinical *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]. Oxidative stress and inflammation are considered to play an important role in the tumour development. Because of this relationship pro-inflammatory cytokines, chemokines and iNOS are considered potential molecular targets for chemoprevention [Habib *et al.* 2008].

For a review of the cancer preventive properties of ginger, see Shukla & Singh [2007].

Assessor's comment

There is much evidence from in vitro and in vivo studies to suggest that ginger root extracts and several of its phenolic constituents have antineoplastic therapeutic and prophylactic potential. The exact mechanisms are not known.

3.1.8. Anti-infectious properties

Aqueous and organic extracts from ginger root have repeatedly been shown to possess broad *in vitro* antibacterial properties against both Gram positive and Gram negative human pathogenic bacteria, *e.g.*, *Escherichia coli*, Staphylococcus, Pseudomonas, Proteus, Porphyromonas [Park *et al.* 2008; Singh *et al.* 2008; Sunderland *et al.* 2009]. In addition, alcoholic and aqueous ginger extracts have been shown to inhibit the growth of several strains of *Helicobacter pylori* [Mahady *et al.* 2003; Mahady *et al.* 2005; Nanjundaiah *et al.* 2009; Nostro *et al.* 2005; Siddaraju & Dharmesh 2007], an aetiological agent in many gastrointestinal diseases, including gastric ulcer and gastritis, and possibly gastric cancer and mucosa associated lymphoid tissue lymphoma. Further, ginger extract may enhance the antibacterial

effect of some commonly used antibiotics [Nagoshi *et al.* 2006; Nostro *et al.* 2006]. Antibacterial properties have been ascribed to the gingerols contained in ginger [Mahady *et al.* 2003]. Ginger also seems to possess antifungal [Agarwal *et al.* 2008; Ficker *et al.* 2003a; Ficker *et al.* 2003b], antiviral [Koch *et al.* 2008; Schnitzler *et al.* 2007] and antihelminthic [Sanderson *et al.* 2002] properties.

Assessor's comment

Ginger root extracts and its pungent principles have demonstrated in vitro antibacterial, antifungal, antiviral and antihelminthic properties; however, its potential anti-infectious properties have not been examined in experimental infections in animals. The mechanism of action has not been examined sufficiently.

3.1.9. Thermogenic properties

The pungent principles of ginger, the gingerols and shogaols have thermogenic properties in pharmacokinetic studies [Westerterp-Plantenga *et al.* 2006]. Perfusion of the rat hindlimb with extracts of fresh and dry ginger resulted in an increased oxygen consumption, partly associated with vasoconstriction, which was partially caused by 6-gingerol [Eldershaw *et al.* 1994].

Assessor's comment

There is presently not sufficient scientific evidence to suggest a thermogenic effect of ginger root.

3.1.10. Analgesic properties

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].

Assessor's comment

There is presently not sufficient scientific evidence to suggest an analgesic effect of ginger root.

3.1.11. Pharmacodynamic interactions

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.

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

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.

3.2.1. Pharmacokinetic interactions

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 halftime ($t_{½}$: 12.7 *vs.* 8.6 hours), and decreased the elimination rate constant K_{el} 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].

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

3.3.1. Single dose acute toxicity

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 mice acute toxicity tests LD_{50} values for intravenous, intraperitoneal and oral administrations of 6-shogaol were respectively 50.9 (38.9-66.6; 95 % confidence intervals), 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. Repeated dose toxicity

Rong *et al.* [2009] evaluated the safety of powdered Japanese ginger (mainly containing 6-gingerol and galanolactone) by conducting a 35-day toxicity study in rats. Both male and female rats were

treated with 500, 1000 and 2000 mg/kg body weight/day by gavage. The results demonstrated that oral administration up to 2000 mg/kg to male and female rats was not associated with any mortalities and abnormalities in general conditions, behaviour, growth, and food and water consumption in the animals. Various parameters of haematology and blood biochemistry, except for a significant LDH decrease in male rats, were similar in both control and treated animals. The results of necropsy showed that all of the examined organs except for the testes of rats were normal. Only at high doses, 2000 mg/kg, ginger caused a reduced absolute and relative weight of testes (14.4 % and 11.5 %, respectively).

The effects of oral and intraperitoneal administration for 28 days of an aqueous extract of ginger root were investigated in female rats at dose levels of 50 mg/kg and 500 mg/kg for haematological parameters (haemoglobin, haemotocrit), 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 & Dairo [2007] administered 1 ml daily for 1 month of an ethanolic ginger extract in 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.

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]. 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. Another 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.

An alcoholic extract of ginger 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.

3.3.3. Genotoxicity

There are no reports available for an eventual genotoxicity of ginger.

3.3.4. Mutagenicity

In *Salmonella typhimurium* strains TA 98, TA 100 and TA 1535, an ethanol extract of ginger [Soudamini *et al.* 1995] and an essential oil from ginger [Sivaswami *et al.* 1991] demonstrated mutagenic activity at concentrations of 25-50 mg/plate and 5-10 mg/plate, respectively. Likewise, an ethanolic ginger extract at concentrations between 10 and 200 µg/plate, and gingerol and shogaol were mutagenic in strains TA 100 and TA 1838 with metabolic activation by rat liver S9 fraction, while zingerone did not display mutagenic effects [Nagabhushan *et al.* 1987]. Nakamura & Yamamoto [1982] found that rhizome juice of ginger contained both mutagen and anti-mutagen, and that 6-gingerol in particular was a powerful mutagen. 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 & Yamamoto 1983]. Capsaicin, the alkaloid present in chilli, is structurally related to gingerol and shogaol, and is also found to be mutagenic [Nagabushan & Bhide 1985]. The urine of rats fed diets containing 0.5, 1 and 5 % powdered ginger during 1 month and exposed to benzo(a)pyrene was found to display a significant reduction in the mutagenecity as indicated by a reduced number of TA98 and TA100 revertants at all ginger concentrations [Nirmala *et al.* 2007].

3.3.5. Reproductive and developmental toxicity

EV.EXT33, a standardised 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 & 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 and visceral and skeletal damages showed no embryotoxic or teratogenic effects of ginger. No differences were seen in foetal body weight or sex 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 (quantity of grated ginger root in boiling water for 10 minutes equivalent to those advocated for the treatment of morning sickness) via their drinking water from gestation day 6 to day 15. 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.

In a study by Dissabandara & Chandrasekara [2007] pregnant rats were administered dried powder extract of ginger orally 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.

Assessor's comment

Toxicity studies have generally been few and non-concordant. The acute toxicity studies indicate that ginger dosages to elicit acute toxicity are high and higher than usually employed dosages of ginger root. There is insufficient evidence that ginger root may cause testicular weight changes. Genotoxicity of ginger root has not been studied. Ginger root has mutagenic as well as antimutagenic properties in microbial test systems. Reproductive and developmental toxicity has been investigated in 3 studies in rats. Findings of advanced skeletal development in one study and increased embryo resorption in another study in the absence of any maternal toxicity or gross foetal toxicity or defects are difficult to interpret (one study using ginger tea and the other using powdered ginger in large daily dosages); however they seem not to suggest any major concerns with respect to reproductive and developmental safety of ginger root.

3.3.6. Overall conclusions on non-clinical data

In vivo animal experiments have demonstrated that ginger root extracts increase gastric emptying and gastrointestinal transit suggesting a role in the treatment and prevention of nausea and emesis. The mechanism is peripheral, by blocking 5-HT_3 receptors – and most likely other (cholinergic, vanilloid) peripheral receptors involved in smooth muscle contraction in the gastrointestinal tract. Also, anti-inflammatory – and antioxidant and antineoplastic – effects of fresh ginger root and extract have repeatedly been shown. The anti-inflammatory effects are at least partly derived from an inhibition of arachidonic acid metabolism via the COX-2 (prostaglandins, thromboxanes) and lipoxygenase (leukotrienes) products pathways. The administered dosages of ginger root have been similar (on a weight basis) to those taken by humans. Ginger extract can inhibit *in vitro* thromboxane formation in platelets; however the *in vivo* effect on blood coagulation is not known. Ginger extracts may have a beneficial effect on lipid and glucose metabolism, and may have anti-infectious properties against several strains of bacteria, viruses, helminths and fungi. Gingerols and shogaols seem to be active components; however other components have not been examined as extensively. There is presently not sufficient scientific evidence to suggest a cardiotonic or hypotensive, a thermogenic or an analgesic effect of ginger root.

The ginger extract dosages to provoke acute toxicity are high and much higher than usually employed dosages (factor 10-15 for an adult). There is some evidence that ginger root may cause testicular weight increase by repeated high dosages of ginger root extract (2000 mg/kg). Ginger root has mutagenic as well as antimutagenic properties in microbial test systems. Developmental toxicity studies in rats are difficult to interpret, however it is probably not a cause for concern. In general, toxicity studies of ginger are considered inadequate at least regarding genotoxicity, carcinogenicity and, partially, reproductive and developmental toxicity.

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

Gastrointestinal motility

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 (2 capsules) 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. In a third test ground ginger (940 mg) was tested using combined (visual and vestibular) emetic stimuli. 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. 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 again 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 on gastric dysrhythmias (that are involved in the pathogenesis of motion sickness) and nausea of ginger 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 subjects were 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. 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, the latency before the onset of gastric dysrhythmia after vector initiation and the duration of nausea after vector cessation were recorded. The subjects were asked to evaluate the severity of nausea at different time-points after vection on a 100 mm visual analogue scale (VAS). Ginger pre-treatment significantly reduced the maximal nausea score. Ginger prolonged latency before nausea onset, and it took subjects longer time to overcome nausea during placebo than during ginger. Tachygastric activity significantly increased during vection, however ginger significantly 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 containing 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 results showed 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 significantly 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.

Assessor's comment

Ginger extract in single dosages of 1000-2000 mg seems to modify gastric muscular contractions and increase gastric emptying, although two small studies (one non-randomised) did not demonstrate this effect. Indirect tests for gastric emptying are (by necessity) used which may not reflect real physiological conditions.

Vestibular system

A placebo-controlled, cross-over, double-blind study including 8 healthy volunteers studied the effect of powdered ginger root upon nystagmus following caloric stimulation of the vestibular system [Grøntved & Hentzer 1986]. Ginger, 1 g, and placebo (lactose), 1 g, was administered one hour prior to irrigating the ear with 44°C warm water 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.

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 results demonstrated that powdered ginger did not affect nystagmus responses compared to placebo, while expectedly dimenhydrinate reduced nystagmus responses compared to placebo and ginger.

Assessor's comment

The studies suggest that ginger root does not have an effect on the vestibular system.

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 B_2 production after ingestion of 5 g fresh ginger daily for 1 week [Srivastava 1989]. However, 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 informed) no effect on maximum *ex vivo* platelet thromboxane B_2 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 rhizomes (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 & Bordia [2001] studied the effect on fibrinolysis after oral intake of 5 g of powdered ginger rhizomes *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 is, however, difficult to interpret, because of lack of description of 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] 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 study is difficult to interpret because the researchers did not perform 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 (study described in section 5.5.2) [Jiang *et al.* 2005].

Assessor's comment

Pharmacodynamic 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.

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 insufficient evidence to document a pharmacodynamic effect of ginger root on blood lipids and blood sugar.

Other effects

Only one small study has investigated the thermogenic properties of ginger in humans [Henry & Piggott 1987]. Eight healthy volunteers on separate days ingested a breakfast meal with and without the addition of ginger sauce (containing 30 g of fresh ginger). The metabolic rate measured by oxygen consumption demonstrated that the ginger breakfast did not have an additional effect on the metabolic rate compared to the non-ginger breakfast.

The effects of ginger on the DNA content of gastric aspirates in 10 healthy volunteers showed that a filtrate from 6 g or more significantly increased the exfoliation of gastric cells suggesting a gastric irritant effect of ginger [Desai *et al.* 1990].

Pharmacodynamic studies that have examined ginger's effect on inflammation or infection and oxidation or free radical generation have not been disclosed.

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.

4.2. Clinical Efficacy

4.2.1. Dose response studies

No dose response studies have been performed.

4.2.2. Clinical studies (case studies and clinical trials)

Nausea and vomiting

Non-randomised studies and case studies

No studies were found.

Systematic reviews and meta-analyses

In a systematic review of double-blind, placebo-controlled studies of the efficacy of ginger against nausea and vomiting published before November 1997 Pittler & Ernst [2000] found 6 studies which fulfilled their inclusion criteria. Three studies dealt with the efficacy on postoperative nausea and vomiting, and 1 study each on chemotherapy-induced nausea and vomiting, pregnancy-induced nausea and vomiting (morning sickness) and motion sickness (seasickness). The pooled absolute risk reduction for postoperative nausea and vomiting was 0.052 (95 % CI: 0.082-0.186; ginger *vs.* placebo). The authors found ginger a promising antiemetic herbal remedy, however the clinical data were insufficient to draw firm conclusions.

Betz *et al.* [2005] published a systematic review of the effect of ginger in nausea and vomiting. Randomised studies up to June 2003 were included. Sixteen studies with a total of 801 patients fulfilled the inclusion criteria. The dosage of ginger was between 0.5 g and 2 g daily. Jadad scores were mean 4 and varied between 1 and 5. Six studies concerned the effect on postoperative nausea and vomiting (PONV), 4 studies on pregnancy-induced nausea and vomiting and 6 studies on motion sickness. The authors concluded that there was no clear evidence for the efficacy of ginger for the treatment of nausea and vomiting in motion sickness and PONV. With respect to the effect on pregnancy-induced nausea and vomiting results were promising; however, ginger was recommended only to be used in controlled clinical studies.

Postoperative nausea and vomiting

Non-randomised studies and case studies

No studies were found.

Systematic reviews and meta-analyses

Morin *et al.* [2004] identified 6 randomised studies including 538 patients (placebo: n = 223; ginger: n = 315) in their systematic review of the effect of ginger compared to placebo in postoperative nausea and vomiting (PONV). The literature search was ended in December 2003. The ginger dosage used in the included studies was between 0.5 g and 2 g daily. The summary relative risk of PONV

within the first 24 hours after surgery was 0.84 (95 % CI: 0.69-1.03; ginger *vs.* placebo). The number needed to treat (NNT) was 11 (95 % CI: 6-250).

Chaiyakunapruk *et al.* [2006] performed a systematic review and a meta-analysis of the efficacy of ginger in PONV. Criteria for trial inclusion were that 1) the trial should be randomised and placebo-controlled; 2) should evaluate the anti-emetic effects of ginger for the prevention of PONV; 3) at least 1 g of ginger was administered; 4) and the data were sufficient to calculate the incidence of 24-hours PONV or postoperative vomiting (POV). The authors included 5 studies (including 1 study that had not been published) with a total of 363 patients. Jadad-scores ranged from 3 to 4. The meta-analysis found that ginger was significantly better than placebo for the prevention of PONV and POV. Summary relative risks of ginger for PONV were 0.65 (95 % confidence interval (CI): 0.51-0.84) and for POV 0.62 (95 % CI: 0.46-0.84). None of the included studies reported the amount of active ingredients or the quality of ginger preparations. Although it is stated in the publication that heterogeneity and publication bias were assessed, the results of these tests are not given.

Randomised studies

Bone *et al.* [1990] randomised 60 women who were scheduled to undergo major gynaecological surgery. They were randomised to receive: 1: ginger root (flavoured with ginger essence; preparation not described), 1 g, and placebo injection (sterile water); 2: placebo (lactose flavoured with ginger essence) and metoclopramide injection, 10 mg; or 3: placebo capsule and placebo injection.
The capsules were taken orally at the time of pre-medication and the injection was administered intravenously (iv) at induction of anaesthesia. The study was double-blinded and similar anaesthetic techniques were employed in the 3 groups. The patients were questioned for the occurrence of nausea and vomiting and nausea was graded as none, mild, moderate or severe in the recovery and at 4, 12, and 24 hours after operation. There were significantly fewer episodes of nausea at the assessment 4 hours postoperatively in group 1 and group 2 compared to placebo. Further, more patients scored greater degrees of nausea in the placebo group compared to those who received either ginger or metoclopramide (NS). The postoperative administration of metoclopramide was significantly greater in the placebo group compared to the other groups.

The efficacy of ginger for the prevention of PONV was examined in patients scheduled for elective gynaecological laparoscopy using the ASA 1 or 2 physical status classification system [Arfeen *et al.* 1995]. One-hundred-and-eight women were included in this double-blind, placebo-controlled study with 3 treatment arms: group 1 received 2 placebo capsules; group 2 received 1 placebo and 1 ginger capsule; and group 3 received 2 ginger capsules. Each ginger capsule contained 500 mg of ginger powder. All patients received diazepam 10 mg as oral pre-medication, and pre-medication and test drugs were administered 1 hour before induction of anaesthesia with thiopentone followed by vecuronium. The duration of the operation was around 30 minutes. Postoperative pain was treated by administering small intravenous doses of morphine as required, and metoclopramide 10 mg intravenous was given only in case of severe nausea or vomiting. Three hours post-operatively patients were questioned to determine if they had experienced any nausea and vomiting, and when present nausea was graded categorically (no nausea; mild nausea; moderate nausea; severe nausea) and vomiting graded as yes/no. Six patients who entered the study were replaced. The study showed that ginger was ineffective in preventing PONV. In fact, the incidence of PONV tended to increase as the dose of ginger increased from 0 to 1 g.

Visalyaputra *et al.* [1998] studied 120 women with ASA grade 1 or 2 scheduled for gynaecological diagnostic laparotomy. They were randomly allocated into 4 groups: 1) a placebo group received 2 capsules of placebo (spray dried rice starch) and an intravenous injection of 0.5 ml saline 1 hour before induction of anaesthesia; 2) a droperidol group received 2 placebo capsules and droperidol

1.25 mg in 0.5 ml saline before induction; 3) a ginger group took 2 capsules of ginger each of 0.5 g and saline 0.5 ml iv; and 4) a ginger + droperidol group who received 2 capsules of ginger and droperidol 1.25 mg. Thirty minutes before discharge, all patients received 2 capsules (1 g) of either ginger or placebo. Anaesthesia was induced with thiopentone and fentanyl followed by suxamethonium. The incidence and severity of nausea (on a 4-point scale), and the frequency of vomiting were recorded by an investigator during 24 hours after discharge. Nine patients were not studied. In a per protocol analysis, there were no significant differences in the incidence of nausea and vomiting frequency between the 4 study groups.

A total of 184 women undergoing gynaecological laparoscopies were included in a placebo-controlled trial by Eberhart *et al.* [2003]. Included women were randomised to 1 of 3 groups: 1) a placebo group (as 3 x 2 capsules); 2) a group that took a total of 300 mg of ginger extract (as 3 x 1 ginger and 3 x 1 placebo); and 3) a group that took 600 mg ginger (as 3 x 2 ginger). Ginger and placebo was administered 1 hour pre-operatively, and 3 and 6 hours post-operatively. All patients were pre-medicated orally with 20 mg of clorazepate, and anaesthesia was induced with propofol, fentanyl, atracurium and in some patients with succinylcholine. Desflurane in nitrous oxide/oxygen and additional fentanyl were used for maintenance. Post-operatively pain was treated with small doses of opioid. If a patient requested therapy for PONV or had nausea for at least 10 minutes or had more than 2 emetic episodes, droperidol was followed by tropisetron, if droperidol was ineffective. Patients were assessed 1, 3, 6 (while admitted) and 24 hours post-operatively (by telephone). Patients were asked to rate nausea and post-operative pain since the last visit using a 4-point verbal rating scale, and to quantify episodes of vomiting or retching. Because of uncertainty with respect to the efficacy and dose responsiveness, it was decided to make an interim analysis (after inclusion of half the calculated number of patients = 180), and stop the trial if there was no realistic chance to detect a clinical relevant difference with continuation of the study. Of the 184 women, 180 women were randomised and further 5 women were subsequently excluded for surgical reasons. The interim analysis demonstrated no difference between groups in PONV. There was also no difference with respect to nausea, vomiting and the need for anti-emetic rescue among the 3 groups.

Nanthakomon & Pongrojpaw [2006] performed a double blind, placebo-controlled trial of the effect of ginger in women in ASA 1 or 2 who were scheduled to undergo elective exploratory laparotomy. The verum group took 2 capsules (1000 mg) of powdered ginger and the placebo group took 2 capsules of lactose (1000 mg) 1 hour prior to surgery. Induction of anaesthesia was with thiopental, followed by alcuronium or vecuronium. Morphine was not used. PONV was treated with metoclopramide upon request from the patient and diclofenac was administered on request for pain. Nausea was recorded on a 100 mm linear visual analogue scale (VAS). The number of vomiting episodes was recorded. Patients were assessed at 0, 2, 6, 12 and 24 hours after completion of surgery. In total 120 patients were included and there were no non-completers. Scores of nausea at 2, 6, 12, and 24 hours post-operatively were lower with ginger than with placebo and significantly lower at 2 and 6 hours Significantly fewer patients in the ginger group complained of nausea compared to the placebo group (48.3 % *vs.* 66.7 %). The number of patients with vomiting was significantly lower with ginger (28.3 %) than with placebo (33 %). The need for post-operative anti-emetics was non-significantly lower with ginger than with placebo (18.3 % *vs.* 33 %).

Apariman *et al.* [2006] included 60 patients who were admitted for elective non-cancer gynaecological laparoscopy. Included patients were randomised into treatment with 1.5 g of powdered ginger administered as 3 capsules of 0.5 g, or 3 capsules of placebo. Ginger or placebo was taken 1 hour before starting the operation. Patients were instructed to score nausea symptoms according to a 100 mm VAS and patients were assessed for the presence of vomiting at 2 and 6 hours after surgery. Similar anaesthetic technique and agents were used. Postoperative analgesics were given according to patients' requirements and metoclopramide was given if more than 2 episodes of vomiting occurred.

There were no statistical significant differences in both nausea and vomiting at 2 hours post-operation. At 6 hours post-operatively median Visual Analogue Scale (VAS) was significantly lower in the ginger group than in the placebo group. Incidence of vomiting was also lower in the ginger group (23.3 %) compared to placebo (46.7 %).

The aim of the study by Tavlan *et al.* [2006] was to compare the prophylactic effect of dexamethasone plus ginger with dexamethasone alone on PONV in patients undergoing thyroidectomy. One-hundred-and-twenty patients were included. The patients received 1 dosage of 0.5 g of ginger (preparation not described) or placebo (preparation not described) with oral pre-medication with diazepam 1 hour prior to surgery. Both groups received 150 µg/kg of dexamethasone intravenously before induction of anaesthesia that was induced with propofol and fentanyl. Postoperative pain was treated with intravenous fentanyl and tenoxicam. Nausea and vomiting were assessed in the first 24 hours after surgery. Nausea and vomiting were assessed on a 4-point scale from no nausea to multiple episodes of vomiting. At the end of the observation period, patients evaluated the severity of nausea on a numerical scale ranging from 0 to 2. The results showed that dexamethasone plus ginger did not significantly reduce nausea and vomiting occurrence, and the severity of nausea, compared with dexamethasone alone.

One-hundred-and-twenty patients with ASA scores 1 and 2 undergoing non-emergency surgery were randomised to 6 treatment groups: 1) shavings of fresh ginger, powdered, 250 mg; 2) metoclopramide, 10 mg; 3) prochlorperazine, 5 mg; 4) promethazine, 20 mg; 5) ondansetron, 4 mg; and 6) placebo, all in similar looking capsules [Nale *et al.* 2007]. Capsules were administered 1 hour prior to surgery, and subsequently at 8 hours intervals for a total of 24 hours pre-medication, induction and maintenance anaesthesia were similar in all groups. Nausea severity was assessed with a 100 mm VAS scale and episodes of vomiting were counted for a period of 48 hours postoperatively. The intensity of nausea was significantly lower with ginger than with placebo. The frequency of vomiting was also lower with ginger; however, it is difficult to interpret the results as no statistics are given.

Assessment of the studies' quality is given in Table 1 in the annex to this assessment report.

Assessor's comment

A total of 8 randomised studies are presented of the effect of ginger on nausea and vomiting on PONV. Most studies used ginger as single dosages of 1000 mg 1 hour before induction of anaesthesia with nausea measured on a VAS-scale and vomiting measured as number of episodes during the first 24 hours after elective and/or minor surgery. Powdered ginger was administered orally 1 hour before anaesthesia induction. Four studies demonstrated a significant, albeit minor but clinical relevant, decrease in nausea and/or vomiting, while four other studies did not demonstrate a significant efficacy of ginger root. One recent meta-analysis demonstrated efficacy of ginger against postoperative nausea and vomiting. According to the general guideline of clinical documentation a well established use of ginger root in the prevention of PONV is suggested.

Pregnancy-induced nausea and vomiting

Non-randomised studies and case studies

No studies were found.

Systematic reviews and meta-analyses

A Cochrane review from 2003 found 28 randomised trials that measured the effect of different methods on pregnancy-induced nausea and vomiting [Jewell & Young 2003]. Only 2 trials on ginger use were included; too few to assess collectively.

A systematic review that 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) has been published by Borelli *et al.* [2005]. A total of 675 pregnant women participated. In 4 of the 6 randomised trials ginger was superior to placebo; the remaining 2 trials demonstrated that ginger was as effective as the reference treatment (vitamin B_6) in relieving the severity of nausea and vomiting. Five of the six studies were judged to have a maximum Jadad score of 5. 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. The conclusion from the systematic review was that ginger might be an effective treatment in managing nausea and vomiting symptoms in pregnancy.

Randomised studies

Thirty women admitted for hyperemesis gravidarum took part in a randomised cross-over study to examine the efficacy of powdered ginger root against placebo [Fischer-Rasmussen *et al.* 1990]. Three patients were withdrawn. At inclusion of the study and at the second treatment period the severity of nausea was assessed by a scoring system that evaluated the degree of nausea, vomiting and weight loss (maximum 10 points). The patients were given capsules containing 250 mg of ginger or placebo containing 250 mg of lactose 4 times daily for 4 days interspersed by a 2 days' wash-out period. For the evaluation of treatment effect a (slightly different) scoring system for symptom relief was applied including a subjective assessment by the patient about her opinion of the treatment after each period. The scoring systems were adopted from a validated (details not known) report on hyperemesis and ACTH. The mean values of the severity scores decreased equally in the two groups from the first to the second period. A significantly greater relief on hyperemesis symptoms was demonstrated after ginger compared to placebo (P = 0.035). Specifically a reduced number of attacks of vomiting and decreased nausea were obtained by the ginger treatment. Nineteen women (70.4 %) preferred the ginger treatment and 4 women (14.8 %) preferred placebo treatment (P = 0.003).

Vutyavanich *et al.* [2001] studied women before 17 weeks of gestation who attended an antenatal clinic and complained of nausea with or without vomiting. They were randomised into two groups: a ginger group who received one 250 mg capsule of powdered ginger 4 times daily for 4 days and a placebo group that received identical-looking capsules and the same dosage regimen. Ginger (and placebo; contents not described) capsules were prepared by a pharmacist using fresh ginger root as starting material. The primary outcome was the improvement in nausea symptoms that were measured by 2 independent scales; a 100 mm VAS scale and a Likert scale. The VAS scale was filled in at start of the study and twice daily during the treatments. The 5-item Likert scale (much worse, worse, same, better, much better) was used at a 7-day follow-up visit to assess the women's response to treatment. Secondary endpoints were the change in the number of vomiting episodes. Seventy women were randomised and three women were non-completers. The median change in nausea scores (average over 4 days) in the ginger group was significantly greater than that in the placebo group in the per protocol (PP) analysis (P = 0.014), but not in the intention-to-treat (ITT) analysis (P = 0.082). After 4 days of treatment the proportion of women with vomiting in the ginger group (12 of 32; 37.5%) was significantly less (P = 0.021) than that in the placebo group (23 of 35; 65.7%). With respect to the average number of vomiting episodes during the treatment periods, the ginger group was significantly better than the placebo group, both in the PP analysis and in the ITT analysis. At the follow-up visit 28 of 32 (87.5 %) ginger treated women reported that their symptoms had improved compared to 10 of 35 (28.6 %) in the placebo group.

A small study including 26 women in the first trimester of pregnancy examined if ginger was a more effective remedy for the relief of nausea and vomiting than a placebo [Keating & Chez 2002]. The ginger consisted of 1 tablespoon of ginger syrup containing 250 mg ginger, honey and water while the

placebo contained lemon oil, honey and water. Patients were instructed to drink 1 tablespoon of syrup mixed in 4-8 ounces of water 4 times a day for 2 weeks. The level of nausea and the number of vomiting episodes were quantified daily using a numerical scale. Four women (1 at day 11) dropped out during the study. Ten of the 13 patients who received ginger had at least a 4-point improvement on the nausea scale on day 9, whereas only 2 of the 10 women in the placebo group had the same improvement. Eight of the 12 women in the ginger group who were vomiting daily at the beginning of the treatment stopped vomiting by day 6, while only 2 of the 10 women in the placebo group who originally were vomiting stopped by day 6. Due to the small number of patients statistical analyses were not performed.

Sripramote & Lekhyananda [2003] compared the efficacy of ginger to vitamin B_6 during 3 day treatment for nausea and vomiting during pregnancy at an antenatal clinic in a randomised, double-blind, parallel design. One-hundred-and thirty-eight pregnant women before 17 weeks of gestation, and who had nausea with or without vomiting and who requested antiemetics were included. They were allocated to receive capsules of powdered ginger root, 500 mg, or identical looking capsules of vitamin B_6, 10 mg, 3 times daily for 3 days. The primary outcome was improvement in nausea measured using the VAS. The measurement at the first enrolment to the study was the baseline score. During the 3-day treatment, the women were asked to record the severity of nausea 3 times daily in the morning, at noon and at bedtime. The average daily nausea scores and the average nausea score over 3 days were calculated. The number of vomiting episodes in the 24 hours before treatment and then on each subsequent day of treatment were also recorded. Of the 138 included women, 10 women did not return for follow-up. Both groups showed significant improvement in nausea comparing baseline score with the average score (14 mm; SD 22.2 in the ginger group *vs.* 20 mm; SD 21.9 in the vitamin B_6 group), however with no significant difference between groups. Vomiting episodes similarly declined in both groups comparing baseline to average vomiting episodes, however with no difference between groups.

Willetts *et al.* [2003] studied the effect of ginger extract in 120 women who experienced morning sickness in a parallel group, double-blind, placebo-controlled study. The study medication was supplied in identically looking capsules, the active treatment (EV.EXT35) containing 125 mg ginger extract (equivalent to 1.5 g of dried ginger) and the placebo containing soy bean oil. Women were required to take the capsules 4 times daily for 4 days and to record their symptoms on the day before study start and 1 hour after taking the capsules using the Rhodes Index of Nausea, Vomiting and Retching 8-item, 5-point Likert scale. Of the 120 women included, 21 women were excluded due to adverse events (n = 12) and non-compliance (n = 9). The nausea experience score was significantly less for the ginger extract group compared to the placebo group after the first day of treatment, and this difference was present for each treatment day (except for day 3). No significant effect was found for vomiting.

A randomised equivalence study was performed by Smith *et al.* [2004] to examine whether the use of ginger to treat nausea and vomiting in pregnancy was equivalent to vitamin B_6. Women between 8 and 16 weeks of pregnancy were randomly allocated to receive either ginger 1 capsule (350 mg) or vitamin B_6 1 capsule (25 mg) 3 times daily for 3 weeks. Both products were provided with a certificate of analysis ensuring that the products were standardised and quality controlled (no further information is provided). Women completed the Rhodes Index of Nausea and Vomiting form for 3 days as a baseline before randomisation. The primary outcome assessed the equivalence and examined change in women's experience from nausea, retching, and vomiting from baseline at days 7, 14 and 21 by the Rhodes Index. Two-hundred-and ninety-one women were randomised and 56 were lost to follow-up. The study demonstrated that ginger was therapeutically equivalent to vitamin B_6. No difference was found between proportions of women completely free of their symptoms between treatment groups. Women's perception of an overall reduction in their symptoms was not found to differ between groups.

Data on blinding suggested that more women were aware that they were allocated to ginger than to vitamin B_6.

One-hundred-and-twenty-six women attending an antenatal clinic who had nausea with or without vomiting requiring treatment took part in a parallel-group, double-blind study in which treatment with capsules with ginger was compared with vitamin B_6 [Chittumma *et al.* 2007]. Each capsule contained 325 mg of powdered ginger prepared by a pharmacist in a registered herbal factory or 12.5 mg of vitamin B_6, and the dosage was 4 capsules per day for 4 days. Patients were requested to record their symptoms at first enrolment 24 hours before treatment, then at noon of each subsequent day during the trial. Nausea and vomiting scores were assessed by 3 physical symptoms (episodes of nausea, duration of nausea and numbers of vomits) modified from a full Rhodes score (lowest score was 3, highest 15). Of the 126 women randomised 3 dropped out. Nausea and vomiting scores decreased in both groups (PP-analysis), however the average decrease was significantly higher in the ginger group compared to the vitamin B_6 group (3.3 *vs.* 2.6; P = 0.042).

Pongrojpaw *et al.* [2007] studied pregnant women with less than 16 weeks of gestation attending an antenatal clinic with symptoms of nausea and vomiting in a double-blind, parallel-group, controlled study. The women were randomised to receive either 1 capsule containing 0.5 g of powdered ginger twice daily or 50 mg of dimenhydrinate twice daily for 1 week. The primary outcome was the improvement in nausea and vomiting symptoms. Nausea severity was measured using a 100 mm VAS. Nausea was assessed twice daily and the average daily nausea score calculated. The frequency of vomiting was recorded daily. One-hundred-and seventy women were included and 19 women were lost to follow-up. In the PP-analysis the daily mean nausea score decreased in both groups during the 7 days' study period with no statistically significant difference between groups. Also the daily number of vomiting decreased in both groups. The daily mean vomiting in the dimenhydrinate group on day 1 and 2 were less than the ginger group, however on day 3-7 the differences were non-significant.

Ozgoli *et al.* [2009b] conducted a randomised (the method of randomisation not described) single-blind study including 70 pregnant women under 20 weeks of gestation who complained of nausea and vomiting. Twenty-four hours before treatment and twice daily during ginger treatment they filled out a 100 mm VAS to measure severity of nausea. Vomiting frequency was measured at the same time points. Four ginger capsules, each containing 250 mg of ginger root powder, were prescribed daily for 4 days. The placebo capsules contained lactose. Three women were excluded, which left 32 women in the experimental group and 35 women in the placebo group. The ginger users demonstrated a higher rate of improvement in nausea than the placebo users (85 % *vs.* 56 %; P < 0.01) and the decrease in vomiting frequency was also greater among ginger users than among placebo users (50 % *vs.* 9 %; P < 0.05). Only PP-analyses were made.

Ginger was compared to vitamin B_6 in a double-blind, parallel-group study including 70 women who were 17 weeks of gestation or less, and had experienced nausea with or without vomiting in a study by Ensiyeh & Sakineh [2009]. Those in the ginger group received 1 g/day (2 capsules) of powdered ginger and those in the vitamin B_6 received 40 mg/day (2 capsules) for 4 consecutive days. Ginger and placebo were prepared by the hospital's pharmacist. A 100 mm VAS was used to quantify the severity of nausea at baseline and 3 times daily during study. At 1-week follow-up a 5-point Likert scale (much worse, worse, same, better, much better) was used to assess treatment response. Of the 70 women included, 1 dropped out. The median change in the nausea score (baseline minus average post-therapy score) in the ginger group was significantly greater (P = 0.024) than that in the vitamin B_6 group. There was no significant difference between groups in the number of vomiting episodes. In the ginger group 82.8 % reported an improvement in their symptoms compared with 67.6 % in the vitamin B_6 group (P = 0.52).

Assessment of the studies' quality is given in Table 1 in the annex to this assessment report.

Assessor's comment

A total of 10 randomised studies were found on the efficacy of ginger root in pregnancy-induced nausea and vomiting (including one study that examined the efficacy on hyperemesis gravidarum). In 5 studies the efficacy was compared with placebo and in 4 studies with vitamin B_6 (in the remaining study the comparator drug was dimenhydrinate). Vitamin B_6 might not be the best comparator due to its uncertain efficacy. Different scales to measure efficacy were used; most used the validated Rhodes score or a VAS. Most often powdered ginger was used in dosages varying between 1000 and 1500 mg. The length of treatment was mostly 3-4 days; 1 study treated patients for 3 weeks. Most studies demonstrated that ginger was better than placebo or similar to vitamin B_6 in relieving nausea and vomiting during the first trimester of pregnancy. In general, the effects of ginger in nausea and vomiting were small, albeit significant and clinically relevant. A systematic review also demonstrated efficacy of ginger root. According to the general guideline of clinical documentation, a well established use of ginger root in the prevention of pregnancy-induced nausea and vomiting is suggested.

Chemotherapy-induced nausea and vomiting

Non-randomised studies and case studies

In a non-randomised study including 11 patients undergoing photopheresis for cutaneous T-cell lymphoma receiving the emetogenic drug 8-MOP, and who complained of nausea after 8-MOP ingestion, 1590 mg of ginger (as capsules, preparation not described) taken ½ hour before 8-MOP ingestion had markedly reduced nausea scores compared to their scores when not taking ginger [Meyer *et al.* 1995].

Randomised studies

Sontakke *et al.* [2003] carried out a double-blind, cross-over study in patients treated with cyclic (3 weeks) combination chemotherapy including cyclophosphamide, 500-1000 mg iv, who had at least 2 episodes of vomiting in previous chemotherapy cycle (the anti-emetic treatment during previous cycles not described). A total of 60 patients were included and 50 patients completed the study. The patients randomly were treated with one of the following antiemetic regimens: 1) 2 capsules, each containing 500 mg of ginger powder (preparation not described) orally, 2 ml of normal saline intravenously, 20 minutes prior to chemotherapy; 2 capsules of ginger were repeated 6 hours after chemotherapy; 2) 2 capsules of lactose orally and metoclopramide 20 mg iv, 20 minutes prior to chemotherapy; 2 capsules of 5 mg metoclopramide each orally after 6 hours; and 3) 2 capsules of lactose orally and ondansetron 4 mg iv, 20 minutes prior to chemotherapy and 2 capsules of ondansetron of 2 mg each orally after 6 hours The patients were randomised to first treatment, however had a fixed treatment order. Nausea was graded as none (complete control), mild to moderate and severe, and vomiting was graded as no vomiting (complete control), 1 or 2 episodes and 3 or more episodes for 24 hours during admission. The study showed that ondansetron was significantly better than ginger or metoclopramide to achieve complete control of nausea and vomiting. The difference in antiemetic effects of ginger and metoclopramide was not statistically significant.

Manusirivthaya *et al.* [2004] conducted a double-blind, cross-over study of the effect of ginger compared to placebo on cisplatin induced emesis. Eligible patients were in-patients receiving cisplatin containing chemotherapy either alone or in combination with other chemotherapeutic agents. The wash-out period was 3-4 weeks corresponding to the next cycle of chemotherapy. Patients received 2 capsules of ginger (or placebo) 30 minutes before and 1 capsule at 6 and 12 hours after chemotherapy together with standard antiemetics (metoclopramide, dexamethasone and lorazepam) on day 1. From day 2 to day 5 they received 1 capsule of ginger (or 1 capsule of metoclopramide)

4 times daily. Each capsule of ginger contained 250 mg of powdered ginger root, while placebo consisted of 250 mg of corn starch and one capsule of metoclopramide contained 10 mg. Assessment of nausea and vomiting in the acute phase were completed by the investigators while during the delayed phase patients recorded their symptoms in diary cards. Intensity of nausea was recorded daily by a 100 mm VAS. Emetic episodes were counted. Of the 48 patients who were included, 5 patients did not receive the second antiemetic treatment. The PP-analysis showed that the nausea score was not significantly different between treatment groups neither during the acute phase nor during the delayed phase. Vomiting episodes did not differ between groups. At the end of the study 41.9 % of patients expressed no preference, while 39.5 % preferred ginger and 18.6 % preferred the metoclopramide regimen (P <0.001).

Zick *et al.* [2009] did a double-blind, placebo-controlled trial in 162 patients with cancer who received chemotherapy and had experienced chemotherapy-induced nausea and vomiting during at least 1 previous round of chemotherapy. Patients were randomly assigned to receive a ginger extract, 1 g (4 capsules of ginger and 4 capsules of placebo), 2 g (8 capsules daily) or a matching placebo (8 capsules daily). Each capsule of ginger contained 250 mg dry ethanol extract of ginger root standardised to 15 mg total gingerols. Placebo consisted of lactose. All participants were receiving a 5-HT_3 receptor antagonist and/or aprepitant. Ginger was taken for 3 days, and the first dose was taken within 1 hour of the completion of chemotherapy. Effect on the severity and prevalence of nausea and vomiting was assessed by a modified validated Morrow Assessment of Nausea and Emesis questionnaire. Among the 162 patients included there were 33 non-completers. There were no differences (ITT-analyses) between groups in the prevalence of delayed nausea or vomiting, the prevalence of acute nausea and vomiting, or severity of delayed vomiting or acute nausea and vomiting. However, patients prescribed aprepitant and either dose of ginger had significantly more severe delayed nausea. Test for blinding efficiency showed that participants were able to accurately guess which treatment they had received.

Children and young adults, aged 8-21 years, with newly diagnosed bone sarcomas undergoing high emetogenic chemotherapy (a combination of cisplatin and doxorubicin for 3 days), were administered either ginger powder (no specifics with respect to formulation is given) or placebo (starch powder), in combination with ondansetron and dexamethasone used as standard antiemetic. The unit of randomisation was the cycle of chemotherapy [Pillai *et al.* 2011]. Patients weighing between 20 and 40 kg received 1000 mg per day (6 capsules per day, each containing 167 mg of either ginger or starch), while those weighing over 40 kg received 2000 mg per day (5 capsules per day containing 400 mg) from days 1 to 3 of the cycle. Patients or guardians were asked to complete a diary with questions of degree of nausea and vomiting as measured by Edmonton's Symptom Assessment Scale (a Likert scale) and the National Cancer Institute's Guidelines (the number of episodes and amount of vomitus per day), respectively, from days 1 to 10 of the chemotherapy cycle. The study parameters were the incidence and severity of acute (occurring within 24 hours of the start of chemotherapy) and delayed (occurring more than 24 hours after completion of chemotherapy) nausea and vomiting. Sixty of 61 consecutive cycle (number of patients = 31) were assigned to either oral ginger or placebo, and the number of cycles treated with ginger or placebo were similar. Acute severe to moderate nausea was observed in 93.3 % of the cycles in the control group compared to 55.6 % in the ginger group (P = 0.003). Also, moderate to severe vomiting occurred significantly more often in the control group compared to the experimental group. Delayed moderate to severe nausea was observed in 73.3 % of the cycles in the control group *vs.* 25.9 % in the ginger group (P < 0.001), and moderate to severe vomiting occurred significantly more often in the control group compared to the experimental group. One major drawback of the study was that the randomisation was done as per cycles rather than a prospective and consecutive inclusion of subjects.

Assessment of the studies' quality is given in Table 1 in the annex to this assessment report.

Assessor's comment

Four randomised studies were found that examined the efficacy of ginger root on nausea and emesis induced by chemotherapy. One study demonstrated non-inferiority to metoclopramide, and another study (of dubious methodology) in children demonstrated superiority to placebo. The 2 remaining studies were unable to demonstrate an effect of powdered ginger in daily dosages of up to 2000 mg taken in connection with chemotherapy. There is thus insufficient evidence for an effect of ginger root on chemotherapy-induced nausea and vomiting.

Motion sickness

Non-randomised studies and case studies

No studies were found

Randomised studies

Mowrey & 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 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.

Grøntved & Hentzer [1986] examined the degree of vertigo, by using a Likert scale (1-5), after irrigation of the ear with 44° C warm water 3 times at 20 minutes intervals in 8 healthy volunteers. The study was conducted as a double-blind, placebo-controlled, cross-over study with a wash-out period of 48 hours Ginger was taken as capsules of powdered ginger root, 1 g, or lactose, 1 g, about 1 hour prior to water instillation. The study showed that ginger root reduced vertigo significantly better than placebo.

In a randomised, double-blind, placebo-controlled trial 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 (68 %) noted symptoms of seasickness, equally distributed in the verum and placebo group. In a distribution made according to the severity of symptoms showed ginger to be significantly better than placebo in reducing the frequency of vomiting and cold sweating. The severity of nausea and vertigo showed no significant difference between the treatments.

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 end-point was determined using the Graybiel scale of motion sickness symptoms. The results showed that the 3 ginger doses were not significantly different from placebo.

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 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 effect of ginger was found to be significantly better and faster than dimenhydrinate. No patients in the ginger group complained of any side effects, while side effects occurred in two thirds treated with dimenhydrinate. The 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.

The effect of ginger on experimentally induced motion sickness has been examined in 2 additional randomised studies [Stewart *et al.* 1991; Lien *et al.* 2003]. The results from these studies have been discussed in the clinical pharmacology section

Assessment of the studies' quality is given in Table 1 in the annex to this assessment report.

Assessor's comment

Seven randomised studies (1 study – of inferior quality – in children) have examined the efficacy of ginger on motion sickness. Five of the studies were in experimentally induced motion sickness (e.g., rotating chair), while 1 study examined the efficacy in a "real life" situation. Mostly single dosages of 1000 mg (in children repeated dosages of 250-500 mg over 2 days) of powdered ginger root were administered prior to the induction of symptoms. In 5 studies ginger was better than placebo to prevent motion sickness. The effect size was generally small, albeit clinically relevant. Further, clinical pharmacology results suggest efficacy of ginger. According to the general guideline of clinical documentation, a well established use of ginger root in the prevention of motion sickness induced nausea and vomiting is suggested.

Musculoskeletal disorders

Non-randomised studies and case studies

Case studies have suggested that a high intake of ginger may be beneficial in relieving symptoms from osteoarthritis, rheumatoid arthritis and other musculoskeletal disorders [Srivastava & Mustafa 1992].

Systematic reviews and meta-analyses

A systematic review by Chrubasik *et al.* [2007] found that the evidence for effectiveness of ginger in osteoarthritis was moderate based on 2 confirmatory intervention studies of high quality with a relatively small effect size and 1 exploratory study of high quality. However, recent systematic reviews by Leach & Kumar [2008] and Rosenbaum *et al.* [2010] found no clear evidence for a beneficial effect

of ginger root on osteoarthritis based on, respectively, 3 and 4 randomised placebo-controlled, clinical efficacy studies.

Randomised studies

Bliddal *et al.* [2000] studied the effect of ginger extract compared to placebo and ibuprofen in patients with osteoarthritis of the hip and knee in a double-blind, double-dummy, cross-over study with a wash-out period of 1 week followed by 3 treatment periods each of 3 weeks' duration with acetaminophen as rescue medication. Treatments were 170 mg EV.EXT-33 ginger extract, ibuprofen 400 mg and placebo 3 times daily. The primary outcome was pain assessment with a 100 mm VAS. Further, the Lequesne Index for either hip or knee was used and the range of motion was recorded. These assessments were performed at study entry and at the end of each treatment period. The consumption of acetaminophen was counted at each visit. A total of 75 patients were initially included and 8 patients were excluded during the wash-out period. Consequently, 67 patients were randomised, and after secondary exclusion of 11 patients 56 were evaluable for treatment. There was a significant ranking of efficacy estimated with the VAS of the 3 treatment periods: ibuprofen>ginger>placebo, and the same trend was found for acetaminophen consumption. Also the Lequesne index changed with the same ranking. Multiple comparison testing, however, showed a significant difference between ibuprofen and ginger as well as ibuprofen and placebo, but not between ginger and placebo.

Two-hundred-sixty-one patients with osteoarthritis were enrolled in a double-blind, placebo-controlled, multicenter, parallel-group 6 week study [Altman & Marcussen 2001]. Admission criteria included the presence of knee pain on standing that had to be between 40 mm and 90 mm on a 100 mm VAS assessed after a 1 week's wash-out period for anti-inflammatory and analgesic medications (acetaminophen was allowed). During the 6 week treatment period patients took 1 capsule twice daily containing 255 mg of EV.EXT 77, extracted from 2,500-4,000 mg of dried ginger rhizomes and 500-1,500 mg of dried galanga rhizomes. Placebo capsules contained lactose. The primary outcome was the proportion of responders experiencing at least a 15 mm reduction in pain between baseline and final visit for knee pain on standing as measured by VAS. Secondary outcome parameters were 1) average improvement in pain on standing; 2) consumption of rescue medication; 3) WOMAC index (VAS); 4) patient assessment of global status (5-point Likert scale); 5) quality of life assessment (SF-12); and 6) pain in knee after walking 50 feet (VAS). High drop-out rates were encountered. Fourteen patients, 8 receiving placebo and 6 receiving ginger dropped out before completing any efficacy evaluation and 55 patients discontinued prematurely, leaving 194 patients who completed without study violation. Analysis was by ITT and PP. With respect to the primary outcome results showed a higher percentage of responders in the ginger group (63 %) than in the placebo group (50 %; $P = 0.048$), both in the ITT-analysis and in the PP-analysis. Among secondary outcome parameters pain after walking and stiffness (WOMAC) significantly improved in the group taking ginger compared to placebo.

Pain relief from osteoarthritis of the knee was also the aim of a double-blind, placebo-controlled, cross-over study [Wigler *et al.* 2003]. Included were patients with pain on knee movement of at least 35 mm on a 100 mm VAS after a 4 days' wash-out period of any previous medication. Twenty-six patients were included and 20 patients completed the study period. The patients were randomised to begin with capsules containing a ginger extract, 250 mg per capsule (containing 10 mg of gingerol) 4 times daily or placebo containing maltodextrin. After 12 weeks treatments were switched without a wash-out period, and continued for another 12 weeks. Outcome parameters were pain and handicap determined by WOMAC (100 mm VAS), and knee circumference measured by a tape. Outcome was measured weeks 4, 12, 16 and 24. During the first 12 weeks of the study VAS of pain on movement and VAS of handicap were reduced in both groups with no significant difference between groups. After cross-over the differences between groups became statistically significant in that the group that switched from

placebo to ginger VAS decreased further while in the group that switched from ginger to placebo VAS of pain and handicap increased. Similar results were found for knee circumference. The marked order effect and lack of wash-out make it difficult to interpret the results.

Haghighi *et al.* [2005] examined 120 outpatients with osteoarthritic pain in the hip or knee. After a 1 - week wash-out period during which treatment with analgesics was discontinued, they were randomised to treatment with capsules containing ginger extract (made from fresh ginger root, dried, powdered and extracted with ethanol), 500 mg 2 times daily; capsules containing ibuprofen, 400 mg 3 times daily, or lactose (placebo). Treatments lasted for 1 month. Before and at the end of trial patients were assessed for severity of pain, by using a 100 mm VAS-score, gelling pain, measurements of joint swelling and joint motion slope measurements. At 1 month the severity of pain score and the gelling pain score were significantly different among the 3 treatment groups. No significant differences were found for joint swelling or joint motion slope. Statistical test for multiple comparisons showed that there were significant differences between the ginger extract and the placebo, as well as ibuprofen and placebo, but not between ginger extract and ibuprofen for both severity of pain and gelling pain.

Ginger has also been used topically in an aromatic oil to relieve knee pain and stiffness in patients with osteoarthritis of the knee. A double-blind, placebo-controlled study was conducted in 59 subjects > 60 years of age with knee joint pain that scored 40 mm or above on a 100 mm VAS scale [Yip & Tam 2008]. Patients were allocated to 1 of 3 groups. Patients in the intervention group received a session of 30-35 minutes of aroma massage on both lower limbs six times within 2-3 weeks. Massage was with ginger essential oil (1 % ginger and 0.5 % orange oil in olive oil) and conventional treatment. The placebo group received massage with olive oil only as well as conventional therapy, while a control group received no massage but conventional treatment solely. The massage treatment was given by a trained nurse. Data were collected at 3 time points: 1) at baseline; 2) 1 week after the completion of treatment; and 3) 4 weeks after the completion of treatment. The primary outcome was knee pain severity measured by WOMAC; and secondary outcomes were knee joint stiffness and physical functioning (measured by WOMAC) and quality of life (SF-36). Of the 59 subjects enrolled 53 completed both post 1-week and 4-week follow-ups. There were significant differences between groups in WOMAC scores or in knee joint stiffness or quality of life scores at 1-week and 4-week follow-ups. Ginger massage intervention demonstrated a better outcome with respect to physical functioning compared to placebo and control groups at 1 week, but not after 4 weeks.

Assessment of the studies' quality is given in Table 1 in the annex to this assessment report.

Assessor's comment

Four studies on the efficacy of oral ginger in osteoarthritis were found. Ginger dosages were around 500-1000 mg daily, administered for 3-12 weeks. Three studies demonstrated some beneficial effect on osteoarthritis pain by ginger. However, the interpretation of the studies is hampered by high drop-out rates, relatively short treatment periods, and, in cross-over studies (n = 3), short (or no) wash-out periods. Recent systematic reviews found no evidence for a beneficial effect of ginger root on osteoarthritis. Thus, the scientific evidence for efficacy of ginger in osteoarthritis is insufficient.

Other conditions

Non-randomised studies and case studies

A double-blind comparative study included students with primary dysmenorrhoea of moderate to severe degree assessed by a self-administered questionnaire [Ozgoli *et al.* 2009b]. The sampling procedure is not properly described. A total of 150 women were alternately (non-randomised) allocated into 3 groups, and each group took their medication 4 times daily for 3 days from the start of

menstruation. One group received capsules containing 250 mg of powdered ginger; the other two groups received capsules with 250 mg or mefenamic acid and capsules with 400 mg ibuprofen, respectively. Severity of pain during menstruation was assessed before and after intervention by a verbal multidimensional scoring system with 4 grades. In addition, a 5-point scale was used to assess pain relief (from considerably better to considerably worse), and patient satisfaction with the treatment was assessed (satisfied, not satisfied). It is not reported whether the assessment tools were validated. The assessment was performed after 1 menstrual period. Results demonstrated no significant differences between groups in severity of dysmenorrhoea before or after treatment, or in pain relief and satisfaction.

A patient is described by Mustafa & Srivastava [1990] who took 500-600 mg of powdered ginger at the onset of a migraine attack and experienced relief of symptoms within 30 minutes.

Randomised studies

The effect of ginger on asthma was examined in a study by Rouhi *et al.* [2006]. Ninety-two patients with asthma of at least 1 year's duration were included. They were randomised into 2 treatment groups: one group received an alcoholic extract of ginger root, 150 mg (25 drops) 3 times daily for 2 months while the other group took placebo (formulation not described) for 2 months. Spirometry and an assessment of clinical symptoms were performed at study start and study end. Ginger treatment significantly reduced dyspnoea, wheezing, chest tightness, nocturnal cough and asthma spray use compared to placebo (no information on statistical method is given). There were no significant differences in the standard parameters FEV1, FVC and FEF25-75 between the groups.

The purpose of a study by Shariatpanahi *et al.* [2010] was to examine the effect of ginger extract on tolerance to tube feeding and development of ventilator-associated pneumonia in 32 patients with adult respiratory distress syndrome. All patients had mechanical ventilation dependence and were fed via a nasogastric tube. Patients were randomised into a group that received 120 mg of ginger extract (preparation not described) 3 times daily and a control group that was treated with coconut oil during tube feeding. Treatment was continued for 21 days. The ginger group had a significantly higher nutritional intake during the first 48 hours compared to the control group. The amount of feeding tolerated and the total period of feeding was not different between the 2 groups. The number of intensive care unit-free days and ventilator-free days was significantly higher in the ginger group while there was a trend toward a decrease in nosocomial pneumonia (P = 0.07) in favour of the ginger-treated group. The beneficial results were ascribed to a reduction in delayed gastric emptying by ginger.

Assessment of the studies' quality is given in Table 1 in the annex to this assessment report.

Assessor's comment

A total of 2 randomised studies of the effect of ginger on asthma and tolerance to tube feeding, respectively, were found. The study on asthma was of inferior scientific quality. The tube feeding study is interesting and does suggest a beneficial effect on the tolerance to feeding, however, for confirmation it should be repeated.

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

Two randomised, double-blind studies have been published where children had been included (reviewed above).

4.3. Overall conclusions on clinical pharmacology and efficacy

Pharmacodynamic studies have demonstrated that powdered ginger in dosages of 1000-2000 mg modifies gastric muscular contractions and probably increases gastric emptying, and hence may have a beneficial effect in conditions associated with nausea and vomiting. 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. The clinical efficacy of ginger root has been examined in randomised controlled studies with respect to postoperative nausea and vomiting, pregnancy-induced nausea and vomiting, chemotherapy-induced nausea and vomiting and motion sickness. Based on these studies there seems to be a modest beneficial short-term effect of ginger in postoperative nausea and vomiting, pregnancy-induced nausea and vomiting and in motion sickness.

Based on ginger's anti-inflammatory and antioxidative effects demonstrated in non-clinical studies, a few randomised studies have examined the efficacy of ginger in human osteoarthritis. The studies suggest some beneficial effect with respect to pain relief. However, recent systematic reviews found no evidence for a beneficial effect of ginger root on osteoarthritis. The interpretation of the results is hampered by inferior study quality, high drop-out rates and short treatment periods. Further, there are no pharmacodynamic studies to back up an eventual efficacy in osteoarthritis.

The preparations and dosages have varied somewhat (generally 1000-2000) mg of powdered ginger root daily), however most preparations were not standardised (*e.g.*, according to gingerol contents or to manufacturing). The treatment duration has also varied: in nausea and vomiting the duration has been
1-5 days; in osteoarthritis the duration has been 3-12 weeks.

Pharmacodynamic studies of the effect of ginger on blood clotting and blood lipids are few and of inferior methodology, and no firm conclusion can be based on these studies. Clinical efficacy of ginger in the treatment and prevention of atherosclerotic diseases is lacking.

5. Clinical Safety/Pharmacovigilance

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

No data available.

5.2. Patient exposure

No data available.

5.3. Adverse events and serious adverse events and deaths

The occurrence of adverse events was demonstrated in many of the randomised studies even in studies where only 1 dosage of ginger was administered. Adverse events are given in Table 2 (in the annex to this assessment report). The adverse events were mainly gastrointestinal complaints and were mild to moderate. Words used by patients have included bad taste, diarrhoea, abdominal discomfort, reflux and heartburn. In 1 randomised study gastrointestinal adverse events, particularly stomach upset, eructation, dyspepsia and nausea, were significantly more common in the ginger group (45 %) compared to placebo (16 %) [Altman & Marcussen 2001]. Severe adverse events have not been encountered which could be ascribed to ginger.

Two small clinical studies report on side effects in children. No side effects from the use of ginger were reported in these studies [Careddu 1999; Pillai *et al.* 2011].

The systematic review by Betz *et al.* [2005] including 15 randomised studies that contained data on side effects showed that of the 777 patients included 3.3 % suffered from slight side effects, mainly mild gastrointestinal symptoms and sleepiness that did not require specific treatments.

Allergic reactions to oral ingestion of ginger root have not been described. 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 & Dieges 1985].

5.4. Laboratory findings

Three randomised studies report laboratory results (see Table 2 in the annex to this assessment report). None found changes in haemoglobin, blood counts, liver function tests or creatinine.

5.5. Safety in special populations and situations

5.5.1. Pregnancy

Because ginger has been found to be a potent thromboxane synthetase inhibitor, it has been hypothesized that it may affect testosterone receptor binding in the foetus and consequently affecting sex steroid differentiation in the foetal brain [Backon 1991].

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 anti-emetics. 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; $P \leq 0.001$). 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 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 B_6. 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. The specific results of the pregnancy outcomes in the 4 studies included in the review by Borelli *et al.* [2005] are described in Table 2 (see Annex).

The study by Ensiyh *et al.* [2009] also presents data for pregnancy outcome (Annex, Table 2). The study found 2 spontaneous abortions in the ginger group and 1 spontaneous abortion in the vitamin B_6 group, and no infants had congenital malformations.

Assessor's comment

Prospective studies have not found a higher incidence of adverse pregnancy outcomes. However, it has to be stressed that treatment durations have been short and only a small number of patients have been included in the prospective studies.

5.5.2. Interactions

Two case reports have been published suggesting that ginger may be associated with over-anticoagulation in patients treated with oral anticoagulants. One case report 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 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 [Jiang *et al.* 2005]. A single 25 mg dose of rac-warfarin was administered to each volunteer with and without pre-treatment of ginger at a dose of 1 capsule 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. Each capsule of ginger contained extract equivalent to 0.4 g of ginger rhizome powder. 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 (PT), (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. They were asked weekly to record their use of complementary and alternative medicine. In a fully adjusted multivariate model the use of ginger (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).

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's 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.

An *in vitro* study demonstrated a significant but variable inhibition of drug marker substrates for human cytochrome P-450 isoforms (2C9, 2C19, 2D6 and 3A4) by aqueous ginger extract (25 mg/ml).

The percent of inhibition ranged from 88 % (3A4) to 53 % (2C9) [Foster *et al.* 2003]. Another *in vitro* study showed that 6-gingerol had inhibitory effects on P-glycoprotein in KB-C2 cells (multidrug-resistant human epidermal carcinoma cell line over-expressing P-glycoprotein) giving it a potential to cause interactions with many commonly used drugs that are substrates for P-glycoprotein [Nabekura *et al.* 2005].

Assessor's comment

Case reports suggesting interaction between ginger and warfarin are indeed few and un-convincing and 1 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.

5.6. Overall conclusions on clinical safety

The adverse events, mainly gastrointestinal, observed in clinical trials which are most probably linked to the study medication are in general mild and occur with low frequency.

Prospective studies have not found a significantly higher incidence of adverse pregnancy outcomes. However, treatment durations in randomised studies have been short and only a small number of patients have been included in the prospective studies.

Interaction with oral anticoagulant drugs is only described in 2 non-convincing case reports.

There is insufficient evidence that ginger has a clinical relevant effect on CYP-450 isoenzymes or p-glycoprotein.

6. Overall conclusions

The medicinal use of powdered ginger root has been used within the Community for the treatment of nausea and vomiting, and osteoarthritis pain relief for at least 10 years.

There is plausible scientific evidence from several randomised clinical studies that oral intake of encapsulated dry powdered rhizome from *Zingiber officinale* (ginger) is better than placebo and non-inferior to some commonly used antiemetics (metoclopramide, dimenhydrinate) in ameliorating pregnancy-induced nausea and vomiting, postoperative nausea and vomiting and motion-induced nausea and vomiting. Therefore, for these conditions ginger could be proposed for well-established use. The beneficial effect is minor to modest, however clinically relevant. Studies are too few and non-consistent to suggest efficacy against chemotherapy-induced nausea and vomiting.

In randomised controlled studies the efficacy of powdered ginger has been demonstrated in several studies most often with the following dosages and treatment durations:

1. Pregnancy-induced nausea and vomiting: 500 mg 3 times daily for 3-5 days.
2. Post-operative nausea and vomiting: 1000 mg 1 hour before induction of anaesthesia.
3. Motion-induced nausea and vomiting: 1000 mg 1 hour before start of travel.

The beneficial effect in nausea and vomiting is supported by experimental animal studies and human pharmacodynamic studies that have shown increased gastric emptying after ingestion of ginger root, probably caused by peripheral blocking of receptors involved in smooth muscle contraction in the gastrointestinal tract by gingerols and shogaols contained in ginger.

Sound scientific evidence for efficacy in osteoarthritis is lacking due to inferior scientific study quality (high drop-out rates, short treatment periods, and, in cross-over studies (3 out of 4), short (or no) wash-out periods). Also, systematic reviews have not shown efficacy.

A traditional use of ginger has been established in the EU (UK) for the indications: 1) symptomatic relief of travel sickness, and 2) symptomatic treatment of mild, spasmodic gastro-intestinal complaints including bloating, and flatulence.

The adverse events from the ingestion of ginger root medicinal products observed in clinical trials, which are most probably linked to the study medication, are mainly gastrointestinal (stomach upset, eructation, heartburn and nausea), in general moderate to mild and occur with low frequency. Severe adverse events have not been encountered that could be ascribed to ginger.

Prospective clinical studies have not found a higher incidence of adverse pregnancy outcomes with ginger treatment; however only a small number of exposed pregnant women (n =490) have been included in the prospective studies. Findings in two experimental animal studies of advanced skeletal development and increased embryo resorption in the absence of any maternal toxicity or gross foetal toxicity or defects with high dose ginger administration are difficult to interpret. Although they do not seem to suggest any definitive concerns with respect to reproductive and developmental safety of ginger root, the usage of ginger in pregnancy is not advocated, due to the possible consequences for adverse foetal development along with the minor clinical benefit in nausea and vomiting.

The oral administration of ginger 1 hour before induction of anaesthesia goes against commonly agreed surgical guidelines that patients undergoing elective surgery should fast 6 hours from solids and 2 hours from liquids to reduce the risk of aspiration. Consequently, a general recommendation to administer ginger before surgery cannot be recommended.

Case reports suggesting interaction between ginger and warfarin are few and unconvincing, and one randomised study in healthy volunteers did not demonstrate warfarin interaction. There is insufficient evidence to suggest induction or inhibition of CYP-enzymes by ginger and its active constituents.

The assessor is not aware whether ginger root products have been subjected to pharmacovigilance and PSURs within or outside the Community.

Consequently, the benefit/risk balance is in favour for the oral use of powdered ginger extract and fulfils the criteria for well established use in the treatment of motion-induced nausea and vomiting.

Annexes

Table 1. Randomised clinical studies, study quality

Table 2. Randomised studies, adverse events

List of references

Table 1. Randomised clinical studies, study quality

Study	Allocation concealment[1]	Success of blinding[2]	Sample size calculation[3]	Description of non-completers[4]	Baseline com-parability[5]	Inclusion/ Exclusion criteria[6]	ITT-analysis[7]	Compliance[8]
Postoperative nausea and vomiting								
Bone 1990	-	-	-	All completed	+	-	All completed	I
Arfeen 1995	-	-	+	All completed	+	+	All completed	I
Visalyaputra 1998	-	-	-	-	+	+	+	I
Eberhart 2003	+	-	+	All completed	+	-	All completed	I
Nanthakomon &Pongrojpaw 2006	-	-	-	All completed	+	+	All completed	I
Apariman 2006	-	-	-	All completed	+	+	All completed	I
Tavlan 2006	-	-	+	-	+	+	+	I
Nale 2007	-	-	-	-	+	+	All completed	I
Pregnancy-induced nausea and vomiting								
Fischer-Rasmussen 1990	-	-	-	+	I	-	-	-
Vutyavanic 2001	+	+	+	+	+	+	+	+
Keating & Chez	+	-	-	+	-	-	No statistics	-
Sripramote & Lekhyananda 2003	+	-	+	+	+	+	+	+
Willetts 2003	+	-	+	+	+	+	-	-
Smith 2004	+	+	+	+	+	+	+	-
Chitumma 2007	+	+	+	+	+	+	-	+

[1] Is the group assignment of the patients concealed to the investigators?
[2] Is the effectiveness of blinding assessed?
[3] Is the number of patients in the trial derived from a sample size calculation?
[4] Are non-completers (leaving study after randomisation) adequately described?
[5] Are data presented with respect to comparability between treatment groups? (I = irrelevant for cross-over studies)
[6] Are the inclusion and exclusion criteria adequately described?
[7] Are the results analysed as intention-to-treat?
[8] Is a pill-count performed to test for compliance? (I = irrelevant in studies where investigators supervised the ingestion)

Study	Allocation concealment[1]	Success of blinding[2]	Sample size calculation[3]	Description of non-completers[4]	Baseline com-parability[5]	Inclusion/ Exclusion criteria[6]	ITT-analysis[7]	Compliance[8]
Pongrojpaw 2007	-	-	-	-	+	+	-	-
Ozgoli 2009a	-	-	-	+	+	+	-	-
Ensiyeh & Sakineh 2009	+	-	+	+	+	+	+	-
Chemotherapy-induced nausea and vomiting								
Sontakke 2003	-	-	+	+	I	+	-	
Manusirivthaya 2004	-	-	-	-	I	+	-	-
Zick 2009	+	+	+	+	+	+	+	+
Pillai 2011	+	-	-	+	+	+	-	-
Motion sickness								
Mowrey & Clayson 1982	-	-	-	All completed	-	-	All completed	I
Grøntved 1988	-	-	-	-	-	-	-	+
Grøntved & Hentzer 1986	-	-	-	All completed	I	+	All completed	I
Wood 1988	-	-	-	All completed	I	+	All completed	I
Stewart 1991	-	-	-	All completed	I	-	All completed	I
Careddu 1999	-	-	-	All completed	+	+	All completed	-
Lien 2003	-	-	-	All completed	I	+	All completed	I
Osteoarthritis								
Bliddal 2000	-	-	-	+	I	+	-	+
Altman & Marcussen 2001	+	-	+	+	+	+	+	+
Wigler 2003	+	-	-	-	I	+	+	-
Haghighi 2005	-	-	-	All completed	+	+	All completed	-
Yip & Tham 2008	+	-	+	+	+	+	All completed	Local therapy
Asthma								
Rouhi 2006	-	-	-	-	-	-	?	-

Study	Allocation concealment[1]	Success of blinding[2]	Sample size calculation[3]	Description of non-completers[4]	Baseline com-parability[5]	Inclusion/ Exclusion criteria[6]	ITT-analysis[7]	Compliance[8]
Tolerance to tube feeding								
Shariatpanahi 2010	-	-	-	All completed	+	+	All completed	I

Table 2. Randomised studies, adverse events

Study	Ginger preparation used	Duration/daily dosage; number randomised	Adverse events
Postoperative nausea and vomiting			
Arfeen 1995	Powdered ginger BP 1988	One dosage Regimen 1: Ginger, 500 mg; n=36 Regimen 2: Ginger, 1000 mg; n=36 Regimen 3: Placebo; n=36	Regimen 1: Flatulence (n=1); Heartburn (n=1) Regimen 2: Burping (n=1); Heartburn (n=1); Nausea (n=1) Regimen 3: Flatulence (n=1)
Eberhart 2003	Standardised extract (drug extract ratio: 10-20:1; acetone extract	1 day Regimen 1: Ginger, 300 mg; n=59 Regimen 2: Ginger, 600 mg; n=57 Regimen 3: Placebo n=59	Adverse effects not described, only number of events Regimen 1: n=8 Regimen 2: n=13 Regimen 3: n=11
Apariman 2006	No information	One dosage Regimen 1: Ginger, 1500 mg; n=30 Regimen 2: Placebo; n=30	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
Pregnancy-induced nausea and vomiting			
Fischer-Rasmussen 1990	Powdered ginger	4 days Regimen 1: Ginger, 1000 mg Regimen 2: Placebo Cross-over study, n =30	Pregancy outcome: 1 patient had spontaneous abortion 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.
Vutyavanich 2001	Powdered ginger made from fresh root, baked and ground by pharmacist	4 days Regimen 1: Ginger 750 mg; n=32 Regimen 2: Placebo; n=35	Regimen 1: Headache, n=6 (19 %) Regimen 2: Headache, n=5 (14 %); Abdominal discomfort, n=1; Heartburn, n=1; Diarrhoea, n=1 Pregnancy outcome: Regimen 1: Spontaneous abortion, n=1 (3.1 %); Term delivery, n=31 (91.4 %); Caesarean deliveries, n=6 (18.8 %).

Study	Ginger preparation used	Duration/daily dosage; number randomised	Adverse events
			Regimen 2: Spontaneous abortion, n=3 (8.6 %); Term delivery, n=32 (96.9 %); Caesarean deliveries, n=4 (11.4 %). No infants had congenital malformations.
Willetts 2003	Ginger extract (Eurovita Extract 35)	4 days Regimen 1: Ginger, 500 mg; n=60 Regimen 2: Placebo; n=60	Exclusions due to AE: Regimen 1: Spontaneous abortion, n=3; Intolerance to treatment, n=4; Worsening of symptoms, n=3; allergic reactions, n=1. Regimen 2: 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.
Smith 2004	Powdered ginger prepared by RP Scherer with a certificate of analysis to ensure that product was standardised and quality controlled.	3 weeks Regimen 1: Ginger, 1050 mg; n=146 Regimen 2: Vitamin B_6, 75 mg; n=145	Regimen 1: Retching, 52 %; Vomiting, 2 %; Burning sensation, 2 %; Belching, 9 %. Regimen 2: Retching, 56 %; Vomiting, 1 %; Burning sensation, 2 %; Belching, 0 %. Significant difference for belching. Pregnancy outcome: Regimen 1: 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. Regimen 2: 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 significant difference in congenital abnormalities. No significant difference in overall risk of pregnancy complications.
Chittumma 2007	Powdered ginger made from fresh root, sun dried and ground by pharmacist	4 days Regimen 1: Ginger, 1300 mg; n=61 Regimen 2: Vitamin B_6, 50 mg; n=62	Regimen 1: Total AE, n=16 (25.4 %); Heartburn, n=8 (12.7 %); Sedation, n=7 (11.1 %); Arrhythmia, n=1 (1.6 %). Regimen 2: Total AE: n=15 (23.8 %); Heartburn, n=2 (3.2 %); Sedation, n=11 (17.5 %); Headache, n=2 (3.1 %).

Study	Ginger preparation used	Duration/daily dosage; number randomised	Adverse events
Pongrojpaw 2007	No information	1 week Regimen 1: Ginger, 1000 mg; n=85 Regimen 2: Dimenhydrinate, 100 mg; n=85	Regimen 1: Drowsiness, n=66 (78 %); Heartburn, n=9 (11 %). Regimen 2: Drowsiness, n=5 (6 %); Heartburn, n=13 (16 %). Significant difference for drowsiness
Ensiyh 2009	Powdered ginger made from fresh root, baked and ground by pharmacist.	4 days Regimen 1: Ginger, 1000 mg; n=35 Regimen 2: Vitamin B_6, 40 mg; n=35	Pregnancy outcome: Regimen 1: Spontaneous abortions, n=2; Term birth, n=29 (82.9 %); Caesarean deliveries, n=4 (11.4 %). Regimen 2: Spontaneous abortions, n=1; Term birth, n=28 (82.4 %); Caesarean deliveries, n=6 (17.6 %). No infants had congenital malformations.
Chemotherapy-induced nausea and vomiting			
Manusirivithaya 2004	Powdered ginger	5 days Regimen 1: Ginger, 1000 mg Regimen 2: Placebo (day 1), metoclopramide, 40 mg Cross-over study, n=48	Regimen 1: Restlessness, n=2 (4.6 %); Diarrhoea, n=6 (14.0 %); Constipation n=3 (7 %); Headache, n=1 (2.3 %); Dizziness, n=6 (14.0 %); Heartburn, n=3 (7.0 %); Palpitation, n=1 (2.3 %); Any side effects, n=8 (18.6 %). Regimen 2: Restlessness, n=8 (18.6 %); Diarrhoea, n=2 (4.6 %); Constipation, n=6 (14.0 %); Headache, n=3 (7 %); Dizziness, n=5 (11.6 %); Heartburn, n=3 (7 %); Palpitation, n=1 (2.3 %); Akathisia, n=1 (2.3 %); Acute dystonic reaction, n=1 (2.3 %); Any side effects, n=12 (27.9 %)
Zick 2009	Ginger (10:1 (v/v) extraction solvent (ethanol) standardised to 5 % total gingerols)	3 days Regimen 1: Ginger, 1000 mg; n=53 Regimen 2: Ginger, 2000 mg; n=52 Regimen 3: Placebo; n=57	A total of 42 AE were reported. No significant differences in total AE, non-serious AE, dyspneu, gastrointestinal AE or laboratory abnormalities. There were significantly more fatigue and miscellaneous AE in the placebo regimen than in the 2 ginger regimens. 3 SAE: UE deep vein thrombosis (n=1); severe diarrhoea and abdominal pain (n=1); anaemia, thrombocytopenia and leucocytopenia (P =0.07 between groups)
Osteoarthritis			
Bliddal 2000	Ginger extract (Eurovita Extract 33)	3 weeks Regimen 1: Ginger, 510 mg Regimen 2: Ibuprofen, 1200 mg Regimen 3: Placebo Cross-over study, n=65	A total of 47 AE were reported in 34 patients. AE mainly gastrointestinal Regimen 1: Bad taste, n=5; Dyspepsia, n=1; Changes in stool/intestinal trouble, n=1; Nausea, n=1; Conjunctivitis, n=1. Regimen 2: Dyspepsia, n=7; Changes in stool/intestinal

Study	Ginger preparation used	Duration/daily dosage; number randomised	Adverse events
			trouble, n=4; Nausea, n=3; Periorbital oedema, n=1. Regimen 3: Dyspepsia, n=1; Changes in stool/intestinal trouble, n=6; Nausea, n=1; Skin allergy, n=1. No change in blood haemoglobin.
Altman & Marcussen 2001	Ginger extract (Eurovita Extract 77)	6 weeks Regimen 1: Ginger, 510 mg; n=124 Regimen 2: Placebo; n=123	A total of 314 AE were reported in 125 patients. Total gastrointestinal AE were more common in regimen 1 than in regimen 2 (116 AE in 59 patients vs. 28 AE in 21 patients), statistical significant for eructation, dyspepsia and nausea. 1 SAE (myocardial infarction) in regimen 2.
Wigler 2003	Ginger extract (Zintona EC, enteric coated designed to release 20 % under gastric conditions in 2 h and the rest under intestinal conditions) standardised to 4 % gingerol	12 weeks Regimen 1: Ginger, 1000 mg Regimen 2: Placebo Cross-over study, n=26	Regimen 1: Heartburn, n=2. Blood counts, liver tests and creatinine remained within normal limits.