EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 July 2013
EMA/HMPC/614586/2012
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Angelica sinensis* (Oliv.) Diels, radix

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)

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Angelica sinensis* (Oliv.) Diels, radix
Herbal preparation(s)	Liquid extract, dried liquid extract
Pharmaceutical forms	Oral solution, tablets
Rapporteur	W. Dymowski
Assessor(s)	

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
An agency of the European Union

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Introduction

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

- Herbal substance(s)

According to European Pharmacopoeia, ed. 7.5 (1), the herbal substance contains the smoke-dried, whole or fragmented root, with rootlets removed, of *Angelica sinensis* (Oliv.) Diels collected in late autumn, containing minimum 0.050 per cent of *trans*-ferulic acid ($C_{10}H_{10}O_4$; M_r 194.2).

Assessor's comments:

The traditional processing of this root in China doesn't contain a washing process, like in the case of other roots used in Europe. There is no information on cleaning of root surface. It is not clear what microbiological flora is present on the surface of the material after smoke-drying. According to data from Korea and Vietnam, for the microbiological decontamination of the Dang gui root, radiation sterilisation is used.

According to the Pharmacopoeia of the People's Republic of China (1977), Radix Angelicae sinensis (Danggui) was used "To enrich blood, activate blood circulation, regulate menstruation, relieve pain and relax bowels".

According to the TCM theory, different parts of Angelicae sinensis radix possess different traditional applications. The whole root (Quan Danggui) is used to quicken, nourish and harmonise blood; root head (Danngui Tou) is used to quicken the blood and to stop bleeding; root body without head (Danggui Shen) consisting of the main body of the root without head and tails is used for nourish the blood when blood quickening properties are not desired; root tails (Danggui Wei) consisting of the primary branch roots is considered to elicit the strongest effect for quickening the blood and breaking up blood stasis; finer roots (Danggui Xu) ("beard") are used to quicken the blood and free the network vessels. In practice, in herbal trade Danggui Tou is actually the two parts of Danggui Tou and Danggui Schen but Danggui Xu is parts of Danggui Tou and Danggui Schen but Danggui Xu is rare on the market.

The species *Angelica sinensis* (Oliv.) Diels was described in Bot. Jahrb. Syst. 29 (3-4): 500.1900 [4 Dec 1900] on the basis of an earlier description of Angelica polymorpha Maxim. var. sinensis Oliv. Hooker's icon. Pl. 20: t. 1999. 1891 [Aug 1891] (IPNI).

According to the Flora of China (China@efloras.org;) the species *Angelica sinensis* (Oliver) Diels (Dang gui) is a perennial plant, 0.4 - 1 m of height, with cylindric branched and succulent roots that have many rootlets and are strongly aromatic. The plant is further described as follows (Zehui & Watson, 2005): Stems purplish green, ribbed, branched above. Basal and lower petioles 5 - 20 cm, sheaths purplish green, ovate, membranous-margined; blade ovate, 10 - 30 × 12 - 25 cm, 2 - 3-ternate-pinnate, pinnae 3 - 4 pairs, proximal and middle pinnae long-petiolulate; leaflets ovate or ovate-lanceolate, 2 - 3.5 × 0.8 - 2.5 cm, 2 - 3-lobed, margin irregularly coarse-cuspidate-serrate, sparse papillate-hairy along nerves and margin. Peduncles 8 - 20 cm, pubescent or subglabrous; bracts absent or 2, linear; rays 10 - 30, unequal, scabrous; bracteoles 2 - 4, linear, 3 - 5 mm; umbellules 13 - 36-flowered; pedicels slender, 1 - 3 cm in fruit. Calyx teeth obsolete, rarely minute, ovate. Petals white, rarely purplish red. Fruit ellipsoid or suborbicular, 4 - 6 × 3 - 4 mm; dorsal ribs filiform, prominent, lateral ribs broadly thin-winged, wings as wide as or wider than the body; vittae 1 in each furrow, 2 or absent on commissure. Flowering from June to July, fruiting from July to September. Plant wild or cultivated in forests, on altitudes 2500-3000 m, in provinces Gansu, Hubei, Shaanxi, Sichuan, Yunnan.

According to the IPNI database, there is one officially recognised variety: *Angelica sinensis* (Oliv.) Diels var. wilsonii (H.Wolff) Z.H.Pan & M.F.Watson. Acta Phytotax. Sin. 42(6): 562. 2004 [Nov 2004]. In the Flora of China, (Zehui & Watson, 2005), there is also a second variety: *Angelica sinensis* var. sinensis (differing in shape of fruits and vittae), however it was not officially published and recognized by international databases.

According to the new phylogenetic taxonomy, the species *Angelica sinensis* does not seem to belong to the Angelica group *sensu stricto*, and it belongs to a different clade containing *Levisticum officinale* with *Angelica sinensis* and *Angelica tianmuensis* with *Angelica peoniifolia*, for practical reasons morphological and carpological classification is used.

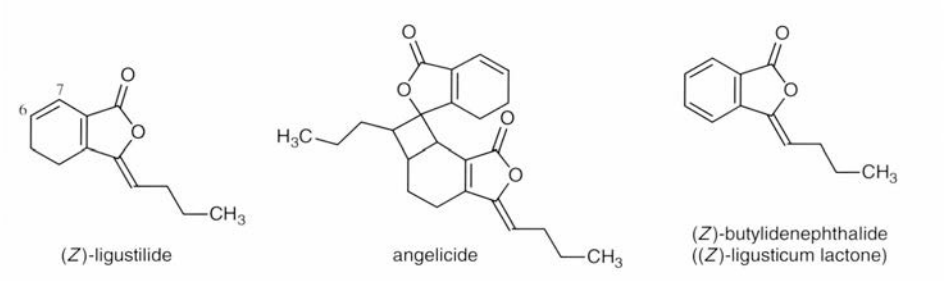
Apart from the species *Angelica sinensis* (Oliv.) Diels, the roots of two other species: Angelica *dahurica* (Hoffm.) Benth. & Hook. f. ex Franch. & Sav. (Angelicae dahuricae radix) and Angelica pubescens Maxim. f. *biserrata* R.H.Shan et C.Q.Yuan (Angelicae pubescentis radix) are used in Traditional Chinese Medicine and described in the European Pharmacopoeia.

Nomenclature

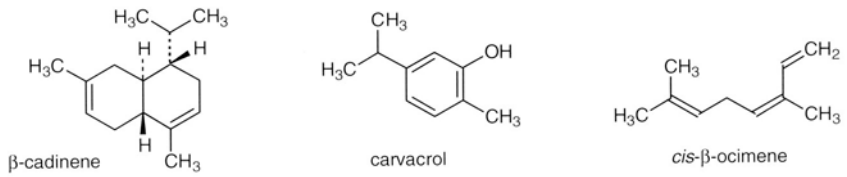
The Pharmacopoeia of the People's Republic of China (1977) uses for Angelicae sinensis radix the name: 'Danggui', the Flora of China (Zehui & Watson, 2005) 'dang gui', while in textbooks and literature often 'Dang Gui' is used (Chen & Chen 2004). In European and American literature names such as 'Dong Quai', 'Tang Kui' (Merck) or 'Tang kuei' were used.

Constituents

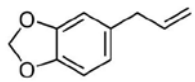
According to the WHO Monograph (2002) the characteristic components are the simple alkyl phthalides (ligustilide, (Z)-ligustilide, (Z)-6,7-epoxyligustilide, angelicide, (Z)-butylidenephthalide, butyl-phthalide, 2,4-dihydrophthalic anhydride), which are the major components of the essential oil of the roots.



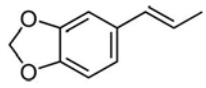
Characteristic components of the oil are terpenes (β-cadinene and cis-β-ocimene).



Also aromatic compounds are present: phenol, *o*-cresol, *p*-cresol, guaiacol, 2,3-dimethylphenol, *p*-ethylphenol, *m*-ethylphenol, 4-ethylresorcinol, isoeugenol, carvacrol, 2,4-dihydroxyacetophenonecadinene (Hagers 1998),



safrole (Hagers 1998, EFSA Compendium 2009),

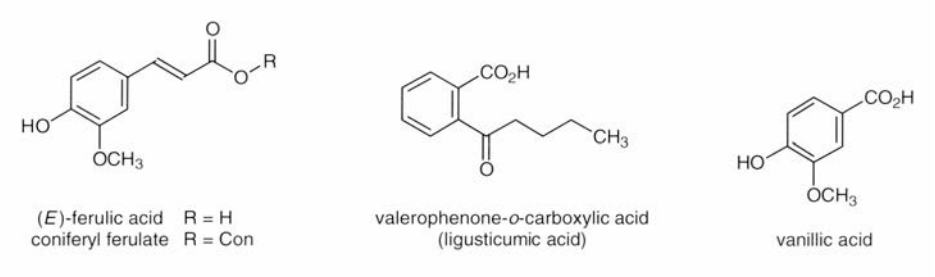


isosafrole (Hagers 1998, EFSA Compendium 2009) and vanillin.

Assessor's comments:

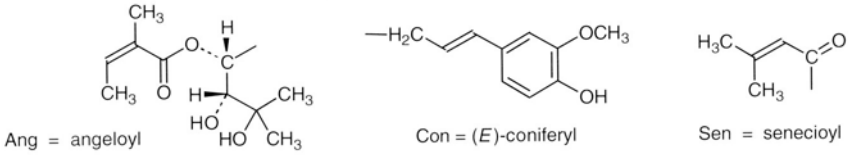
There are no quantitative data on the content of safrole and isosafrol.

Among characteristic non-volatile constituents are phenylpropanoids ((E)-ferulic acid, coniferyl ferulate); benzenoids (valerophenone-o-carboxylic acid and vanillic acid)



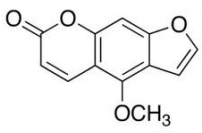
and coumarins (angelol G, angelicone and umbelliferone),

	R^5	R^6	R^7	R^8
umbelliferone	H	H	H	H
angelicone	OCH_3	H	CH_3	Sen
angelol G	H	Ang	CH_3	H

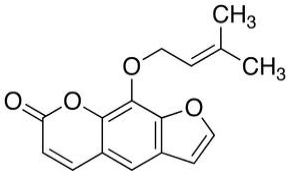


and also 6-methoxy-7-hydroxycoumarin (scopoletin), 6-ethoxycoumarin (Deng 2005).

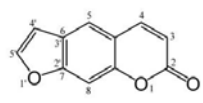
Furthermore have been found osthole (Hagers 1998, Gruenwald 2004) and furocoumarins: bergapten (5-methoxypsoralen, 5-MOP)(Hagers 1998), imperatorin (Deng 2005, Gruenwald 2004), psoralen, oxypeucedanin (Hagers 1998, Deng 2005, Gruenwald 2004).



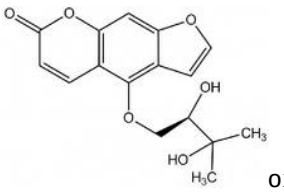
bergapten (5-MOP)



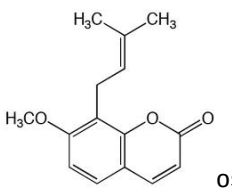
imperatorin,



psoralen



oxypeucedanin



osthole

Assessor's comments:

Angelica sinensis radix contains a number of furocoumarins that induce photosensivity. There are no systematic data on the content of furocoumarins in the root. Data on a furocoumarins profile in the

Angelica sinensis radix are also lacking. Bergapten (5-MOP) in the presence of UV light is probably carcinogenic in humans. A quantity of furocoumarins in the roots was not determined but such a determination would allow using the drug according to 1.5 mg acceptable daily intake of these substances. (EMEA/HMPC/317913/2006)

The essential oil contains also safrole, described in the EFSA compendium on botanicals containing toxic substances of concern (2009) as a weak carcinogen; as well as in rats and mice and a known genotoxic carcinogen, and isosafrole, a weak hepatocarcinogen in rats and mice. There is no quantitative data on the content of these substances in the herbal substance or in preparations. There are however general estimations of population exposure to genotoxic and possible carcinogenic substances in food and spices, which were currently evaluated in a project coordinated by EFSA (PlantLIBRA PLANT) for food supplements (Van den Berg et al., 2011). These models and estimations do not take into consideration the use of herbal medicinal products.

Polysaccharides: The root contains significant amounts of sugars: galactose, glucose, arabinose, rhamnose and xylose. arabigalactan (WHO), saccharose, hypoxanthine-9-beta-D-ribofuranoside, fructose and polysaccharides: X-C-3-III, X-C-3-IV (composed of galactose, arabinose, rhamnose, glucuronic acid and galacturonic acid) and X-C-3-I (composed of arabinose, galactose, glucose and fructose with a molar ratio of 1:1:4:9) (Deng 2005).

- Herbal preparation(s)

Currently there is no information on medicinal products on the European market containing as herbal substance *Angelica sinensis,* radix.

There are historical data on the use of a product 'Eumenol' in Europe between 1899 and 1946. Eumenol was described in the 3rd edition of the Merck's Index as a fluid extract of the Chinese root, named (Tang-kui, Man-mu) supposed to be of the *Araliaceae.* However, genus und species were not yet determined. It was used as emmenagogue in amenorrhoea und dysmenorrhoea, especially when the latter was thought to be of nervous origin. The dose was 3 times daily 1 coffee spoon, i.e. 3 x 2 = 6 g. In 1907, Eumenol was also mentioned in Merck's Index in the United States. The product was first available in form of an oral liquid. Since 1907, Eumenol was referred to as a new medicinal product, and was known also in Central Europe (for example in Poland in Nowiny Lekarskie, 1907, R. 19, nr 12). However the product was not listed on an official lists of medicinal means available in pharmacies, but still it was imported by many pharmacies and was advertised by the agencies of Merck in the medical press (like in Warsaw Medical Journal, *Warszawskie Czasopismo Lekarskie, 1930, R.7, nr 12* and Polish Official Journal of Medical Chambers in 1931 (Dziennik Urzędowy Izb Lekarskich 1931)). In Poland, the product was available in liquid form, in bottles containing 25, 100, 250g and in a form of tablets, in boxes containing 25, 50, 100 units, in following indications: Amenorrhea, Dysmenorrhea, especially in imaginary pregnancy.

Eumenol was authorised in Sweden 1939-1946. It was manufactured by the company Merck in a form of tablets 0.3 g containing dried liquid extract, corresponding 0.6 g of herbal substance, DER (2:1). Extraction solvent was probably 70% ethanol.

Since 1946 the product has not been distributed and detailed data on the composition, according to contemporary criteria, are lacking.

In China at least since 1978, a product Danggui Wan has been available in a form of pellets, obtained by using following method: 700 g of 1000 g of *Angelica sinensis* radix (Danggui Wan) is pulverised, extracted with 70% ethanol [V/V], in proportion 1 to 6.5 parts of extraction solvent. The percolate is concentrated under reduced pressure to obtain a thick paste extract and to this extract the other 300 g

of the original herbal substance are added, dried in 70°C, pulverised (sieve 100-120) and mixed with thick paste extract, adding talc powder and starch *quantum sufficit*, pelleting, drying under 70°C and finally polishing to obtain as final form pellets.

- 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.

In the WHO ADR database, there are mentioned 96 combination products containing *Angelica sinensis* preparations. This assessment report refers only to the use of the single substance.

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

A review of pharmaceutical markets among EU countries demonstrated that there are no monocomponent medicinal products, containing *Angelica sinensis* radix or its preparations.

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no products on the market
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no medicinal products. There are about 150 food supplements containing Dong Quai.
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no medicinal products on the market.
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No data
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no products on the market
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no products on the market
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no medicinal products on the market, there are food supplements.
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no products on the market
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no products on the market
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no products on the market
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no products on the market

Member State	Regulatory Status				Comments
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no products on the market
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No data
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no products on the market
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no products on the market
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no products on the market
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No data
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Such a products have not been sold during last 20 years
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No data
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No data
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no products on the market
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no products on the market.
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no authorised nor registered products on the market
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no products on the market
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no products on the market
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No data
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no medicinal products on the market.
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no products on the market
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no products on the market. During the years 1939-1946 one authorised product Eumenol (Merck, Germany). 1 tablet contained 0.3 g of dried liquid extract, DER (2:1). Extrahent probably 70% V/V ethanol. The average recommended doses 2 – 4 tablets daily,

Member State	Regulatory Status				Comments
					(corresponding to 3.6-7.2 g of plant material). Indications: amenorrhea, dysmenorrhea, menstruation problems. Product was recommended during the menstruation period.
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	There are no authorised products.

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

A first search was performed using Medline PubMed, TOXNET and Cochrain Database; key words *Angelica sinensis*, *Angelica sinensis* clinical, Dong Quai, Tang kui, Eumenol. This first step was followed by a search in Embase (Ovid).

As a third step an additional search was performed in Google scholar, key words: *Angelica sinensis*, *Angelica sinensis* clinical, *Angelica sinensis* safety, *Angelica sinensis* toxicological, *Angelica sinensis* pharmacopoea, *Angelica sinensis* microbiological, Angelica taxonomy, *Angelica sinensis* taxonomy, Dong Quai, Dang gui, Danggui, Dong Quai toxic, Dong Quai safety.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

First reports on the medicinal use of the product Eumenol-Merck containing the extract of Chinese emmenagoge Tang-kui (Man-mu) come from a publication of Dr Arthur Mueller in 1899, in Bavaria. There are historical data indicating the broad use of Eumenol, which was distributed in continental Europe, Germany, Czech Republic, Poland and was authorised last time in the years 1939 – 1946 in Sweden.

Assessor's comments:

There are no data on medicinal use of single products, containing Angelica sinensis root as an active substance among medicinal products in Europe after the year 1946. However, many products containing Angelica sinensis radix appeared on European markets as food supplements after implementation of Directive 2002/46/EC. There are no data that, according to Article 16c.1(c) Angelica sinensis root has been in medicinal use throughout a period of at least 30 years preceding the assessment, including at least 15 years within the Community.

However there is evidence based on monographs of Angelicae sinensis radix (Danggui) in editions of the Chinese Pharmacopoeia that the herbal substance has been in traditional use in China throughout at least 30 years preceding the assessment.

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

Therapeutic actions traditionally attributed to Radix Angelicae sinensis in China:

1. Tonifies blood in heart and liver blood deficiencies with symptoms such as anaemia, pale complexion, brittle nails, dry hair, dizziness, blurred vision, and palpitations. *Dang Gui* (Radicis Angelicae sinensis), warm in nature, is most suitable for cold-type blood deficient patients.
2. Invigorates blood circulation and relieves pain in menstrual disorders: blood deficiency, blood stagnation or qi stagnation all result in menstrual disorders such as irregular menstrual cycle, dysmenorrhea, amenorrhea and other gynaecological disorders. Because of the warm property of Dang Gui and its action to nourish the blood and invigorate circulation, it is most suitable for treatment of cold types of menstrual disorders with blood and qi stagnation.
3. Moistens intestines and unblocks the bowels in constipation due to blood deficiency, when the bowels are not properly nourished by blood, constipation or dry stools result (usually the elderly or those who have chronic constipation, or are postpartum women, or are in late or recovery stages of chronic disorders suffer this type of constipation).
4. Stops cough and treats dyspnoea cough and dyspnoea, often used in combinations with herbs that transform phlegm (Chen & Chen 2004).

According to the Pharmacopoeia of the People's Republic of China (Ch.P.) in 1963, "actions", indications and dosages were following:

Action: to enrich blood, activate blood circulation and relax bowels.

Indications: anaemia with dizziness and palpitation; menstrual disorders, amenorrhea, dysmenorrhea; constipation; traumatic injuries; carbuncles, boils and sores.

Usage and dosage: 4.5-9 g.

And in Ch.P. 1977, the following:

Action: to enrich blood, activate blood circulation, regulate menstruation, relieve pain, and relax bowels.

Indications: anaemia; menstrual disorders, amenorrhea, dysmenorrhea, metrorrhagia, postpartum abdominal pain; constipation; traumatic injuries; carbuncles, boils and sores.

Radix Angelicae sinensis (stir-baked with wine) amenorrhea, dysmenorrhea, rheumatic arthralgia, traumatic injuries.

Usage and dosage: 4.5-9 g.

Traditional indications and specified preparations in Europe:

According to historical data the product Eumenol was largely advertised in Europe, for example in Warsaw Medical Journal in 1930 and 1931, in following indications: amenorrhea, dysmenorrhea, especially in imaginary pregnancy.

Assessor's comments:

The product must have been so popular in continental Europe, that it was mentioned in Czech poetry (Jiři Wolker: Těžká hodina/Balada o nenarozeném dítěti).

Eumenol was authorised in Sweden in years 1939 - 1946 in indications: Amenorrhoea, dysmenorrhoea, menstruation problems and was recommended during menstruation period.

Currently 'Eumenol' is not authorised in Europe as medicinal product and there are no officially recognised medical indications in European Union countries.

According to WHO monograph for Angelicae sinensis radix in Asia, the herbal substance has been used traditionally in treatment of menstrual disorders such as irregular menstruation, amenorrhoea and dysmenorrhoea.

The monograph cites also that the herbal substance has been used traditionally in symptomatic treatment of rheumatic arthralgia, abdominal pain and in the management of post-operative pain, treatment of constipation, anaemia, chronic hepatitis and cirrhosis of the liver and use in folk medicine in dehydration, lumbago, abnormal menstruation, menopausal symptoms (including hot flushes), hypertonia and nervous disorders.

Assessor's comments:

The use in these indications was not known in Europe. There are no data on traditional use of Angelica sinensis radix in the indications: abnormal menstruation, menopausal symptoms (including hot flushes) during the last 15 years in EC countries.

However, J. Ramsden (2011) analysing the use of herbal medicines in Britain found that the root of *Angelica sinensis* was declared to being used by one patient in the indication of endometriosis.

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

According to the Merck's Index in 1902 and 1907 (American edition) Eumenol (liquid) was used in the quantity of 1 coffee spoon (in Europe) and 4 cm^3 (in the United States) 3 times daily. Historically, in the thirties Eumenol was distributed in continental Europe such as Poland, in liquid form, in bottles containing 25, 100 or 250 g and tablets, in boxes containing 25, 50, 100 units. The duration of use was not specified.

Between 1939 – 1946 Eumenol was authorised in Sweden, in form of tablets was containing 0.3 g dried liquid extract, corresponding 0.6 g of herbal substance, DER (2:1). The extraction solvent was probably 70% ethanol. There are no data on the use of Eumenol in Europe after 1946.

According to the in Ch.P. 1963, the used dosages for *Angelica sinensis* radix were the following:

Usage and dosage: 4.5-9 g;

And in 1977, the following:

Usage and dosage: 4.5-9 g.

3. Non-Clinical Data

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

No systematic data are available.

Results of first pharmacological observations were published by Read and Schmidt in 1923. Authors injected intravenously in anesthetised dogs a simple extract (not further specified) of the Tang Kuei and observed: (a) marked circulatory depression; (b) prolonged and striking diuresis; (c) contraction

of uterine, bladder and intestinal muscle. The distillate sometimes caused contraction of uterus or gut, but large doses were required. They observed also that a residue of the extract, after distillation of volatile material, was still effective. They stated that the circulatory depression was due to direct action on the cardiac muscle. The depressant material was precipitated using mercury. The residue after extraction contained sugar, which was removed by glacial acetic acid. From this residue they obtained crystals, which were powerful stimulants to smooth muscles of uterus, intestine, and arteries. The substance (not further specified) caused constriction, followed by dilatation of kidney vessels, with slight diuresis and a prolonged rise in blood pressure, from peripheral constriction. In the dog, 0.5 to 5 mg of the substance caused contraction of the uterus, pregnant or non-pregnant. In the rabbit, similar results were obtained with 0.1 to 0.4 mg. Intestinal muscles were also affected, but larger doses were required. Isolated rabbit uterus was strongly stimulated by one part in two millions of this material. Strips of human uterus responded to one part in one million; isolated rabbit gut showed an increase in rhythmic movement and in tone, but never a tonic spasm, and the effect was not influenced by atropine. In all these preparations, the effect disappeared on substituting fresh solution, and could be brought out repeatedly by adding more of the drug.

The root of Tang Kuei used in these experiments was identified by E. H. Holmes as the root of *Angelica anomala*, var. *chinensis*. It was known to be used in native medicine in the treatment of menstrual and puerperal disorders and sterility in women, being sold as thin slices of a woody root, having a sweetish taste and an aromatic odour. Previous investigators ascribed its action to volatile ingredients, being unable to isolate from it an alkaloid, glucoside, or other active principle.

3.1.1. Primary pharmacodynamics

Because there are many components in herbal substance and in different preparations, and their effects are not definitely established, different substances may play a main role in different kind of extracts. There are also several directions of pharmacological activity.

There is no data on primary pharmacology after oral administration of Angelicae sinensis water extracts.

3.1.1.1. Antithrombotic, antiplatelet activity

Yin Z et al. (1980) reported the effect of ferulic acid on platelet aggregation and serotonin (5–HT) release in rats. Intravenous injection of aqueous extract of Dang-Gui at a dose 20 g/kg inhibited platelet aggregation. The inhibitory effect on platelets aggregation was observed when sodium ferrulate was administered intravenously at doses 0.1 – 0.2 g/kg.

Sun LQ (2005) referred to results of studies on antithrombotic activity. Xu LN et al. (1985) found the aqueous extract of *Angelica sinensis* (20g/kg) given by intravenous injection to have an inhibitory effect (30%) on rat arterial thrombus formation. Sodium ferulate given intravenously (0.3 g/kg) was shown to be one of the active antithrombotic constituents. The thrombus weight of the control group was 22.1 mg, and that of the ferulate treated group was 11.3 mg ($p<0.01$). When the aqueous extract (20 g/kg) or ferulate (0.2 g/kg) were administered intravenously, the plasma recalcification time was prolonged ($p<0.01$). Both, aqueous extract and sodium ferulate, given intravenously, showed a mild anticoagulant effect. The blood platelet aggregation was estimated by the turbidimetric method. *In vitro*, ADP or collagen induced rat platelet aggregation was inhibited by the aqueous extract at doses of 200-500 mg/ml and by ferulic acid at doses of 0.4-0.6 mg/ml. In human platelets, 0.5 mg/ml did not inhibit the initial platelet response to epinephrine but inhibited the second wave of epinephrine induced aggregation. Similar results have been obtained in case of ADP-induced platelet aggregation *in vivo*. Intravenous injection of the aqueous extract at a dose of 20 g/kg inhibited rat platelet aggregation. An inhibitory effect on platelet aggregation was also observed when sodium ferulate was administered

intravenously (0.1-0.2 g/kg). The aqueous extract (500 mg/ml) and sodium ferulate (1-2 mg/ml) inhibited aggregation and release of 5-HT from rat platelets induced by thrombin. When the extract (20 g/kg) or aspirin (15 mg/kg) were given intravenously to rats, platelet aggregation was inhibited by 50% or more. The carotid arterial prostacyclin (PGI2) production remained unchanged after AS treatment, in contrast to aspirin treatment. When rats were treated with sodium ferulate, the collagen-induced platelet aggregation and thromboxane (TXA2) activity were inhibited by 46% and 47%, respectively, while the carotid arterial PGI2 release remained unchanged. The *in vitro* test showed a significant antagonistic effect on collagen-induced rat platelet TXA2 activity. Sodium ferulate at the concentration of 0.5 mg/ml exhibited potentiation effect on inhibition of platelet aggregation by either rat carotid arterial segment incubates or sodium salt of PGI2. Aqueous extract or sodium ferulate elevated the platelet cAMP level. Ferulate showed a mild inhibitory effect on the activity of cAMP phosphodiesterase (DPE).

Zhang L et al. (2009) demonstrated antithrombotic activity of Z-ligustilide and its effect on platelet aggregation on model arterio-venous shunt thrombosis in rats and in a model of platelet aggregation *ex vivo*. Z-ligustilide administered intragastrically in two doses 10 mg/kg and 40 mg/kg, once daily for 3 days showed dose-dependent reduced arterial thrombus weight in an arteriovenous shunt thrombosis in rats and platelet aggregation induced by adenosine diphosphate *ex vivo*. No significant effect on the coagulation time was observed. The antithrombotic effect of Z-ligustilide in the experiment, at a dose of 10 mg/kg was comparable to 40 mg/kg of aspirin.

3.1.1.2. Antispasmodic activities

Tao J-Y et al. (1984) observed inhibition of asthmatic and spasmodic effects in guinea pigs, induced by acetylcholine and histamine at an intravenous dose of 0.08 mg/kg, by ligustilide at a dose of 0.14 mg/kg. The constituent inhibited histamine-induced asthmatic reaction. *In vitro* ligustilide exhibited spasmolytic action on isolated trachea constricted by acetylcholine, barium chloride or histamine and produced relaxation of the uncontracted trachea. Ligustilide exhibited antispasmodic effect on isolated trachea strip of the guinea pig contracted by acetycholine, histamine and barium chloride, and a relaxation effect on trachea strip under normal tension. Addition of propranolol did not affect these actions. The contents of cAMP and cGMP in the pulmonary and intestinal tissues of the guinea pigs were not altered by treatment with ligustilide.

Ko WC (1980) isolated butylidenephthalide which was proved to be most active, in inhibiting rat uterine contractions induced by prostaglandin F2α, oxytocin and Acetylcholine, than ligustilide and butylphthalide. In experiments on guinea pig ileum, vas deferens and taenia coli, butylidenephthalide proved to be non-specific antispasmodic, but weaker than papaverine.

Ko WC et al. (1997) observed that two geometric isomers of butylidenephthalide inhibited Ca^{2+} - induced contractions in depolarised (K^+, 60mM) guinea-pig ileum longitudinal smooth muscle. Z-butylidenephthalide (50-100 µM) non-competentively inhibited contractions in depolarised pD_2' value 3.88 ± 0.20 (n = 5). E-butylidenephthalide (20 – 100 µM) competitively inhibited, with pA_2' value 4.56 ± 0.16 (n = 5) which was significantly greater ($p < 0.05$) than pD_2' of the Z isomer. The two isomers had no stereoselective inhibitory action on Ca^{2+} influx through pre- and post-junctional membranes of cholinergic nerve endings.

Ko WC et al. (1998) studied the effect of butylidenephthalide on calcium mobilization in isolated rat aorta. Synthetic Z-butylidenephthalide has selected anti-anginal effect without changing blood pressure what inspired the authors to perform experiment to study the mechanism of action. Z-butylidenephthalide relaxed phenylephrine induced constrictions of intact and denuded rat aorta rings. The relaxation was endothelium–independent. The substance in concentrations of 30 – 300 µM inhibited concentration-response curves in concentration-dependent manner.

Intra-venous administration to dogs of a Angelica hot aqueous extracts (not further specified) (10 g/kg body weight) stimulated smooth muscle contractions of the bladder, intestine and uterus. Intravenous administration of an aqueous or 95% ethanol extract of the roots to cats, rats and rabbits increased the strength of the contractions and tone of uterine smooth muscles. Ligustilide, a constituent of the essential oil of the roots, inhibited contractions of isolated uteri from various animal models. Ligustilide (32.5-130 µl/ml) inhibited smooth muscle contractions induced by barium sulphate, acetylcholine and histamine in isolated guinea-pig trachea (WHO Monograph, 2002).

Du J et al. (2005) described the influence of essential oil *in vitro* on uterine of normal rats as "two-way effect", dependent on the oil concentration. Lower levels of the oil (0.01-0.02 mg/ml) can increase uterine contraction frequency but at levels higher than 0.04 mg/ml the inhibition is significantly higher than the control group. Between 0.04 – 0.32 mg/ml the oil is described to produce inhibition of the uterine with a dose dependent manner. Oxytocin induced spasms were dose dependently inhibited by the oil in concentrations of 0.01 – 0.16 mg/ml.

Du J et al. (2006) investigated effects of ligustilide on uterine contraction *in vitro*, in a model of isolated rat uterus. The authors observed on the model of isolated rat uterus that at doses of 2-8 µg/ml ligustilide inhibited in a concentration-dependent manner (EC_{50}=4.4µg/ml 95% confidence interval, 2.7 – 6.1 µg/ml) the spontaneous periodic rat uterine contractions, induced by acetylocholine chloride. At a concentration of 8 µg/ml ligustilide nearly completely blocked PGF2α-induced contractions (95.3%). Ligustilide affected also significantly the oxytocin-induced increase in the concentration-dependent inhibition of uterine horns that were incubated not only in Locke solution but also in Ca2+ free medium. The authors concluded that ligustilide possesses a non-specific antispasmodic activity.

3.1.1.3. Oestrogenic activity

Klein KO (2003) used a recombinant cell bioassay to measure the oestrogenic activity of dried herbal extracts (not further characterised). They studied the *in vitro* activity of *Angelica sinensis* radix and extracts of other herbal substances: *Trifolium pretense*, *Cimicifuga racemosa*, *Glycine max*, *Vitex agnus-castus*, *Polygonum multiflorum*, *Humulus lupulus*. Extract of *Angelica sinensis* radix did not have measurable activity in the experiment. However, other substances' extracts: soy, red clover, liquorice, hops and *Polygonum multiflorum* (fo-ti) had a large amount of measurable oestrogenic activity.

Because there are no data on distinct pharmacological data showing oestrogenic effect of extracts of *Angelica sinensis* radix some authors suggested other mechanisms which may explain the traditional use of the herbal substance in premenstrual pain complaints.

Some *in vitro* assays demonstrated that a decoction of the roots stimulated the H_1 receptor of mouse uterus. The active constituent responsible for this activity is an aqueous- and alcohol-soluble, non-volatile component, the structure of which is unknown (WHO Monograph, 2002).

Deng S et al. (2006), performed a serotonergic activity-guided phytochemical analysis of the roots of *Angelica sinensis* and fractionated and isolated twenty one components. Most of them were earlier known substances, among them: p-hydroxyphenetyl trans-ferulate, Z-ligustilide, Z—butylidenephthalide, senkyunolide I, Z-6-hydroxy -7-methoxy-dihydroligustilide and there were new, named: angeliferulate (phenolis ester), angeloylbutylphthalide, sinaspirolide, ansaspirolide (dimeric phthalides). Some of the compounds exhibited affinity toward 5 HT_7 receptors in a competitive binding assay: p-hydroxyphenethyl trans-ferulate, Z—butylidenephthalide, two polyines, (3*R*,8*S*)-falcarindiol, and imperatorin.

Assessor's comments:

Although it was earlier presumed that Angelica sinensis radix has oestrogenic activity; there is no evidence of oestrogenicity in both in vitro and also in clinical studies, which indicates that the substance may act through an alternative mechanism rather than being a phytoestrogen. Preliminary testing of extracts demonstrated that the methanol extract of Angelica sinensis radix has serotonergic activity, what suggests that it may contain serotonergic ligands that act on serotonin receptors and, thus, exhibit pharmacological effects related to improvement of symptoms of moods, behaviours and hot flashes for premenstrual and menopausal women.

3.1.2. Secondary pharmacodynamics

3.1.2.1. Cytotoxicity and antiproliferative effects

Tsai NM et al. (2005) tested the influence of a chloroform extract of *Angelica sinensis* radix on glioblastoma multiforme *in vitro* and *in vivo* on rats. The extract displayed some potency to suppress the growth of malignant brain tumour cells showing a lower cytotoxicity towards fibroblasts.

The same authors (2006) studied the inhibition of malignant brain tumour growth *in vitro* and *in vivo* by n-butylidnephthalide. The IC_{50} of this component indicated activity against several experimental malignant cell systems, especially lower than 20 µg/ml: mouse neuroblastoma N18 15.5 ± 2.5 µg/ml; human teratoma cells PA-1 18.7 ± 1.9 µg/ml; human hepatoma cell J5 19.5 ± 0.4 µg/ml.

Deng S et al. (2008), isolated from the chloroformic extract of the roots of *Angelica sinensis*, under *in vitro* tuberculosis activity control, five polyynes: falcarinol; *9Z*,17-octadecadiene-12,14-diyne-1,11,16-triol,1-acetate, oplopandiol, heptadeca-1-ene-9,10-epoxy-4,6-diyne-3,8-diol and the new polyyne 8-hydroxy-1-methoxy-(*Z*)-9-heptadecene-4,6-diyn-3-one, and characterised by spectroscopic techniques including 1D, 2D NMR and HR-MS. All compounds were tested against two pathogenic strains of *Mycobacterium tuberculosis* (H37R*v* and ERDMAN) *in vitro* in a microplate Alamar Blue assay (MABA). The most potent anti-TB constituents were falcarinol and *9Z*,17-octadecadiene-12,14-diyne-1,11,16-triol,1-acetate, exhibiting MIC values of 1.4-26.7 µg/ml. Notably, none of the five compounds exhibited significant cytotoxicity against VERO cells.

3.1.2.2. Anxiolytic effect of the essential oil

Chen SW et al. (2004) performed three assays of the effects of Angelica essential oil. An activity of the oil in male mice was studied, with diazepam as a positive anxiolytic control. In the elevated plus-maze test, compared to the positive control diazepam. Angelica essential oil (30 mg/kg, orally) had a "modest anxiolytic-like effect" (increased the percentage of open-arm time and reduced the percent protected head dips). In the light/dark test, Angelica essential oil (30 mg/kg) prolonged the time spent in the light area without altering the locomotor activity of the animals. In the stress-induced hyperthermia test, 60 and 70 minutes after the administration, at the same dose the oil inhibited stress-induced hyperthermia. The authors concluded that Angelica essential oil, as does diazepam, exhibits a modest anxiolytic-like effect, but further studies will be required to assess the generality of these findings.

3.1.2.3. Effects on the cardiovascular system

Du JR et al. (2005) reported experiments with expansion of peripheral and coronary vessels by Angelica oil, decreasing the coronary vascular resistance and the total peripheral resistance, as well as increase of blood flow and significant decrease of myocardial oxygen consumption. The volatile oil lowered dose-dependently the blood pressure of dog, cat, and rabbit. Two g/kg of the oil significantly

lowered the blood pressure after 5 minutes intravenous administration for a dog with high blood pressure (177/130 mmHg reduced to 155/110 mmHg) and reduced the limb vascular resistance. Angelica root oil (50 mg/kg i.v.) on empty stomach 80 mg/kg/day showed a protective effect on the vasopressin induced myocardial ischemia in experimental rabbits.

3.1.2.4. Protective effect of a polysaccharide fraction on the gastric mucosa

Ye YN et al. (2001), referred to first data that a crude extract from *Angelica sinensis*, mainly consisting of polysaccharides, significantly promoted migration and proliferation of normal gastric epithelial cells, which suggested wound healing effects on the gastric mucosa. In his study, the authors found that the polysaccharide extract promoted ulcer healing in animal models. The area of the ulcer was reduced. This was accompanied with a significant increase in mucus synthesis when compared with the control. Angiogenesis was inhibited by the treatment. The mechanism, how the extract accelerates ulcer healing in addition to its effect on mucus synthesis, remains to be investigated.

Song M et al. (2009) identified in a water extract of *Angelica sinensis* radix a polysaccharide substance possessing significant analgesic activity.

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

There are no systematic data available on pharmacokinetics of the main active components. There are data on pharmacokinetics in animal models, for substances of known therapeutic activities.

Luo H et al. (2003) detected ferulic acid and paeoniflorin in the serum of mice after intra-gastric administration of a combination Angelic-Paeonia root powder. The concentrations of both substances at different times were determined in serum, using HPLC. The pharmacokinetic parameters of ferulic acid in the experiment were: T_{peak} = 2.606±0.586 h, C_{max} = 6.372 ±1.510 mg.L-1, $t_{1/2(ka)}$ = 1.249 ± 0.365 h, $t_{1/2(ke)}$ = 2.101± 0.665 h, AUC = 41.399± 11.763 mg.h.L-1, K_e = 0.330± 0.085 h-1, K_a = 0.555 ± 0.133 h-1.

Ru Y et al. (2007) observed low oral bioavailability of senkyunolide A in rats. The pharmacokinetics of senkyunolide A, of the essential oil of Rhizoma Chuanxiong (Ligusticum chuanxiong), which is commonly used for the treatment of cardiovascular diseases, was studied in rats. After intravenous administration, senkyunolide A was extensively distributed (V_d/F: 6.74 ± 0.73 L/kg) and rapidly eliminated from the plasma (CL/F: 7.20 ± 0.48 L/h per kilogram and $t_{1/2}$: 0.65 ± 0.06 h). Hepatic metabolism was suggested as the major route of senkyunolide A elimination as indicated by the results of an *in vitro* S9 fraction study. After intraperitoneal administration, senkyunolide A exhibited dose-independent pharmacokinetics. The absorption after IP administration was rapid (T_{max}: 0.04 ± 0.01 h), and the bioavailability was 75%. After oral administration, senkyunolide was also absorbed rapidly (T_{max} 0.21 ± 0.08 h) however its oral bioavailability was low, about 8%. Moreover as contributing factors were determined the instability in the gastrointestinal tract (accounting for 67% of the loss) and a hepatic first-pass metabolism (accounting for another 25%). Pharmacokinetics of senkyunolide A were unaltered when extract was administered, which suggests that components in the extract have insignificant effects on senkyunolide A pharmacokinetics.

Yan et al. (2008) analysed pharmacokinetic parameters of ligustilide, isolated from the essential oil of the root of *Ligusticum chuangxiong* Hort by chromatographic methods. After oral administration of ligustilide to rats, plasma concentration-time profile and pharmacokinetic parameters were only obtained at the highest dose, 500 mg/kg. At lower doses plasma levels of ligustilide were below detectable limits (at 100 mg/kg) or they were not high enough for accurate pharmacokinetic analysis. At the dose of 500 mg/kg ligustilide was rapidly absorbed (T_{max}, 0.36 ± 0.19 h) reaching a C_{max} of

0.66 ± 0.23 µg/ml. The plasma concentration of ligustilide declined in a multiphase manner quickly to approximately 120 ng/ml within 4 h. This level was maintained for another 4 to 8 h before decreasing. The longer-lasting terminal phase (4–8 h) significantly increased the retention of ligustilide (MRT, 5.14 ± 1.56 h) when compared with that of intravenous and intraperitoneal data. CL/F values were significantly higher and the dose normalized AUC lower than those obtained after intravenous and intraperitoneal administration. The oral bioavailability was estimated to be 2.6% at the 500 mg/kg dose. The elimination of ligustilide when administered as extract intravenously was significantly faster than that for its pure form (CL, 20.35 ± 3.05 versus 9.14 ± 1.27 l/h/kg; $p < 0.01$), suggesting interaction between ligustilide and components present in the extract.

Pharmacokinetic parameters of ligustilide in rats after intravenous, intraperitoneal and per os administration (n = 5) (according to Yan et al., 2008)

Pharmacokinetic Parameter	Administration Route				
	intravenous		intraperitoneal		per os
Dose (mg/kg)	15.6	14.9 [a]	26	52	500
T_{max} (h)			0.05 ± 0.02	0.08 ± 0.01	0.36 ± 0.19
C_{max} (mg/l)	13.19 ± 0.84	6.93 ± 0.60***	7.48 ± 1.10***	20.75 ± 2.55###	0.66 ± 0.23***
$T_{1/2}$ (h)	0.31 ± 0.12	0.22 ± 0.07	0.36 ± 0.05	0.44 ± 0.08#	3.43 ± 1.01***
AUC $_{0-\mu}$ (mg/l) [b]	1.81 ± 0.24	0.79 ± 0.10**	0.93 ± 0.07*	1.77 ± 0.23#	0.047 ± 0.012**
V_d/F (l/kg)[c]	3.76 ± 1.23	5.62 ± 1.19	6.54 ± 1.56	6.32 ± 1.81	1641.9 ± 121.6***
CL/F (l/h/kg) [c]	9.14 ± 1.27	20.35 ± 3.05**	16.90 ± 1.21**	9.26 ± 1.04##	411.1 ± 145.7***
MRT (h)	0.30 ± 0.07	0.19 ± 0.03	0.30 ± 0.05	0.41 ± 0.03	5.14 ± 1.56***
F (%)		45.7 [d]	51.7	97.7	2.6

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, compared with intravenous dosing of the isolated ligustilide. # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$, compared with the lower intraperitoneal dose of the isolated ligustilide. *a* Dose of ligustilide in 100 mg/kg of Chuanxiong extract. *b* Normalised with dose. *c* Data represent Vd and CL in the case of intravenous dosing of the isolated ligustilide. *d* Relative bioavailability compared with that of intravenous dosing of the isolated ligustilide.

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

According to Mills S and Bone K (2005), after Wagner H et al. (2001), the LD50 value of Dong Quai extract, concentrated 8-16:1, was 100 g/kg after giving single dose to rats, orally.

According to Mills S and Bone K (2005), after Opdyke DL (1979), the LD50 value of 3-n-butylidene phthalide was 2.45 g/kg after giving single dose to rats, orally.

There are no data on genotoxicity, carcinogenicity and reproductive and development toxicity.

3.4. Overall conclusions on non-clinical data

On the base of available data there are different groups of substances contained in *Angelica sinensis* radix. In a Chinese tradition, Dang gui is used specially to enrich blood, activate blood circulation, regulate menstruation, relieve pain, and relax bowels. The pharmacodynamic and pharmacokinetic data may explain the use to improve blood circulation and probably relieve pain. There are no data explaining the use for “regulate menstruation” and no data confirming distinct oestrogenic activity of

Angelica sinensis, radix or preparations thereof. However, some studies indicate mild spasmolytic activity of the essential oil and unspecific inhibition of uterus contractions, by Z-ligustilide and other phthalides. This may play a role in relieving of painful complaints associated with the pre-menopausal syndrome. The bioavailability of the phthalides is low, what may hamper pharmacological effects.

The antiplatelet activity of ferulic acid may play an important role in diminishing inflammatory complaints.

Angelica sinensis radix contain substances possessing genotoxic properties: safrole and isosafrole and other naturally occuring components – phototoxic furocoumarins: xanthotoxin (8-MOP), bergapten (5-MOP), psoralen, imperatorin and oxypeucedanin. There is no data on the content of these compounds in the herbal substance and it is difficult to evaluate the potential exposure of patients to these substances.

An additional factor which could influence safety considerations as regards the medicinal use of *Angelica sinensis* radix is a traditional method used for adjustment of the plant material. Smoke drying of the roots differs from the method used in Europe, where underground plant organs are usually washed with water before drying, for removing microbiological and mineral pollution. For the traditional Chinese method of preparation, no information on washing the root and drying is available, only smoke-drying seems to be in use.

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

Hirata JD et al. (1997) evaluated oestrogenic effects of dong quai on vaginal cells and on endometrial thickness in postmenopausal women in a double-blind, randomised, placebo-controlled clinical trial. From 116 screened women qualified for the study, 25 refused further participation; remaining 91 women had been postmenopausal for at least 6 months and had symptoms of night sweats or vasomotor flushes (more than 14 events per week and of more than 5 of moderate to severe combined events per week). Further 8 were subsequently excluded because of using other medicines: follicle stimulating hormone, erythromycin or substances to decrease vasomotor symptoms. Another 7 women declined to participate in the initial visit, and 5 were excluded because their initial thickness exceeded 5 mm. The remaining 71 women were randomised, according to the computer generated numbers, to the groups of dong quai (age 44.5 – 59.6 years) or placebo (44.7 – 69.3 years). Each patient was instructed to take 3 capsules 3 times daily. Dong quai was extracted with water and air-dried to obtain a granular powder. This powder was mixed with the residual root material. One gram of the finished product represents 1g of root material (except for volatile substances which evaporate during the drying of an aqueous extract). Placebo (maltodextrin) and dong quai were dispensed in identical capsules. After the initial visits, patients returned for clinical assessment at 6, 12, 24 weeks. During the initial and final visits serum oestrogen levels and vaginal cytology were evaluated. During each visit blood pressure, weight, endometrial ultrasonography were measured. Women in whom transvaginal ultrasonography showed >5 mm endometrial thickness at the final visit, were evaluated by using endometrial biopsy to exclude the possibility of endometrial abnormalities.

Double endometrial thickness as viewed longitudinally was determined by using transvaginal ultrasonography at all visits. Cytologic examinations of vaginal smears was performed at the initial visit and again after 12 weeks of the study.

Menopausal symptoms were recorded by patients in a diary recording the total daily number of vasomotor episodes: vasomotor symptoms, paresthesia, insomnia, nervousness, melancholia, vertigo, fatigue, arthralgia/myalgia, headache, palpitation and formication) in scores: no symptomes = 0, mild complaint = 1, moderate = 2, severe = 3. At each clinic visit, the subject's score was assessed on the Kupperman index.

Six patients receiving placebo (16.6%) dropped out of the study (two because of lack of efficacy, two because of side effects, two because of loss of interest). Four patients (11.4%) dropped out from the dong quai group, two because of lack of efficacy, one because of side effects and one because of other health problems. Both treatment groups, dong quai and placebo, noted similar side effects: burping (22.9% v. 31.4%), gas (22.2% v. 25%), headache (14.4% v. 16.7%). Compliance with study protocol was exellent (>75%), 78.8 in the dong quai group and 83.3% in placebo.

During the 24 weeks of the study endometrial thickness increased by 0.8 mm, from 2.6 mm (± 1.1) in the dong quai group to 3.5 (± 2.2) and by 2.3 mm in the placebo group, from 2.5 (± 0.7) to 4.7 (± 2.4) but the difference between the groups was not significant.

At the initial visit, most patients of the dong quai group had a vaginal cytology pattern that showed dominance of intermediate cells, indicating that few women had an atrophic pattern. The cytologic pattern did not change between the initial and 12–week assessments. No significant increase in percentage of superficial cells or in the maturation value at 12 weeks in either the dong quai group or the control was noted.

During the study, the Kupperman index and number of vasomotor episodes were reduced by about 25% - 30% from initial values, and no significant differences were seen between treatment and placebo. Only 29.4% patients of the placebo group and 33.3% of the dong quai group reported good or excellent diminution of their vasomotor symptoms.

The authors found no differences in menopausal outcomes between dong quai and placebo groups. Dong quai did not promote endometrial proliferation, the mean increase of endometrial thickness tended to be greater among women receiving placebo.

Dong WG et al. (2004) observed in patients with significantly activated platelets that *Angelica sinensis* injection can significantly inhibit platelet activation, relieve vascular endothelial cell injury and improve microcirculation in patients with ulcerative colitis.

Assessor's comment: Form of injections is outside the scope of traditional use legislation.

This observation or experiment on humans with ulcerative colitis was not continued. It may indicate an aspect of anti-inflammatory activities after injection, but it was not confirmed by further experiments or followed by clinical trials. However, this publication -isolated from other data on medicinal use in humans- may have a limited value providing a hint for further experiments on a possible anti-inflammatory effect in humans.

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

There is no pharmacokinetic data from humans.

4.2. Clinical Efficacy

4.2.1. Dose response studies

There are no available dose response data.

4.2.2. Clinical studies (case studies and clinical trials)

Hu CH (2004) described the retrospective observation of the treatment of a group of 200 gynaecological outpatients with dysmenorrhea, irregular menstruations, aged 16 – 46 and treated with the product 'Concentrated Danggui Wan' and another combination of Angelica and Astragalus. One hundred and forty-eight patients were in the treatment group, 52 in the comparator group. Diseases persisted from 6 months to 12 years, average 5 years. Inclusion criteria covered three groups of symptoms, defined as following:

Dysmenorrhea: premenstrual and menstrual abdominal pain affecting work and daily activities, unstable effects of antispasmodic treatment.

Irregular menstrual cycle: menstrual cycle shorter than 20 days or longer than 35 days, or in 2 consecutive months the menstruation lasted for more than 7 days.

Reduced menstrual flow: Menstrual period less than 2 days or progressive decline of menstrual flow.

The treatment group (148 cases) was treated daily with product Concentrated Danggui Wan. Each dose unit "pill" contained 0.25 g of the drug. Twice a day 10-20 pills were taken each time with lukewarm water. Each treatment lasted for 4 weeks, and each patient received 2–3 treatments.

The control group (52 cases) took large honey-based Angelica pills daily (ingredients of the pills were Angelica and Astragalus), twice a day, 9 g each time. Each treatment lasted for 4 weeks, and each patient normally received 2–3 treatments. During the treatment, all other medications for dysmenorrhea and irregular menstruation were prohibited. Effects of the treatment and the side-effects were measured.

Results of treatment were assessed in a 3 - step scale:

Significantly effective: abdominal pain is reduced after the treatment and it no longer affects daily activities and work; menstrual cycle becomes largely normal, i.e., less than 5 days early or late; the flow increases at least one third as compared to before the treatment; menstruation lasts for 5-7 days, and other symptoms have disappeared or been alleviated.

Effective: Abdominal pain is reduced. With the help of painkillers a patient can remain at job. Symptoms of menstrual problem have become less severe but improvements are limited as compared to the "very effective" result.

Ineffective: No improvements with abdominal pain and other problems. Menstrual cycle and flow have shown no changes.

Therapy in treatment group was assessed as significantly effective in 59/148 patients (39%), effective in 81/148 (54%) ineffective 7/148 (4%). Therapy in control group was assessed as significantly effective in 27/52 patients (52%), effective in 18/52 (34%) an ineffective in 7/52 (13%) patients.

The author states that "there have been no clear side-effects in using Concentrated Danggui Wan for treating dysmenorrhea and irregular menstruation". In a few cases the patients developed mild nausea but the symptom quickly disappeared when the treatment was halted; there is no more detailed data.

Assessor's comments:

Groups were not balanced and results in Concentrated Danggui Wan patients group and in comparator group (Angelica and Astragalus) were similar. The scheme of parallel observation of two traditionally used products, without control, cannot give us information on their potential efficacy. On the other

hand Hirata J et al. (1997) earlier concluded that when dong quai is used alone, it is no more helpful than placebo in relieving menopausal symptoms.

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

Not available.

4.3. Overall conclusions on clinical pharmacology and efficacy

In the only evaluation of oestrogenic effects of a water extract of *Angelica sinensis* radix on endometrial thickness, in postmenopausal women, (Hirata et al. 1997) no differences in menopausal outcome between dong quai and placebo groups were observed.

In the retrospective parallel observation of 200 gynaecological outpatients with dysmenorrhea and irregular menstruations by Hu CH (2004) the author concluded that concentrated Danggui Wan "was effective for treating dysmenorrhea and irregular menstruation, meagre and stagnant flow, dark flow, thick flow with clothes". However both groups: verum (148) and control (52) were not balanced and there was no placebo control. Moreover, the two products observed were easy to differentiate by the patients: large honey-based Angelica pills (containing Angelica and Astragalus) used as a control. It is difficult to accept this observation as evidence of efficacy. Taking into account the negative outcome of the study of Hirata, there is no coherence in scientific assessments.

5. Clinical Safety/Pharmacovigilance

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

There are no data on safety clinical trials.

The observational study Hu CH (2004) on 200 gynaecological outpatients did not record distinct side-effects while using *Angelica sinensis* preparation for treating dysmenorrhea and irregular menstruation, but in a few cases the patients developed mild nausea and the symptoms quickly disappeared when the treatment was halted. Quantitative analysis of the data is not available.

The study of Hirata J et al. (1997) was not able to supply information on adverse effects.

5.2. Patient exposure

There are no data on exposure patients on *Angelica sinensis* radix as a substance or preparations, in EU countries.

5.3. Adverse events and serious adverse events and deaths

There are no systematic pharmacovigilance data from European countries.

In the WHO ADR database MedDRA, there are records of 35 adverse reactions: 1 abdominal pain, 1 abnormal level of alanine aminotransferase, 2 amenorrhea, 1 angioedema, 1 blood bilirubin increased, 1 breast pain, 1 coagulopathy, 1 convulsion, 3 Creutzfeld-Jakob disease, 1 diarrhoea, 1 drug ineffective, 1 dystonia, 1 fibrocystic breast disease, 1 gastrointestinal haemorrhage, 1 haematemesis, 1 haemoglobulin decreased, 1 hepatic failure, 1 hepatitis acute, 1 hepatitis toxic, 1 jaundice cholestatic, 1 loss of consciousness, 1 menstruation irregular, 1 multi-organ failure, 1 nausea, 1 oedema peripheral, 1 prothrombin time prolonged, 1 pruritus, 1 rash, 1 somnolence, 1 tongue spasm, 1 urticaria, 1 vaginal haemorrhage.

Most common ADR are: reproductive system and breast disorders 6 ADR, gastrointestinal signs and symptoms 5 ADR, hepatobiliary 4 ADR, nervous system 4 ADR, haematology 4 ADR, skin diseases 4.

Three cases of Creutzfeld–Jakob disease are difficult to explain and difficult to classify.

There were recorded also 9 ADR for combinations products (94). 1 record concerning nephrotic syndrome for product containing: *Angelica sinensis* root, *Bupleurum chinense* root, *Gentiana scabra* root, *Scutellaria baicalensis* root, *Gardenia jasminoides* fruit, *Plantago asiatica* seed, *Akebia quinata* stem, *Alisma plantago-aquatica* var. *orientale* rhizome and *Glycyrriza uralensis* root with rhizome. Eight records for product containing combination of Angelica simemsis and Chamamaelum nobile: 1 nausea, 1 fatigue, 2 jaundice, 1 liver injury, 1 grand mal convulsion, 1 convulsion, 1 pruritus.

Bradley RR et al. (1999) reported about a patient, treated with recombinant human erythropoietin (rHuEPO), but was resistant to this drug. The patient suffered from anaemia. He experienced marked improvement in the anaemia after self-initiating regular consumption of the Angelicae sinensis radix. The significant hematologic amelioration occurred in face of a major decrease in the amount of rHuEPO administered. This surprising hematopoietic effect was not explained.

5.4. Laboratory findings

There are no data.

5.5. Safety in special populations and situations

There are no data.

5.6. Overall conclusions on clinical safety

No data on clinical safety are available. The only clinical trial concentrated on the mechanism of action and was not able to give information on safety.

In the observational study on outpatients using a product containing concentrated Dang gui Wan the records on safety were not systematic nor suitable for the assessment.

Moreover certain possible unwanted effects may be undetectable, because genotoxic potential cannot be detected by pharmacovigilance or long-standing use and experience.

6. Overall conclusions

There are no data on medicinal use of single products, containing *Angelica sinensis* root as an active substance of medicinal products in Europe after the year 1946. However many products containing *Angelica sinensis* radix appeared on European markets, as food supplements, after implementation of Directive 2002/46/EC. There are no data that, according to Article 16c1(c), *Angelica sinensis* root has been in medicinal use throughout a period of at least 30 years preceding the assessment, including at least 15 years within the Community.

However, there is evidence based on monographs for Angelicae sinensis radix (Danggui) in editions of the Chinese Pharmacopoeia that the herbal substance has been in traditional use in China throughout at least 30 years preceding the assessment.

Angelica sinensis radix contains two groups of substances which seem to be most important in exerting pharmacological effects in patients after taking oral forms. The first is trans-ferulic acid, which is present in water extracts, like infusions, and alcoholic extracts. Ferulic acids and other hydrophilic compounds which are present in water extracts may be responsible for anti-inflammatory, antiplatelet

and antithrombotic effects in animal pharmacological models. The other group of components are lipophilic components of the essential oil, especially characteristic mono alkylphthalides and dimeric phthalides. The pharmacodynamic effects in humans of this second substance group may depend on other factors, in particularly those improving absorption, because of the low bioavailability of ligustilides and senkyunolides. The essential oil and monoalkylphthalides, especially Z-ligustilide, possess unspecific antispasmodic properties what may explain the use in symptoms of dysmenorrhaea, such as painful colics.

Angelicae sinensis radix contains a number of furocoumarins that can induce photosensitivity. Some furocoumarins, in the presence of UV light, are considered carcinogenic or probably carcinogenic to humans. There are no systematic data on the content of furocoumarins in the herbal substance and generally more detailed data on content and profile of furocoumarins in the *Angelica sinensis* radix are lacking.

The essential oil contains also safrol, which is described as weak carcinogen in rats and mice and a known genotoxic compound; furthermore isosafrol, a weak hepatocarcinogen in rats and mice (EFSA compendium 2009). There are no data on the content of these substances in the herbal substance and in preparations thereof.

In Chinese tradition, dang gui is used mostly to enrich blood, activate blood circulation, regulate menstruation, relieve pain, and relax bowels. The available pharmacodynamic and pharmacokinetic data may explain its use to improve blood circulation and probably relieve pain. There are no data explaining the use for “regulate menstruation” or data confirming distinct oestrogenic activity of *Angelica sinensis* radix or derived preparations. However some studies indicate mild spasmolytic activity of the essential oil and unspecific inhibition of uterus contractions by Z-ligustilide and other phthalides, which may play a role in relieving pain associated with complaints of pre-menopausal syndrome. Because the bioavailability of the phthalides is low, hampering potential pharmacological effects, ferulic acid instead may play an important role in the effects observed.

Retrospective observation of the treatment of a group of 200 gynaecological outpatients with dysmenorrhea and irregular menstruations, treated with Concentrated Danggui Wan (148 patients) and a combination of Angelica and Astragalus (52 patients) described by Hu CH (2004), resulted in similar therapeutic effects in both groups. The scheme of parallel observation of two traditionally used products, without placebo control, cannot give us information on their potential efficacy. In the only controlled clinical trial assessing the oestrogenic effect of a water extract of *Angelica sinensis* radix on endometrial thickness, in postmenopausal women (Hirata et al. 1997), no difference in menopausal outcomes between the group taking the extract of *Angelica sinensis* radix and the placebo group was observed.

Clinical data are not sufficient to accept a well-established use, because the substance is not documented in all pharmacological and clinical aspects as required by Art. 10a of Dir. 2001/83/EC and further described in Annex 1, Part. II, 1 Well-established medicinal use (Commission Directive 2003/63/EC) in particular regarding the degree of scientific interest in the substance (reflected in the published scientific literature) and the coherence of scientific assessments.

Annex

List of references