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Committee on Herbal Medicinal Products (HMPC)

## Assessment report on *Curcuma longa* L., rhizoma

Final

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Curcuma longa</i> L., rhizoma
Herbal preparation(s)	A) Powdered herbal substance B) Comminuted herbal substance C) Tincture (Ratio of herbal substance to extraction solvent 1:10), extraction solvent ethanol 70% (V/V) D) Dry extract (DER 13-25:1), extraction solvent ethanol 96% (V/V) E) Dry extract (DER 5.5-6.5:1), extraction solvent ethanol 50% (V/V) F) Tincture (Ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 70% (V/V)
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use.  Herbal preparations in liquid or solid dosage forms for oral use.
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## ABBREVIATIONS

ADI	Acceptable Daily Intake
CMS	Chronic Mild Stress
b-FGF	Basic Fibroblast Growth Factors
DBP	di-n-butylphthalate
DMBA	7,12-dimethylbenz(a)anthracene
FGF	Fibroblast Growth Factor
GRAS	Generally Recognised As Safe
GSH	Glutathione
G6PD	Glucose-6-Phosphate Dehydrogenase
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MDA	Malondialdehyde
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
PAF	Platelet-Activating Factor

# 1. Introduction

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

- Herbal substance(s)

The European Pharmacopoeia defines *Curcuma longae* rhizoma or turmeric rhizome as the whole, cured (by boiling or steaming), dried rhizome of *Curcuma longa* L. (syn. *Curcuma domestica* Valetton) with roots and outer surface removed (European pharmacopoeia 8th ed. 2017).

Other documented synonyms of *C. longa* are *C. aromatica* Salisbury and *Amomum curcuma* Jacq. (Blumenthal 1998, WHO 1999). Common names for *C. longa*: turmeric, curcuma.

Besides *C. longa* also *C. rotunda* is mentioned in some older references. Nowadays *C. rotunda* is considered to be a former trade name for the product containing the primary rhizomes (bulb or round turmeric) in distinction to the product consisting of the thinner and longer secondary rhizomes (longa-form), both originating from *C. domestica* L. (List and Horhammer 1973, Bisset 1994).

Other names: Curcuma, Indian saffron, Haridra (Sanskrit, Ayurvedic), Jianghuang (=yellow ginger in Chinese), Kyoo or Ukon (Japanese) (Häringer 2004).

The monographs of ESCOP and Commission E mention that the herbal substance contains not less than 2.5 resp. 3% dicinnamoylmethane derivatives, calculated as curcumin, and not less than 2.5 resp. 3 % volatile oil, both calculated on a dry-weight basis of the drug (ESCOP Monograph 2003, German Commission E Monograph - Bundesanzeiger 1985).

For *Curcuma xanthorrhiza* Roxb. (*C. xanthorrhiza* D. Dietrich), another species of the genus *Curcuma*, and having similar properties as *C. longa*, a HMPC monograph was established in 2014. The European Pharmacopoeia describes in the monograph for *Curcuma xanthorrhizae* rhizoma a TLC-test for *C. domestica* and its modifications for identifying *C. xanthorrhiza* (European pharmacopoeia 6<sup>th</sup> ed. 2009).

**Constituents** (see also Fig. 1)

Carbohydrates: 69.4% of total mass (Kapoor 1990).

Curcuminoids: this is a mixture of curcumin (diferuloylmethane), monodexmethoxycurcumin and bis-desmethoxycurcumin (ASEAN 1993, Bisset 1994, Bruneton 1995, Osawa *et al.* 1995, Sreejayan and Rao 1997a). Curcumin makes up approximately 90% of the curcuminoid content in turmeric (Ruby *et al.*, 1995).

The phenolic groups in the structure of curcumin explain the ability of curcumin to eliminate oxygen-derived free radicals (Priyadarsini 1997). The free radicals which can be eliminated by curcumin are hydroxyl radical (Reddy and Lokesh 1994), singlet oxygen (Rao *et al.*, 1995), superoxide radical (Sreejayan and Rao 1996), nitrogen dioxide and NO (Sreejayan and Rao 1997b, Unnikrishnan and Rao 1995).

The curcumin content of the *C. longa* rhizome varies from 0.6 to 5% of the dry mass (Cronin 2003). The dry turmeric rhizomes contain 3-5% curcumin, the curcumin content of turmeric oleoresin is 40% (Govindarajan 1980).

Essential oil: 5.8% of total mass, constituents are:  $\alpha$ -phellandrene 1%, sabinene 0.6%, cineol 1%, borneol 0.5%, zingiberene 25%, and sesquiterpenes 53% (Kapoor 1990). The mono- and sesquiterpenes include zingiberene, curcumene, aromatic turmerone (*ar*-turmerone) and  $\alpha$ - and  $\beta$ -turmerone (ASEAN 1993, Bisset 1994, Bruneton 1995, Osawa *et al.* 1995, Sreejayan and Rao 1997a).

Mineral matter: 3.5% of total mass (Kapoor 1990).

Moisture: 13.1% of total mass (Kapoor 1990).

Polypeptides: (Osawa *et al.* 1995, Sreejayan and Rao 1997a).

Protein: 6.3% of total mass (Kapoor 1990) and Fatty oil (Srimal 1997).

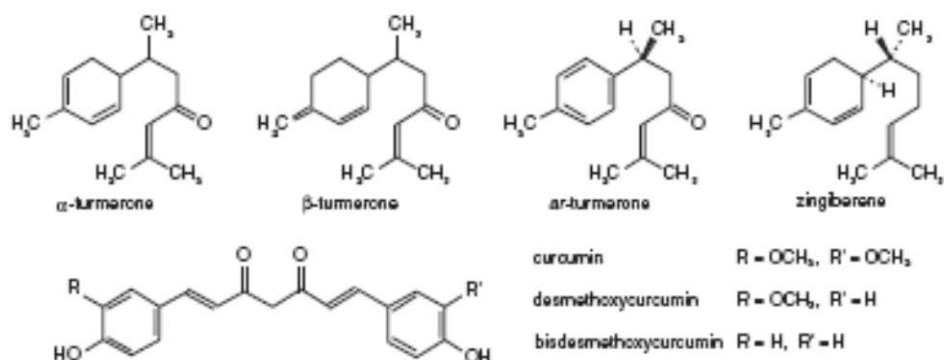


Fig. 1: Structures of main components of *Rhizoma Curcumae longae* (WHO 1999).

### Treatment of the herbal substance immediately after harvesting

According to some handbooks the plant material is processed before drying (Blumenthal 1998, ESCOP Monograph 2003, German Commission E Monograph - Bundesanzeiger 1985).

Hager's Handbuch describes that after harvest, the rhizomes are cooked for a short time or heated with hot water (Frerichs *et al.* 1949, List and Horhammer 1973). The Indian and Japanese Pharmacopoeias also describe the 'curing', consisting of boiling and (sun) drying of the rhizomes as well as identification by different color reaction tests. The Chinese Pharmacopoeia mentions: collection of rhizomes, washing, boiling or steaming, cutting in thick slices, sun drying and separation from roots (Herbal Medicine).

Max Wichtl's Herbal Drugs mentions that the yellowish brown color of the herbal substance is due to the steaming or scalding treatment after harvesting (Bisset 1994).

As pharmacological and (pre)clinical studies do not contain any data on the pretreatment of the plant material, and research data on the scalding effect are missing, the impact of the scalding treatment on the active compounds and on the efficacy of *C. longa* preparations remains unclear. The scalding treatment is considered to be a traditional procedure mainly for food purposes.

- Herbal preparation(s)

The following herbal preparations are mentioned in literature: Powdered *C. longa* rhizoma (ESCOP Monograph 2003, German Commission E Monograph - Bundesanzeiger 1985, The Indian pharmaceutical codex 1953, WHO 1999); Ethanolic (80%) extract (Commandeur and Vermeulen 1996, Deshpande *et al.* 1998, Khattak *et al.* 2005, Kim *et al.* 2005, Kuroda *et al.* 2005, Lee 2006, Nishiyama *et al.* 2005, Rafatullah *et al.* 1990, Xia *et al.*, 2007); Aqueous extract (supernatant of mixture of 50 mg turmeric and 5 ml boiling distilled water): (Azuine *et al.* 1992, Soni *et al.* 1992); Tincture (1:10) (WHO 1999); Paste: turmeric powder in petroleum jelly (Kundu *et al.* 2005), or a mix of turmeric powder and neem leaves (*Azadirachta indica*) (Charles and Charles 1992); Oil (by distillation of rhizoma with water

vapour)(Frerichs *et al.* 1949); Oleoresin powder (containing turmeric oleoresin (acetone/ethanolic extract of turmeric root) at 40% (w/w) and auxiliary substances such as zein, corn starch, and dextrin at 20% (w/w) each (Honda *et al.* 2006).

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable

## 1.2. Search and assessment methodology

The databases that have been searched for relevant information on toxicological, pre-clinical and clinical data are EMBASE, PUBMED, TOXNET. Search terms were '*Curcuma longa*', 'curcuma' and 'curcumin' and date until 2016.

For information on traditional use herbal books in EMA library, containing herbal compendia and monographs were searched for '*Curcuma longa*'.

## 2. Data on medicinal use

### 2.1. Information about products on the market

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

##### Information on medicinal products marketed in the EU/EEA

**Table 1:** Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
Dry extract (DER 13-25:1) Extraction solvent: ethanol 96% V/V	WEU: Dyspeptic complaints, particularly based on functional affections of the biliary tract  TU: Traditional used to promote the digestion	WEU: >12 years, 90-162 mg daily: 1 tablet (30 mg/tablet), 3-5 times daily  or 1 capsule (81 mg/capsule), 2 times daily  TU: >12 years, 40.5 mg daily: 1 capsule (13.5 mg/capsule), 3 times daily	WEU, DE, at least from 1976 to 2011  WEU, DE, since 1976  TU, DE, at least from 1976 to 2011
Dry extract (DER 5.5-6.5:1) Extraction solvent:	Symptomatic treatment of mild digestive disturbances due to biliary dysfunction	>18 years 1-2 tablets (100 mg/tablet) 2 times daily	ES Authorised in 2002, not specified

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
ethanol 50% V/V			
Tincture (1:5) Ethanol 70% V/V	treatment of mild digestive disturbances and minor biliary dysfunction	TU: >18 years: 10 ml once daily or 5 ml in 60 ml water 3 times daily  TU: 12-18 years: 5 ml in 60 ml water once daily	TU, PL  Authorised in 1977

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

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

##### Member state: Belgium

Product: coated tablet, containing *C. longa* 148.0 mg/Hyoscyamine Sulfate 0.02 mg/Boldine 1.0 mg/Bovine Gall, depurated extract 50.0 mg.

Indication/posology: unknown

On the market: since 1962-1981

Product: oral solution containing *C. longa* 1.5 mg/ml, Chloroform 1.25 mg/ml, Menthae Essential Oil 0.1 mg/ml, *Anemone Nemorosa* 1.5 mg/ml

Indication: traditional used to facilitate the elimination of bile

Posology: unknown

On the market: since 1961/1983

Product: herbal tea containing *C. longa* 78.67 mg/g, Greater Celandine 49.26 mg/g, *Marrubium Vulgare* L. 75.0 mg/g, Senna Leaf 122.05 mg/g, Peppermint Leaf 166.91 mg/g, Taraxacum Herbs 122.05 mg/g, Barberry 34.55 mg/g, Birch Tar 75.0 mg/g, Boldo 78.67 mg/g, Achilleae Millefolli Herba 83.08 mg/g, Agrimony 78.67 mg/g

Indication: normal working of the digestive system and support of the bile ducts

Posology: 5–10 drops three times daily

On the market: since 1969

##### Member state: Czech Republic

Product: WEU authorisation, oral drops containing Frangula emodinum 9 mg, Curcuma rhizomatis pigmenta 22.5 mg, Magnesii salicylas 100 mg, Eucalypti aetheroleum 1926 mg, Menthae piperitae aetheroleum 3600 mg, Levomentholum 9 mg/10 ml.



Indication: cholelithiasis, chronic cholecystitis, dyspeptic disorders in chronic hepatitis and after surgery in biliary duct

Posology: 5–10 drops three times daily

On the market: since 1969

Member state: Denmark

Product: tablets and pills, combination products with 10 active substances

Indication: as laxative

On the market: at least between 1956 and 1993 (no further details)

Member state: Slovakia

Product: WEU authorisation, oral drops containing: Curcuma rhizomatis pigmenta 22.5 mg, Magnesii salicylas 100 mg, Menthae piperitae aetheroleum 3600 mg, Eucalypti aetheroleum 1926 mg, Frangula emodinum 9 mg.

Indication: cholelithiasis, chronic cholecystitis, and dyspeptic disorders.

### Information on other products marketed in the EU/EEA

Dried *C. longa* rhizoma powder is a very common dietary spice and is marketed as health product and food supplement under Food Law, either as single component or in combination products. No information on non-medicinal use was collected.

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

Not Applicable

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

**Table 2:** Overview bibliographic information on historical oral use in EU

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
Powdered herbal substance	stomach and liver complaints (hepatitis)	0.5-1 g, 2-3 times daily	German Com E monograph- Bundesanzeiger 1985 Hagers handbuch by Hänsel <i>et al.</i> , 1992
	Cholagogum and cholericum; Stomach and liver disorders		Schneider, 1974, refers to presence in German pharmacies 17 <sup>th</sup> and 18 <sup>th</sup> century
Comminuted herbal substance	Dyspeptic complaints	0.5-1 g, 2-3 times daily as infusion (in 150 ml boiling water)	German Com E monograph- Bundesanzeiger 1985

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
			Hagers handbuch by Hänsel <i>et al.</i> , 1992
	Liver and gall disorders	Daily 22-25 g fresh rhizome as infusion (in 500 ml boiling water) or 8-10 tablets (0.125 g dried rhizoma)	Madaus, 1979 refers to an original publication from 1938
	Liver, gall and stomach disorders		Hoppe, 1943 Refers to DAB Erg.B 1941
	Stomach and liver complaints (hepatitis)		Hagers handbuch by Frerichs <i>et al.</i> , 1949
	Stomach and liver complaints (hepatitis)		Hagers handbuch by List and Horhammer, 1973
	Dyspeptic complaints; coloring agent for foods	0.5-1 g for tea	Hiller and Melzig (Publication year unknown)
	Stimulates stomach and gall production	Rhiz. Curcuma conc. 200,0 D.S. boil 1 spoon with 1 glass water, 3 times daily	Weiss, 1974
	Cholagogum and cholericum; Stomache and liver disorders		Schneider, 1974, refers to presence in German pharmacies 17 <sup>th</sup> -19 <sup>th</sup> century and DAB 1872
	Dyspeptic complaints	Daily dose: 1.5-3 g of drug; equivalent preparations	German Com E monograph-Bundesanzeiger 1985
	Dyspeptic complaints	Oral, 1.5-3.0 g	Hagers handbuch by Hänsel <i>et al.</i> , 1992
Tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent ethanol 70% V/V	Dyspeptic complaints	10-15 drops in water, 3 times daily	Hagers handbuch by Hänsel <i>et al.</i> , 1992
Tincture (ratio of herbal substance to extraction solvent 1:5), ethanol 70% V/V	Dyspeptic complaints and coloring agent	Refers to maceration of powder with alcohol	Hagers handbuch by Frerichs <i>et al.</i> , 1949

## Information on period of medicinal use outside the European Union

Experience with *C. longa* in traditional medicinal systems outside the EU:

In many Asian countries the use of turmeric has a long tradition as a food spice, colorant and medicine.

### China, Japan, Korea, Vietnam, Nepal

Turmeric is used extensively in traditional Chinese medicine. It is official in the Pharmacopoeia of the People's Republic of China as well as in the Japanese Herbal Medicines Codex and is used in these countries and Korea for a range of indications including abdominal fullness, kidney pain, and amenorrhoea. In China an aqueous decoction dosage form is ingested orally and applied topically (Herbal Medicine, 2008).

### India

Turmeric is used extensively in the Indian systems of medicine (Ayurvedha, Unani, and Siddha) and is official (Haridra) in the Ayurvedic Pharmacopoeia of India (API, 1989). In Ayurvedic medicine turmeric has a long history of use as an anti-inflammatory drug for arthritis. In both the Ayurvedha and Siddha systems of medicine, turmeric paste is used topically to treat ulcers and scabies.

The Swami Prakashananda Ayurveda Research Centre lists as indications for turmeric: urticaria and skin allergy, viral hepatitis, inflammatory conditions of joints, sore throat and wounds (Kapoor 1990).

## **2.3. Overall conclusions on medicinal use**

Both historical data on medicinal use and actual marketing information confirm that *C. longa* has a longstanding use for the relief of several dyspeptic complaints.

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

<b>Herbal preparation Pharmaceutical form</b>	<b>Indication</b>	<b>Posology, Strength</b>	<b>Period of medicinal use</b>
Powdered herbal substance	Stomach, dyspeptic complaints	0.5-1 g, 2-3 times daily	German Com E monograph- Bundesanzeiger 1985  Hagers handbuch by Hänsel <i>et al.</i> , 1992
Comminuted herbal substance	Liver, gall and stomache disorders;	0.5-1 g in 150 ml boiling water as infusion, 2-3 times daily	German Com E monograph- Bundesanzeiger 1985
Tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent: ethanol 70% V/V	Dyspeptic complaints	10-15 drops (0.5-1 ml), 3 times daily	Hagers handbuch by Hänsel <i>et al.</i> , 1992

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Dry extract (DER 13-25:1) Extraction solvent: ethanol 96% V/V	Dyspeptic complaints, particularly based on functional affections of the biliary tract	30 mg, 3-5 times daily	At least from 1976 to 2011 (DE)
	Dyspeptic complaints, particularly based on functional affections of the biliary tract	81 mg, 2 times daily	Since 1976 (DE)
	Traditional used to promote the digestion	13.5 mg, 3 times daily	At least from 1976 to 2011 (DE)
Dry extract (DER 5.5-6.5:1) Extraction solvent: ethanol 50% V/V	Symptomatic treatment of mild digestive disturbances due to biliary dysfunction	100-200 mg, 2 times daily	Since 2002 (ES)
Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent: ethanol 70% V/V	treatment of mild digestive disturbances and minor biliary dysfunction	10 ml once daily or 5 ml in 60 ml water, 3 times daily	Since 1977 (PL)

According to the reported literature and information provided by Member States, all herbal preparations mentioned above, except the dry extract (DER 5.5-6.5:1) and the tincture (ratio herbal substance to extraction solvent 1:10) have been in medicinal use for 30 years or more.

The dry extract (DER 5.5-6.5:1) was already included in the monograph which was published in 2009. It was decided to maintain this herbal preparation in the revised monograph because the extraction solvent and the posology is in the range of the other preparations listed in the monograph (e.g. daily intake of corresponding herbal substance is 1.1-2.3 g, posology of the powdered or comminuted herbal substance is 1-3 g daily). The tincture (ratio herbal substance to extraction solvent 1:10) was also maintained because it was already accepted during adoption of the previous version of the monograph. Moreover, there is no safety concern considering also the broad use of turmeric and turmeric preparations in the food area.

The indications reported in the medicinal use can be reworded as a general indication for a "Traditional herbal medicinal product used for the relief of digestive disturbances, such as feelings of fullness, slow digestion and flatulence."

### 3. Non-Clinical Data

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

##### 3.1.1. Primary pharmacodynamics

###### Herbal substance

*In vivo*: In a study of Najafzadeh *et al.* (2011) choleric effect, the bile accumulation in gall bladder of mice, was compared between aqueous suspension of *C. longa* and calcium channel blocker Verapamil. This animal model is approved and used for evaluation and screening pharmacological effect of agents on bile production or secretion. The mice were divided in 3 groups. Saline was administrated in group 1, an aqueous suspension of *C. longa* and Verapamil was orally administrated in groups 2 and 3 respectively. One hour after drug administration, the mice were euthanized and gall bladder was immediately removed. Verapamil as well as *C. longa* significantly increased the accumulation of bile in gall bladder in comparison to saline. Similar action on bile secretion (possibly via p-glycoprotein) was observed by Verapamil and *C. longa* (Najafzadeh *et al.*, 2011).

###### Isolated compound- Curcumin

*In vivo*: Siegers *et al.* (1997) observed that intravenous application of curcumin or bis(desmethoxy)curcumin to rats at a level of 25 mg/kg bw, the bile flow increased by 80 and 120%, respectively after a period of 2 hours; the authors concluded that the observed effect on bile secretion was due to the presence of curcumin (Siegers *et al.*, 1997).

**Table 4:** Overview of the main non-clinical data/conclusions

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
<i>C. longa</i> aqueous suspension	0.5 ml oral administration	<i>In vivo</i> bile accumulation in gall bladder of mice	Najafzadeh <i>et al.</i> , 2011	<i>C. longa</i> significantly increased the accumulation of bile in gall bladder in comparison to saline, similarly to Verapamil
Curcumin or bis(desmethoxy)curcumin	25 mg/kg bw i.v.	<i>In vivo</i> In rats	Siegers <i>et al.</i> , 1997	Bile flow increased by 80 and 120%, respectively after a period of 2 hours

##### 3.1.2. Secondary pharmacodynamics

###### Preparations

###### Anti-depressant effect

*C. longa* aqueous extract has antidepressant effects mediated through inhibition of monoamine oxidase A (Yu *et al.*, 2002).

*C. longa* ethanolic extract reversed the decrease in serotonin, noradrenalin and dopamine concentrations as well as the increase in serotonin turnover, cortisol levels and the *in serum* corticotrophin-releasing factor (Xia *et al.*, 2007).

#### Effect on blood glucose level

The effect of an ethanolic extract of turmeric on blood glucose levels in type 2 diabetic KK-Ay mice and stimulated human adipocyte differentiation was investigated by Kuroda *et al.* The extract was prepared by a two time extraction of powdered turmeric, with five volumes of ethanol. The extract was concentrated under reduced pressure to give 12.2 g of ethanolic extract. In the experiment on the human adipocytes a stimulation of adipocyte differentiation was observed. The activity of 5.0 µg/ml and 10.0 µg/ml ethanolic extract was more potent than that of 0.22 µg/ml and 0.44 µg/ml of troglitazone, which was therapeutically used as anti-diabetic and anti-inflammatory drug in humans, until it was withdrawn in 2000 for causing drug-induced hepatitis (Kuroda *et al.* 2005).

Nishiyama *et al.* studied the influence of three turmeric extracts on blood glucose levels in type 2 diabetic KK-Ay mice. The extracts used were ethanolic extract (DER and concentration not specified) containing *ar*-turmerone, curcumin, demethoxycurcumin and bisdemethoxycurcumin, a hexanic extract (DER not specified) containing *ar*-turmerone, and an ethanolic extract from the residue of the hexane extraction (ethanol concentration not specified) containing curcumin, demethoxycurcumin and bisdemethoxycurcumin. The ethanolic extract and hexanic extract were obtained from powdered *C. longa* by extracting twice with five volumes of ethanol or hexane and filtration and evaporation of the solvent. The ethanolic extract from the residue of the hexane extraction was obtained using the same method. To determine the mechanism of action the extracts were tested for adipocyte differentiation. No differences in bodyweight were observed between treated and control animals. The ethanolic extract stimulated adipocyte differentiation dose-dependently. The hexanic extract and the ethanolic extract from the residue of the hexane extraction showed similar effects but at higher concentration as the ethanolic extract. The results indicate that turmeric ethanolic extract containing both curcuminoids and sesquiterpenoids is more strongly hypoglycemic than either curcuminoids or sesquiterpenoids (Nishiyama *et al.*, 2005).

#### Antifungal, antibacterial, phytotoxic, cytotoxic and insecticidal activity

Khattak *et al.* studied the antifungal, antibacterial, phytotoxic, cytotoxic and insecticidal activity of an ethanolic extract of *C. longa* (extract preparation not specified). The extract showed antifungal activity towards *Trichophyton longifusus* and *Microsporum canis* and weak antibacterial activity against *Staphylococcus aureus*. Toxic activity was observed against *Lemna minor*. The LD<sub>50</sub> in a brine shrimp lethality bioassay *C. longa* was 33 µg/ml. Curcuma showed no insecticidal activity (Khattak *et al.*, 2005).

#### Antioxidant activity in atherosclerosis

A high-cholesterol diet given to New Zealand White rabbits leads to development of atherosclerosis in the rabbits. Rabbits given a dietary supplement of a *C. longa* extract (no further detail) in combination with a high-cholesterol diet showed a positive effect on the animals' antioxidant status compared to controls. Curcumin has shown to mobilize α-tocopherol from adipose tissue, thus protecting their body against oxidative damage produced during the development of atherosclerosis. Also more LDL cholesterol could be transported in plasma, increasing levels of α-tocopherol. Overall the fatty acids in the animals were less susceptible to oxidation in the vessel wall (Ramirez-Tortosa *et al.*, 1999).

#### Inhibition of aflatoxin induced liver necrosis

Soni *et al.* (1992) investigated the preventive effect of aqueous and alcoholic extracts of turmeric on liver damage in ducklings induced by aflatoxin. The extract was prepared by boiling 1 g of turmeric

powder in 100 ml water. After concentration it was made up to 10 ml. The aqueous extract (10 mg/ml) inhibited toxin production by 99%. An alcoholic extract of turmeric showed also inhibition though on a much lower level. Turmeric and curcumin treatment showed almost complete reversal of fatty changes and necrosis induced by aflatoxin (Soni *et al.*, 1992).

#### Myocardial apoptosis

The effect of *C. longa* on myocardial apoptosis in experimentally induced myocardial ischemic-reperfusion injury was investigated by Mohanty *et al.* (2006) Wistar rats were fed 100 mg/kg *C. longa* once a day, for one month. *C. longa* treated rats demonstrated significant anti-apoptotic property, which might contributed to the observed preservation in cardioprotective effects and cardiac function (Mohanty *et al.* 2006).

#### Inhibition of ulcer formation

Kim *et al.* (2005) investigated the protective effect of *C. longa* ethanolic extract against gastric ulcers by blocking H<sub>2</sub> histamine receptors (H<sub>2</sub>R) of male Sprague-Dawley (pylorus-ligated) rats. The extract was prepared by refluxing 100 g *C. longa* with 80% ethanol. This was shaken at room temperature for 24 hours, this was performed twice. After extraction, the fluid was concentrated with rotary vacuum evaporator. The ethanolic extract was dissolved in 100 ml H<sub>2</sub>O and fractionated with organic solvents, n-butanol and ethyl acetate. For *in vitro* tests the dried material was resuspended in DMSO, for *in vivo* tests the dried material was resuspended in saline. The *C. longa* ethanolic extract fractions were found to protect the gastric mucosal layer as effective as ranitidine. Orally administered ethanolic extract (unknown amount) inhibited gastric acid, gastric juice secretion and ulcer formation comparable to the effects of ranitidine. *C. longa* ethanolic extract also suppressed histamine-induced cAMP production, caused by direct inhibition of H<sub>2</sub> histamine receptors, curcumin however had no effect on cAMP formation (Kim *et al.*, 2005).

Rafatullah *et al.* (1990) investigated the ulceration induced by indomethacin or reserpine administration. Hypothermic-restraint stress reduction of gastric wall mucus was inhibited by turmeric extract treatment. Treatment with turmeric extract reduced the severity of lesions induced by various necrotizing agents. Turmeric antiulcer activity of an ethanolic extract of turmeric in inbred Wistar albino rats. The extract tested was a dried 96% ethanol extract. Administration of turmeric extract led to a significant decrease in ulcer index and acidity of stomach contents. Turmeric extract not only increased the gastric wall mucus significantly but also restored the non-protein sulfhydryl (NP-SH) content in the glandular stomachs of the rats (Rafatullah *et al.*, 1990).

#### Wound healing

Kundu *et al.* studied the wound healing effects of *C. longa* paste in rabbits. The *C. longa* treated group showed a significant higher mean value for contraction of the wound compared to controls. Furthermore the wounds showed less inflammation and an increasing trend in the formation of collagen (Kundu *et al.* 2005).

### **Isolated compounds: curcumin(oids), *ar*-turmerone**

#### Anti-inflammatory activity

Curcuminoids inhibit LOX, COX, phospholipases, leukotrienes, prostaglandins, thromboxane, nitric oxide (Bundy *et al.*, 2004, Chainani-Wu 2003), elastase, hyaluronidase, collagenase, monocyte chemoattractant protein-1, interferon inducible protein, TNF and interleukin-12 (Chainani-Wu 2003).

Curcuminoids decrease prostaglandin formation and inhibit leukotriene biosynthesis via the lipoxygenase pathway (Bisset 1994).

### Neurochemical effect

Xu *et al.* (2006) investigated the effect of orally administered curcumin on behavior in a chronic stress model of depression in rats. The antidepressant imipramine was used as a control. Curcumin administration showed similar properties as imipramine. The authors suggested that the findings suggest that the properties of chronic administration of curcumin on the behavior of chronic stressed rats may be related to the modulating properties of the dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, through selective increase in brain-derived neurotrophic factor in the frontal cortex and the hippocampus of the rats (Xu *et al.*, 2006).

### Anti-oxidant activity

Curcumin mobilizes  $\alpha$ -tocopherol from adipose tissue, this results in protection against oxidative damage produced during atherosclerosis development. Curcumin increases VLDL cholesterol transport in plasma, which results in increasing levels of  $\alpha$ -tocopherol (Ramirez-Tortosa *et al.*, 1999).

Curcumin was found not to be an efficient hydroxyl radical scavenger or quencher of superoxide (Khar *et al.*, 2001).

### Hepatoprotective activity

Curcumin protects cells against lipid peroxidation induced by paracetamol. This may be due to the antioxidative effects of the phenolic groups of curcumin (Donatus *et al.*, 1990).

Curcumin was found to decrease serum aspartate transaminase and alkaline phosphatase activity, and free fatty acid, cholesterol and phospholipid levels. The mechanism of action is still unclear (Rajakrishnan *et al.*, 1998).

Tacrine is known for its T-cell destructive activity and hepatotoxicity. In a study with cultures of human hepatocytes, which had been destroyed by tacrine, curcumin showed to be nearly ten times more effective than the regular treatment, ascorbic acid (Song *et al.* 2001). However, a study on carbon tetrachloride toxicity in mice, performed in 1996, showed no protective effects due to curcumin administration at dosages of 200 mg per kg (Zhao and O'Brien, 1996).

Donatus *et al.* (1990) investigated the effect of curcumin on the cytotoxic effect of paracetamol in rat hepatocytes. Curcumin showed no protective effect against paracetamol induced glutathione (GSH)-depletion in hepatocytes of 3-methyl-cholanthrene pretreated rats. Curcumin in a concentration of  $5 \times 10^{-5}$ ,  $5 \times 10^{-4}$  and  $5 \times 10^{-3}$  M protected the cells against lipid peroxidation induced by paracetamol. This effect may be due to the two phenolic groups of curcumin, which give it strong anti-oxidant effects (Donatus *et al.*, 1990).

The effect of curcumin on alcohol induced hepatotoxicity in alcoholic rats were studied by Rajakrishnan *et al.* Compared to the control group curcumin administration resulted in a decrease of serum aspartate transaminase and alkaline phosphatase activity. The levels of serum free fatty acids, cholesterol and phospholipids decreased as well (Rajakrishnan *et al.*, 1998).

### Antiplatelet property

Lee (2006) studied the antiplatelet property of *ar*-turmerone. *ar*-turmerone showed strong inhibitory activity against platelet aggregation mediated by collagen and arachidonic acid.

At higher concentrations curcumin showed the same effect. However, only a weak or no inhibitory effect was observed against PAF or thrombin activated platelets. The other components in the ethanolic extract showed no inhibitory effects (Lee 2006).

Comparison between *ar*-turmerone and aspirin showed that *ar*-turmerone inhibited platelet aggregation induced by collagen more effectively than aspirin (Lee 2006).



### Cancer related activity

Curcumin was found to inhibit *in vitro* tumor cell growth by inhibiting expression of basic fibroblast growth factor (FGF) in breast cancer-cell cultures and the angiogenesis factors vascular endothelial growth factor (VEGF) and basic fibroblast growth factors (b-FGF) (Shao *et al.* 2002). Effects of curcumin on inhibition of angiogenesis and induction of apoptosis of cancer cells was also observed (Jiang *et al.*, 1996, Thaloor *et al.*, 1998).

Curcumin was effective in squamous-cell carcinoma model. The study of Li *et al.* showed a reduced occurrence of chemically induced tumors by 50% (Li *et al.* 2002).

Curcumin blocks cyclosporine A-resistant phorbol myristate acetate+anti-CD28 pathway of T-cell proliferation and thus may be a potential adjuvant immunosuppressive agent for the treatment of cancer (Ranjan *et al.*, 1998).

Farombi *et al.* carried out a study to determine the ameliorative effects of curcumin and kolaviron (a biflavonoid from the seeds of *Garcinia kola*) on the DBP-induced testicular damage in rats. The level of GSH, the glucose-6-phosphate dehydrogenase (G6PD) activity and the decreased testosterone levels were significantly increased (Farombi *et al.*, 2007). The increased levels of malondialdehyde (MDA) were decreased, which is in agreement with Ishihara *et al.* (Ishihara *et al.*, 2000). The authors concluded that is may be due to the intrinsic antioxidative abilities to combat oxidative damage induced by DBP.

Mice exposed to human prostate cancer cells were treated with curcumin. The curcumin-treated animals showed a decrease in microvessel density and cell proliferation and an increase in apoptosis compared to controls (Dorai *et al.*, 2000).

Incubation of endothelial cells from bovine aorta with curcumin (in a concentration range of 5-15  $\mu\text{M}$ ) showed induction of heme oxygenase expression. Heme oxygenase is an enzyme that reacts to oxidative stress, by producing the antioxidant biliverdin, and it enhances resistance to oxidative damage to cells (Motterlini *et al.*, 2000).

The efficacy of curcumin or turmeric extract in reducing chemically-induced tumours in male Swiss albino mice was studied by Soudamini and Kuttan. The extract was prepared by extraction of 5 g of powdered turmeric with 100 ml acetone/methanol (45:55). The extract was filtered using filter paper. 40 mg of curcumin was dissolved in 5 ml acetone/methanol (45:55). 7.12-dimethylbenz(a)anthracene (DMBA) was used to induce tumors. Single application of curcumin or turmeric extract failed to inhibit papilloma formation. A small, non significant, reduction in papilloma formation was seen in the turmeric extract treated group, compared to the control group. Application of both curcumin and turmeric extract during carcinogenesis and promotion resulted in less papilloma production, compared to controls. This indicates that both curcumin and turmeric extract produce their best effects during tumour promotion (Soudamini and Kuttan 1989).

The effect of dietary curcumin (0.2% and 1.0%) on DMBA and 12,O-tetradecanoylphorbol-13-acetate (TPA)-promoted skin tumor formation in Swiss albino mice was investigated by Limtrakul *et al.* They found a significant lower number of papillomas in the curcumin treated group compared to the control group. The enhanced expression of ras-p21 and fos-p62 oncogenes were decreased dose dependently in the curcumin treated group (Limtrakul *et al.*, 2001).

Curcumin reduces the testicular damage caused by exposure to di-n-butylphthalate (DBP), by increase in GSH, testosterone levels and G6PD activity and decrease in MDA levels. These effects may be due to intrinsic antioxidative abilities of curcumin (Farombi *et al.*, 2007).

### Anti-mutagenic activity

Nagabhushan *et al.* (1987) tested curcumin against tobacco products and several environmental mutagens in a Salmonella/microsome test with or without Aroclor 1254-induced rat liver homogenate (S-9 mix), in order to determine the difference between mutagens which require metabolic activation and those who do not. Curcumin inhibited the mutagenicity of bidi smoke condensate, cigarette smoke condensate and masheri (a tobacco product) and tobacco extracts in a dose-dependant manner. Curcumin is only antimutagenic against mutagens which require metabolic activation (Nagabhushan. *et al.*, 1987).

### Diabetes

Arbiser *et al.* (1998) and Okamoto *et al.* (2002) reported that curcumin reduces the destructive angiogenesis associated with diabetic retinopathy (Arbiser *et al.*, 1998, Okamoto *et al.*, 2002).

### **3.1.3. Safety pharmacology**

No data available.

### **3.1.4. Pharmacodynamic interactions**

The poor bioavailability of curcumin if applied as single component is well known and described in literature. However regarding the complex composition of herbal preparations and the interplay of the many constituents (actions of synergy and inhibition), adequate general conclusions on pharmacodynamic interactions after intake of curcuma (extracts) cannot be drawn.

### **3.1.5. Conclusions**

For curcumin the studied amounts after oral administration are many times higher than the human daily posology used in traditional herbal medicinal products. Based on this finding it is not likely that a significant effect of curcumin on human bile secretion is obtained at doses traditionally used.

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

### **Curcumin**

#### Absorption and bioavailability

In rodents, curcumin demonstrates a poor systemic bioavailability, because of low absorption by the gastrointestinal tract and rapid metabolism. Oral administration of a single dose of 2 g of curcumin to rats resulted in very low concentrations in plasma (less than 5 µg/ml) indicating a poor absorption from the gut (Leisher *et al.*, 2013). After oral administration of curcumin to rats at 1 g/kg bw about 75% was excreted in the faeces and only traces in the urine; concentrations in plasma and bile were negligible. Blood levels were less than 5 µg/ml, these indicating a poor absorption from the gut (Lukita-Admadja *et al.*, 2002, Volak *et al.*, 2013).

Oral administration of radio-labelled curcumin to rats resulted in radioactivity being found only in the liver and kidneys (Ravindranath and Chandrasekhara 1980, Ravindranath and Chandrasekhara 1982). Curcumin administered intravenously was excreted in the bile (Wahlstrom and Blennow 1978). 3H-labelled curcumin administered orally to rats at 0.6 mg/kg led to faecal excretion of about 89% of the radioactivity in 72 hours; about 6% was excreted in the bile. After intraperitoneal administration about 73% of the radioactivity was excreted in the faeces and about 11% in the bile (Holder *et al.* 1978).

When a single 400 mg dose of curcumin was administered orally to rats about 60% was absorbed and 40% excreted unchanged in the faeces over a period of 5 days. No curcumin could be detected in urine and only traces were found in the portal blood, liver and kidney (Ravindranath and Chandrasekhara 1980).

Recently research has focussed on the preparation of nanocurcumin because it has a higher solubility than curcumin and therefore a better bioavailability (Sarkar *et al.*, 2010). Also fytosome-curcumin in which curcumin is linked to phosphatidylcholine has been observed to result in a better bioavailability and activity after oral administration in rats (Kidd 2009, Saraf 2010).

### Metabolism

After p.o. dosing, curcumin undergoes metabolic O-conjugation to curcumin glucuronide and curcumin sulfate and bioreduction to tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol in rats and mice *in vivo* and in suspensions of human and rat hepatocytes (Ireson *et al.*, 2002).

Studies with isolated perfused rat liver and isolated rat intestine suggested an initial metabolism of curcumin in the intestine, producing easily absorbable metabolites, and intensive second metabolism in the liver. Major metabolites were glucuronides of tetrahydrocurcumin and hexahydrocurcumin, with dihydroferulic acid and traces of ferulic acid as further metabolites, all of which were excreted in the bile (Ravindranath and Chandrasekhara 1980, Wahlstrom and Blennow 1978).

LC-MS analysis of plasma after oral administration of curcumin to rats showed that the predominant metabolites were glucuronide and glucuronide-sulphate conjugates, which reached maximum plasma concentrations about 1 hour after administration (Asai and Miyazawa 2000).

There is increasing evidence that in rodents and humans the intestinal tract substantially contributes to the overall metabolite yield. Metabolism of curcumin to curcumin glucuronide, curcumin sulfate, tetrahydrocurcumin, and hexahydrocurcumin was demonstrated in intestinal fractions from humans and rats, and its conversion to curcumin sulfate was demonstrated *in situ* in intact rat intestine (Ireson *et al.* 2002).

Certain curcumin metabolites, such as tetrahydrocurcumin, possess anti-inflammatory (Ammon *et al.*, 1993) and antioxidant activities similar to those of their metabolic progenitor (Cohly *et al.*, 1998, Romiti *et al.*, 1998).

Metabolism also appeared to be rapid *in vivo*. After intravenous dosing more than 50% of the dose was excreted in the bile within 5 h. This finding was interpreted as evidence in support of the hypothesis that curcumin undergoes biotransformation during absorption in the intestinal tract and enterohepatic recirculation (Ravindranath and Chandrasekhara 1982). Major metabolites included the glucuronides of tetrahydrocurcumin and hexahydrocurcumin, with dihydroferulic acid and ferulic acid present as minor metabolites (Holder *et al.*, 1978).

### Metabolic transfer through lactation

Singh *et al.* (1995) followed dams and their suckling neonates to determine the modulatory influence of turmeric and curcumin on hepatic biotransformation system enzymes. Turmeric and curcumin induced a significant increase in hepatic levels of glutathione S-transferase (GST) and sulfhydryl (SH) levels. Cytochrome b5 and cytochrome P450 levels were significantly elevated as well. This indicates that turmeric and/or curcumin metabolites can be transferred through lactation (Singh *et al.*, 1995).

### Drug Interactions

Animal studies revealed that green tea enhances the effect of curcumin. In mice and hamster tumor models the combination of catechin and turmeric was more effective than the individual components

(Azuine and Bhide 1994). Li *et al.* suggested that curcumin and green tea extract have synergistic effect in reducing oral squamous-cell carcinomas in hamsters (Li *et al.*, 2002).

The interpretation of the clinical relevance of the findings retrieved from animal studies and/or effects of isolated substances (as curcumin) is difficult and may lead to doubtful conclusions; therefore no interactions are included in the monograph.

Curcumin is a potent inhibitor of cytochrome P450 (CYP 2C9 and CYP3A4) and a moderate inhibitor of CYP2B6, CYP1A2 and CYP2D6, with IC<sub>50</sub> values ranging from 4.3 to 50.3 µM (Appiah-Opong *et al.* 2007). These CYPs are responsible for the hepatic metabolism of about 80% of drugs currently on the market and notably CYP3A4 is also abundant in the intestine. The inhibitory activity of curcumin towards CYP3A4 may well have implications for drug-drug interactions in the intestine, rather than in the liver when the intestines are exposed to high concentrations upon oral ingestion together with drugs metabolised by this enzyme. Curcumin is also a potent inhibitor of the three major human glutathione S-transferases (GSTs), i.e. GSTA1-1, GSTM1-1 and GSTP1-1. Curcumin is also an inhibitor of the bile acid transporter P-glycoprotein 1 (P-gp). The IC<sub>50</sub> value is in the range of 50 -100 µM (Aurade *et al.*, 2010).

After the combined oral administration of 4 g curcuminoids and 24 mg piperine to healthy volunteers in a randomised placebo-controlled crossover study no effect on the metabolism of midazolam, flurbiprofen or paracetamol was observed, indicating that a clinically significant interaction is not likely (Volak *et al.*, 2013).

*Assessor's comment:*

*Curcumin demonstrates poor systemic bioavailability, because of low solubility and poor absorption by the gastrointestinal tract and rapid metabolism, which already starts in the intestinal mucosa. Secondary metabolism occurs in the liver.*

*The observed interactions of curcumin with other herbal preparations is not considered relevant for the traditional use of C. longa, while the maximum daily dose of curcumin is much lower than the dose for which interactions have been observed. Therefore it is not likely that interactions will occur during the use of the traditional herbal products as described in the monograph.*

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

#### **3.3.1. Single dose toxicity**

##### **Herbal substance**

The study of Majeed *et al.* revealed that a single feeding of 30% turmeric diet to rats had no toxic effects (Majeed *et al.*, 1995).

##### **Isolated compound- Curcumin**

The oral median lethal dose (LD<sub>50</sub>) of curcumin in mice is higher than 2.0 g/kg bw (Itokawa *et al.* 2008). Single oral doses of curcumin at 1-5 g/kg bw induced no toxic effects in rats (Wahlstrom and Blennow 1978).

### 3.3.2. Repeat dose toxicity

#### Herbal substance/Extracts

In a subchronic toxicity study liver toxicity had been reported, but most of these incidents involved large dietary doses (turmeric 0.2%, 1.0%, 5.0%) or turmeric ethanolic extract (0.05%, 0.25%) given to mice or rats. In mice fed for 14 days with a diet containing 1% and 5% turmeric hepatotoxicity was observed. Rats fed with turmeric 1% for the same period showed no adverse affect. The rats fed turmeric at a dose of 5% of their diet for a period of 90 days showed a reduction in body weight gain and hepatotoxicity (Deshpande *et al.*, 1998, Kandarkar *et al.*, 1998).

#### Isolated compound- Curcumin

Gastric ulceration was observed after oral administration of curcumin to rats at 100 mg/kg bw for 6 days; but not at 50 mg/kg bw (Gupta *et al.*, 1980).

### 3.3.3. Genotoxicity

#### Herbal substance/Isolated compound- Curcumin

No effects on chromosomal damage, and mutagenic effects were observed in mice fed with turmeric (herbal substance) (0.5%) or curcumin (0.015%) (Vijayalaxmi 1980).

#### In vitro

Curcumin showed no mutagenic potential in the Ames test, in *Salmonella typhimurium* strains TA1535, TA100 and TA98, with or without metabolic activation (Jensen 1982).

No mutagenic effects were found in the Ames tests for curcumin and turmeric extracts (information on preparation could not be found) (Nagabhushan and Bhide 1986).

No mutagenic activity was demonstrated in bacteria treated with curcumin preparations of purity up to 85%, or of unknown purity. A 79-85% purity preparation induced chromosomal aberrations and sister chromatid exchanges *in vitro* (Jain *et al.* 1987).

Donatus *et al.* (1990) found curcumin to be moderate cytotoxic. At a concentration of  $5 \times 10^{-3}$  M curcumin slightly increased LDH-leakage from rat hepatocytes. This increase was accompanied by an increase in GSH-depletion, which can result in increased susceptibility to cytotoxicity (Donatus *et al.* 1990).

#### In vivo:

Curcumin given to mice at 0.015% of their diet for 12 weeks induced no genotoxic effects as measured by the incidence of micronucleated polychromatic erythrocytes and chromosomal aberrations in bone marrow cells (Vijayalaxmi 1980). *In vivo*, a curcumin preparation (unknown purity) administered to mice by intraperitoneal injection did not induce micronuclei in bone marrow cells, whereas a low level of chromosomal aberrations was reported in the same cell population (Jain *et al.*, 1987). In another *in vivo* study in mice injected i.p. with curcumin of unknown purity, there was some evidence of sister chromatid exchanges induction at low frequency above 25 mg/kg, while in rats fed curcumin of unknown purity there was equivocal evidence for the induction of chromosomal aberrations (Giri *et al.*, 1990).

Based on these data, the JECFA concluded that there was no adequate evidence for the genotoxicity of curcumin. In reaching this conclusion, the sister chromatid exchange data in particular was considered to be of little relevance in the evaluation, while other studies could not be reliably interpreted because of the impurities in the curcumin preparations used (JECFA, JECFA 2004).

### 3.3.4. Carcinogenicity

#### Preparation (turmeric oleoresin)

Long-term (103-weeks) carcinogenicity studies have been performed in mice and rats, fed *ad libitum* diets containing 0, 2000, 10.000 or 50.000 mg/kg turmeric oleoresin (79%-85% curcumin). These doses were equal in males/females to daily doses of 0, 220/320, 1520/1620 or 6000/8400 mg turmeric oleoresin/kg in mice and to 0, 80/90, 460/440 or 2000/2400 mg turmeric oleoresin /kg per day in rats. These results showed marginal increases in hepatocellular adenomas and carcinomas in mice and in clitoral gland adenomas in rats. These effects were not considered to be treatment related and it was concluded that turmeric-oleoresin is not carcinogenic (National Toxicology Program 1993).

### 3.3.5. Reproductive and developmental toxicity

No effects on pregnancy rate, number of dead embryos, total implants were observed in mice fed with turmeric (0.5%) or curcumin (0.015%) (Vijayalaxmi 1980).

The reproductive toxicity of curcumin, was studied in Wistar rats (Ganiger *et al.* 2007). It was concluded that the no observed adverse effect level (NOAEL) for reproductive toxicity of curcumin, fed in the diet for two successive generations to rats in this study was 847 and 959 mg/kg bodyweight (bw) per day for male rats and 1043 and 1076 mg/kg bw for females for F0 and F1 generations, respectively. This study was the final toxicology study on curcumin reviewed by JECFA at the 61st Meeting, 2003. The JECFA group considered that the small body weight reduction in the F2 pups of the highest dose group prevented this from being regarded as a no adverse effect level, and so allocated an ADI for curcumin of 0–3 mg/kg bw based on the intake of 250–320 mg/kg bw in the mid-dose group as the NOAEL (JECFA, JECFA 2004).

There is one report indicating that rats fed high doses of turmeric (4 g/kg per day) or curcumin (0.4 g/kg per day) for 14-21 days can pass sufficient quantities of these compounds (or their metabolites) into milk to cause the induction of hepatic enzymes in exposed offspring (Singh *et al.*, 1995).

### 3.3.6. Local tolerance

No data available.

### 3.3.7. Other special studies

The finding that curcumin can cause gastrointestinal irritation in rats (ulcers, hyperplasia and inflammation) has been shown at doses of 100 mg/kg bw (Gupta *et al.*, 1980) and therefore is not relevant for the daily doses of curcumin that are contained in the products that are described in the monograph (based on a content of 3.14%, the maximum daily dose is 126 mg curcumin), therefore no warning is taken up for individuals with gastrointestinal diseases (peptic ulcer disease, ulcerative colitis, Crohn's) (Tayyem *et al.*, 2006).

### 3.3.8. Conclusions

In absence of toxicological data on the herbal substance and only one report on single dose toxicity on rats fed with 30% turmeric diet, which showed no toxic effects, data on the constituents can give an indication about the safety of the herbal substance. The isolated constituents do not appear to be toxic or mutagenic. No reproductive toxicity has been observed. However because it is known that curcumin and/or metabolites are transferred to sucklings via lactation it is not recommended to use *C. longa* or preparations thereof during breastfeeding. The JECFA established an ADI of 0-3 mg/kg bw for

curcumin, based on the NOAEL of 250-320 mg/kg bw per day from the reproductive toxicity study for a decreased body weight gain in the F2 generation observed at the highest dose level and an uncertainty factor of 100. Currently curcumin is an authorised food color in EU with maximal allowed use levels varying from 20-500 mg/kg food according to the food type. Curcumin is also allowed in beverages at levels upto 200 mg/l (EFSA 2010).

The estimated maximum daily intake of curcumin with the posology recommended in the monograph is 126 mg. For an adult of 60 kg this corresponds with an intake of 2.1 mg/kg bw, which is within the established ADI.

The finding that curcumin can cause gastrointestinal irritation (ulcers, hyperplasia and inflammation) has been shown in rats at doses of 100 mg/kg bw (Gupta *et al.*, 1980) and therefore is not relevant for the daily doses of curcumin that are contained in the products that are described in the monograph (maximum daily dose is 126 mg curcumin), therefore no warning is taken up for individuals with gastrointestinal diseases (peptic ulcer disease, ulcerative colitis, Crohn's).

### **3.4. Overall conclusions on non-clinical data**

The primary pharmacodynamic data presented supports the proposed traditional use indication: "Traditional herbal medicinal product used for the relief of digestive disturbances such as feelings of fullness, slow digestion and flatulence".

A warning is taken up that the use of the product is not recommended in case of biliary obstruction and other liver function disorders. For curcumin an ADI of 0-3 mg/kg bw has been established. The estimated maximum daily intake of curcumin recommended in the monograph is 126 mg. For an adult of 60 kg this corresponds to 2.1 mg/kg bw; therefore the proposed traditional posology is considered safe.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have mainly been performed with curcumin or herbal preparations and not with the herbal substance. Nonetheless, neither the chemical composition nor the long-term widespread uses in the European Union suggest that there is a high risk associated with the use of *C. longa*. In absence of genotoxicity data, a list entry cannot be recommended.

## **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**

No data available.

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

##### **Curcumin**

In a small study observing the influence of curcumin on blood lipids with 10 healthy volunteers was found that oral intake of 500 mg per day curcumin for 7 days resulted in a significant decrease in the level of serum lipid peroxides (33%) and increase in HDL cholesterol (29%) and a decrease in level of total serum cholesterol (12%) (Soni and Kuttan 1992).

After oral administration the bioavailability of curcumin was estimated to be 65% (Commandeur and Vermeulen 1996).

In a Phase I clinical study, low systemic bioavailability of curcumin following oral dosing has been demonstrated. Efficient first-pass metabolism and some degree of intestinal metabolism, particularly glucuronidation and sulfation of curcumin, might explain its poor systemic availability when administered via the oral route. A daily oral dose of 3.6 g of curcumin is compatible with detectable levels of the parent compound in colorectal tissue (7-20 nmol/g). There appears to be negligible distribution of the parent drug to hepatic tissue or other tissues beyond the gastrointestinal tract (Hatcher *et al.*, 2008, Sharma *et al.*, 2001, Sharma *et al.*, 2007).

In another Phase I clinical trial, patients with high risk or pre-malignant lesions were treated with curcumin for 3 months. The serum concentration of curcumin usually peaked at 1 to 2 hours after oral intake of curcumin and gradually declined within 12 hours. The average peak serum concentrations after taking 4-8 g of curcumin were 0.51-1.77 µM, respectively. Urinary excretion of curcumin was undetectable (Cheng *et al.*, 2001). The authors concluded that the levels demonstrated might be sufficient to exert pharmacological activity.

*Assessor's comment:*

*The amounts of curcumin that were tested in these studies (4-8 g of curcumin) exceed by far the theoretical maximal amounts of curcumin on the basis of literature values in the products containing C. longa L. that are mentioned in the monograph.*

## **4.2. Clinical efficacy**

### **4.2.1. Dose response studies**

#### ***Curcuma longa* (preparations)**

No data available.

#### **Curcumin**

In a randomised, single-blind, three phase, cross-over study on 12 healthy volunteers the effect of different dosages of curcumin on the gall bladder contraction was measured against placebo (amylum) over an observation time of 2 hours. Dosages of 20-80 mg curcumin were taken orally. A dosage of 40 mg produced 50% decrease in the volume of the gall bladder, indicating an increase in the contraction of the gall bladder, 2 hours after intake. No side effects were reported by the participants in this study (Rasyid *et al.*, 2002).

### **4.2.2. Clinical studies**

In the published literature 12 clinical studies conducted with *C. longa* preparations or curcumin were found. Details of these studies and the outcomes are presented in the following tables.





**Table 5:** Clinical studies on humans, in dyspeptic disorders, and other applications with *C. longa* preparations

Type (aim)	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
<b>Dyspeptic disorders</b>							
Thamlikitkul <i>et al.</i> 1989	MC R P DB <sup>1</sup> 3-arm,	2 g powder of dried turmeric rhizome (2x250 mg capsules 4 times) or "traditional medicine" (containing extracts of cascara and Nux vomica, asafoetida tincture, capsicum powder, and ginger powder)  7 days	116	Patients with dyspepsia (acid/flatulent /atonic)	Response: Placebo: 53%, traditional medicine: 83%, <i>C. longa</i> : 87% improvement of symptoms, compliance & acceptance	not known	Only placebo controlled trial with <i>C. longa</i> ; very little information on the medical protocol used; no information on blinding of the clinical assessors; no difference was observed with regard in the patient's satisfaction. Comparator is not a standard treatment
Prucksunand <i>et al.</i> , 2001	Phase II, uncontrolled	2 capsules of 300 mg turmeric, 5 times daily  oral intake  4 weeks	45 (24 males, 21 females)  Age: 16-60 y	Patients with peptic ulcers/symptoms indicating peptic ulcers	Abdominal pain and discomfort subsided in 1 <sup>st</sup> and 2 <sup>nd</sup> week, no significant changes in blood chemistry	not known	Methodological shortcomings (e.g. baseline, not all patients endoscoped)

Type (aim)	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Häringer, 2004	MC <sup>1</sup> observational study	2.8 g (2 tablets of 81 mg dry extract (DER 13-25:1), extraction solvent ethanol 96% (V/V))	221	Patients with functional dyspepsy (Rome II criteria)	154 patients finished trial; after 6 weeks 33%, after 12 weeks 54% less symptoms	Not known	No placebo, subjective assessments; Methodological short comings
Kammerer & Fintelmann, 2001	Observational study	2 tablets of 81 mg dry extract (DER 13-25:1), extraction solvent ethanol 96 % (V/V)  Oral use  28 days	440	Patients with dyspepsy, functional disorders of bile ducts	64% reduction of symptoms; 36% of patients symptom free; 56% continued treatment; 7% ended prematurely, for no relief	Not known	No placebo, subjective assessments; Methodological short comings
Bundy <i>et al.</i> , 2004	Pilot study, partially blinded  R <sup>1</sup> two-doses,	1 or 2 tablets of 72 mg standardised turmeric extract (no further details)  Oral use  8 weeks	207	Volunteers selected with IBS (Rome II criteria)	IBS prevalence reduced in both groups, significant reduction in abdominal pain / discomfort score by 22% and 25% in 1-tablet and 2-tablets groups resp., symptoms improved, no significant differences between groups	Student's <i>t</i> -test analysis	No data on preparation, no placebo

Type (aim)	Study Design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
<b>Skin disorders</b>							
Kuttan <i>et al.</i> , 1987	Study design unknown	Ethanol extract of <i>C. longa</i> (not specified)/ointment of curcumin  Topical use	62	Patients with external cancerous lesions	Reduction in smell (90% of cases) Reduction of itching (all cases), dry lesions (70% of cases) Reduction in lesion size and pain (10% of cases)	Not known	No details on study, formulation, application
<b>Other applications- Urinary excretion of tobacco mutagens</b>							
Polasa <i>et al.</i> , 1992	Uncontrolled	2 tablets of 750 mg turmeric  oral use  30 days	22	Normal men (16 chronic smokers, 6 non-smokers)	Urine testing after 0, 15, 30 days, biochemical parameters, and mutagenicity assay revealed reduction of urinary excretion of mutagens in smokers	Not known	Clinical relevance is not clear

<sup>1</sup> R=randomised, P=placebo-controlled, DB=double blind, MC=multi centre, CO=cross-over

**Table 6:** Clinical studies on humans with curcumin.

Type (aim)	Study Design	Test Product(s)	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Comments
Soni and Kuttan, 1992	Un-controlled;	500 mg curcumin Oral use 7 days	10	Healthy volunteers	Decrease serum lipid peroxides (33%), increase in HDL cholesterol (29%), decrease in total serum cholesterol (12%)	Not known	Follow-up study needed of curcumin as preventive substance against arterial diseases
Rasyid and Lelo, 1999	R DB P CO <sup>1</sup>	20 mg curcumin/placebo (amylum) Oral use Wash-out period: 1 week	12 Age: 24-48 years Weight: 45-65 kg	Healthy volunteers	Significant reduction of gall bladder volume after 0.5 h-2.0 hours: 12-29%, respectively	Student's <i>t</i> -test analysis	Further dose-responding studies needed to find optimal dose of curcumin to induce 50% contraction
James, 1996	Design unknown	Curcumin Oral intake 8 weeks	40	AIDS patients	No evidence that curcumin reduced viral load	Not known	No clinical relevance

<sup>1</sup> R=randomised, P=placebo-controlled, DB=double blind, MC=multi centre, CO=cross-over

**Table 7:** Clinical studies on humans, in other indications with *C. longa* containing combination preparations

Type (aim)	Study Design	Test Product(s):	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Comments
Kulkarni <i>et al.</i> , 1991	R DB P CO <sup>1</sup>	3 x 2 capsules of 650 mg of <i>C. longa</i> containing Ayurvedic formulation (corresponding to 50 mg turmeric each) / placebo, oral use  Duration of both treatments: 3 months	42	Patients with osteoarthritis	Significant drop in severity of pain ( $p < 0.001$ ) and disability score ( $p < 0.05$ )	CI 95%	Efficacy was not assessed because efficacy of a combination can not be extrapolated to mono-preparations and no detail on formulation is given
Charles and Charles, 1992	Pilot study	Paste of 'neem' and 'turmeric' (Ayurvedic formulation)  Topical use	814	Patients with scabies	Number, size and type of lesions: cure within 3-15 days in 97% of cases	Not known	Efficacy was not assessed because efficacy of a combination can not be extrapolated to mono-preparations and no detail on formulation is given

<sup>1</sup> R=randomised, P=placebo-controlled, DB=double blind, MC=multi centre, CO=cross-over

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

No data available.

### **4.4. Overall conclusions on clinical pharmacology and efficacy**

The available clinical data are not sufficient to support a “well established use” indication for curcuma. The clinical data suggest some possible effects of curcumin on the depletion of the gallbladder, and reduction of symptoms in dyspeptic disorders. These are partially supportive for the traditional use of *C. longa* for digestive complaints.

## **5. Clinical Safety/Pharmacovigilance**

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

No side effects were reported during a study in which 12 healthy volunteers took 20 mg curcumin (Rasyid and Lelo 1999).

In a study with 8 healthy volunteers no adverse effects have been reported after oral doses of 2 g curcumin and also not after combining curcumin with piperine and thereby raising the serum level of curcumin (Shoba *et al.*, 1998).

In a phase I trial with 25 subjects, who had various high-risk cancerous conditions, no toxic reactions were observed. The subjects received up to 8 g of curcumin a day for 3 months (Cheng *et al.*, 2001).

In a clinical study, two of 19 patients treated with 2500 mg of curcumin per day, complained of gastric irritation. No other adverse effects were reported (James 1994).

Mild side effects (nausea, dermatitis, pain in abdomen) were also reported by participants in the study of Kulkarni after oral intake of a turmeric containing combination product, corresponding to 300 mg turmeric daily, however the side effects did not necessitate discontinuation of the treatment (Kulkarni *et al.* 1991).

Rare cases of allergic contact dermatitis have been reported (Goh and Ng 1987, Hata *et al.* 1997). In an 18-month study on the topical use of curcumin to treat skin and mucous membrane cancers, scalp itching was observed in 1 patient of 62 patients (Kuttan *et al.* 1987). Patch testing led to allergic reactions (not further classified) in persons who were regularly exposed to the substance or who already had dermatitis of the finger tips. Few allergic reactions (skin rash) occurred in people not previously exposed to curcumin (Seetharam and Pasricha 1987).

In a phase II study, a gastro-protective action was observed in patients with peptic ulcer disease after oral intake of 600 mg curcumin 5 times daily (Prucksun *et al.*, 2001). Therefore no contraindication for duodenal/gastric ulcers was included in the monograph.

A dietary supplement containing curcumin has received a GRAS (Generally Recognised as Safe) notification from the FDA up to 1000 mg per day for a 60 kg person (GRAS notification from FDA, 2018).

According to the EFSA panel, the daily intake of curcumin from the normal diet amounts to less than 7% of the ADI of 3 mg/kg per day, with a theoretical maximum daily exposure of 6.9 mg/kg bw per day for adults and of 11.9 mg/kg per day for a typical 3 year-old child (EFSA 2010).

## **5.2. Patient exposure**

No data available.

## **5.3. Adverse events, serious adverse events and deaths**

In the database of the Dutch Pharmacovigilance Centre LAREB no adverse events were reported for *C. longa*.

The Food and Drug Administration classifies turmeric as a substance Generally Recognized as Safe (GRAS notification from FDA, 2018).

No major side effects have been reported in the cited clinical studies after oral intake of curcuma extracts and curcumin in doses up to 8 g per day for 3 months (Bundy *et al.*, 2004, Cheng *et al.*, 2001, Deodhar *et al.*, 1980, Rasyid *et al.*, 2002).

In a clinical study in patients with irritable bowel syndrome dry mouth and flatulence was reported by approximately 25% of the patients (Bundy *et al.*, 2004). In another study two of 19 patients treated with 2500 mg of curcumin per day, complained of gastric irritation (James 1994). In another study mild side-effects as nausea, diarrhoea, headache, tiredness and sleepiness have been reported in the turmeric group (2 g per day) as well as in the other groups (placebo and comparative herbal combination) (Thamlikitkul *et al.*, 1989).

With respect to topical use, rare cases of allergic contact dermatitis have been reported (Goh and Ng 1987, Hata *et al.*, 1997). In an 18-month study on the topical use of curcumin to treat skin and mucous membrane cancers, scalp itching was observed in 1 patient out of 62 patients (Kundu *et al.* 2005). Patch testing led to allergic reactions (not further classified) in persons who were regularly exposed to the substance or who already had dermatitis of the finger tips. Few allergic reactions (skin rash) occurred to people not previously exposed to curcumin (Seetharam and Pasricha 1987). Pharmacovigilance issues have been reported for a product containing curcuma and an amino acid. Further study revealed that the observed liver toxicity was not due to curcuma.

## **5.4. Laboratory findings**

No data available.

## **5.5. Safety in special populations and situations**

### **5.5.1. Use in children and adolescents**

No data available. Therefore in the section "Special Warnings and precautions for use" the following sentence is included: "The use in children and adolescents under 18 years of age has not been established due to lack of adequate data".

### **5.5.2. Contraindications**

The available data do not justify including a contraindication, apart from the general contraindication on hypersensitivity to the active substance. The warning concerning the potential effect on bile secretion reported in the first version of the monograph was moved to "Special warning and precautions of use" to align with the *Curcuma xanthorrhiza* monograph.

### 5.5.3. Special Warnings and precautions for use

Because of a potential effect on bile secretion, *C. longa* is not recommended in case of obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases (Blumenthal 1998, ESCOP Monograph 2003, Rasyid *et al.*, 2002, WHO 1999). Therefore, as a precautionary measure a warning is taken up into the monograph.

### 5.5.4. Drug interactions and other forms of interaction

Turmeric may interact with NSAIDs (Non-Steroidal Anti-inflammatory Drugs), antiplatelet agents or antihyperlipidemics, and a case report mentions interaction with warfarin. These findings are mainly based on *in vitro* data, animal studies or individual case reports. More studies are needed to confirm and assess the clinical significance of these potential interactions (Bowman 2005, Fetrow and Avila 1999, Heck *et al.*, 2000). As clinical data is lacking, these effects are not included in the monograph.

Several studies reported interactions between curcumin and other phytochemicals.

Fetrow suggested that curcumin could decrease the effect of immunosuppressants, but also here no supporting clinical data was provided (Fetrow and Avila 1999).

Shoba *et al.* demonstrated that the bioavailability of curcumin increased twenty-fold when healthy human subjects took a 2 g dose of curcumin in combination with 20 mg of piperine, extracted from black pepper, compared to subjects who took only 2 g of curcumin (Shoba *et al.*, 1998).

The interpretation of the clinical relevance of the findings retrieved from animal studies (see Section 3.2) and/or effects of isolated substances (as curcumin) is difficult and may lead to doubtful conclusions; therefore no interactions are included in the monograph.

### 5.5.5. Fertility, pregnancy and lactation

Safety during pregnancy and lactation has not been established. However, because it is known that curcumin and/or metabolites are transferred to sucklings via lactation (Singh *et al.*, 1995) it is not recommended to use *C. longa* or preparations thereof during breastfeeding.

No fertility data is available.

### 5.5.6. Overdose

No toxic effects were observed in patients after three months oral daily intake of 8,000 mg or 2.2 g of turmeric (equivalent to max. 110 mg of curcumin) for four months (Cheng *et al.*, 2001, Sharma *et al.*, 2007).

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

No data available.

### 5.5.8. Safety in other special situations

Not applicable



## 5.6. Overall conclusions on clinical safety

No serious side effects have been reported up to now. Furthermore the chemical composition of *C. longa* does not give any reason for concerns regarding safety.

Potential interactions between *C. longa* and NSAIDs, antiplatelet agents, antihyper-lipidemics and immunosuppressants have been described and reported, but clinical evidence for these effects is lacking (Bowman 2005, Fetrow and Avila 1999).

The use of *C. longa* in pregnant women and during lactation is not recommended while there are signs that curcumin and/or metabolites can be transferred through lactation.

Because of possible effect on bile secretion, as a precautionary measure, *C. longa* preparations are not recommended in case of obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases.

## 6. Overall conclusions

*C. longa* is in use in Europe for a long time, mainly for dyspeptic complaints, skin problems and liver diseases and infections. The available data is not sufficient to support a “well established use” indication for curcuma. As the medicinal use has been documented continuously in European handbooks, *C. longa* fulfils the requirements of Directive 2004/24 EC for classification of traditional herbal medicinal products. The use of *C. longa* is considered plausible in the treatment of dyspeptic complaints on the basis of bibliography and pharmacological data.

The initial indication: ‘Traditional herbal medicinal product used to increase bile flow for the relief of symptoms of indigestion (such as sensation of fullness, flatulence and slow digestion’ was slightly amended for the revision to align it with with the *Curcuma xanthorrhiza* monograph. Reference to a lack of bile secretion was not considered to fulfill the criteria as laid down in Article 16a of Directive 2004/24 EC, because this is a potential effect and can only be diagnosed with the help of a medicinal practitioner.

Therefore the proposed indication for traditional monograph reads as follows: ‘Traditional herbal medicinal product used for the relief of digestive disturbances, such as feelings of fullness, slow digestion and flatulence’.

Although the (topical) use for skin diseases is also described in authoritative texts, it is not included in the monograph because no information is available that *C. longa* containing products are currently on the market of EU Member States for such indications and data on the preparations and posology is lacking.

The pharmacological activity is attributed to the whole preparation; however the majority of activities were observed with curcumin.

*C. longa* is used in the following pharmaceutical preparations and posology:

- powdered herbal substance: 0.5-1 g, 2-3 times daily
- comminuted herbal substance as herbal tea (infusion): 0.5-1 g in 150 ml boiling water, 2-3 times daily
- tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent ethanol 70% V/V: 0.5-1 ml, 3 times daily

- dry extract (DER 13-25:1) extraction solvent: ethanol 96% V/V: 90-162 mg daily, divided in 2-5 partial doses
- dry extract (DER 5.5-6.5:1) extraction solvent: ethanol 50% V/V: 100-200 mg, 2 times daily
- tincture (ratio of herbal substance to extraction solvent 1:5) extraction solvent ethanol 70%, V/V: 10 ml once daily or 5 ml in 60 ml water, 3 times daily

Only mild side effects have been reported for *C. longa* such as dry mouth, flatulence, and gastric irritation. No serious side effects have been reported.

Due to lack of data, the use of *C. longa* in children and adolescents under the age of 18 years cannot be recommended.

As relevant data on the use during pregnancy and lactation is lacking, *C. longa* cannot be recommended in these conditions.

Due to the nature of the potential effect on bile secretion it is not recommended to use *C. longa* preparations in case of obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases.

A European Union list entry is not supported due to lack of adequate data on genotoxicity.

## **Annex**

### ***List of references***