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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Curcuma xanthorrhiza* Roxb. (*C. xanthorrhiza* D. Dietrich)., rhizoma

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

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Curcuma xanthorrhiza Roxb. (C. xanthorrhiza* D. Dietrich*)., rhizoma*
Herbal preparation(s)	Comminuted herbal substance for infusion; Dry extract (20-50:1), extraction solvent: ethanol 96% (v/v) Dry extract (9-12:1), extraction solvent: acetone
Pharmaceutical forms	Oral dosage forms
Rapporteur	
Assessor(s)	

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

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1. Introduction

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

- Herbal substance(s)

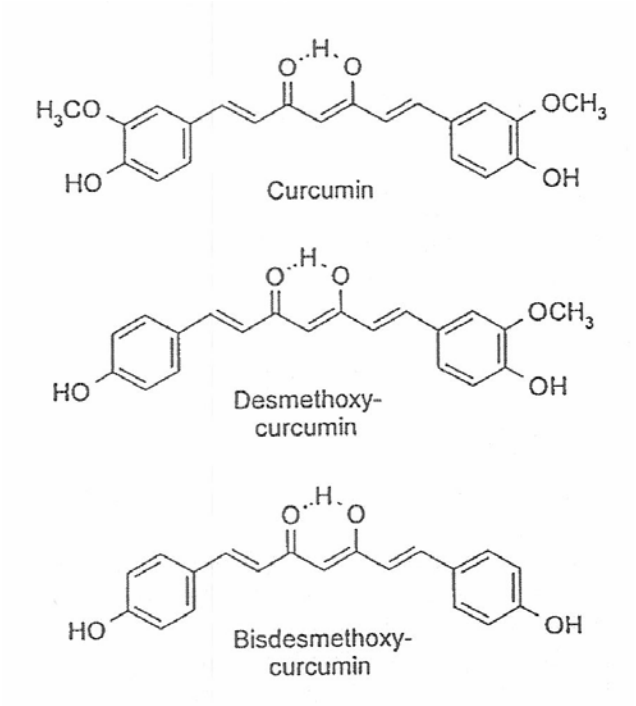
Curcumae xanthorrhizae rhizoma consists of the dried rhizome, cut in slices, of *Curcuma xanthorrhiza* Roxb. (*C. xanthorrhiza* D. Dietrich). The raw material is described in the Ph. Eur. Monograph 1441 Curcumae xanthorrhizae rhizoma (Ph. Eur. 1441).

Synonyms: *Curcuma xanthorrhiza* is also known as Javanese Turmeric or Temoe Lawak.

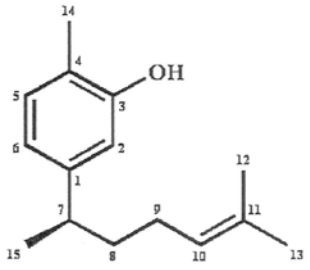
Constituents:

The root contains two classes of characteristic constituents:

- curcuminoids (1-2%), a mixture of dicinnamoylmethane derivatives such as curcumin (diferuloylmethane), monodemethoxycurcumin (feruloyl-*p*-hydroxycinnamoylmethane) and bisdesmethoxycurcumin (bis-(*p*-hydroxycinnamoyl)methane) (Ruslay et al. 2007), and other phenolic and non-phenolic diarylheptanoids (Uehara et al. 1987)



- volatile oil (3-12%), composed mainly of sesquiterpenes (e.g. β-curcumene, ar-curcumene), xanthorrizol (44.5%) and a small amount of camphor (1.39%) (Zwaving and Bos, 1992; Jantan et al. 1999; Jarikasem et al. 2005).



xanthorrhizol

A test for both classes of constituents is taken up in the Ph. Eur. Monograph 1441 of *C. xanthorrhiza,* rhizoma:

- e*ssential oil*: minimum 50 mL/kg (anhydrous drug);
- *dicinnamoyl methane derivatives, expressed as curcumin* ($C_{21}H_{20}O_6$; M_r 368.4): minimum 1.0 per cent (anhydrous drug).

The presence of xanthorrhizol and absence of bisdemethoxycurcumin are species-specific, distinguishing *C. xanthorrhiza* (Javanese turmeric) from *C. longa* (turmeric) (Wichtl 2002; Lechtenberg et al. 2004).

Furthermore, abundant non-gelatinized starch is present (Wichtl, 1994) and in a methanolic extract the following flavonoids have been identified: 5.12 mg/g catechin, 3.42 mg/g epicatechin; 107.83 mg/100g quercetin; 169.43 mg/100g myricetin; 8.60 mg/100g kaempferol; 300.38 mg/100g apigenin; 13.23 mg/100g luteolin and 2.60 mg/100g naringenin (Mustafa et al. 2010).

In a hexane soluble fraction the sesquiterpene lactone germacrone was identified (Ozaki 1990). From the chloroform-soluble fraction four bisabolane sesquiterpenoids were isolated (Uehara et al. 1990).

Pandji et al. (1993) identified β-curcumene, ar-curcumene, xanthorrhizol, germacrole, furanodienone and curcumin.

- Herbal preparation(s)

Dry extract (DER 20-50:1), extraction agent: ethanol 96% (v/v)

Dry extract (DER 9-12:1), extraction solvent: acetone

1 g of comminuted drug in 100 ml of boiling water as an infusion, up to 3 cups per day (Fytotherapeutisch Vademecum, 1979; Fytotherapeutisch Formularium, 1990)

- 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.

A combination preparation containing 600 mg Curcuma aromatica 100 mg powder of *Curcuma xanthorrhiza* and 30 mg powder of *Rhamnus purshianae* is in medicinal use (Fytotherapeutisch Vademecum, 1979).

However, the monograph and this assessment report exclusively refer to *Curcuma xanthorrhiza*, rhizoma as single active substance only.

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

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	As combination
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

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

The databases that have been searched for tox and pre-clinical data are EMBASE, PUBMED, TOXNET and International Pharmaceutical abstracts. Search terms were <Curcuma xanthorrhiza> <xanthorrhizol> <curcumin> and date until 2011.

For information on traditional use herbal books in EMA library, containing herbal compendia and monographs were searched for <Curcuma xanthorrhiza>.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

There are three preparations on the German market at least since 1976, two of which are ethanolic extracts in hard capsules and one being an acetone extract in a soft capsule.

Curcuma xanthorrhiza, rhizoma is on the Dutch market as a combination product at least since 1963.

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

Preparation	**Period of use**	**Pharmaceutical form/posology**	**posology**	**curcumin**[1]
Dry extract (20-50:1), extraction agent: ethanol 96% (v/v)	Since 1976 in Germany	Hard capsules for oral use in adults and adolescents over 12 years	3 x daily 1 capsule containing 23.3 mg dry extract	70 mg
Dry extract (9-12:1), extraction solvent: acetone	At least since 1976 in Germany	Soft capsules for oral use in adults and adolescents over 12 years	2 x daily 1 capsule containing 100 mg dry extract	48 mg
Infusion (1:100); in boiling water	Since 1979 in the Netherlands	Infusion	Up to 3 cups daily	60 mg
Combination preparation containing 600 mg Curcuma aromatic, 100 mg powder of *Curcuma xanthorrhiza* and 30 mg powder of Rhamnus purshianae	Since at least 1963 in the Netherlands	Tablets for oral use in adults and adolescents over 12 years	1 or 2 tablets up to 4 x per day	nd

Traditional indication in Germany:

"dyspeptic complaints, particularly based on functional affections of the biliary tract"

Traditional use indication in the Netherlands contains:

"unsatisfactory functioning of the liver and biliairy tract and indigestion due to insufficient bile secretion"

[1] The daily dose of curcumin is calculated using a maximum of 2% curcuminoids value from the literature

The use of Curcuma xanthorrhiza, rhizoma has been included in the following handbooks:

Reference	Traditional Use
Benedum J. et al. (2006) Medicinal plants in Traditional medicine.	Antiflatulent, digestive and cholagogue
Blumenthal et al. (1998) Commission E monographs	Has a choleric action and is used in peptic disorders
Bruneton J. (1999) Pharmacognosy phytochemistry medicinal plants.	Cholagogue and choleretic
ESCOP monographs supplement 2009	Symptomatic treatment of mild digestive disturbances and minor biliary dysfunction
Fleming T. (1998) PDR for herbal medicines.	Liver and gallbladder complaints; loss of appetite; used for dyspepsia, particularly feelings of fullness after meals and meteorism (accumulation of gas in the abdomen or the intestine).
Fytotherapeutisch Formularium (1990)	As choleretic and cholagogue during chronic cholangitis and cholecystitis; as stomachic en carminative; against bilesones
Fytotherapeutisch Vademecum (1979)	As cholagogue and antispasmodic
Hänsel R. and Sticher O. (2006) Pharmakognosie – phytopharmazie.	Cholagogue and choleretic action
Hoppe (1975) Drogenkunde	Liver and biliary complaints; choleretic and cholagogue action
Wagner H. and Wiesenauer M. (1995) Phytotherapie	Choleric and Cholagogue
Wichtl M. (1994) Herbal drugs and Phytopharmaceuticals	Choleretic and cholagogue action and as carminative and stomachic effect
Wyk van B.E. and Wink M. (2004) Medicinal plants of the World,	Used in dyspeptic complaints and as stomachic and carminative

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

Reference	Strength and posology	Route of administration	Duration of use	indication
PDR for herbal medicines (1998)	½ tsp of drug in 1 cup of boiling water; 2-3 times daily	Oral use	-	Liver and gallbladder complaints; loss of appetite; used for dyspepsia, particularly feelings of fullness after meals and meteorism
Commission E monograph (1990)	2 g dried root or equivalent preparations	Oral use	-	Peptic disorders (choleretic action)
ESCOP monograph 2009	2 g of drug or corresponding extracts	Oral use	No restriction	Symptomatic treatment of mild digestive disturbances and minor biliary disfunction
Fytotherapeutisch Formularium, 1990	0.5-1 g of drug in 150 ml of boiling water, several times daily	Oral use	-	As choleretic
Fytotherapeutisch Formularium, 1990	0.5-1 g of drug in 150 ml of boiling water, 3 times daily	Oral use	-	As stomachic and carminative
Fytotherapeutisch Vademecum, 1979	Infusum (5:500), 3 times daily 2 cups	Oral use	-	As cholagogue and antospasmodic

3. Non-Clinical Data

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

The principal components of *Curcuma xanthorrhiza* are curcumin and xanthorrhizol. These components have a wide range of pharmacological activities, which overlap and synergistic effects have been observed. In this section data are presented that support the traditional use of *Curcuma xanthorrhiza*. Also an overview is given of the other activities that have been observed.

Primary pharmacodynamics

Extracts:

No data available.

Powdered herbal substance:

In-vivo:

When rats were put on a diet containing 5% powdered *Curcuma xanthorrhiza* root for two weeks (eq. 3,67 g/kg bw and 73 mg curcumin/kg bw, based on the assumption that dried *Curcuma xanthorrhiza* contains 2% curcumin) the fecal excretion of total bile acids was decreased significantly (30%) in comparison to the cellulose control, indicating a decrease in pool size of total bile acids (Yasni et al. 1991). The level of bile acid increased at the cost of deoxy-bile acid.

Essential oil:

In-vivo:

Ozaki and Liang (1988) observed that oral administration of the essential oil, obtained by steam distillation from the rhizome of *Curcuma xanthorrhiza*, to anesthetized rats, caused a persistent but transient (5h) increase of bile secretion, the essential oil of *C. xanthorrhiza* being slightly more active than that of *Curcuma longa* (both 300 mg/kg). The effect of curcumin (300 mg/kg) was weaker than both essential oils. The active principle of the essential oil of *C. xanthorrhiza* was shown to contain *d*-camphor. The fraction of the essential oil containing *d*-camphor (at doses of 100 and 300 mg/kg) and *d*-camphor (at doses of 30 and 100 mg/kg) gave a persisting cholagogic effect. The results suggest that the cholagogic effect of the essential oil is attributable for a major part to d-camphor contained in it and that the increase in bile secretion induced is partly due to the increase in the total bile acids in the excretive bile.

Single substances:

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, indicating that the observed effect on bile secretion was due to the presence of curcumin.

Assessor's comment:

The data shown above indicate that components from Curcuma xanthorrhiza, exert a transient increase on bile secretion within 2 hours after oral consumption. The main active components have been shown to be curcumin and camphor. For curcumin the studied amounts after oral application are 70 times higher than the human daily posology used in traditional herbal medicinal products (paragraph 2.2). Based on this finding it is not likely that a significant effect of curcumin on bile secretion is obtained at doses traditionally used.

Secondary pharmacodynamics

Extracts:

Anti-oxidant properties

Curcumin acts as a scavenger of oxygen species, such as hydroxyl radical, superoxide anion, and singlet oxygen (Sharma 1976, Subramanian 1994, Tonnesen 1992, Kunchandy 1990, Reddy 1994; cited by Ireson et al 2002), and it interferes with lipid peroxidation (Donatus 1990, Mukhopadhyay 1982, Sharma 1972; cited by Ireson et al 2002).

Chanwitheesuk *et al* (2005) observed a limited antioxidant activity with a methanolic fraction of *Curcuma xanthorrhiza*. In a methanolic extract the antioxidant activity was correlated to the presence of phenolic compounds and flavonoids (Mustafa et al. 2010). In neuronal and microglia cells antioxidant activity has been shown by 10 µM xanthorrhizol (Lim et al. 2005). Isolated curcumin inhibited liposomal peroxidation (70% at 300 ng/ µl) and peroxide-induced DNA damage (Shalini and Srinivas, 1987).

Anti-inflammatory and immunomodulatory properties

The observed anti-inflammatory effect of *Curcuma xanthorrhiza* has been attributed to curcuminoid-derivatives and dependent on the appropriate substituents on the phenylrings. It has been observed that curcumin is a more potent anti-inflammatory agent than the demethoxy- or bisdesmethoxy-form (Nurfina et al. 1997). The inhibition of oedema formation (as an experimental model for inflammation) in the hind paw of rats by a hexane fraction (75 mg/kg bw) has been attributed to the presence of non-phenolic linear diarylheptanoids (Ozaki et al 1990). External application of these compounds (0.1-1000 µg/ear) showed anti-inflammatory activity (Claeson et al. 1996). This may suggest a role in treatment of acne and skin-inflammation.

Also xanthorrhizol has been observed to exert an anti-inflammatory effect. In vitro application of 10 µM xanthorrhizol induced anti-inflammatory activity in neuronal and microglia cells (Lim et al. 2005). Five milligrams methanolic extract and 0.1 – 2.0 µmol xanthorrhizol/50 µL applied topically inhibited TPA-induced oedema in rat ears, which has a direct correlation with inflammation (Chung et al. 2007; Park et al. 2008). The mode of action is probably multi-targeted via immunomodulation, for 18.2 µg xanthorrhizol/ml inhibitied PAF-receptor binding (Jantan et al. 2004). Another mode of action is via modulation of cell adhesion molecules (CAMs), for a methanolic extract (12,5 µg/ml) stimulated ICAM-1 in M1 Murine cells *in vitro* (Tanaka et al. 2001; Spelman et al. 2011). Yasni et al. (1993) observed that dietary intake of powdered root of *Curcuma xanthorrhiza* (2% of dietary intake) increased mitogenic responses of splenic lymphocytes in rats and altered populations of the lymphocytes in mice. Furthermore, Jantan et al. (2011) observed *in vitro* that a methanolic extract inhibited the release of reactive oxygen species (ROS) and chemotactic migration of phagocytes (IC_{50} 0.7 µg/ml).

Anti-mutagenic and anti-carcinogenic properties

The anti-inflammatory action has often been brought into relation with prevention of cancer. In the first decade of this century research has focussed on the anti-cancer effect of xanthorrhizol and curcumin:

Xanthorrhizol

Chung et al. (2007) observed that topical application of 2 and 6 µmol xanthorrhizol in rats inhibited TPA-induced tumour formation correlated with reduction in protein levels of ODC, iNOS and COX-2. Also Lee et al. (2002) observed inhibitive action of xanthorrhizol on inducible COX-2 and i-NOS in mouse (IC_{50} = 0.2 µg/ml and 1.0 µg/ml respectively), which are important mediators of the inflammation process and carcinogenesis. Choi et al. (2005) observed that injection of 0.2-1.0 mg xanthorrhizol/ kg bw had an anti-metastatic effect in a mouse lung metastasis model. *In vitro* experiments showed induction of apoptosis via upregulation of Bax and p53 in HeLa cells (EC_{50} 6.16 µg/ml; Ismail et al. 2005) and in HCT116 human colon cancer cells also apoptosis and growth arrest have been observed (IC_{50} = 54.8 µM; Kang et al. 2009). Park et al. (2008) observed inhibition of DMBA- and oxidation-induced bacterial mutagenesis using 0.5-2.5 µg of a methanolic extract/plate.

Curcumin

In nude mouse that had been injected subcutaneously with prostate cancer cells, a diet of 2% curcumin caused a marked decrease in the extent of cell proliferation, a significant increase of apoptosis and micro-vessel density (Dorai et al. 2001). Also it has been observed that green tea enhances the effect of curcumin in reducing oral squamous-cell carcinomas in hamsters (Li et al. 2002). Cheah et al (2009) observed that when xanthorrhizol and curcumin were added together to human breast cancer cells *in vitro* there was an increase in growth inhibition via apoptosis (GI_{50} = 5 µM) as compared to xanthorrhizol alone (GI_{50} = 15 µM), indicating a synergistic effect of these two substances. Synergistic activity was commenced from the combination xanthorrhizol-curcumin 3:7 to 1:9, reflecting the vital involvement of curcumin in the sensitivity of test cells towards the test agents.

Curcumin suppresses a number of key elements in cellular signal transduction pathways pertinent to growth, differentiation, and malignant transformation (Ireson et al. 2002; Hatcher et al. 2008). Among signaling events inhibited by curcumin are protein kinases (Liu et al. 1993), c-Jun/AP-1 activation (Huang et al, 1991), prostaglandin biosynthesis (Huang et al 1992), and activity and expression of the enzyme cyclooxygenase (COX)-2 (Huang et al 1991). Curcumin inhibits the enzymes COX-1 and COX-2 with IC_{50} values (3.57 µM and 29.3 µM) which are in the same range as that for acetylsalicylic acid (18.1 µM and 15.9 µM, respectively) (Gafner et al 2004).

Hepatoprotective properties

Studies in rats and mice have demonstrated that oral application of *Curcuma xanthorrhiza* (100 mg/kg bw) has a hepatoprotective effect from a variety of hepatotoxic insults, including galactosamine and carbon tetrachloride, as shown by significant reduction of serum transaminases (Linn et al. 1995, 1996). This hepatoprotective effect was confirmed by histopathological examination: necrosis and vascular congestion were less profound in livers of the treated animals. Furthermore an increase in binuclear hepatocytes was ovserved in the mid-zone, indicating regeneration of hepatocytes. This hepatoprotective effect is considered mainly a result of its antioxidant properties, as well as its ability to decrease the formation of pro-inflammatory cytokines. Kim et al. (2004 and 2005) observed that oral application of 200 mg xanthorrhizol/kg bw attenuated cisplatin-induced nephrotoxicity and hepatotoxicity in mice (cisplatin is often used in chemotherapy). A possible mode of action being attenuation of phosphorylation of c-Jun N-terminal kinases (JNKs) (Hong et al. 2005).

Curcumin also reversed biliary hyperplasia, fatty changes, and necrosis induced by aflatoxin in ducklings (Sony et al, 1992) and dietary treatment of chicks with curcumin ameliorated the adverse effects of aflatoxin B1 on the liver (Gowda et al 2008). Sodium curcuminate, a salt of curcumin, also exerts choleretic effects by increasing biliary excretion of bile salts, cholesterol, and bilirubin, as well as increasing bile solubility, therefore possibly preventing and treating cholelithiasis (Akram et al 2010).

When rats were fed with 0.1-0.5% curcuminoids a preventive effect on deposition of cholesterol in the liver was observed, however, no effect on serum lipids was found with a diet containing 0.2% curcuminoids (Subba et al. 1970). Yasni *et al* (1993) observed an inhibitive effect on liver fatty acid synthase when rats were put on a diet containing 4% powdered *C. xanthorrhiza* rhizome resulting in a decrease of the triglyceride content of the liver. In a follow-up experiment it was observed that the essential oil from *Curcuma xanthorrhiza* had a lowering effect on the hepathic triglyceride content and additionally that application of the hexane fraction resulted in a lowering of the hepathic triglyceride content and the serum triglyceride level. This activity was attributed to α-curcumene (Yasni et al. 1994). Suksamrarn *et al* (1994) observed inhibition of hepatic triglyceride secretion by curcuminoids.

Hypolipidaemic and hypocholesterolic properties

Curcumin at a level of 0.1% in the diet was reported to lower serum and liver cholesterol in rats fed 1% cholesterol-containing diets for 7 weeks (Rao et al., 1970).

Anti-microbial, -fungal and -insecticidal properties

In vitro studies have shown that xanthorrhizol exerts anti-microbial, anti-fungal and anti-insecticidal activities. In the table below the studies are cited that have been performed in this field:

study	xanthorrhizol	application	effect
Anti-microbial and anti-fungal activity			
Lee et al. 2008	8-18 µg/ml	In vitro	Antimicrobial activity against foodborne pathogens
Rukuyadi and Hwang, 2006	MIC 0.25-1.25 µg/ml; MFC 2.5-5 µg/ml	In vitro	Anti-malessezia (dandruff) activity
Rukayadi and Hwang, 2007	MIC 1.0-4.0 µg/ml; MFC 2.0-8.0 µg/ml	In vitro	Activity against opportunistic filamentous fungi
Jantan et al. 2003	MIC 10-40 µg/µl	In vitro	Antifungal activity
Oral health			
Hwang et al. 2000	2-4 µg/ml	In vitro	Minimum inhibitory concentration of Streptococcus spp. (oral pathogen)
Rukuyadi and Hwang, 2006	5 µg/ml	In vitro	Inhibition of biofilm formation of Streptococcus mutans (anti plaque)
Kim et al. 2007	MIC 5 ppm	In vitro	Inhibitory effect on S. mutans and A. viscosus (human dental caries)
Yanti et al. 2009	2-10 µg/L	In vitro	Anti-biofilm activity (anti plaque)
Anti-mycotic effect (Candida spp.)			
Rukayadi et al. 2009	2-16 µg/ml	In vitro	Minimum inhibitory concentration of Candida spp.; synergy with ketoconazole and amphotericin B
Rukayadi et al. 2006	MIC 1.0-25.0 mg/L MFC 10-30 mg/L	In vitro	Anti-candidal activity
Rukayadi et al. 2011	8-64 µg/ml	In vitro	Activity against Candida spp. Biofilm formation
Anti-insecticidal effect			
Pandji et al. 1993	LD_{50} = 6.92-8.13 µmol/kg fr.wt	Topical treatment	Insecticidal activity

Structure-activity relation study results suggested that the antibacterial activity of phenolic compounds like xanthorrhizol, is likely exerted by multiple functions, primarily comes from its ability to act as a non-ionic surface-active agent therefore disrupting the lipid-protein interface (Greenberg et al, 2008).

Improvement of insulin resistance

When streptozotocin-induced diabetic rats were put on a diet containing 5% powdered *Curcuma xanthorrhiza* for two weeks an improvement of diabetic symptoms such as growth retardation, hyperphagia, polydipsia, elevation of glucose and triglyceride in the serum, and reduction of the ratio of arachidonate to linoleate in the liver phospholipids was observed (Yasni et al. 1991).

Anti-aging and estrogenic properties

Recent investigations have observed that xanthorrhizol (0.01 – 0.5 µg/ml) inhibited matrix metalloprotease and procollagen *in vitro*, suggesting role in anti skin aging (Oh et al. 2009). Furthermore Anggakusuma et al. (2009) observed *in vitro* that 0.5-5 µM xanthorrhizol induced estrogen dependent gene expression, suggesting that this compound may have estrogenic activity. Also for curcumin it has been observed that 100 nM curcumin activates gene expression in the breast

cancer cell line MCF7 in the same direction as 17-β-estradiol does, indicating that curcumin may have low estrogenic activity (Bachmeier et al, 2010).

Anti-coagulation properties

Curcumin shows inhibition of arachidonic acid-induced platelet aggregation with IC_{50} ranging from 37.5 to 60.9 µM (Jantan et al. 2008) up to 125 µM (Raghavendra et al 2009). With these IC_{50} values, curcumin is less potent than acetylsalicylic acid which has an IC_{50} value of 14.5 µM. The clinical relevance of this observation is not clear.

Assessor's comment:

The primary pharmacodynamic data presented indicate that Curcuma xanthorrhiza may increase bile secretion several hours after oral intake. This may be considered to support the traditional use of Curcuma xanthorrhiza in digestive disturbances due to lack of bile secretion, such as feelings of fullness, slow digestion and flatulence. However, the amount of substance necessary to exert this effect seems to be much larger than the dose traditionally used. Therefore the reference to the effect on bile secretion should be omitted from the indication. The proposed traditional use indication therefore is: "Traditional herbal medicinal product used for the relief of symptoms of digestive disturbances such as feelings of fullness, slow digestion and flatulence".

Based on this consideration, a contra-indication for biliary obstruction is not necessary. However, a warning is taken up in case of biliary obstruction.

Curcumin has been observed to inhibit platelet aggregation in vitro. However, the daily dose of curcumin for the products in the monograph is estimated to be maximally 70 mg, which is considerably lower than doses used in bioavailability studies in humans and animals (minimum dose is 4 g; Anand et al, 2007). Therefore a warning in relation to this observation is not considered necessary.

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

Xanthorrhizol

There are no pharmacokinetic data for xanthorrhizol.

Curcumin

In rodents, curcumin demonstrates poor systemic bioavailability, because of poor 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 (Leiherer 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 of less than 5 µg/ml indicate poor absorption from the gut (Yegnanarayan et al 1976; Lukita-Atmadja et al, 2002).

Oral administration of radio-labelled curcumin to rats resulted in radioactivity being found only in the liver and kidneys (Ravindranath and Chandrasekhara, 1980 and 1982). Curcumin administered intravenously was excreted in the bile (Wahlström and Blennow, 1978). ^{3}H-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 an 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 (Sarkar et al 2010) because it has a better solubility than curcumin and therefore a better bioavailability. Also fytosome-curcumin in which curcumin is linked to phosphatidylcholine has been observed to result in a better bioavailability and activity after oral application 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 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 (Wahlström and Blennow, 1978; Ravindranath and Chandrasekhara, 1980).

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 (Cohly et al, 1998; Romiti et al, 1998) similar to those of their metabolic progenitor.

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 et al., 1982). Major metabolites included the glucuronides of tetrahydrocurcumin and hexahydrocurcumin, with dihydroferulic acid and ferulic acid present as minor metabolites (Holder et al., 1978).

Drug Interactions

Interactions between curcumin and other phytochemicals have been observed. When healthy human subjects took a 2 g dose of curcumin in combination with 20 mg of piperine, extracted from black pepper, the bioavailability of curcumin increased twenty-fold compared to subjects who took only 2 g of curcumin (Shoba et al.,1998).

Curcumin is a potent inhibitor of cytochrome P450 (CYP) 2C9 and CYP3A4 and a moderate inhibitor of CYP2B6, CYP1A2 and CYP2D6, with IC_{50} 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 metabolized 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_{50} value is in the range of 50 -100 µM (Aurade et al 2010). After the combined oral application 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:

There are no pharmacokinetic data for xanthorrhizol. 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 herbs is not considered relevant for the traditional use of Curcumin xanthorrhiza , 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

Single dose toxicity

Extracts:

An aqueous extract of *Curcuma xanthorrhiza* did not produce any signs of toxicity in mice or rats up to an oral dose of 2 g/kg bw (Lin *et al* 1995).

Single substances:

Curcumin

The oral median lethal dose (LD_{50}) of curcumin in mice is higher than 2.0 g/kg bw (Itokawa, 2008). Single oral doses of curcumin at 1-5 g/kg bw induced no toxic effects in rats (Wahlström and Blennow, 1978).

Donatus *et al.* (1990) observed curcumin to be moderately cytotoxic *in vitro*, inducing slightly increased LDH-leakage from rat hepatocytes, accompanied by an increase in GSH-depletion.

Xanthorrhizol

No mortality was observed after a single oral administration of xanthorrhizol to mice at 500 mg/kg (Yamazaki *et al*, 1988).

The *in vitro* GI_{50} value of both xanthorrhizol and curcumin on human breast cancer cell lines was around 20 mg/ml. Simultaneous application of xanthorrhizol and curcumin has been observed to inhibit cell growth in human breast cancer cells (GI_{50} = 5 µM) and xanthorrhizol alone (GI_{50} = 15 µM) (Cheah *et al*, 2009).

Repeated dose toxicity

Extracts:

No data available.

Single substances:

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). For the national toxicity programme long-term (103-weeks) dietary exposure studies were performed in rats and mice. Based on the findings in rats

the NOEL for gastrointestinal irritation (ulcers, hyperplasia and inflammation) was established at 440 mg curcumin/kg/day. In mice, there were absolute and relative increases in liver weights after 15 months of treatment, with a NOEL of 220 mg/kg/day (NTP, 1993). Based on these results and reckoned with a safety factor of 200, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established at its 44th meeting the temporary ADI to 0–1 mg/kg for human, pending submission of the results of a study on reproductive toxicity.

Genotoxicity

Extracts:

No data available.

Single substances:

Curcumin

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 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).

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 of 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.

Carcinogenicity

Extracts:

No data available.

Single substances:

Curcumin

Curcumin is considered to be not carcinogenic (JECFA). 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) (NTP 1993). 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/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 curcumin is not carcinogenic.

Reproductive toxicity

Extracts:

No data available.

Single substances:

Curcumin

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 the Joint FAO/WHO Expert Committee on Food Additives (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 NOEL.

There is one report indicating that rats fed high doses of turmeric (4 g/kg/d) or curcumin (0.4 g/kg/d) 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).

Assessor's comment:

In absence of toxicological data on the herbal substance and only one report on single dose toxicity on an aqueous extract, which showed low toxicity, data on the constituents can give an indication about the safety of the herbal product. The constituents do not appear to be toxic or mutagenic in traditional use doses. No reproductive toxicity has been observed, however while it has been established that curcumin and/or metabolites are transferred to sucklings via lactation it is not recommended to use Curcuma xanthorrhiza or preparations thereof during breastfeeding. For curcumin an ADI of 0-3 mg/kg bw has been established. The maximum daily dose in the monograph is 70 mg curcumin. For an adult of 60 kg this means 1.17 mg/kg bw, and therefore the proposed human traditional use dose can be used safely.

The finding that curcumin can cause gastrointestinal irritation (ulcers, hyperplasia and inflammation) has been shown at doses of 100 mg/kg bw 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 70 mg curcumin and 1.17 mg/kg bw), 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 indicate that *Curcuma xanthorrhiza* may increase bile secretion several hours after oral intake. This may be seen to supports the traditional use of *Curcuma xanthorrhiza* in digestive disturbances due to lack of bile secretion, such as feelings of fullness, slow digestion and flatulence. However, the amount of substance necessary to exert this effect seems to be much larger than the dose traditionally used. Therefore the reference to the effect on bile secretion should be omitted from the indication. The proposed traditional use indication therefore is: "Traditional

herbal medicinal product used for the relief of symptoms 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.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have only been performed with curcumin, but not with the herbal substance. Nonetheless, neither the chemical composition nor the long-term widespread use in the European Community suggests that there is a high risk associated with the use of *Curcuma xanthorrhiza* preparations. In absence of reproductive toxicity, genotoxicity and carcinogenicity data, a list entry cannot be recommended from a non-clinical point of view.

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

Xanthorrhizol

No data available.

Curcumin

No data available.

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

Xanthorrhizol

No data available.

Curcumin

In a Phase I clinical study, low systemic bioavailability 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 (Sharma et al, 2007; Hatcher et al. 2008).

In a 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 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 Curcuma xanthorrhiza L. that are mentioned in the monograph (maximum daily dose of curcumin is 70 mg). Therefore, it is not likely that the resulting plasma level of curcumin causes physiological activity.

4.2. Clinical Efficacy

4.2.1. Dose response studies

Xanthorrhizol

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 (Rasyid et al. 2002).

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.

4.2.2. Clinical studies (case studies and clinical trials)

No data available.

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

No data available.

4.3. Overall conclusions on clinical pharmacology and efficacy

The presented clinical data suggest some effect of curcumin on the depletion of the gallbladder, supporting the traditional use of *Curcuma xanthorrhiza* for digestive complaints related to a lack of bile secretion.

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 80 mg curcumin (Rasyid et al. 2002).

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).

Rare cases of allergic contact dermatitis have been reported (Hata et al. 1997; Goh and Ng, 1987). 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 (Seetharan 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 [Prucksunand *et al.*, 2001]. Therefore no contraindication for duodenal/gastric ulcers was included in the monograph.

A dietary supplement containing curcumin has received a GRAS notification from the FDA up to 1500 mg per day for a 60 kg person.

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/day, with a theoretical maximum daily exposure of 6.9 mg/kg bw/day for adults and of 11.9 mg/kg/day for a typical 3 year-old child (EFSA 2010).

Although there is no evidence that dietary consumption of curcuma extract as a spice adversely affects pregnancy or lactation, the safety of curcumin supplements in pregnancy and lactation has not been established (Reprotox 2012).

5.2. Patient exposure

No data available.

5.3. Adverse events and serious adverse events and deaths

Germany (BfArM) reported the following adverse reactions:

gastrointestinal complaints like feeling of fullness, heartburn, vomiting, diarrhoea; longer use may cause gastric pain; hypersensitivity reactions of the skin.

Frequency unknown.

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

An analysis has been made of the side effects of herbal products in Thailand that have been reported between 2000 and 2008 to the Thai Health Products Vigilance Center (Saokaew et al. 2011). For *Curcuma xanthorrhiza* 12 spontaneous reported adverse events have been found.

The reported adverse events were not serious and consisted of urinary system disorders (6; face oedema), gastrointestinal system disorders (2; abdominal pain), skin and appendages disorders (2; erythema multiform and urticaria), body as a whole/general disorders (1; eyelid oedema) and reproductive disorders (1; female, leucorrhoea). Due to the lack of accurate information, causality could not be established.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

Intrinsic/extrinsic factors

Due to the nature of the effect on bile secretion *Curcuma xanthorrhiza* is not recommended in case of obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases. Therefore a warning is taken up into the monograph.

Drug interactions

Germany (BfArM) reported:

No reports of clinical interactions. However there are insufficient human data concerning possible interactions. Animal tests indicate that there may be an influence of different phases of the CYP 450 system. If medicinal products which are metabolised by these systems, are taken concomitantly, therapy has to be supervised carefully.

Pregnancy and lactation

There are no reports on the use of curcumin during pregnancy and lactation in humans (Cronin, 2003, Blumenthal, 1998).

Overdose

No data available.

Ability to drive or operate machinery

No data available.

Impairment of mental ability

No data available.

5.6. Overall conclusions on clinical safety

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

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

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

6. Overall conclusions

Curcuma xanthorrhiza (Javanese turmeric) has been used in Europe at least since 1963, mainly against dyspepsia, skin and liver diseases and infections. The available data are not sufficient to support a “Well Established Use” indication for Javanese Turmeric. As the medicinal use of *Curcuma xanthorrhiza, rhizoma* has been documented continuously in European handbooks, specified preparations fulfill the requirements of Directive 2004/24/EC for use in products classified as Traditional Herbal Medicinal Products. The use of *Curcuma xanthorrhiza, rhizoma* is considered plausible in the treatment of “digestive complaints related to insufficient bile secretion” on the basis of bibliography and pharmacological data. Nonetheless reference to a lack of bile secretion is not considered to fulfill the criteria as laid down in Article 16a of Directive 2004/24 EC, because this cannot be diagnosed without the help of a medicinal practitioner. Therefore the proposed indication for traditional monograph reads as follows: “Traditional herbal medicinal product used for symptomatic treatment of digestive disturbances, such as feelings of fullness, slow digestion and flatulence”.

Although the use for skin diseases is also described, it is not included in the monograph because no information is available that *Curcuma xanthorrhiza, rhizoma* containing products are currently on the market of EU Member States for such indications.

Curcuma xanthorrhiza is used in the following strengths and posologies:

- Dry extract (DER 20-50:1): 23-70 mg daily;

- Dry extract (DER 9-12:1): 100-200 mg daily;
- Comminuted herbal substance as an infusion (1:100), in boiling water.

Only mild side effects have been reported for *Curcuma xanthorrhiza*: dry mouth, flatulence, and gastric irritation. No serious side effects have been reported.

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

Due to the possible effect on bile secretion it is not recommended to use the described herbal preparations in case of biliary obstruction, cholangitis, liver disease, gallstones and any other biliary diseases.

As relevant data on the use during pregnancy and lactation is lacking, *Curcuma xanthorrhiza* can not be recommended in these cases.

Annex

List of references