13 September 2011
EMA/HMPC/369801/2009
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Chelidonium majus* L., herba

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

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Chelidonium majus* L., herba
Herbal preparation(s)	Internal Use a) Chelidonii herba: comminuted b) Chelidonii tincture: 1:10, 45% ethanol (V/V) c) Chelidonii extractum fluidum: 1:1, 25% ethanol (V/V) d) Chelidonii extractum siccum (concentration not specified) e) *Chelidonium majus* M.T. (ø) prepared with 70% ethanol (HAB) External Use a) Eye-drops: (preparation not specified) b) Ointment: (concentration not specified)
Pharmaceutical forms	Herbal preparations in solid or liquid dosage form or as an herbal tea for oral use. Herbal preparation in solid or liquid dosage form for external use.
Rapporteur	Gert Laekeman
Assessor(s)	Pieter-Jan Corne, Frederic Vandewalle

Table of contents

1. Introduction

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

- Herbal substance(s)

The European Pharmacopoeia (01/2008:1861) monograph provides the following definition for Chelidonii herba: dried, whole or cut aerial parts of *Chelidonium majus* L. collected during flowering. Content: minimum 0.6 per cent of total alkaloids, expressed as chelidonine ($C_{20}H_{19}NO_5$; Mr 353.4) (dried drug).

Chelidonium majus L. is known under the synonyms:

English: greater celandine, devil's milk, rock poppy, tetterwort, swallow-wort
Italian: celidonia, erba di porri, cinerognola, erba maistra, erba nocca
German: Schöllkraut, Schellkraut, Schwalbenkraut, Goldwurz, Blutkraut, Gelbes Millkraut
French: chélidoine, Herbe d'éclaire, Herbe de l'hirondelle, Felougue, herbes de Sainte Claire, Herbe hirondalle
Dutch: stinkende gouwe
Spanish: celidonia
Portugal: celidonia
Polish: ziele glistnika, złotnik, jaskółcze ziele, glistnik pospolity

There are over 20 different *Chelidonium* alkaloids identified. According to Barnes *et al. (*2007) and Bruneton (1999), the different groups of chemical molecules which are present in the herb of *Chelidonium majus* are:

- Benzylisoquinoline type (0.01-1%): with at least three subgroups:

Benzophenanthridines: chelerythrine, chelidonine, sanguinarine, isochelidonine
Protoberberines: berberine, coptisine, dihydrocoptisine, stylopine
Protopine

- Acids: chelidonic, malic, citric, caffeic (0.4%) ferulic (0.02%), p-coumaric (0.06%), gentisic and p-hydroxybenzoic acids

- Hydroxycinnamic acid derivates: (-)-2-(E)-caffeoyl-D-glyceric acid, (-)-4-(E)-caffeoyl-L-threonic acid, (-)-(2)-(E)-coffeoyl threonic acid lactone, (+)-(E)-caffeoyl-L-malic acid

- Others: a saponine, carotenoids, a phytocytostatin (chelidocystatin), sparteine and flavonoids.

Chelidonium majus L. belongs to *Papaveracecae* family and is widely distributed across the world. It can be found in Europe, Asia, Northwest Africa and North America. It is a typical ruderal plant that grows on nitrogenous grounds.

Historically, *Chelidonium majus* was already used in the Middle Ages. It was mentioned by Plinius and Dioscorides. The name Chelidon (χελιδον) in Greek means swallow because the plant begins to flower when the swallows return.
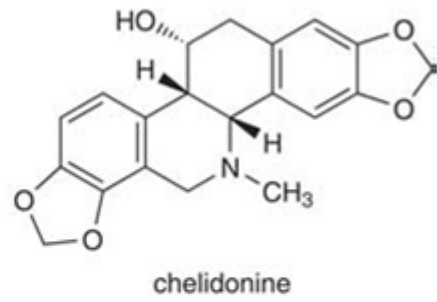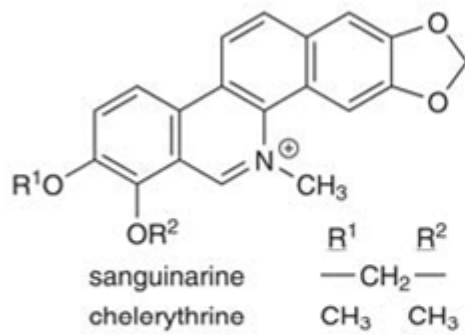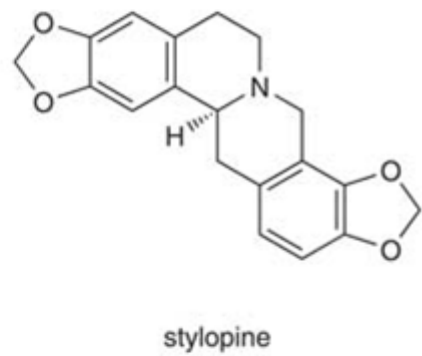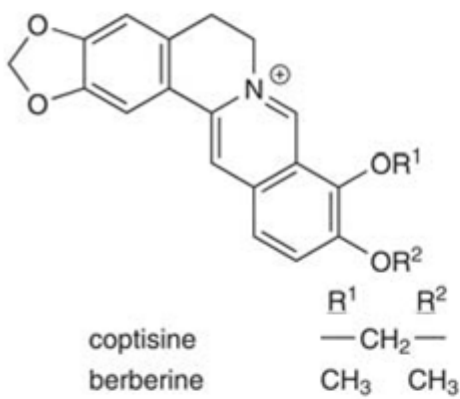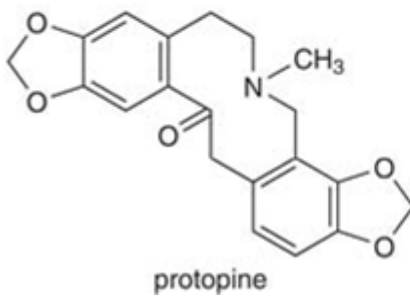
Figure 1. Alkaloids of *Chelidonium majus* (Barnes *et al.* 2007)

Acids

chelidonic acid

Caffeic acid esters

(−)-2-(E)-caffeoyl-
D-glyceric acid

(−)-4-(E)-caffeoyl−
L-threonic acid

(−)-2-(E)-caffeoyl-
L-threonic acid lactone

(+)-(E)-caffeoyl-
L-malic acid

R =

Figure 2. Acids of *Chelidonium majus* (Barnes *et al.* 2007)

- Herbal preparation(s)

Internal use:

- Chelidonii herba comminuted: 1.2-3.6 g as a tea infusion (ESCOP 2003)

- Chelidonii tinctura (45% Ethanol V/V): 2-4 ml of a 1:5 preparation daily or 2-4 ml of a 1:10 preparation three times daily (Barnes *et al.* 2007)

- Chelidonii extractum fluidum (25% ethanol V/V): 1-2 ml of a 1:2 preparation daily or 1-2 ml of a 1:1 preparation three times daily (Barnes *et al.* 2007)

- Chelidonii extractum siccum (concentration not specified): 100-200 mg three times daily (Van Hellemont 1985; Delfosse 1998)

- *Chelidonium majus* M.T. (ø) (70% ethanol HAB): three times 15 drops daily (Van Hellemont 1985; Delfosse 1998)

External use:

- Eye-drops, one drop three times daily (Kommission C 1992; linked to anthroposophic medicine):

Chelidonium, volatile grade of dilution D4 to D30
Chelidonium Rh, volatile grade of dilution D4 to D30
Chelidonium Flos (ethanol), volatile grade of dilution D4 to D30
Chelidonium Flos Rh, volatile grade of dilution D4 to D30

- Ointment, apply 1-2 times daily on rash (Kommission C 1992; linked to anthroposophic medicine)

Chelidonium majus M.T. (ø)
Chelidonium e radice ferm 34b, volatile grade of dilution D3 to D30
Chelidonium ex herba cum radice ferm, volatile grade of dilution D3 to D30

- 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 few herbal preparations in combination with *Chelidonium majus* are described in the *Deutschen Rezeptformeln*: Tinctura Cholagoga (DRF) (a combination of *Chelidonium majus* tincture with *Silybum marianum* tincture and *Strychnos nux-vomica* tincture) and Tinctu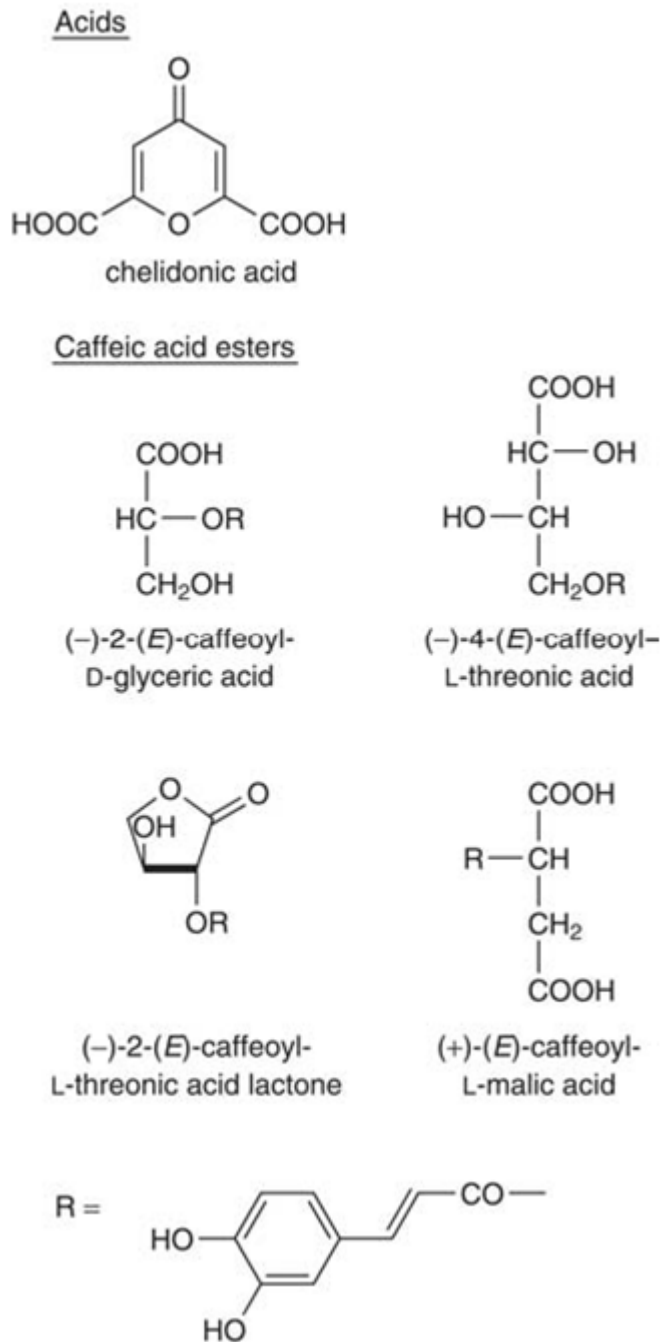ra Cholagoga Fortis (DRF) (a combination of *Chelidonium majus* tincture, *Silybum marianum* tincture, *Atropa belladonna* tincture and *Mint* Oil) (Van Hellemont 1985; Weiss & Fintelman 1999).

Another common combination product is a liquid formulation that consists of nine herbs. Iberogast[®] contains a fixed combination of hydroethanolic herbal extracts from bitter candy tuft (Iberis amara totalis), peppermint leaves (Menthae piperitae folium), chamomile flower (Matricariae flos), liquorice root (Liquiritiae radix), angelica root (Angelicae radix), caraway fruit (Carvi fructus), milk thistle fruit (Silybi mariani fructus), lemon balm leaves (Melissae folium) and greater celandine herbs (Chelidonii herba). Each of them is reported to have multiple pharmacological properties relevant in gastrointestinal pathophysiology (Wegener and Wagner 2006). According to Wegener and Wagner (2006), it is a prokinetic that is indicated for irritable bowel syndrome and dyspepsia. The composition of 100 ml liquid is the following:

Extracts from:

Iberis amara (fresh whole plant) (1:1.5-2.5) 15.0 ml, extraction solvent: ethanol 50% (V/V)
Angelicae radix (1:2.5-3.5) 10.0 ml
Matricariae flos (1:2-4) 20.0 ml
Carvi fructus (1:2.5-3.5) 10.0 ml
Cardui mariae fructus (1:2.5-3.5) 10.0 ml
Melissae folium (1:2.5-3.5) 10.0 ml

Menthae piperitae folium (1:2.5-3.5) 5.0 ml
Chelidonii herba (1:2.5-3.5) 10.0 ml
Liquiritiae radix (1:2.5-3.5) 10.0 ml

Extraction solvent for all: ethanol 30% (V/V)

- Vitamin(s)

Not applicable

- Mineral(s)

Not applicable

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

Austria

Combination product containing 9 herbal preparations including Chelidonii herba 30% ethanolic extract (DER 1:2.5-3.5) 10 ml/100 ml. (See composition under section 1.1.)

Belgium

Preparation

A combination product contains the tincture of *Chelidonium majus* 45 mg, the tincture of Thuja species 45 mg, acetic acid 80 mg, lactic acid 20 mg, salicylic acid 135 mg in 9 ml solvent.

Indication: topical treatment of warts.

Regulatory

According to the Belgium Royal Decree of 1997, *Chelidonium* is included in list 3 that includes substances which can be used in medicines as well as in food supplements. There is no restriction with regard to maximum doses specified.

Bulgaria

Combination product containing 9 herbal preparations including Chelidonii herba 30% ethanolic extract (DER 1:2.5-3.5) 10 ml/100 ml.

Czech Republic

Combination product containing 9 herbal preparations including Chelidonii herba 30% ethanolic extract (DER 1:2.5-3.5) (See composition under section 1.1.)

Estonia

Combination product containing 9 herbal preparations including Chelidonii herba 30% ethanolic extract (DER 1:2.5-3.5) 10 ml/100 ml.

Germany

Combination product containing 9 herbal preparations including Chelidonii herba 30% ethanolic extract (DER 1:2.5-3.5) 10 ml/100 ml.

Hungary

Preparation

Chelidonii herba extract ethanolic 30 ml, DER 1:10, extraction solvent ethanol 40% (V/V)

On the market since 1999 as a solution for external use.

Indication: for removing warts and corns.

Posology

Warts, corns should be painted 2-3 times daily with the help of a little stick with cotton on the top of it.

Safety: no adverse effects have been known until now.

Ointment

Composition: 5 ml extractum fluidum alcoholicum ex Bardanae radix-, Calendulae flos-, Matricariae flos-, Chelidonii herba-, et Hyperici herba.

Indication: alleviation systems associated with mild or moderate psoriasis.

The ointment should be applied to the affected skin twice daily.

The product has been on the market since 1989 as a registered "healing product".

Gel

Composition: 0.400 g extract which is an alcoholic extractum from Melissae herba, Matricariae flos, Chelidonii herba, Solidaginis herba, Pulminariae folium, Thymi herba and 0.1% Zinci sulfas heptahydricus/g.

Indication: for the topical treatment of herpes simplex infections of the perioral, perinasa region.

From onset of vesicles and slough the affected area should be smeared 1-3 times daily.

The product has been on the market since 1988 as a registered "healing product".

Tea mixture

50 mg Chelidonii herba, 250 mg Solidaginis herba, 250 mg Urticae folium, 200 mg Equiseti herba, 250 mg Agrimoniae herba/filter

Indication: diuretic, prevents the formation of renal calculi.

As infusion 3-4 times 1 filter daily.

The product has been on the market since 1996 as a registered "healing product".

Lithuania

Comminuted herbal substance for tea preparation. No further details reported.

According to ESCOP (2003): 1.2-3.6 g as a tea infusion

Slovenia

Combination product containing 9 herbal preparations including Chelidonii herba 30% ethanolic extract (DER 1:2.5-3.5) 10 ml/100 ml

Spain

Preparations

Combination of an extract of *Chelidonium* with a tincture of Thuja (1:10), salicylic acid, iodine and acetic acid.

Indication: topical treatment of warts.

Regulatory

There are other combined preparations with 7 to 9 herbal substances for use as an herbal tea. The herbal substance is included in a list of plants restricted to be used as medicinal products and should not be used in food supplements.

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Combination prep
Belgium	☐ MA	X TRAD	☐ Other TRAD	☐ Other Specify:	Combination prep. External use
Bulgaria	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Combination procuct on the market
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Combination prep
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	No authorised or registered preparations *Chelidonium* not allowed in food supplements
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Combination prep.
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☐ MA	☐ TRAD	☐ Other TRAD	X Other Specify:	Combination prep.
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	X TRAD	☐ Other TRAD	☐ Other Specify:	Mono preparation for external use
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	No authorised or registered preparations
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Voluntary withdrawal of products for oral use
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not allowed in food supplements
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Comminuted

Member State	Regulatory Status				Comments
					Chelidonium for tea infusion
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered preparations
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered preparations
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Herb can be sold on prescription
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered preparations
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Combination prep
Spain	☐ MA	☐ TRAD	☐ Other TRAD	X Other Specify:	No authorised or registered preparations for internal use Topical preparation only
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered preparations
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorised or registered preparations

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

Not specified by the Rapporteur.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

See market information in EU member states (section 1.2).

Chelidonium majus has been used since the Middle Ages. It was used for bile and liver disorders. The fresh latex was used in the treatment of warts but also for other skin complaints such as corns, Tinea

infections, eczema and tumours of the skin. The fresh latex was dabbed on the warts (Barnes *et al.* 2007).

In another literature source it is mentioned that in 1896 a Russian doctor injected 1.50-5 g of an extract (concentration not specified) in combination with equal parts glycerine and distilled water in a tumour of the skin. The tumour decreased partially or disappeared completely. Further research showed that this painful method did not have an effect on the tumour but did only decrease secretion and hemorrhages (Leclerc 1954).

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

See section 1.2

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

See section 1.2

3. Non-Clinical Data

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

In vitro studies

Anti-viral effect

Amoros *et al.* (1977): Extracts of the whole plant of *Chelidonium majus* were tested for their anti-viral properties. Alcoholic (96% ethanolic extract, 1 ml of the aqueous solution corresponds to 1 g of the fresh plant) and alkaline (50 g of the dried and pulverised plant was eluted with ammonia solutions and extracted with chloroform) extracts were tested on the herpes simplex and the polio virus. The alkaline extract showed activity against the herpes simplex virus but not against the polio virus, whereas the alcoholic extract did not show any inhibitory effect. The authors noted that this was only a preliminary search on anti-viral properties of certain plants.

Sethi (1981, 1983 and 1985): Protoberberine and benzophenanthridine alkaloids were tested for inhibition of reverse transcriptase (RT) activity of RNA tumour viruses. Inhibition of reverse transcriptase activity was correlated with the structure and anti-leukemic activity of the protoberberine alkaloids.

Table 1. Comparison of inhibition of reverse transcriptase and anti-leukemic activities of protoberberine and benzophenanthridine alkaloids (Sethi 1985)

	RT-activity (50% inhibition)		Anti-leukemic activity	
	µg/ml	µM	%	Dose (mg/kg)
coralyne acetosulfate	30	60	176	100
8-Et coralyne ethosulfate	35	72	219	100
8-Pr coralyne proposulfate	95	170	100	100

	RT-activity (50% inhibition)		Anti-leukemic activity	
2,3-Me dioxy-10,11dimethoxy dibenzoquinolizinium acetosulphat	50	103	122	50
2,3- dimethoxy-10,11methylene dioxydibenzo quinolizinium acetosulphat	45	92	121	100
10- demethoxycoralyne acetosulphat	45	92	145	100
13-methylpalmatine iodide	80	158	116	100
palmatine chloride	60	124	107	12,5
norcoralyne chloride	30	70	/	/
stracoralyne acetosulfate	45	111	154	80
isocoralyne acetosulfate	60	115	180	80
fagaronine chloride	70	139	177	40
isomers of fagorine	6	16	265	100
isomers of fagorine	80	209	107	100
isomers of fagorine	12	32	147	100

The phenolic and methoxy groups on the structure of the benzophenanthridine are important for an anti-RT activity, so individual alkaloids showed very different activities. The presence of the quaternary nitrogen in the molecule is necessary for the activity. Compounds like chelidonine (IC_{50}=200µg/ml) which do not have a quaternary nitrogen are very weakly active against RNA tumour viruses.

Kéry *et al.* (1987): The squeezed juice and a sodium chloride extract of the aerial parts of the plant were subjected to bioassays test activity against adenoviruses and herpes simplex virus type I (HSV-I). Subfractions were taken from the aerial parts and the root and tested also for the activity. After incubating the fractions with cells infected with adenovirus type 12, the subfraction with concentration of 35 µg/ml showed anti-viral activity. This fraction also showed virucidal activity against HSV-1, achieving 100% loss of virus infectivity after 90 min of incubation (75% after 30 min, and only 25% of the cells were infected with the virus after 60 min). Although adenoviruses 5 and 12 were less sensitive, they retained 50% infectivity after 120 min incubation (75% infections after 60 and 90 min for adenovirus 5 and 12.). This alkaloid fraction would belong to the benzophenanthridine fraction of *Chelidonium majus*.

Tan *et al.* (1991): Chelidonine on itself is only a weak inhibitor against human immunodeficiency virus type-I reverse transcriptase (IC_{50} around 200 µg/ml). Berberine chloride showed a moderate inhibitory activity against the same enzyme (IC_{50} around 100 µg/ml).

Rogelj *et al.* (1998): An extract, with tris-HCl buffer pH 7, was prepared from the green parts of a mature *C. majus* plant. The extract showed an inhibitory activity (no concentrations were reported) against cysteine proteinases. Chelidocystatin was isolated from this extract and was the inhibitor of the cysteine proteinases cathepsin L ($Ki = 5.6 \times 10^{-11}$ M), papain ($Ki = 1.1 \times 10^{-10}$ M) and cathepsin ($Ki = 7.5 \times 10^{-9}$ M). The values are typical for phytocystatins since similar values were obtained for inhibition of the papain, cathepsin L and cathepsin H with phytocystatin from *Phaseolus vulgaris* seed.

Anti-microbial activity

Mitscher *et al.* (1978): The anti-microbial activity was found for pseudoalcoholates of sanguinarine and chelerythrine, which have greater intercellular penetration than the polar benzophenanthridine itself

and are active (MIC= 6.25 µg/ml) against *Staphylococcus aureus, Escherichia coli, Salmonella gallinarum, Klebsiella pneumoniae, Mycobacterium smegmatis* and *Candida albicans.*

Lenfeld *et al.* (1981): Fractions of *C. majus* containing chelerythrine and quaternary benzophenanthridine showed activity against some *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Candida albicans*. There was a significant anti-microbial effect on gram-positive bacteria and on *Candida.* Minimal inhibitory concentrations (MIC) and minimal bactericidal concentrations (MBC) of the quaternary benzophenanthridine fraction (QBF) and of chelerythrine are shown in the following table 2.

Table 2. (Lenfeld *et al.* 1981).

Organism	QBF		*Chelerythrine*	
	MIC (µg/ml)	MBC (µg/ml)	MIC (µg/ml)	MBC (µg/ml)
S. aureus	5	40	10	40
S. beta A	10	10	10	10
S. alfa	20	40	20	40
C. albicans	5	>160	5	>160

Mahajan *et al.* (1982): *Alternaria, Aspergillus flavus, A. fumigatus, Candida albicans, Curvularia, Drechslera, Fusarium, Mucor, Penicillium, Rhizopus orizae* and *Scopulariopsis* growth was inhibited by Berberine in concentrations of 10-25 µg/ml.

Fik *et al.* (1997): Drug resistant *Staphylococci* and *Enterococci* were found sensitive for a glycoprotein isolated from the juice of *C. majus* leaves and roots *in vitro*. The minimal bactericidal concentration, MBC, values of various methicillin-sensitive *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), mupirocin-resistant MRSA, aminoglycoside-resistant *E. faecium* and aminoglycoside-resistant *E. faecium* were established, and were found 31-125, 31-250, 31-125, 125-500, 250-500 mg/l, respectively.

Matos *et al.* (1999): The anti-fungal activity *in vitro* was documented for *C. majus* extracts against *Fusarium* strains. A methanolic extract of the whole plant showed the highest anti-fungal activity. After five days of inoculation, the growth of the strain was reduced to less than 40% as compared to the control, but this was seen only in one strain with an alcoholic extract and no reduction was seen with a water extract. *Fusarium oxysporum cubense* strain was most sensitive to the methanolic extract; *F. solani* was the most sensitive strain to all three extracts. A methanolic root extract achieved better inhibition of growth in comparison with extracts from the aerial parts: growth of *F. oxysporum cubense, F. oxysporum melonis* and *F. solani* was reduced to less than 30% of that seen with control, although *F. culmorum* seemed rather insensitive. In further experiments, chelerythrine and sanguinarine were found to be active against *F. solani and F. culmorum*. *F. solani* was sensitive to berberine, but there was no activity found for chelidonine.

Ma *et al.* (2000): Chelidonine, dihydrochelerythrine and dihydrosanguinarine, isolated from an extract of *C. majus* roots, have activity against *Cladosporium herbarum*. The lowest concentrations which showed activity against *C. herbarum* were 10, 6 and 4 µg/ml respectively (determined by TLC).

Zuo *et al.* (2008): Extracts and compounds isolated from the aerial part of *C. majus* were tested for their anti-bacterial activity against strains of methicillin-resistant *Staphylococcus aureus* (MRSA). Bioassays led to the isolation of four benzophenanthridine-alkaloids (8-hydroxydihydro-sanguinarine (hhS), 8-hydroxydihydro-chelerythridine (hhC), dihydro-sanguinarine (hS) and dihydro-chelerythrine (hC)), which showed activity against MRSA strains, with MIC$_{50/90}$ values of 0.49/1.95; 0.98/7.81 µg/ml

for hhS and hhC respectively. hS and hC showed moderate to no inhibitory effects at concentrations up to 3 mg/ml.

Anti-tumour effect

Krey and Hahn (1969): Berberine has been shown to interact with nucleic acids by optical methods. They suggested that berberine binds to DNA because calf-thymus DNA produced changes in absorption spectrum of berberine. It is concluded that the planes of berberine lie parallel to those of purine and pyrimidine pairs in DNA (double, single DNA and ribosomal RNA).

Hladon *et al.* (1978): The cytotoxic activity of chelidonine, sanguinarine and berberine was tested in HeLa cell cultures; ED_{50} values were respectively 0.27; 0.54 and 3.5 to 30.0 µg/ml. ED_{50} values in normal rabbit kidney cell cultures were 1.35 µg/ml for chelidonine and 0.66 µg/ml for sanguinarine. Only a weak activity in Erlich ascites carcinoma cell cultures was observed for chelidonine and sanguinarine.

Caolo and Stermitz (1978): The anti-tumour activity of some quaternary benzophenantridine alkaloids was tested to determine the structure-activity relationship. It was found likely that the iminium site was involved in the biological activity of these compounds; a high iminium ion concentration (90-98%) in 50% ethanol is correlated with good anti-tumour activity. Sanguinarine and chelerythrine (resp. 3% and 10% iminium ion at pH7 in 50% EtOH) are inactive against P388 and L1210 mouse leukaemia.

Maiti *et al.* (1982): The anti-leukaemic activity of cytotoxic protoberberine alkaloids could be related to the structural conformation of the molecule and its DNA-binding properties. Free calf thymus DNA showed an absorption maximum of 325 nm, whereas bound DNA-sanguinarine showed an absorbtion of 342 nm. These results were evaluated against a control with ethidium (free showed an absorption max of 480 nm, whereas bound ethidium-DNA showed an absorption maximum of 520 nm). The melting points were also documented; they were 68°C and 91°C respectively. The biologic effects of sanguinarine can be attributed to the formation of a complex of sanguinarine with DNA.

Smekal *et al.* (1984), Smekal and Kubova (1984), Faddejeva *et al.* (1984): DNA is intercalated by sanguinarine, the neutral form intercalates partially while cationic form intercalates totally into the DNA double helix. There is a strong interaction with DNA, this indicates (like ethidium) that sanguinarine is involved into the DNA base pairing. Ethidium and sanguinarine are affecting the circular dichroism spectrum of DNA in the same manner.

Smekal *et al.* (1985): Chelerythrine binding differs from sanguinarine which suggests steric-hindrance effects of the substituents on ring D.

Ishii *et al.* (1985): The anti-tumour activity of chemically synthesised and natural non phenolic benzophenanthridine occurring alkaloids was evaluated using sarcoma 180 cell lines. The results showed that the iminium site in the molecule was determinant for the activity against these cells. Chelerythrine was found less active than sanguinarine, when tested *in vitro* against Kb cells and *in vivo* against L1210 and P288 leukaemias. Chelerythrine, used in doses of 3 and 1 mg/kg/5days, gave respectively 26% and 81% tumour growth relative to the control. Sanguinarine used in doses of 10 and 3 mg/kg/5 days gave 1 and 87% tumour growth, respectively (compared with the control).

Vavreckovà *et al.* (1996a and 1996b): *C. majus* anti-proliferative effects were subjected to *in vitro* studies with rapidly multiplying human keratinocyte cell lines (HaCaT cells). A dry extract (0.68% alkaloids calculated as chelidonine) inhibited HaCaT cell growth with an IC_{50} value of 1.9 µmol/l. Sanguinarine, chelerythrine and chelidonine respectively gave IC_{50} values of 0.2; 3.2 and 3.3 µmol/l. The potency of sanguinarine was similar to that of the anti-psoriatic agent anthralin ($IC_{50} = 0.7$

µmol/l), whereas berberine showed a low potency (IC$_{50}$ = 30 µmol/l). Further investigation, by following lactate dehydrogenase release in the culture, showed more evidence for the cytostatic activity than for the cytotoxic activity.

Song *et al.* (2002): A polysaccharide fraction from a water extract inhibited the proliferation of several tumour cell lines *in vitro*. A 100 µg/ml fraction showed over 50% cytotoxicity for the P815 and B16F10 cell lines.

Anti-spasmodic activity

Kardos *et al.* (1986): Protopine, cryptopine and allocryptopine enhance [^3H]-GABA binding to rat brain synaptic membrane receptors, in comparison with diazepam binding. The following table gives the concentrations and % enhancement of the GABA binding. The effect of diazepam is more significant than the effect of the protopine alkaloids, indicating that the enhancement of GABA binding and binding to benzodiazepine receptor may be independent phenomena.

Table 3. Effect of diazepam and protopine alkaloids on ^{3}H-GABA binding (Kardos *et al.* 1986).

Conc (µmol/L)	% of control			
	Diazepam	Protopine	Cryptopine	Allocryptopine
0.01	1%	/	/	/
0.1	5%	0%	0%	0%
1	14%	7%	5%	10%
10	39%	31%	24%	30%
100	46%	/	/	/

Boegge *et al.* (1996): An aqueous-methanolic extract of the flowering aerial parts of *C. majus* and the isolated constituents coptisine and (+)-caffeoylmalic acid have been evaluated for their anti-spasmodic activity. *In vitro* tests involving isolated rat ileum was used. The extract contained 0.81% alkaloids, 2.00% flavonoids, 1.20% hydroxycinnamic acid derivates and 0.06% (+)-caffeoylmalic acid. The extract showed anti-spasmodic activity of 12.7% (SEM= 4.0) in comparison to the control group (Ach). Coptisine (at concentration of 1.0x10^{-5} g/ml organ bath) and (+)-caffeoylmalic acid (at concentration of 2.5x10^{-5} g/ml) were found to be the two constituents that contributed to the total anti-spasmodic activity of the extract. They exerted a mean anti-spasmodic activity of 16.5% (SEM= 3.0) and 6.9% (SEM= 2.6) at these concentrations respectively. A lower concentration of coptisine (0.5x10^{-5} g/ml organ bath) did not exhibit any statistically anti-spasmodic activity.

Häberlein *et al.* (1996): *In vitro* tests demonstrated effects of an extract of *C. majus* herb and certain constituent alkaloids at GABA$_A$ receptors. Radio receptor assays were evaluated with high concentrations of a dry ethanolic extract of the herb, which inhibited 50% of specific [^3H]-muscimol binding. At lower concentrations, specific binding of 115% indicated induction of positive co-operation. The alkaloid content (mg/100mg dry extract) of the extract was determined allocryptopine 0.076, chelerythrine 0.009, protopine 0.465, sanguinarine 0.003 and stylopine 0.154. Further studies showed that allocryptine, stylopine and protopine are responsible for the positive cooperative effect, mainly contributed by protopine. Concentrations of chelerythrine and sanguinarine were considered to be too low to contribute.

Hiller *et al.* (1998): Two hydro alcoholic (ethanol 70% w/w) extracts of *C. majus* (at concentration of $5x10^{-4}$ g/ml organ bath) relaxed isolated guinea-pig ileums which had been contracted using barium-chloride. The alkaloid content of both extracts was determined (by HPLC) as containing chelidonine (0.38%), protopine (0.41%) and coptisine (0.32%); the second extract contained 0.59%, 0.48% and 0.26% respectively. Individual constituents were also tested and the mean percent of relaxation was 68.8% and 54.8% for chelidonine and protopine, both at concentrations of $1x10^{-5}$ g/ml organ bath. Coptisine, up to a concentration of $3x10^{-5}$ g/ml organ bath, showed no significant relaxation. Further experiments using these two active substances together and individually produced a concentration-dependent reduction of carbachol and electric-field-induced contractions. These results indicate that the anti-spasmodic effects of the herb comprise both musculotropic and neurotropic mechanisms.

Reports on prokinetic effects of a combined preparation (Iberogast) and its components:

- Schemann *et al.* (2006): Stomach smooth muscle preparations, incubated in 24 to 188 µg/ml of a dried *Chelidonium majus* fluid extract (1:2.5-3.5, extraction solvent 30% ethanol) showed a dose-dependent increase of tonic (corpus, fundus) resp. phasic (antrum) contractions, pointing to a prokinetic effect in the stomach.

- Sibaev *et al.* (2006): *Chelidonium majus* fluid extract (1:2.5-3.5), 2 ml/100 ml, significantly increased resting membrane potential and frequency and amplitude of myoelectrical slow waves of the smooth muscle of mouse colon.

Choleretic activity

Vahlensieck *et al*. (1995): Total ethanolic (70% EtOH) extract (total alkaloid content 1.6%, caffeic acid esters 1.9%), the phenolic and alkaloid fraction of *C. majus* herb were evaluated for their choleretic activity using isolated perfused rat livers. Choleresis was induced by the total extract (concentration of 10 mg/ml/minute). There was a significantly increased bile flow, and after 40 min the amount of bile was doubled as compared to the pre-treatment value. The two other fractions showed a slight increase of the bile flow, but it was not significant. Even when used together, they gave an increase of 20% over pre-treatment value, which was not significant.

Anti-inflammatory effect

Chung *et al.* (2004): Effects related to an anti-inflammatory activity have been evaluated for *C. majus* water extracts and for some alkaloids (specific plant parts not reported). The yield of the decoction was approximately 9%. Mouse peritoneal macrophages were used *in vitro*, and nitric oxide production levels showed a significant increase when these cells were incubated with water extracts of the herb at different concentrations (0.01; 0.1; 1 mg/ml) together with recombinant murine interferon-gamma. This was compared to the treatment with recombinant murine interferon-gamma only. The increased NO levels indicate that there is a cooperative induction of NO production. The increased NO levels were progressively inhibited by incubation with increasing levels of N-monomethyl-L-arginine and by addition of the anti-oxidant compound pyrrolidine dithiocarbamate (PDTC) (concentration: 100µM). Furthermore, incubation of mouse peritoneal macrophages induced by *C. majus* extract plus rIFN-gamma increased tumour-necrosis-factor-alpha (TNF-a) production in a concentration dependent manner. When nuclear factor kappa B inhibitor PDTC was added, there was a significant decrease in production of TNF-a, so *C. majus* extract increases TNF-a production via NF-kB activation.

Vavrecková *et al.* (1996a): The alkaloids sanguinarine and chelerythrine, and a total extract of the herb showed inhibition of 5-lipoxygenase (5-LO) in isolated bovine polymorphonuclear leukocytes

(PMNL) with IC_{50} values of 0.4; 0.8 and 1.9 µmol/L respectively. Sanguinarine and chelerythrine also inhibited 12-LO (from mouse epidermis; IC_{50} values 13 and 33 µmol/l respectively), whereas *C. majus* extract was inactive at a concentration of 170 µg extract/ml test solution. Chelidonine was also tested, but did not show any activity against 5-LO (IC_{50} = >100 µmol/l).

Vasopressin effect

Granger *et al.* (1992): Chelerythrine and sanguinarine exhibited affinity for rat liver vasopressin V_1-receptors. [^3H]-vasopressin was inhibited by those two alkaloids within the micromolar range (K_i, inhibition constant, $4x10^{-6}$M and $7x10^{-6}$M respectively). The interaction on the V_1-receptor is based on the position of the alkoxy group and the quaternary ammonium function.

Immunomodulatory activity

Song *et al.* (2002): Polysaccharide fractions of a water extract of *C. majus* were incubated for five days with spleen cells. Results showed an increase in the lytic activity of spleen lymphocytes to Yac-1 tumour cells from 0.9% to 30.0% and 34.2% for the fractions CM-Al and CM-Ala respectively. The optimal concentration for generation of activated T_c-cells was 5 µg/ml for both fractions. The second test, now with mouse peritoneal macrophages cultured with CM-Ala (10-100µg/ml), gave also an increase in cytotoxicity, compared with the control test. The results were determined by the uptake of radio-labelled thymidine by the tumour cells.

Analgesic activity

Kim *et al.* (2001): The analgesic activity was investigated by testing a receptor activity for GABA receptors. An aqueous extract of *C. majus* (no details specified) was used in patch-clamp experiments using fresh periaqueductal grey (PAG) neurons isolated from rats. The extract was applied every 2 minutes at concentrations of over 0.3-10 mg/ml and elicited chloride ion current in a concentration-dependent manner. Bicuculline, a $GABA_A$ antagonist, reversibly inhibited this effect. Further tests showed the same results with lower concentrations of *Chelidonii herba* (0.03 and 0.1 mg/ml).

Shin (2002): These tests have demonstrated that low concentrations (0.03 and 0.1 mg/ml) of a aqueous extract of *Chelidonii herba* (no details specified) suppress glycine-activated and increase glutamate-activated ion current in PAG (periaqueductal gray) rat neurons.

Receptor binding activity

Simmen *et al.* (2006) measured the IC50 values for the binding of a *Chelidonium majus* fluid extract (1:2.5-3.5) to rat intestinal 5-HT3, 5-HT4 and Muscarine M3-receptors using dilutions of 1:1,000, > 1:10,000 and 1:3,500. In a human recombinant 5-HT4 receptor IC50 was 1:350. These receptors are involved in the aetiology of functional gastrointestinal diseases.

In vivo studies

Anti-viral activity

Lozyuk (1977): In influenza-virus-induced pneumonia mice, the total alkaloid extraction was injected. Total alkaloids given were therapeutically effective when the quantity of virus injected in the mice was low.

Anti-microbial activity

Zhu and Ahrens (1982), Pitea and Marginanu (1972): Berberine has been successfully used to control the intestinal secretions enhanced by *E. coli* enterotoxin. Berberine has positive influence because of the quaternary ammonium group.

Anti-inflammatory activity

Lenfeld *et al.* (1981): Anti-inflammatory activity was screened for sanguinarine, chelerythrine and a quaternary benzophenanthridine fraction in assays involving carrageenan-induced rat paw oedema. Sanguinarine (5 mg/kg body weight, applied subcutaneously) showed the highest anti-phlogistic activity, chelerythrine (10 mg/kg body weight) was found less active, in comparison to control, what may be explained by the different oxygen electro-donating group.

Anti-tumour effect

Sokoloff (1968): Chelidonine and protopine were tested for an anti-tumour therapy in the treatment of sarcoma 180 and Erlich carcinoma. The total dose of 50 µg/kg body weight of the mouse chelidonine administered over 7 days showed an insignificant tumour inhibition (respectively 25% and 22% with mild cytotoxicity). Total dose of 350 µg/kg of protopine administered intraperitoneally in 7 days exerted only a mild tumour inhibition (respectively 15% and 26%).

Kim *et al.* (1969): An ethanol-water (1:1) dry extract of *C. majus* roots and rhizomes was inactive in animal models of leukaemia (L-1210 mice) and carcinosarcoma (Walker 256 rats). In contrary, the extract had cytotoxic activity in an assay utilising Eagle's 9KB carcinoma of the nasopharynx ($ED_{50}<15$ µg/ml). Coptisine and another alkaloid (name not cited) also displayed a cytotoxic activity.

Kim *et al.* (1997): N-methyl-N'-nitro-N-nitrosoguanidine (MNNG, 200 mg/kg body weight), a carcinogenic agent was given to rats together with a saturated sodium chloride solution or a 0.9% saline, for three weeks. A water methanol extract of *C. majus* (0.1% or 0.2% in the diet for 16 weeks) or no further treatment was combined; the rats were killed after 20 weeks. Pepsinogen-1-altered glands (PPAGs) in the pyloric mucosa of the stomach occurred in all groups of rats, but the mean number of PPAGs was significantly lower in animals treated with 0.1% *C. majus* herb extract, compared with MNNG and saturated sodium chloride alone. However, the results did not show a significant difference in rats with a 0.2% *C. majus* extract. There were also no significant differences between the groups in the number of animals with papilloma and squamous cell carcinoma lesions of the fore stomach.

Immunomodulatory activity

Song *et al.* (2003): The protein bound polysaccharide, CMAla, isolated from a water extract of *C. majus*, was given to mice (50 mg/kg) intraperitoneally 24 hours before sub-lethal doses of irradiation. Results showed a significant increase in platelet numbers in mice treated with *C. majus* extract (evaluation: 5 days post radiation). The white blood cells were also significantly increased in CM-Ala treated mice, compared to the control (9 days post radiation). This indicates a haematopoietic recovery. In other experiments, mice were radiated with lethal doses of irradiation (9Gy), the survival rate for mice treated with CM-Ala (50 or 100 mg/kg) was 80% at 30 days post-irradiation, whereas all mice in the control group were dead after 15 days.

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

Only few studies have been conducted on the pharmacokinetics of *Chelidonium* alkaloids.

Sanguinarine and chelerythrine

In a study with adult rats, a single dose of sanguinarine (10 mg/kg body weight) in 1 ml water was administered orally. Dihydrosanguinarine was identified as a sanguinarine metabolite in the plasma and liver, and significantly higher levels of dihydrosanguinarine were found compared to levels of sanguinarine. Sanguinarine and dihydrosanguinarine were not detected in the urine (Psotova *et al.* 2006).

Sanguinarine (6,403 mg/kg body weight) and chelerythrine (2,199 mg/kg body weight) were applied via the feed to rats for 109 days.

Table 4. Concentrations of sanguinarine (Psotova *et al.* 2006).

Sample	sanguinarine (µg/g)	chelerythrine (µg/g)
Diet	42.4	34.9
Feces	138.5	86.0
Plasma	0.008	n.d.
Liver	0.083	0.024
Kidney	0.004	0.009
Muscle	0.004	n.d.
Myocardium	0.005	n.d.

The limit of detection/quantification was 0.003/0.004 µg/g

Liver concentrations were more than a factor of 3 below the concentration of 1 µM (0.330/0.348 µg/g) not being toxic in human liver cells *in vitro*. It was evidenced that 2% of benzoquinoline alkaloids were absorbed through the gastro-intestinal tract while 98% were excreted in the faeces (Psotova *et al.* 2006).

Extrapolation from Psotova *et al.* (2006):

- Starting from absorption of alkaloids of 2%;
- The rats received a daily dose of 8.6 mg/kg, which puts the human equivalent (70 kg bodyweight) on 602 mg alkaloids;
- The concentration in rat liver reached 0.107 µg/g ≈ 1/3 of the toxic threshold;
- If a person takes daily 6 x 2 g *Chelidonium majus* powder equivalent with a minimal concentration of 0.6% of total alkaloids, a total of 72 mg alkaloids is ingested. As compared to the amount ingested by the experimental rats, this is a 8.36 x lower dose with which a concentration in the liver was reached more than a factor 3 below the non toxic level in human liver cells;
- This leads to an extrapolated concentration 25 x lower (3 x 8.36) than the no effect level.

Kosina *et al.* (2004) applied 5 mg/kg body weight of an alkaloid fraction, corresponding to 3.2 mg/kg sanguinarine and 1.1 mg/kg chelerythrine, to pigs for 90 days. Concentrations of sanguinarine/chelerythrine were determined in muscle (below limit of detection), plasma (traces), liver (0.019/0.010 µg/g) and gingiva (0.079/0.048 µg/g) as well as in the faeces (0.990/1.730 µg/g). The values in the liver are more than 10 times lower the concentrations of 1 µM (0.330/0.348 µg/g), shown to be non toxic in human hepatoma cells. It can be concluded, that these alkaloids are very poorly absorbed.

According to the monograph of the German Commission E (Blumenthal 1998), the dose of 3.2 mg/kg sanguinarine and 1.1 mg/kg chelerythrine, calculated for an adult human of 70 kg body weight, corresponds to a dose of 224 mg sanguinarine and 77 mg chelerythrine, which is 30-60 fold the alkaloid dose applied with high-dose *Chelidonium majus* preparations. In addition, both these benzo[c]phenanthridine alkaloids have the highest toxic potential, but the lowest content of all alkaloids in *Chelidonium majus* extracts.

Extrapolation from Kosina *et al.* (2004):

- Starting from an absorption of alkaloids of 2%;
- The experimental pigs received a dose of 5 mg/kg, which is a human equivalent (70 kg) of 350 mg total alkaloids;
- A pig liver concentration of 0.029 µg/g was obtained ≈ 1/10 of the no effect threshold;
- If a person takes daily 6x2 g *Chelidonium majus* powder equivalent with a minimal concentration of 0.6% of total alkaloids, a total of 72 mg alkaloids is ingested. As compared to the amount ingested by the experimental pigs, this represents a 4.86 times lower total alkaloid amount ingested daily.
- The liver concentrations expected are 49 times (10 x 4.86) lower than the no effect threshold.

Coptisin

Coptisine was isolated from a traditional Chinese medicine and was administered intravenously at a dose of 10 mg/kg in rats. The plasma-drug concentration time profile can be described as a two compartmental model. Coptisine was quickly eliminated with systemic clearance of 0.08 l/min/kg, which is 147% of the hepatic blood flow (0.055 l/min/kg in rats), suggesting that the alkaloid was quickly cleared via hepatic clearance. The elimination half-life of coptisine was 288 minutes. The volume of distribution (Vd) at terminal phase was 30.07 l/kg. This is greater than total body water at 0.67 l/kg, suggesting that coptisine may be widely distributed into extra vascular systems. However, it should be considered that the oral administration is the normal one, and that the relatively high Vd could be related to the way of administration. The pharmacokinetics of coptisine after the oral administration at a dose of 10 mg/kg can also be described as a two compartmental model. The terminal elimination half-life was 307.8 minutes. The oral bioavailability of coptisine was 7.8% and the time to reach the maximum plasma concentration was 14 minutes. The percentage of coptisine excreted in the urine was 5.16% following an intravenous administration and 0.26% after an oral administration. The significantly lower excretion following oral rather than an intravenous administration showed that coptisine may undergo the first pass effects. This low percentage strongly suggested either a strong first-pass effect or poor absorption (Li *et al.* 2006).

Berberine

The pharmacokinetic assay of berberine was executed on rabbits, using intravenous and intramuscular administration at a dose of 2 mg/kg. The plasma concentration of berberine as function of time can be described as a two compartmental model with a terminal elimination half-life of 5.28 hours, a total plasma clearance of 5.64 l/h and a volume of distribution of 38.30 l. The amount of berberine excreted unchanged into urine was found to be only 4.93 % of the dose given. Berberine was also excreted biliary into the intestine and this may be one of the other major elimination pathways. The biliary excretion of berberine was found to be 0.5 % of the dose given.
Berberine was also given by the intramuscular route. The bioavailability was evaluated by comparison with an intravenous bolus dose of 2 mg/kg. The absolute bioavailability of i.m. administration was 99.77%. After an oral administration, less than 0.1% of a dose is excreted in the urine unchanged in

24 hours. A reason for this finding may be intensive metabolism (elimination), but also poor absorption from the gastro-intestinal tract cannot be excluded (Chen *et al.* 1995; Moffat *et al.* 2004).

Miyazaki *et al.* (1978) administered a dose of 100 mg tritiated berberine orally to human volunteers, with 0.043% of the dose excreted in the urine within 24 h. This result supports the assumption that animal data on alkaloid pharmacokinetics can be transferred to humans.

Alkaloids in general

In summary, all studies documenting organ distribution as well as faecal excretion of *Chelidonium* alkaloids show very high faecal and very low hepatic concentrations, thus clearly showing that despite quick hepatic clearance there is no accumulation in the liver. Urinary excretion is consequently low, as has also been shown in humans. This strongly suggests that a very poor absorption, but not the high first pass effect, is mainly responsible for the low systemic bioavailability.

This view is also supported by the high sensitivity of the alkaloids sanguinarine, chelerythrine and coptisine to nucleophilic attack, shown e.g. by Debiton *et al.* (2003) and Ulrichova *et al.* (2001), which hinder their intestinal absorption. As these publications suggest, metabolic inactivation by conjugation with glutathione also seems to play an important role for the low bioavailability (Schrenk 2011).

Other components

An existing *in vitro* study of the absorption of chelidonic acid, as characteristic component of the extracts, was done by Kelber *et al.* (2006). In this study, the uptake of chelidonic acid by rat small intestinal preparations *in vitro* has been shown, with a linear dependency of the uptake rate from the concentration on the luminal side. Even if the role of chelidonic acid for the clinical efficacy of *Chelidonium* is not known, the study suggests the bioavailability of another component of *Chelidonium*, besides the alkaloids.

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

Single/repeated dose toxicity

In an animal experimental study, the anti-tumour properties of *Chelidonium majus* L. were investigated. It was found that the fresh plant can cause acute toxicity due to the latex. Drying of the plant considerably reduces the toxicity. The use of therapeutic doses is safe due to the low quantity of alkaloids in the plant preparations. Large doses can irritate the gastro-intestinal tract. An excessive use for long periods should be avoided because of the risk of hepatotoxic effects, including severe hepatitis, severe cholestasis and fibrosis. A mechanism for *C. majus* induced hepatotoxicity has not been established. In the literature, deadly poisonings have been described with children after eating the plant (Hänsel *et al.* 1992).

The LD_{50} in mice was tested and determined as 1300 mg/kg, while in rats it was more than 2000 mg/kg (ESCOP monograph 2003).

Sokoloff *et al.* (1964) describes intraperitoneal application of 350 mg/kg body weight of a methanolic extract in mice resulting in a 20% mortality rate. Studies using the intraperitoneal route of application for herbal extracts are generally of low scientific value, as unspecific effects of non-absorbable components can severely confound the outcome. In addition, they are of no direct use for evaluations of toxicological exposure limits for medicinal products for oral use, as they do not reflect intestinal

absorption and bioavailability. Irrespective of that, the study rather points out to a low toxicity of the extract tested, given a LC_{50} above 350 mg/kg body weight.

Other studies with intraperitoneal application of sanguinarine are reported by Dalvi *et al.* (1985), where increases of liver enzymes in blood of rats 24 hours after intraperitoneal application of 10 mg/kg body weight were described. Ulrichova *et al.* (1996) reported on liver damage 24 hours after intraperitoneal application of a dose of 10 mg/kg body weight in rats, while no histological changes occurred in the liver of rats after intraperitoneal treatment with 0.2 mg/kg body weight over 14, 28, 42 or 56 days.

Mheddhbi (2002) performed a 4-week toxicity study by oral route (gavage) in rats.
The oral toxicity of repeated doses of *Chelidonium majus* extract (mother tincture according to HAB, containing 0.147% total alkaloids, calculated as chelidonine) over 4 weeks was determined in 20 rats per group (10 males and 10 females) under GLP conditions and according to EU recommendations. Daily doses of 0, 730, 1270 and 1820 mg/kg body weight were applied solubilised in 70% ethanol. 2 ml/kg of the solution (70% ethanol) were applied. The control group received 70% ethanol under the same conditions. Clinical signs, mortality, body weight and food consumption were recorded during the study. After necropsy, haematology, blood chemistry (including complete liver function parameters) and urine analysis were performed. In controls and the high dose group, ophthalmological examinations were performed at the beginning and the end of the study. The main organs were studied histologically. No test-related mortalities or changes of any other parameters studied, including liver, were observed.

The NOEL of *Chelidonium* fluid extract is the highest administered dose, 1820 mg/kg body weight/day, corresponding to 2.68 mg/kg body weight total alkaloids.

Table 5. (Mheddhbi 2002).

	Species: SD rats		Route: oral gavage	
	Period: 4 weeks; Schedule: 7 days/7			
	Control	Gr. 1	Gr. 2	Gr. 3
No of animals/sex	10	10	10	10
Daily dose of extract (mg/kg)	0	730	1270	1820
Daily dose of total alkaloids (mg/kg)	0	1.07	1.87	2.68
Deaths	7*	0	2*	0
Symptoms	No treatment related symptoms			
Body weight	No dose-related effects			
Food consumption	No dose-related effects			
Clinical chemistry	No abnormal values, no dose-related effects			
Ophthalmoscopy	No changes			
Anatomy/Pathology	No histopathological findings, including the liver			

*Attributed to the regurgitation of the test item or the vehicle (ethanol 70%)

Mazzanti *et al.* (2009) tested hepatotoxicity of *Chelidonium majus* in Wistar rats, in a 4 weeks feeding experiment. The authors tested the same batch used by one of the two patients for whom a hepatotoxic reaction was reported by the Italian Surveillance System. As a result, the study suggested that *Chelidonium majus*, at doses about 50 and 100 times higher than those generally used in human, does not alter the hepatic function. The results excluded the possibility of cellular hepatic toxicity, cholestasis, inflammation, or other hepato-biliary disease that could affect liver functions. High doses of Greater Celandine led to a reduction of GSH levels and SOD activity which is indicative of a dose-

dependency. In adverse drug reactions involving overdoses, such an effect is simply an extension of the pharmacological effect, and not an effect of idiosyncratic drug reaction.

Genotoxicity

Sanguinarine was shown to induce DNA damage in mouse bone marrow cells (Ansari *et al*. 2006). *In vitro* DNA adducts formation with sanguinarine and chelerythrine in the presence of rat hepatic microsomes has been described (Stiborova *et al.* 2002). Sanguinarine elicited weak positive responses in the *Salmonella* mutagenicity test after metabolic activation (Frankos *et al*. 1990).

Genotoxicity *in vivo* of *Macleaya cordata* (Willd.) R.Br. (*Papaveraceae*) was tested. The plant species contains sanguinarine. An isoquinoline mixture made from the plant was given to rats (5,330 or 660 ppm isoquinoline alkaloids), mixed with the food. DNA adducts formation in liver was analysed. No DNA damage was seen to rat lymphocytes or hepatocytes after 90 days administration (Stiborova *et al.* 2008).

In the study by Kosina *et al.* (2004) in pigs, 3.2 mg/kg sanguinarine and 1.1 mg/kg chelerythrine were applied over 90 days. No DNA adducts were observed.

The same applies to the study by Psotova *et al.* (2006) that found that sanguinarine (6,403 mg/kg body weight) and chelerythrine (2,199 mg/kg body weight) applied via the feed to rats for 109 days did not cause DNA damage.

Haddouk (2001) performed a bacterial reverse mutation test (Ames-Test). *Chelidonium majus* extract (mother tincture according to the German Homeopathic Pharmacopoeia (HAB), extraction solvent ethanol 70%, containing 0.147% total alkaloids, calculated as chelidonine) was tested according to all current regulations in five strains of *Salmonella typhimurium*, in two independent experiments according to the preincubation method, using metabolic activation with S9-mix. Concentrations were between 312.5 and 5,000 µg/plate, and no precipitate being observed. Adequate positive controls were used. No relevant increases of numbers of revertants occurred with the test substance. The *Chelidonium* extract tested had no mutagenic properties in this test.

Cytotoxicity

This study tested the cytotoxicity of sanguinarine and chelerythrine on human hepatoma cells. Concentrations of 0.01, 0.1, 1µM were found not to be cytotoxic. It was also shown that these benzophenanthridine alkaloids do not interfere with the expression of the important P450 enzyme, CYP1A1 and that they do not affect the AhR (Aryl hydrocarbon receptor) transcriptional activity in human hepatoma cells. Chelidonine did not show a significant cytotoxicity or DNA damage (Zdarilova *et al*. 2006; Dvorak 2005; Kaminskyy *et al*. 2007).
Cytotoxicity of chelidonine and protopine were investigated and cytotoxic activity was not observed for alcoholic and water extracts (Saglam *et al*. 2003).

Recently, a hepatotoxic assessment of *Chelidonium* has been executed in primary hepatocyte cultures of different species. The aim was to elucidate the potential hepatotoxicity of *Chelidonium* in human, rat, canine and monkey hepatocyte cultures. For this purpose water-soluble extracts were used. The liquid extract showed a concentration-dependent toxicity in human hepatocytes and at concentrations of 7.5 mg/kg for animal hepatocytes (Runge *et al.* 2009).

The involvement of sanguinarine and chelerythrine was investigated in cell cycle regulation and cell death in various cell lines. Results were mainly published from 1995 to 2006. These alkaloids seemed to be good candidates for chemotherapeutic regimens. They could also contribute to the development of successful immune therapies of some carcinomas due to their apoptotic potential. However, the

complete signalling cascade in which sanguinarne and chelerythrine treatment induces apoptotic cell death is not yet understood (Malikova *et al.* 2006).

Studies undertaken with *Chelidonium* extracts:

- An extract made with 30% (V/V) ethanol and containing 5.9 mg/g total alkaloids displayed a 24 h IC50 on human hepatocytes of 0.83 mg/ml (corresponding to an alkaloid concentration of 4.9 µg/ml) (Adler *et al.* 2006).

- An extract of Chelidonii herba (1.25-3.5, extraction medium 30% ethanol) was tested as native extract (total alkaloids 6.15 mg/g) and with reduced alkaloid content (0.67 mg/g) in human Chang liver cells. For comparison, the respective alkaloid fraction a Ginkgo biloba extract and paracetamol were tested. Test substances were dissolved completely. Vitality was determined by the MTT test, cell integrity by microscopy. EC50 over 24 h for the native extract was 0.96, for the extract with reduced alkaloid content 1.60 (corresponding to alkaloid contents of 5.9 mg/ml and 1.1 µg/ml). Cytotoxicity of the alkaloid fraction was, depending from the mode of dissolution, 86 to 189 µg/ml. EC50 of the Ginkgo biloba extract and paracetamol were 0.31 mg/g and 2.49 mg/ml. The findings proved that Chelidonii herba extract has no special hepatotoxicity, compared to other accepted medicinal products, and its hepatotoxic properties depend from its alkaloid content only to a very limited extent (Pascolo *et al.* 2005).

Carcinogenicity

No data available.

Reproductive and developmental toxicity

The alkaloid sanguinarine potently suppresses angiogenesis by inhibition of the VEGF signalling pathway in the angiogenic process. In this *in vitro* study, cytotoxicity of sanguinarine was observed with a concentration of 500 nM (0.017 µg/ml) sanguinarine. Suppression of angiogenesis by inhibition of VEGF signalling was described in primary pig granulose cells and in porcine endothelial cells (AOC cells) after incubation with 300 nM (0.01 µg/ml) sanguinarine for up to 192 h. Cytotoxicity of sanguinarine in primary pig granulose cells was observed with a concentration of 500 nM (0.017 µg/ml) sanguinarine. Given the low difference between cytotoxic concentrations and concentrations inhibiting parameters of angiogenesis, the specificity of the results and therefore their relevance for reproduction and developmental toxicology is unclear (Basini *et al.* 2007).

Local Tolerance

Contact dermatitis has been reported in a woman who had used *Chelidonium majus* to treat warts. The woman experienced severe itching and erythema with papules at the application site. The reaction resolved within a few days without treatment (Etxenagusia *et al.* 2000).

3.4. *Overall conclusions on non-clinical data*

Pharmacology

Viruses

Total alkaloid extracts of *Chelidonium majus* showed activity against multiple viruses (herpes simplex virus, polio virus, several adenoviruses) *in vitro*. HIV-I virus was found to be less or more sensitive to berberine. There was only one study by Lozyuk (1977), which investigated activity against influenza virus. Results showed an activity in mice, when pneumonia was induced by a low quantity of *influenza*

virus. Protoberberine was found active against reverse-transcriptase enzyme of RNA-tumour viruses, whereas its activity is dependent of the quaternary nitrogen in its structure. Chelidocystatin on its own has proved activity against cysteine proteinases. All these findings report a good indication for anti-viral activity of *C. majus* extracts, but further investigations are necessary, especially *in vivo* trials.

Bacteria

Multi-drug resistant bacteria and MRSA strains were submitted in trials to test their sensitivity for *C. majus* extracts. Two benzophenanthridine alkaloids were found to be responsible for the activity, but neither in vivo nor clinical trials were conducted to date. Total extracts and pure substances (berberine, sanguinarine, chelerythrine and chelidonine) were tested for their anti-microbial activity against many strains (gram positive, gram negative and dermatophytes). Berberine, containing a quaternary nitrogen, showed *in vivo* activity against the enterotoxin production of *E. coli.*

Cancer

Most results of *in vitro* anti-tumour activity trials are pointing towards sanguinarine, chelidonine, chelerythrine and berberine for the anti-tumour effect of *C. majus* extracts. The iminium group in the structure of the molecules is hold responsible for the activity. The strongest anti-tumour agent of *C. majus* was found to be sanguinarine, which intercalates strongly with DNA. The activity is comparable with the anti-psoriatic agent anthralin. Chelerythrine, berberine and chelidonine are also active but are less potent. Nevertheless, *in vivo* trials did not show any significant result for the anti-tumour activity. The results of the *in vitro* tests are very promising but they are not proven in *in vivo* studies. There is a need for additional studies.

Gastro-intestinal

Coptisine, chelidonine and (+)-caffeoylmalic acid (as single components or in combinations) show an anti-spasmodic activity. Studies are indicating that there is a musculotropic and neurotropic effect and also an effect on the GABA receptor. A choleretic activity was also evaluated but did not show any significant results with the total alkaloid extract of *C. majus*. This suggests that all the components of the total extract are necessary for the activity, rather than the alkaloids only. Sanguinarine and chelerythrine extracts also showed a vasopressin receptor activity, inhibiting vasopressin binding to its receptor.

Inflammation

C. majus extract increases TNF-a production via NF-kB activation, so it plays a role in the anti-inflammatory proceses. 5- and 12-lipoxygenase are inhibited by sanguinarine and chelerythrine but not by the total extract or chelidonine. These enzymes are involved in leukotriene B_4 and 12-hydroxyeicosatetraenoic acid synthesis, so they have anti-inflammatory properties. These results were also shown in an *in vivo* study (Lenfeld 1981).

Miscellaneous

A water extract of *C. majus* gave a significant increase in the cytotoxicity of C_T cells in a few *in vitro* studies. *In vivo* trials are showing also a positive immunomodulatory effect, but there are too few studies to draw general conclusions. Analgesic activity was evaluated via the effect on GABA receptors. Results showed an inhibition of GABA chloride currents which indicates an indirect mechanism for analgesic activity. The activity on glycine, an inhibitory neurotransmitter, and glutamate, an excitatory neurotransmitter, suggests also a nociceptive activity.

Pharmacokinetics

Rats, rabbits and pigs were used as species to investigate the pharmacokinetics of *Chelidonium* alkaloids. The main alkaloids in *Chelidonium majus* may be intensively metabolised and/or poorly absorbed. The plasma concentration of the alkaloids as function of time can be described as a two

compartmental model. The high volume of distribution suggests a penetration into the extravascular system.

Tissue concentrations were measured after an oral administration of alkaloid fractions of *Chelidonium*. When experimental data are extrapolated to human conditions, concentrations in liver cells are relatively distant from the no effect levels (rats and pigs).

Up to now, pharmacokinetic data on the components of *Chelidonium majus* are scarce. Sanguinarin, one of the alkaloids studied, is mainly present in the roots of *Chelidonium* but not in the aerial parts. Further investigation on the pharmacokinetics of alkaloids and other components of *Chelidonium majus* is necessary, if possible with preparations clinically used. This would contribute to the plausibility of a safe therapeutic use.

Toxicology

When the dried parts of *Chelidonium* are used in normal dose the toxicity is limited. Severe and irreversible hepatotoxicity can occur after chronic administration of high doses. Further investigation is needed on the mechanisms of action. Four alkaloids, sanguinarine and chelerythrine, chelidonine and protopine were found not to be cytotoxic. The other components of *Chelidonium* need more investigation to make a conclusion on cytotoxicity of *Chelidonium*. A recent study also suggested that human hepatocytes seemed to be more sensitive to *Chelidonium* extracts than canine, rat and monkey hepatocytes. Further evaluation of possible toxicological effects on human hepatocytes is needed. It was found that sanguinarine and chelerythrine can induce DNA damage in rat and mouse cells. One case of contact dermatitis has been reported after topical application suggesting a hypersensitivity to one of the components. In summary, the toxicity of *Chelidonium majus* can be assumed to be low and the plant can be considered as relatively safe to use. Nevertheless, further investigation is needed to exclude some toxic effects when the substance is used under normal administration and conditions of use.

4. Clinical Data

4.1. Clinical Pharmacology

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

There are no intentional pharmacodynamic studies undertaken.

Assessor's overall conclusions on pharmacodynamics

No studies available.

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

No data available on humans.

Assessor's overall conclusions on pharmacokinetics

Not applicable.

4.2. Clinical Efficacy

4.2.1. Dose response studies

No dose-finding studies available.

4.2.2. Clinical studies (case studies and clinical trials)

Boulwere *et al.* (1985): The *C. majus* alkaloids sanguinarine and chelerythrine were found effective in the control of the production of bacterial sulphur compounds responsible for a halithosis. Subjects (five females, two males, average age 34 years old) were asked to use an oral rinse (15 ml rinse for 15 seconds each day at 9 am). Saliva samples were taken at 8:15 am and one hour after application. The subjects could not use any products like coffee, tea or could not have any morning mouth hygiene. Saliva samples were then worked on and incubated. The reduction of thiols available to react with reagents was evaluated for the different substances. Results are summarised in the following table.

Table 6. Percent reduction of measurable volatile sulphur compounds from fermenting saliva by four commercial mouth rinses (Boulwere *et al.* 1985).

Substance	Concentration	% of thiol reduction
Sanguinarine extract + ZnCl	0.030% / 0.20%	65.4%
ZnCl	0.22%	44.5%
Cetylpyridinium chloride + Domiphen Bromide	0.045% / 0.005%	43.9%
Essential oils	16.4 mM	15.6%

Thus, rinses capable of lowering populations of anaerobic bacteria, who produce volatile sulphur compounds or those which are capable of covalently trapping sulphur, can be used to reduce bad breath compounds.

Southard *et al.* (1987): Benzophenanthridine alkaloids are used in the treatment of periodontal disease and they are integrated into toothpastes and mouth rinses. The subjects (five females, eight males, average age 29 years old) received a test irrigation fluid containing 22.5 μg/ml and 90 μg/ml or an oral rinse solution with a concentration of 0.03% or placebo. The subjects used the solutions twice daily for 14 days, without any other oral hygiene preparation. After day 4, 7 and 14, plaque and gingivitis score was evaluated in comparison with day 0. After this first period, the subjects did a cross-over with the other test solution after a two week resting period that included optimal oral hygiene. Results are aligned in the following table, containing the kind of used preparation and the plaque and gingivitis score.

Table 7. Preparations in order to the concentration and the plaque and gingivitis score (Southard *et al.* 1987).

		Plaque score				Gingivitis score			
		Day 0	Day 4	Day 7	Day 14	Day 0	Day 4	Day 7	Day 14
oral rinse	0.03%	0	0.37	0.53	0.74	0.17	0.33	0.47	0.79
	PLACEBO	0	0.68	1.00	1.28	0.17	0.65	0.95	1.48
supragingival irrigation	22.5μg/ml	0	0.37	0.56	0.83	0.4	0.34	0.42	0.67
	90μg/ml	0	0.29	0.33	0.55	0.4	0.25	0.26	0.37

Ritter *et al.* (1993): Tablets containing *C. majus* extract (containing 66.0 to 167.2 mg native dry extract, equivalent to 4 mg total alkaloids, calculated as chelidonine) or placebo pills were evaluated in a randomised, double-blind, placebo-controlled trial in 60 patients with functional epigastric complaints. The patients received two tablets, three times daily for six weeks (yielding 24 mg total alkaloids). The reduction in symptom score, assessed using the Zerssen list, at the end of the trial was evaluated and was significantly greater in the *C. majus* group, compared with the placebo group (p=0.003). The physician's assessment of efficacy was that 18/30 patients in the treatment group improved or were symptom free, compared with 8/30 in the placebo group.

Under verum treatment, adverse drug reactions (restlessness or sleeplessness 4x; dryness of the mouth 3x) were reported for 3 patients and, in the placebo group, for 5 patients (sleeplessness 1x; urticaria or eczema 3x; somnolence 3x).

Niederau & Göpfert (1999) studied the action of capsules containing dry extract of celandine and curcuma rootstock on upper abdominal complaints. One capsule contains 45 mg dry extract from curcuma rootstock and 131-104 mg dry extract from celandine standardised to 4 mg total alkaloids calculated as chelidonin.

76 patients (61 female and 15 male, 39 verum and 37 placebo) were recruited in a total of 8 practices. Those patient who showed organic diseases of the bile duct system, pancreas or of other upper abdominal organs were excluded. Further exclusion criteria were cholestasia (bilirubin > 2.5 mg/dl), severe gall colic at the time of admission, condition after cholecystectomy, vagotomy and stomach resection as well as disorders of kidney function, leukopenia and thrombopenia. Furthermore, patients with classical symptoms of an irritable bowel syndrome including flatulence, stool irregularities and abdominal pains at several locations were not admitted to the clinical trial. The patients with these relevant diagnoses were excluded by means of comprehensive clinical, chemical laboratory, sonographic and radiological diagnostic procedures. Another reason for exclusion was application of therapeutic agents for bile ducts and spasmolytics.

The intervention was made as a prospective, randomised, placebo-controlled, double-blind pilot clinical trial. Patients were randomly assigned to treatment groups in blocks of 4 patients. They were treated as outpatients with a capsule three times daily over a period of 3 weeks with interim examinations after 1 or 2 weeks.

The main outcome variable "frequency of cramp-like and dull upper abdominal complaints" was determined prospectively and evaluated by means of a visual analogue scale (VAS, 0 to 100 mm) by daily questioning and monitoring in a diary. Secondary variables were: intensity of the subjective symptom "pain"; assessment of the frequency and intensity of accompanying variables of the upper abdominal complaints; postprandial feelings of pressure and fullness, meal intolerance, nausea, vomiting, flatulence; laboratory variables and adverse events. The reduction of the symptoms (per day) at the end of the first week as well as after 2 and 3 weeks was evaluated in comparison to placebo as the therapeutic effect for all variables. The difference between the data of the first two diary days (mean) and those at days 6 and 7 (after week 1), at days 8-14 (after week 2) or at day 15-21 (after week 3) was determined. The parameters were analysed with the two-sided U test of Wilcoxon, Mann and Whitney for independent random samples. All p-values were interpreted descriptively in accordance with the character of the clinical trial. All adverse events and pathological changes in the laboratory variables bilirubin, creatinine, glucose, calcium, sodium, total protein, albumin, protein electrophoresis, ALT, AST, alkaline phosphatase, *gamma*-GT, cholinesterase, ESR, haemoglobin, haematocrit, erythrocyte, leukocyte and thrombocyte numbers as well as the Quick value were documented both before and after the therapy.

All the patients could be included in the tolerability evaluation, 73 in the efficacy evaluation (excluded: 1 verum and 2 placebo patients, 2 due to revocation of consent and 1 because of a tumour, all without medication). Neither the demographic data nor the findings of the anamnesis and basic examinations showed differences between the treatment groups. A marked reduction in the frequency of cramp-like

and dull upper abdominal complaints was observed in comparison to placebo even after one week. The maximum was attained in the verum group even after one week whereas the reduction under placebo treatment still continued in weeks 2 and 3. With regard to the primary outcome, the difference to placebo was small to moderate (p|x > y = 0.62; no confidence intervals given) in terms of cramp-like pain (p = 0.069). Secondary outcomes were more outspoken: dull upper abdominal complaints (p|x > y = 0.67; p = 0.009); combined pain parameters (p|x > y = 0.67; p = 0.011). The intensity of the complaints comparably decreased in the two treatment groups. A small to moderate difference was found in favour of verum for the parameters "dull upper abdominal complaints" (p = 0.20) and "feelings of pressure and fullness" (p = 0.21) (p|x > y = 0.59). All other secondary variables showed similar courses for the two groups.

No patient in the verum group showed adverse events, however, in the placebo group 4 adverse events (nausea, retching, stomach pains, and colic in the left lower abdomen) with 3 patients occurred. The changes in vital parameters lay in the range of normal variation and were comparable for both groups. Changes in single laboratory values were clinically not relevant and gave no indication of a connection with the two therapies.

A series of clinical studies presented below has been conducted with a product called Panchelidon® either in form of drops or capsules. The information on the composition of this product is insufficient and inconsistent (e.g. containing fresh plant extract with '20 mg%' *Chelidonium* alkaloid, daily dose: 0.2 to 0.3 mg *Chelidonium* alkaloid; extraction solvent not specified) and therefore the brand name instead of the correct herbal preparation has been used in the following.

Neuman-Mangold (1977) performed an open clinical trial with 77 patients (45 women and 32 men, average age 47.1 years). They suffered from diseases of the bile ducts and gall stone complaints. The patients were treated differently: cholangitis (A, 15 Panchelidon® vs. 10), cholelithiasis (B, 25 vs. 15) and dyskinesia (C, 12): 3 times daily with 20-30 drops of Panchelidon® in comparison to commonly available synthetic spasmolytics with analgesic admixture (the numbers in brackets give the patient distribution in the groups). The duration of the treatment was adapted to the therapy success; on average 50 days in Group A and 43 and 52 days in the Groups B and C, respectively. The comparative therapy was not specified.

The investigation parameters encompass both subjective complaints (long-term pain; pain attacks, feeling of fullness; obstipation or diarrhoea, meal intolerance) as well as investigation findings of the physician (pressure pain, muscular defence, meteorism, liver palpation finding and icterus) and laboratory findings (blood sedimentation, urobilinogenuria and transaminases in selected cases). In Groups A and B, 9 out of 12 possible positive changes of the findings were evaluated as "very good", 6 to 8 as a "good" result and 4 to 5 represented an "improved" state. The condition was regarded as "uninfluenced" with 3 and less. In the Group C, the laboratory parameters were not applicable for determination of improvement of the condition. The improvement was rated as "very good" by 7 and more than 8, as "good" by 5 to 6, "improved" by 3 to 4 and as uninfluenced by 2.

Panchelidon® was found to be effective in the treatment Groups A and B, however, less for dyskinesia of Group C. 4 Patients showed an improved state in the Group A, the treatment success was good in 8 and very good in 3. No case remained uninfluenced. The transaminases improved in 10 of the investigated patients, 7 of whom however were under anti-biotic therapy. The SGOT activity in these patients sank from an average of 15.3 to 9.4 and the SGPT from 18.4 to 9.3 I.U. In the Group B, 3 patients had to undergo an operation in spite of improvement. The improvement was slight in the case of 5 patients, clear in 3, good in 10 and very good in 7. An anti-biotic therapy was carried out in 4 cases. Determination of transaminases was carried out in a further 12 patients. The SGOT activity sank on average from 13.1 to 8.5 and that of SGPT from 14.9 to 9.2 I.U.

The possible side effects of a spasmolytic were carefully observed and Panchelidon® was found to be

indifferent regarding blood pressure. No further decrease was found even among constitutional hypotonic patients. The blood picture remained unchanged and the general tolerability was good. The author concludes regarding the positive transaminase change: "as little as this permits us to assume an improvement in liver function by the preferred spasmolytic activity of the *Chelidonium* extract, it can be certainly ruled out that the metabolism of Panchelidon® does not burden the liver".

Ardjah (1991) carried out an open clinical trial with 236 patients with varying upper abdominal symptoms such as, pain, pressure and feeling of fullness or digestive disorders due to dysfunction or hindrance of flow in the area of the gall bladder and bile ducts. Patients with clinical – sonographic – radiological assured diagnosis were admitted to the clinical trial in the course of almost 3 years of control and supervision. The patients' population consisted of 155 women (19 to 88 years) and 81 men (32 to 84 years). 49 (38 women, 11 men) of these suffered from cholelithiasis, 37 (25 vs. 12) from complaints due to a cholecystitis-cholangitis without evidence of concrement, 44 (32 vs. 12) from a postcholecystectomy syndrome, 64 (43 vs. 21) from dyspeptic complaints due to gall bladder dyskinesia, 6 patients (4 vs. 2) from an upper abdominal syndrome with disorders of digestion on the basis of a double gall bladder, 7 (2 vs. 5) from a porcelain gall bladder with upper abdominal syndromes and digestion disorders, 7 (5 vs. 2) from functional upper abdominal complaints due to septum formation of the gall bladder with gall bladder dyskinesia, 21 (6 vs. 15) from various digestion disorders such as diarrhoea, obstipation, meteorism, upper abdominal pain with the anamnesis of alcohol toxic liver parenchyma damage. An enlarged gall bladder was found by sonography in the latter with wall thickening and occasionally an extension or thickening of extrahepatic and intrahepatic bile ducts. The classification of the complaints was made by means of three degrees of severity as described in the following: severity grade 3: anamnestic gall colic, pain in the right upper abdomen with at least 2 other symptoms such as feeling of fullness, obstipation, diarrhoea, meteorism and sonographic or chemical laboratory finding; severity grade 2: no anamnestic gall colic but enduring pain or pressure in the right upper abdomen, otherwise like grade 3; severity grade 1: neither anamnestic gall colic nor pain in the right upper abdomen. Meteorism, feeling of fullness, obstipation or diarrhoea were the most mentioned complaints (1 or more symptoms). Patients were treated 2 to 3 times daily with a capsule or 3 times 20 drops of Panchelidon® (alkaloid content approximately 0.20 mg C*helidonium* alkaloids per daily dose). A smaller group of 30 patients were treated under the same conditions with a cholinergic and spasmolytic (no further specifications).

A total of 106 patients were treated with Panchelidon®; 80 received a capsule 3 times daily and 26 received 20 to 30 drops 3 times daily. 21 patients with alcohol toxic liver received capsules. The patients suffering from cholelithiasis were divided into 2 groups (with and without colic) and treated either with Panchelidon® or in the case of 20 patients with a cholinergic plus spasmolytic (one capsule 3 times daily). A further 10 patients of the comparative treatment involved patients with a postcholecystectomy syndrome and were compared with 34 Panchelidon® patients. They were observed over a period of 6 months with examinations at the beginning, during the investigation and at the end. Finally, the patients could be divided into 2 groups with 206 Panchelidon® patients and 30 patients (20 cholecystolitiasis, 9 with and 11 without colic and 10 patients with postcholecystectomy syndrome and dyspeptic complaints) who were treated with a spasmolytic and cholinergic.

The therapeutic effectiveness was measured in terms of improvement to disappearance of the subjective parameters of the change of the colic-free intervals to freedom from colic and improvement of meal intolerance. The findings were rendered objective by sonographic investigations (signs of blockage in the gall bladder and bile ducts, removal of the veiling, thickening and tendency to deposition).

Cholinergic and spasmolytic effects were evaluated by means of improvement of subjective parameters such as upper abdominal complaints with periodic or lasting pain, feeling of fullness and digestive disorders based on a classification involving three degrees of severity as well as objectively considered

by means of sonographic findings and laboratory values.

In addition, laboratory parameters such as ESR, *gamma*-GT, bilirubin and cholesterol were determined. The emphasis of the evaluation with patients suffering from cholecystolithiasis was the spasmolytic analgesic action. The patients were questioned regarding their constant or intermittent attacks of pain, their nature and intensity, their dependence on eating food before and after therapy with Panchelidon®. The frequency of colics before, during and after therapy was of particular importance here. In the case of patients with postcholecystectomy, 29 out of 35 patients showed a clear improvement of the complaints after 3-6 days up to complete remission in the course of the following weeks. They continued the long-term therapy with 1 capsule twice daily. The remaining patients continued the therapy in spite of only a slight improvement. The effects in the control group were comparable.

In the case of patients with cholecystolithiasis, 7 out of 10 were free of colic after 6 months of therapy and 3 had mild attacks of upper abdominal pain, twice in 6 months. Out of the 9 patients in the comparison group, 7 were likewise free from colic and 2 had uncharacteristic upper abdominal pains twice in 6 months.

Out of the 37 patients with cholecystic or cholangistic complaints, 28 reported clinically relevant and above all sonographic and chemical laboratory objective improvement up to complete freedom from symptoms after 5 weeks. A slight improvement was observed only in 2 patients, the first showed only a slight improvement in spite of an unimproved sonographic and chemical laboratory finding, the second one showed only a slight therapy success and one was hospitalised and underwent surgery due to a confirmed cholelithiasis in spite of improvement in the upper abdominal complaints.

Out of 64 patients with dyskinesia, porcelain, double gall bladder and septum formation, 53 reported a clear improvement of the complaints after 4 to 7 days at the beginning and, after 2 weeks. A further 9 patients showed a moderate effect, and 2 no effect. Patients suffering from porcelain bladder (7) only showed a moderate improvement.

Out of 21 patients with dyspeptic complaints with alcohol toxic liver parenchyma damage, 20 reported an essential improvement of the complaints after 2 weeks. Only in the case of one patient, the therapy was completely unsuccessful. The average values of the ESR improved from 16/40 mm almost to normal values (9/17 mm). The *gamma*-GT was reduced from an average of 39.8 U/l to 20.7 U/l.

In the case of 206 patients treated with Panchelidon®, 3 prematurely terminated the clinical trial due to a stomach disease, 2 with *ulcus ventriculi* and one patient with *ulcus duodeni* due to intolerability. Patients however resumed taking Panchelidon® after the ulcers had healed successfully and with very good tolerability. Other adverse drug reactions were not observed.

Knöpfel (1991) studied 92 patients with the selection diagnosis chronic gall bladder inflammation and/or occurrence of gallstones in an open non comparative multicentre clinical trial (8 centres, 10-20 patients per centre). The patients (70 women and 22 men) with average age of 58 years and the average illness duration amounted to 39 months showed an average of 1.7 colic attacks per month (18% arising without diet, 20% with diet and 62% with diet errors).

The selection diagnoses included cholecystitis (25), solitary (16), multiple (15), Gries (12) cholelithiasis, both diagnoses together without differentiation (1), solitary (2), multiple (16), Gries (3) and without diagnosis (1). Patients who underwent with Panchelidon® treatment during 2 months before beginning of the clinical trial were excluded as well as patients with analgesic and anti-cholinergic pre-treatment. The investigation parameters encompassed both subjective criteria (constant – irregular, casewise – regularly after meals occurring pain; feeling of fullness; meal intolerance; diet yes/no) as well as objective findings (pressure pain, muscular defence, Blumberg's sign, meteorism, icterus) and laboratory findings (bilirubin; blood sedimentation).

The patients received 20 drops (1 ml) 3 times daily (Panchelidon® (standardised to 5 mg chelidonine/100 ml, daily dose: 150 µg chelidonine) before meals over a period of 4 weeks with

controls at the beginning of the clinical trial, after 2 and 4 weeks (final). A validated scale ranging from 0 (no complaints) to 5 (intense complaints) was used to assess the subjective and objective investigation parameters.

At the end of the investigation, 20% of the patients were completely free of pain and complaints. In this respect, the average degree of pain was reduced from 3.10 by 2.08 to 1.02 units (p = 0.001). The feeling of fullness decreased from 52% to 3% of the patients and was reduced in intensity by 2.07 points. Some of the patients with constant meteorism (27%) showed symptoms only "after meals" (increase from 47 to 74%). The remaining patients (22%) became completely free of complaints. The percentage of patients with meal intolerances shifted in favour of the group with "meal intolerance only for single gall typical foods" or in favour of a group without intolerances. The objective parameters were likewise statistically significantly improved.

According to Lorkowski (2011), more than 1,000 patients, who have been treated with celandine preparations, have been documented in the published literature. The results of a further approximately 8000 patients are evaluated in the unpublished investigations (see Table 1 under section 5.3 Adverse events).

All unpublished investigations belong to so-called post-marketing surveillance studies, for which the German Medicines Act (AMG) required that marketed preparations are to be monitored in everyday practice for their risk potential. Of particular importance here is the documentation of the treatment of problematic patients. They cannot be sufficiently investigated in the clinical trials to demonstrate the efficacy with clearly defined eligibility or inclusion criteria. On the other hand, the results provide the physician with necessary safety information. The efficacy evaluation is positive in all investigations and was notably observed in the lower dose range too.

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 reported clinical studies are characterised by a considerable heterogeneity. Patients included have different pathological conditions, interventions are made with mono- and combined preparations and different outcomes are measured. Controlled clinical trials are performed with a limited number of patients and without power calculation. An extensive number of patients have been included in observational studies with different preparations. One study was performed with Panchelidon®, a mono preparation on the market before 1977. The daily intake of total alkaloids remains below the threshold of 2.5 mg (according to German pharmacovigilance measures, see section 5.2).

The number of patients taken into well conducted controlled clinical trials is too low to accept a well-established use. The extract used in Panchelidon® seems to be used since at least 1977, but the solvent and the way of preparation is not in the public domain.

5. Clinical Safety/Pharmacovigilance

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

Not specified by the Rapporteur.

5.2. Patient exposure

In Germany, there is a graduated plan (grade II) concerning *Chelidonium*-containing medicinal products for internal use, which came into force on 9 April 2008. The report is only available in German, therefore only the key elements are mentioned:

1. All marketing authorisations for medicinal products are withdrawn which lead to a daily intake of more then 2.5 mg alkaloids from *Chelidonium majus* according to the posology of the SPC.

2. For medicinal products which lead to a daily intake of 2.5 µg to 2.5 mg alkaloids from *Chelidonium majus* according to the posology of the SPC the marketing authorisation is changed.

The following information has to be included in the package leaflet and the SPC:

Contraindications:

The intake of the medicinal product is contraindicated for people who suffer from liver diseases or who had liver diseases in history or in cases of concomitant intake of other liver damaging medicinal products.

Special warnings and precautions for use

If signs of liver damage occur, the intake of the product should be stopped immediately and medical advice should be sought.

Undesirable effects

Cases of liver damage (increase of liver enzymes and bilirubin up to drug-mediated hepatitis) as well as cases of liver failure occurred.

Pregnancy and lactation

The intake during pregnancy and lactation is contraindicated.

Duration of use

If the duration of use is longer than 4 weeks liver function test (transaminases) should be conducted.

For those medicinal products that are also authorised for the use in children, the maximum limit of alkaloids is to adjust according to the body weight (starting from 2.5 mg for a 70 kg adult).

The necessity for the graduated plan was justified with several cases of undesirable effects connected to liver diseases reported after the intake of *Chelidonium*-containing medicinal products. The maximum permissible value is based on preclinical studies (Notox project 320211 and 330222; Mheddhbi 2002). It is emphasised that for the dosage of 2.5 µg-2.5 mg alkaloids/day no valid studies for the proof of efficacy exist.

Post marketing surveillance

In a post-marketing surveillance by Kniebel and Urlacher (1993), 608 cases from 60 centers (practitioners, internists and general practitioners) were evaluated in the course of 3 months treatment. The aim of the surveillance was to determine the incidence of adverse events. An event occurring with a frequency of at least 1:200 involving 600 observed cases can be statistically assured with 95% certainty.

The therapy of cramp-like complaints in the gastrointestinal tract and/or of the bile ducts was given as the indication for the selection of patients. The patients received 1-2 tablets containing a standardised celandine extract (total alkaloids 2.85 mg of which chelidonine: 0.79 mg, daily dose 12-24 mg of total

alkaloids), 3 times daily for a period of mainly 3-4 weeks but also up to 2.5 months. Pain intensity, frequency of the occurring pain and duration of the persisting pain were registered at the beginning of the investigation. Nausea, vomiting, feeling of fullness and flatulence were determined as concomitant symptoms. A global judgement of the efficacy based on the reduction of symptoms of cramp-like complaints in the gastrointestinal tract and/or bile ducts for all patients, both with and without concomitant medication, was made at the end of the treatment. Furthermore, the time it took for the onset of an effect was determined. The evaluation of the tolerability was made based on the judgement of the patient and the recording of any adverse events as well as measurement of blood pressure at the beginning and at the end of the investigation with an evaluation with or without concomitant medication.

The evaluation involved 608 patients (403 women and 205 men) with an average age of 59 ± 16 years for women and 55 ± 14 years for men. The eligibility diagnoses were distributed as follows: "essential NUD" (59%), cholelithiasis (25.5%), colon irritabile (10.0%), hepatopathy/pancreopathy (4.1%) and ulcers (1.3%). The localisation of the complaint symptoms in the gall area (48.2%) in comparison to that in the gastrointestinal tract was attributed to the preference of occurrence among younger people. Feeling of fullness occurred the most frequently (78.6%), followed by flatulence (58.6%) and nausea (55.9%). Obstipation (34.4%) was an important concomitant symptom that was treated in 29% of the cases (209) with laxatives. The rest received ballast-rich food or were changed. The complaints indicate a "post-cholecystectomy syndrome" in the 23.2% of patients with cholecystectomy. Of these patients, 35% had a cholelithiasis and 53.1% received a concomitant therapy including laxatives and cardiovascular medication. In patients aged below 48, ulcer therapeutics and spasmolytics dominated in addition to cardiovascular medicines. Interactions were not found.

The initial average daily dose was 4 tablets and a dose reduction was made with one third of the patients, 81% of these as a reduction to an average dose of 3 tablets per day. The average treatment duration amounted to 22 days. One third (34%) were treated over 3 weeks and one fifth (20%) over 4 weeks as well as up to 2.5 months in isolated cases. The efficacy was rated as "very good" by 49.1% of patients without concomitant therapy and only 38.8% by those undergoing concomitant therapy. The therapy success was only unsatisfactory in 3.8% of the cases. Eight patients prematurely discontinued the observation due to the lack of effectiveness. The good efficacy is partly founded on the rapid occurrence of an effect which in 62.3% of cases occurred after 30 minutes, in 27% of cases after 60 minutes and only in 7.4% of cases after 90 minutes. The effect lasted for at least 3 hours with 75.5%. The tolerability was rated "good" to "very good" by 97.4% of all patients. Blood pressure remained unchanged even among constitutional hypotonics. Only 6 suspected cases of an adverse drug reaction (3 cases of diarrhoea or soft stools, 2 cases of nausea and one case of mild tiredness) were reported. A connection with the medication was not claimed in any case (Kniebel and Urlacher 1993).

Gutsche (1977) made a retrospective long-term surveillance (at least 0.5 year up to 10 years) involving 162 treated patients suffering from chronic gall bladder and bile duct complaints, chronic non-active liver disease, excretory pancreas function disorders and chronic obstipation. A granulate (combination preparation) was used at a dose of 0.5 to 2 bags per day (alkaloid content: 0.15 to 0.6 mg *Chelidonium* alkaloids per daily dose). Chronic active (aggressive) hepatitis, liver failure at every stage, bile duct occlusion and gall bladder empyema were regarded as exclusion criteria.
The average daily dose amounted to 1 bag per day (127 patients). The daily dose had to be increased for 17 patients from 1.5 to 2 bags mostly after 1 to 2 years. The dose for 11 patients had to be reduced to 0.5 bag due to the occurrence of diarrhoea. Bowel movement had to be regulated over the period of the surveillance with 1-2 bags when taken after meals among 43 patients, who mostly complained for years about obstipation.
The following laboratory tests were carried out irregularly on average once per year for 97 out of 162

patients: SGOT, SGPT, *gamma*-GT, alkaline phosphatase, haematology, blood cell sedimentation, electrophoresis, in some cases the oral glucose tolerance test; furthermore in blood serum: sodium and potassium, iron, urea, creatinine, uric acid, cholesterol and neutral fats. No negative findings were reported which were attributed to the medicine. In order to safely exclude any damaging effects, the serum enzyme values of SGOT, SGPT, *gamma*-GT and alkaline phosphatase in 53 patients were statistically conservatively evaluated during a 4-year treatment period. The laboratory values showed only slight deviations from the norm over 4 years. The reduction of the standard deviation was evidence for a stabilisation of liver function.

In the case of 28 patients having a histologically assured chronic liver ailment determined by biopsy and who were not evaluated due to the small number and the broad variation of the investigated laboratory parameters, return of the complaints after discontinuation and reexposition and a new reduction of the symptoms could be observed.

The complaints are reduced among the majority of patients even during the first days of treatment due to the pharmacological effects. The treated symptoms correspond to the indication mentioned in the monograph. It should be noted that the investigation was carried out with a combination containing a small proportion of celandine. Effects were found in particular among patients with bile duct diseases.

The physicians recorded the prescribed temporary or continuous concomitant medication of 127 patients and the subjective evaluation of the efficacy is put in relative perspective by the very long therapeutically active treatment.

Interactions and liver toxic reactions were not found. The physician documented his therapy experience and did not use clearly documented measuring methods or questionnaires in view of the long and successful treatment. Therapy success is documented by the compliance of the patient.

The clinical data are only descriptive but the laboratory values of the patients selected by set criteria have been statistically evaluated. Laboratory tests were carried out in 97 patients, which showed no unusual results. A statistical evaluation was carried out for assurance purposes in 53 patients selected based on the described criteria (at least 1 non-pathological value per criterion, taking the sum, limits for women also for men). Another 28 patients with histologically assured chronic liver ailment were likewise described. The number of patients with laboratory investigations amounted to 92 so that investigation results were not documented for a maximum of 70 patients (Gutsche 1977).

5.3. Adverse events

Table 1 Summary of spontaneous reports (*n* = 47) of adverse drug reactions associated with single-ingredient *Chelidonium majus* preparations held in the Vigisearch database of the World Health Organization's Uppsala Monitoring Centre for the period up to end of June 2005.[a, 64]

System organ class. Adverse drug reaction name (number)	Total
Central nervous system. Paraesthesia (1)	1
Foetal. Biliary atresia (1)	1
General. Asthenia (3); death (1); fatigue (2); malaise (1); necrosis ischaemic (1)	8
Gastrointestinal. Abdominal pain (4); diarrhoea (2); faeces, discoloured (3); mouth dry (1); nausea (6); pancreatitis (1); tongue oedema (1); vomiting (3)	21
Liver-biliary. Bilirubinaemia (11); cholelithiasis (1); gamma-GT increased (6); hepatic enzymes increased (13); hepatic failure (1); hepatic function abnormal (1); hepatitis (19); hepatitis, cholestatic (8); hepatitis, viral (1); hepatocellular damage (4); jaundice (16); SGOT increased (7); SGPT increased (7)	95
Metabolic. Cholinesterase decreased (1); LDH increased (2); phosphatase alkaline, increased (5)	8
Psychiatric. Anorexia (1); insomnia (1); nervousness (2)	4
Respiratory. Dyspnoea (1); larynx oedema (1)	2
Skin. Pruritus (3); skin discoloration (1)	4
Urinary. Urine abnormal (3)	3
Total number of adverse drug reactions	**147**

Key: GT = glutamyl transferase; LDH = lactate dehydrogenase; SGOT = serum glutamic-oxaloacetic transaminase (= aspartate transaminase/aspartate aminotransferase); SGPT = serum glutamate pyruvate transaminase (= alanine transaminase/alanine aminotransferase)
[a]Caveat statement. These data were obtained from the Vigisearch database held by the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden. The information is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction. Any information included in this report does not represent the opinion of the World Health Organization

(Barnes et *al.* 2007)

Generally, the VigiSearch database may serve for the detection of signals of potential safety issues by data-mining. The causality assessment is often hampered by poor reporting. Underreporting must also be taken into consideration.

Spontaneous reporting can be illustrated by published case reports:

Acute hepatitis

A 42-year-old woman was diagnosed with severe acute hepatitis 2 weeks after she started using a preparation with herbal ingredients (a.o. *Chelidonium majus herba* and *Curcuma longa rhizoma*) for dermatological conditions.
The following complaints were reported: high fever (40.5°C), epigastral pain, headache, hypersensitivity of the eyes, muscle pain and tiredness. The patient became icteric, her urine had a dark colour and faeces were discoloured. The patient declared that she had only taken 1 tablet of 500 mg paracetamol as co-medication.
Transaminases strongly increased: aspartate aminotransferase (ASAT): 838 U/l (0-40); alanine aminotransferase (ALAT): 1490 U/l (0-30); lactatedehydrogenase (LDH): 389 U/l (114-235); gamma glutamyltransferase (γ-GT) 286 U/l (0-65). Total bilirubine 200 µM/l (3-26). Viral infection with hepatitis A, B or C was excluded. Paracetamol intoxication was excluded by serum analysis.
After the patient discontinued the medication, her situation normalised within 2 months.
Causal relationship with *Chelidonium* was hypothesised but no causality scale or scoring was used (Crijns *et al.* 2002).

10 cases of acute hepatitis were observed over 2 years, probably induced by *Chelidonium majus,* frequently described to treat gastric and biliary disorders. The course of the hepatitis was mild to severe, with marked cholestasis observed in 5 patients. In all cases, other possible causes of hepatitis were excluded (viral, autoimmune, hereditary, alcohol) by laboratory tests and imaging procedures. Liver biopsies were consistent with drug-induced damage. After discontinuation of greater celandine, rapid recovery was observed in all patients and liver enzymes levels returned to normal within 2-6 months. Unintentional rechallenge led to a second flare of hepatic inflammation in 1 patient. No causality scales were used (Benninger *et al.* 1999).

A 82-year-old male patient was admitted to the geriatric ward of a local hospital. Cognitive impairment had become worse during the last months. There was a decline in Mini-Mental-State (MMS) from 24/30 to 14/30. When admitted to the hospital, a MMS of 12/30 was found. There were no hepatic preconditions known. The liver had normal dimensions as was shown by sonography and magnetic resonance imaging. The patient used a herbal tea preparation with self-collected *Chelidonium* as main component. Liver enzymes were enhanced in serum: GGT 197 U/l; GOT 687 U/l; GPT 904 U/l; LDH 297 U/l; bilirubine 2.32 mg/dl.
The diagnosis toxic hepatitis caused by *Chelidonium* was made. The patient declared practicing herbal medicine as told by friends and that he probably made his tea too concentrated. Five months after discontinuation, liver enzymes were returned to normal. There were no signs of hepatic damage (Bichler 2009).

Moro *et al.* (2009) investigated one case of a 65-year-old man with a sudden onset of asthenia, dyspepsia and jaundice. The first symptoms emerged 3 days before admission to the hospital and the patient noticed hyperchronic urine and scleral jaundice. A laboratory test showed a strong enhancement of transaminases and bilirubin levels: e.g. AST 3253 U/l (5-38); ALT 4765 (5-41). Apart from hepatitis C virus antibodies (HCV), the remaining for hepatic viruses were negative. The positive screening for HCV was most probably due to contact with the patient's brother-in-law who died 5 years earlier of HCV-related hepatic cirrhosis. The patient was taking lansoprazole (15 mg/d) at that time. Because of a persistent pyrrosis, patient's wife recommended to take a cup of a *Chelidonium majus*

decoction daily (boiling 4-5 spoons of dried leaves in 150 ml of water, straining and leaving it overnight). This treatment continued for one month preceding the hospital admission. *Chelidonium majus* was identified by thin layer chromatography. The tea preparation as well as lansoprazol was discontinued after admission, infusions with normal saline were started, as well as treatment with glutathione (600 mg i.v.-2x/d) and ursodeoxycholic acid (300 mg p.o. 2x/d for 30 days). The patient was discharged from the hospital after 10 days. He recovered completely, though a mild pyrosis persisted, and the liver parameters normalised within 2 months.

Additionally to this case, 16 cases of *Chelidonium majus* hepatitis from the literature were analysed. Typical symptoms of cholestatic hepatitis (jaundice, itching and fatigue) usually arose after 2 or more months since the beginning of greater celandine oral consumption. The onset seems to be independent from dosage. Typical manifestations are hepatomegaly, serum transaminases and bilirubin level over the normal range. Patients were mostly tested negative for antibodies against hepatitis viruses (sometimes slight positive hepatitis-C viruses reactions were detected). A possibility of a celandine-drug interaction must be considered because a majority of patients took other (herbal or conventional) medicines. When the consumption of greater celandine was interrupted, symptoms regressed and liver parameters normalised until complete recovery within 2 to 3 months (rarely after more than 5 months), although recovery could also be seen after 2 weeks. Rechallenge occurred in 2 patients leading to liver impairment (Moro *et al.* 2009; Stickel *et al.* 2001).

A 58-year-old woman went for a consultation because of painless jaundice with dark urine and pale stools. The jaundice started one week before the consultation. There was no medication used besides tablets of medicinal herbs for muscular pain since 6 weeks and – started after the jaundice – supplements of vitamins. The patient took capsules with 50 mg of greater celandine, 50 mg of gentian and 100 mg of curcuma root.
The abdomen revealed a palpable and tender liver edge just beneath the costal arc. The gallbladder was also palpable. Liver enzymes were strongly increased: GOT (AST) U/l (1740 U/l; on day 14 lowered to 55 U/l); GPT (ALT) 1566 U/l; on day 14 lowered to 45 U/l) (Hardeman *et al.* 2008).

Schmidt (2011) made an overview of case reports with comments and evaluation according to the CIOMS criteria[1]. The CIOMS scale, used in the table, is a validated tool for the assessment of liver injury. Although still in need for further refinement, the CIOMS scale is judged as a reliable and reproducible tool, providing a maximum level of objectivity (Garcia-Cortes *et al.* 2008).

The analysis by Dr. Schmidt points out two cases with highly likely causality (≥ 9 points) by the herbal product, but not necessarily by greater celandine: one of the products was a combination preparation where the effect cannot be attributed to any of the constituents.
No information regarding dose can be derived from these two cases, as in both cases there was no data available allowing the calculation of daily alkaloid exposure. In both cases the reaction occurred within a reasonable period after commencing the herbal treatment. An idiosyncratic reaction type was not confirmed.

There are seven cases with probable causality (6-8 points). Of these cases, two referred to the intake of a tea infusion, one of which was composed of more herbs than just greater celandine.
In all cases with available information, the daily alkaloid dose exceeded 9 mg. All cases occurred within the usual and typical 90 day period for toxic hepatitis.

There are 29 cases with possible causality (3-5 points), among them five cases observed with combination products. The majority of these cases (n = 18) has only a weak possible association (3

---

[1] http://www.cioms.ch/publications/g4-benefit-risk.pdf (last access on 3 May 2011): Benefit-risk balance for marketed drugs: evaluating safety signals.

points), see also below. Among these cases, there are four with an unusual long latency period, which is *de facto* strongly speaking against greater celandine as the causative factor.

The remainder of the cases is unlikely related with greater celandine. With the poor documentation of the case reports, weak to moderate causality or less, a further analysis of these cases is not justified.

With the regard to the assessment of methodological cases, it has to be taken into account that greater celandine presence in the event was rated with 5 points; usually 2 points for the onset of the hepatic reaction within 90 days post initiation are given. Another point was given when there had been symptoms already present or developed within less than 14 days after the preparation was discontinued. 2 points were attributed for the fact that liver adverse reactions are labeled for greater celandine. One additional point is attributed when a patient is older than 54 years, without discrimination (Schmidt 2011; Schrenk 2011).

5.4. Serious adverse events and deaths

Not specified by the Rapporteur.

5.5. Laboratory findings

See the graduated plan (Germany) under section 5.2

5.6. Safety in special populations and situations

See the graduated plan (Germany) under section 5.2.

Intrinsic (including elderly and children) /extrinsic factors

See the graduated plan (Germany) under section 5.2.

Drug interactions

See the graduated plan (Germany) under section 5.2.

Use in pregnancy and lactation

Because of some cytotoxicity, the herbal substance or preparations thereof are not recommended during pregnancy. See also the German graduated plan under section 5.2.

Overdose

No systematic data reported.

Drug abuse

Not applicable.

Withdrawal and rebound

Not applicable.

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

Not reported.

5.7. Overall conclusions on clinical safety

The main concern is a possible hepatic damage. In the Vigisearch database, 95 cases of hepatic complications are indexed and hepatic toxicity has been repeatedly reported in the literature. This concern led to a graduated plan in Germany in 2008. This plan has been communicated to the EMA. It essentially consists of limiting the daily intake of total alkaloids from *Chelidonium* to 2.5 mg.

Apparently causality analysis points to a dose-dependent toxicity. According to one expert, no clear relationship between *Chelidonium* and hepatotoxicity was seen with a daily intake of alkaloids lower than 9 mg.

6. Overall conclusions

Chelidonium extracts have a well documented anti-viral activity. *Herpes simplex*, polio as well as several adenoviruses are affected. There is even an *in vivo* anti-influenza activity. Protoberberine was found active against reverse transcriptase of RNA-tumour viruses. The anti-microbial activity and anti-tumour activity were mostly tested with isolated compounds of *Chelidonium*. The choleretic activity seems to be linked to the totality of the components. Furthermore, in different experimental models there are indications for anti-inflammatory and analgesic properties.

The alkaloids of *Chelidonium* are poorly absorbed and seem to be intensively metabolised. A high volume of distribution should be taken into consideration.

Although the acute toxicology of the total extract is low, some alkaloids such as sanguinarine induced DNA damage in bone marrow cells. The same can be stated for the cytotoxicity.
There are a limited number of clinical studies with total extracts in patients with epigastric complaints. These studies are done with small numbers of patients and are partially observational. On the other hand, there are warnings against possible hepatotoxicity of *Chelidonium* containing preparations. These warnings were translated into marketing authorisation restrictions in Germany, especially with regard to the daily intake of alkaloids.

A risk-benefit analysis can be made for the herbal preparations containing *Chelidonium*. The herbal substance is described in the European Pharmacopoeia with a minimum of 0.6% of total alkaloids. The herbal substance as well as the alkaloids can be characterised. Adulteration of the herbal substance is no a point of concern.

Although voluntary intoxications with the herbal substance and preparations thereof are not reported, there is a concern with regard to possible hepatotoxicity. Indications for weak genotoxicity or foetotoxicity are known for single alkaloids of *Chelidonium*.

Chelidonium preparations are used for epigastric discomfort and superficial warts. Warts are mostly treated with preparations containing several plants, which complicates the characterisation of mono preparations in the monograph. The fresh latex is traditionally used in folk medicine and cannot be considered in an industrial context.

The evidence to support a safe oral daily dose limit of not more than 2.5 mg alkaloids could be considered. However, the scientific rationale or the information available is not reassuring. Evidence of clinical efficacy is lacking and a well established use indication cannot be supported. Traditional use for *Chelidonium majus* is hampered by a high number of spontaneously reported liver-biliary adverse drug reactions and the withdrawal of products in Member States due to safety concerns. Therefore the benefit-risk assessment of oral use of *Chelidonium majus* must be considered negative.

Moreover, safer herbal medicinal products are available in the indication in question.

If new information on clinical safety and efficacy of *Chelidonium majus* herba as a single ingredient for oral use were to be made available, such documentation may be re-assessed.

With regard to the cutaneous use, the indication is currently not sufficiently supported by market information on monotherapy.

Annex

List of references