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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Solanum dulcamara* L., stipites

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)	*Solanum dulcamara* L., stipites
Herbal preparation(s)	Comminuted herbal substance
Pharmaceutical forms	Comminuted herbal substance for infusion or decoction preparation for cutaneous use
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1. Introduction

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

- Herbal substance(s)

Solanum dulcamara L., stipites consists of the dried 2- to 3-year-old stems of the plant, harvested in spring prior to leafing or in the late autumn after leaves have dropped (Blumenthal *et al.*, 1998).

The plant is a subshrub from 30 to 150 cm in height with a creeping, branched rhizome. The stem is twining or creeping, woody below, angular and usually glabrous. The leaves are petiolate, the upper and lower ones are usually cordate and acute. The middle leaves are usually pinnatesect with one pair of lateral segments and a large terminal segment. The violet flowers are arranged in 10-20 blossomed, hanging, long-peduncled, panicle-like forms. The calyx is fused, 5-tipped and does not drop. The corolla has a very short tube and 5 long tips, which become revolute when mature. At the base of each tip, there are 2 green spots surrounded by white. There are 5 stamens with golden yellow anthers, which lean toward each other, and 1 superior ovary. The fruit is an oblong, scarlet, and many-seeded berry (Gruenwald *et al*., 2004).

Constituents:

Steroid alkaloid glycosides

Solanum dulcamara L. contains several different types of steroid alkaloid glycosides. The tomatidenol type has the aglycone Δ^5 –tomatidenol. Representative glycosides are: α-solamarine and β-solamarine. The aglycone of the soladulcidine type is soladulcidine and a representative alkaloid is the soladulcidinetetraoside. The solasodine type has the aglycone solasodine. Representative glycosides are solasonine and solamargine. The content in the stem is 0.07-0.4% (Hänsel *et al*., 1994).

Steroid saponines

The herbal substance also contains steroid saponins with yamogenin, tigogenin and diosgenin as aglycones. The content in the stem is 0.18% (Hänsel *et al*., 1994).

Polyhydroxynortropane alkaloids

The compounds calystegine A_3, A_5, B_1, B_2 and N_1 have been isolated from the whole plant. The total amount of calystegines in the plant material was 0.048% (Asano *et al*., 2001).

- Herbal preparation(s)

Comminuted herbal substance for infusion or decoction preparation for cutaneous use (Blumenthal *et al.*, 1998).

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

Not applicable.

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

Belgium

Preparations: Herbal teas (combination products)

Preparations on the market: Authorised since 1962 (in the revision phase) and food supplements.

Pharmaceutical form: Herbal teas

Bulgaria

Preparation: Extract (1:4-5), extraction solvent: ethanol 30% m/m, 9 g/100 g of the final product.

Preparation on the market: Since 2006 (marketing authorisation).

Pharmaceutical form: Ointment

Therapeutic indication and posology: For supporting treatment in case of chronic eczema, 3-5 times daily.

Czech Republic

Preparation: Extract (1:5), extraction solvent: ethanol 30% m/m, 10 g/100 g of the final product.

Preparation on the market: Since 2008 (other national traditional systems of registration).

Pharmaceutical form: Ointment

Therapeutic indication and posology: Adjuvant therapy of chronic eczemas, 3-5 times daily.

Germany

1) *Preparation:* Extract (1:5), extraction solvent: ethanol 30% m/m, 70 g/100 g of the final product.

Preparation on the market: Since 1990.

Pharmaceutical form: Oral drops

Therapeutic indication and posology: Adjuvant therapy of chronic eczemas, 30-40 drops 4-5 times daily.

2) *Preparation:* Dry extract (5:1), extraction solvent: ethanol 30% m/m, 200 mg

Preparation on the market: Since 1991.

Pharmaceutical form: Film-coated tablets

Therapeutic indication and posology: Adjuvant therapy of chronic eczemas, 1-3 times daily.

3) *Preparation:* Extract (1:5), extraction solvent: ethanol 30% m/m, 10 g/100 g of the final product.

Preparation on the market: Since 1993.

Pharmaceutical form: Ointment

Therapeutic indication and posology: Adjuvant therapy of chronic eczemas, 3-5 times daily.

Spain

*Preparation*s: Herbal tea (combination product) with 6.25% *Solanum dulcamara* L. and herbal substance (combination product) with 75 mg of *Solanum dulcamara* L.

Preparations on the market: Two combination products according to former national traditional systems of registration; currently revoked.

Pharmaceutical forms: Herbal teas and capsules.

Therapeutic indication and posology: Herbal tea for digestive complaints. Capsules 3 times daily for the treatment of acne or dermatitis (depurative activity).

Sweden

Preparation: Extract (1:5), extraction solvent: ethanol 30% m/m, 10 g/100 g of the final product.

Preparation on the market: Since 2006 (other national traditional systems of registration) and re-classified in 2010 (Traditional use registration, Article 16 of Directive 2001/83/EC).

Pharmaceutical form: Ointment

Therapeutic indication and posology: For the relief of mild chronic eczemas, 3-5 times daily.

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No auth or reg products
Belgium	☒ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Auth product & food suppl, combn products
Bulgaria	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	One authorised product (extract 1:4-5, extracted with ethanol 30% m/m 9 g/100 g of the final product) since 2006
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	One reg product (extract 1:5, extracted with ethanol 30% m/m 10 g/100 g of the final product) since 2008
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No auth or reg products
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No auth or reg products
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No auth or reg products
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No auth or reg products
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No auth or reg products

Member State	Regulatory Status				Comments
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No auth or reg products
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No auth or reg products
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No auth or reg products
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No auth or reg products
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No auth or reg products
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No auth or reg products
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No auth or reg products
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No auth or reg products
Sweden	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	One reg product (extract 1:5, extracted with ethanol 30% m/m 10 g/100 g of the final product) since 2010
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No auth or reg products

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

1.3. Search and assessment methodology

Traditional medicinal use of *Solanum dulcamara* L., stipites has been documented in several handbooks that are included in the list of references. From the references listed in the handbooks, additional scientific literature on *Solanum dulcamara* L. were found. PubMed and Toxnet were searched in the beginning of August 2011 using the terms [solanum AND dulcamara OR dulcamara]. The abstracts of the references retrieved were screened manually and all articles considered relevant were assessed and included in the list of references. Additionally, the cosmetic ingredients database CosIng of the European Commission was searched in August 2011 for information on *Solanum dulcamara.*

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Solanum dulcamara L., stipites has a long history of traditional use in the treatment of different skin diseases. It has been used in the European Union (EU) for more than 30 years and was for example included in the British Pharmaceutical Codex 1934, Ergänzungsbuch zum DAB 6 1953 and the Commission E 1998.

Dulcamara stipites have been official in France, Austria, Portugal, Spain, Mexico and Venezuela (Madaus, 1938).

The dried stem of *Solanum dulcamara* L. has been included in the United States Pharmacopoeia (USP) 1820 to 1905 and in the USP National Formulary (NF) 1916 to 1936 (Claus, 1956).

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

According to the 'Commission E monograph', the dried 2- to 3-year-old stems of *Solanum dulcamara* L. harvested in spring prior to leafing or late autumn after leaves have dropped are used as supportive therapy for chronic eczema (Blumenthal *et al.*, 1998).

According to 'Hagers Handbuch' 1975, *Solanum dulcamara* L., stipites has been used for the treatment of chronic itching eczema, chronic bronchitis and asthma (Frerichs *et al*., 1975).

In 'Drogenkunde' 1975, *Solanum dulcamara* L., stipites is presented as a traditional treatment for chronic itching eczema, rheumatism and gout (Hoppe, 1975).

The dried stems and branches of *Solanum dulcamara* L. have been a popular remedy for chronic rheumatism and obstinate skin eruptions (Martindale, 1967, 1972 and 1982).

An ointment containing an extract of *Solanum dulcamara* L., stipites (1:5), extraction solvent: ethanol 30% m/m, 10 g/100 g of the final product, is registered in the Czech Republic for the adjuvant therapy of chronic eczemas and in Sweden for the relief of mild chronic eczemas.

In Spain, the herbal tea was used for digestive complaints and the herbal substance for the treatment of acne and dermatitis.

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

The comminuted herbal substance is used for herbal teas and other galenical preparations for internal use and for compresses and rinses (Blumenthal *et al.*, 1998). For internal use: 1-3 g daily dosage of the herbal substance. For external use: infusions or decoctions equivalent to 1-2 g of herbal substance per 250 ml of water (Blumenthal *et al.*, 1998). This supporting evidence does not give the specified daily dose, however the HMPC considered it possible to recommend an administration 1 to 5 times daily for the cutaneous use accepted in the monograph for the comminuted herbal substance for infusion or decoction preparation.

According to 'Hagers Handbuch' 1975, a decoction of the herbal substance is used cutaneously in impregnated dressings and rinses. The dosage for internal use is 1 g of herbal substance as infusion 1:10, 30-60 ml or as liquid extract 1:1, 2-4 ml (Frerichs *et al*., 1975).

The dried stems and branches of *Solanum dulcamara* L. were administrated as an infusion (1:10; dose 30-60 ml) or a liquid extract (1:1; dose 2-4 ml) (Martindale, 1965, 1972 and 1982).

For the adjuvant therapy of chronic eczemas, the ointment containing an extract of *Solanum dulcamara* L., stipites (1:5), extraction solvent: ethanol 30% m/m, 10 g/100 g of the final product, should be applied 3-5 times daily (information from the Czech Republic).

For the relief of mild chronic eczemas, the ointment containing an extract of *Solanum dulcamara* L., stipites (1:5), extraction solvent: ethanol 30% m/m, 10 g/100 g of the final product, should be applied 3-5 times daily (information from Sweden).

For the treatment of acne and dermatitis, the posology was 1 capsule (containing 75 mg of *Solanum dulcamara* L.) 3 times daily (information from Spain).

3. Non-Clinical Data

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

Herbal substance and herbal preparations

No pharmacological data on the herbal substance or herbal preparations are available.

Information on other plant parts of *Solanum dulcamara* L.

In mice, an ethanol-water solution of an ethanol extract of the stem and leaves of *Solanum dulcamara* L., in an i.p. dose corresponding to 1 mg extract/animal, stimulated the phagocytosis of *Escherichia coli*, applied by i.p. 24 hours following the injection of the extract (Delaveau *et al*., 1980).

The water extract of the aerial parts of *Solanum dulcamara* L. showed high inhibition of platelet activating factor (PAF)-induced exocytosis *in vitro.* Since steroid alkaloid glycosides have shown cytotoxic effects in *in vitro* test, the authors concluded that the effect might be a false inhibitory activity in the PAF-test (Tunón *et al*., 1995).

The ethanol extract (50% ethanol) of fresh shoots of *Solanum dulcamara* L. inhibited the production of PGE_2 by COX 1 (IC_{50} = 40 µg/ml) and COX 2 (IC_{50} = 150 µg/ml) but not the production of leukotriene LTB4 by 5-LOX (Jäggi *et al*., 2004).

The water extract of *Solanum dulcamara* L. aerial parts showed inhibitory activity against *Streptococcus pyogenes*, *Staphylococcus aureus* and *Staphylococcus epidermidis* in a screening of antibacterial activity (Turker & Usta, 2008).

Constituents and other structurally similar substances

In the literature, there are some pharmacological studies on isolated steroid alkaloid glycosides or their aglycones on different *in vitro* models. Most studies have been performed on solanine and chaconine, steroid alkaloid glycosides present in *Solanum tuberosum* L. (potato) but not in *Solanum dulcamara* L., stipites. The effects of the steroid alkaloid glycosides present in *Solanum dulcamara* L. are qualitatively comparable to those of solanine and chaconine, although at equal concentrations the *Solanum dulcamara* alkaloids are less potent (Hänsel *et al*., 1994).

Membrane-disruption properties

The steroid alkaloid glycosides have membrane-disrupting properties on a variety of structures ranging from synthetic membranes through organelles and cells to living organisms including humans. They have therefore haemolytic and cytotoxic activity (Roddick *et al*., 1989; Hänsel *et al*., 1994).

Antimicrobial activity

Steroid alkaloid glycosides were extracted from *Solanum dulcamara* L. and screened for their antibacterial activity. Human pathogenic bacteria were selected for the study. The alkaloids inhibited the growth of *Escherichia coli* and *Staphylococcus aureus*. However, no significant activity was observed against *Enterobacter aerogenes* (Kumar *et al*., 2009).

Antiviral activity

The infectivity of herpes simplex virus Type I in tissue culture was inhibited by prior incubation with aqueous suspensions of steroid alkaloid glycosides, in order of activity α-chaconine > α-tomatine > α-solasonine, but not by the corresponding aglycones, solanidine, tomatidine and solasodine. (Thorne *et al*., 1985).

Acetylcholinesterase inhibition

α-solanine and α-chaconine significantly inhibited bovine and human acetylcholinesterase at a concentration of 100 µM. Tomatine was less inhibitory, whereas solasonine and solamargine showed very much reduced activity. The aglycones solanidine, tomatidine and solasodine produced only slight to negligible inhibition (Roddick, 1989).

Inotropic effect

Steroid alkaloid glycosides have a positive inotropic effect on isolated frog hearts. The positive inotropic dose, PID_{50} (the dose which causes a 50% increased contraction force in 3 minutes), is 1.5 µg/ml for tomatine, 3.1 µg/ml for α-chaconine, 4.5 µg/ml for α-solanine, 16.8 µg/ml for β-chaconine and 11 µg/ml for solanidine. This should be compared to the dose for k-strophantosid which is 0.7 µg/ml. Solasodine has a positive inotropic effect on cat hearts *in situ* (Hänsel *et al*., 1994).

Vascular and anti-allergic effects

In rats, i.m. administration of solasodine (10 mg/kg) 3 hours before an i.m. dose of a 6% ammonium chloride solution (5 ml/kg) delayed the development of lung oedema from 8 minutes (control) to 25 minutes. All control animals died but none of those treated with solasodine. In guinea pigs, sensitised for horse serum, solasodine (5 mg/kg) delayed or prevented the death by anaphylactic shock, caused by i.p. or i.v. administration of the serum. Also histamine-induced shock or heat shock was prevented by solasodine (Hänsel *et al*., 1994).

Pharmacodynamic interactions

The biotransformation of barbiturates was inhibited by solanine at 10 mg/kg body weight (b.w.) i.p., causing prolonged sleeping time in rats given pentobarbital (Hänsel *et al*., 1994).

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

No pharmacokinetic data on the herbal substance or herbal preparations are available.

Nishie and co-workers have published a comprehensive study for the steroid alkaloid glycoside solanine (Nishie *et al*., 1971). This alkaloid does not appear to be present in *Solanum dulcamara* L., stipites, but the structure of solanine is closely related to the steroid alkaloids reported from *Solanum dulcamara* L., stipites and the information below is included for information.

In the rat, small oral doses of steroid alkaloid glycoside solanine (5 mg/kg) are poorly absorbed after oral administration (Nishie *et al*., 1971).

Following oral or i.p. administration of ^{3}H labelled solanine to rats, radioactivity was detected in all organs. The activity following oral doses was much lower than that following i.p. doses. The ratio i.p dose/oral dose ranged from 2.4 to 12.2. High activities were found in kidneys, thymus, liver, spleen, adrenals and pancreas (Nishie *et al*., 1971).

Following doses of 5 mg/kg of ^{3}H labelled solanine to rats, 72% of the dose was excreted in the faeces and 6% in the urine within the first 24 hours. Administration of higher doses (15-25 mg/kg) showed a decreased faecal and urinary elimination during 24 hours, accompanied by increased concentration in the organs, particularly in the liver and spleen (Nishie *et al*., 1971).

Following oral administration of ^{3}H labelled solanine to rats, 65% of the radioactivity in the faeces was identified as un-metabolised solanine. Following i.p. administration 45% in faeces was solanidine and in addition two non-identified metabolites were detected. In urine after oral administration 72% of the tritium was present in basic compounds. Only 6% was identified as solanidine and most of the activity was seen in two other basic compounds with intermediate polarity between solanine and solanidine (Nishie *et al*., 1971).

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

Single/repeat toxicity

No information on the toxicity of the herbal substance or herbal preparation is available. However, toxicological data on other plant parts are presented below.

Information on other plant parts of Solanum dulcamara L.

8 out of 10 Syrian hamsters died after orally administered fruits of *Solanum dulcamara* L. and had gastric glandular mucosal necrosis and small intestinal mucosal necrosis with little inflammation. The total alkaloid concentration as percent dry matter of the fruits was 0.030%. The fruit contained the steroidal alkaloid in the glycoside form of which 50% had the aglycone solasodine (Baker *et al*., 1989).

The toxicity of the fruits was studied by gavaging mice with a preparation of lyophilised fruits, ripe and unripe, collected at various times of the year. Mice receiving unripe fruit from early in the season had gastrointestinal tissue changes consistent with solanine toxicity. Animals dosed with unripe fruit from the latter part of the year showed behavioural signs suggestive of solanine toxicity, however gastrointestinal lesions were not observed. In no case did the ripe fruit produce behavioural or histologic toxicity (Hornfeldt & Collins, 1990).

Constituents and other structurally similar substances

The toxicity of α-solamargine, one of the steroid alkaloid glycosides present in *Solanum dulcamara* L. has been studied in rats. The i.p. LD_{50} was 42 mg/kg b.w. No animal died earlier than 6 hours. At 60 mg/kg b.w. the rats died within 3 hours. The chronic and subchronic toxicity investigations indicated that the size of the steroid alkaloid glycoside dose was more important than the total steroid alkaloid glycoside intake. No appreciable toxic effects were observed at doses below 35 mg/kg b.w. as indicated by blood parameters, enzyme levels and histological sections of kidney, liver and cardiac muscle. The steroid alkaloid glycoside did not affect the weight of the testes and epidymis or the number of spermatozoa but produced a slight irritation and congestion in the epidymis and testes at doses up to 50 mg/kg b.w. (Al Chami *et al*., 2003).

Using osmotic minipumps, calystegines A_3, B_2 and C_1 were administered to mice in doses of 1, 10, and 100 mg/kg/day for 28 days. The animals were clinically normal at all doses. After completed treatment, the mice were euthanized, necropsied and examined using light- and electron microscopy. Mice treated with high-dose calystegine A_3 had increased numbers of granulated cells in the hepatic sinusoids. The granules contained glycoproteins or oligo-saccharides with abundant terminal N-acetylglucosamine residues. Mice treated with the other calystegines were histologically normal (Stegelmeier *et al*., 2008).

Constituents of toxicological interest are the steroid alkaloid glycosides, the saponines and the calystegines. Most studies have been performed on solanine and chaconine, steroid alkaloid glycosides present in *Solanum tuberosum* L. (potato) but not in *Solanum dulcamara* L., stipites. The effects of the steroid alkaloid glycosides present in *Solanum dulcamara* L. are qualitatively comparable to those of solanine and chaconine, although at equal concentrations the *Solanum dulcamara* alkaloids are less potent (Hänsel *et al*., 1994).

The following data for steroid alkaloid glycosides are available (Hänsel *et al*., 1994):

Alkaloid	**Species**	**LD_{50} (mg/kg) Oral**	**LD_{50} (mg/kg) Intraperitoneal**	**LD_{50} (mg/kg) Intravenous**
α-solanine	Mouse	> 1000	32-42	-
	Rat	590	67-75	-
	Sheep	> 225, <500	-	<50
	Rhesus monkey	-	<20	-
	Rabbit	-	<10-30	-
α-chaconine	Mouse	-	10-28	-
	Rat	-	84	-
solanidine	Mouse	-	> 500	-

For steroid alkaloid glycosides in general, 'Hagers Handbuch' 1994 states that an oral dose of 20 mg (total) in man is safe. Doses of 2-5 mg/kg b.w. are toxic and doses > 3-6 mg/kg b.w. can be lethal (Hänsel *et al*., 1994).

In Syrian Golden hamsters, daily oral doses of 100 mg α-solanine induced death in 2 of 4 hamsters within 4 days. Oral doses of 100 mg/kg b.w. of α-chaconine alone or α-solanine and α-chaconine, combined in a ratio of 1:2.5, in doses of 75 or 100 mg/kg b.w. induced death in 1 of 4 hamsters within the same period (Langkilde *et al*., 2008).

Genotoxicity

No information on genotoxicity of the herbal substance or herbal preparation is available.

Constituents and other structurally similar substances

In Ames test (using *Salmonella typhimurium* strains TA98 and TA100, with and without metabolic activation), α-chaconine (0.07-2.3 mM/plate), α-solanine (0.04-0.58 mM/plate) and solanidine (0.07-2.3 mM/plate) showed no mutagenicity. In adult and foetal erythrocyte micronucleus assays, α-chaconine (0.01-0.045 mol/kg), α-solanine (0.02-0.09 mol/kg) and solanidine (0.01-0.045 mol/kg) showed no clastogenicity (Friedman & Henika, 1992).

Carcinogenicity

No information available.

Reproductive and developmental toxicity

No information on teratogenic effects of the herbal substance or herbal preparation is available.

Constituents and other structurally similar substances

Toxic doses of solasodine (1184-1628 mg/kg), administered by tube to pregnant hamsters caused malformations in 7% of the new-born animals (spina bifida, exencephalie and anophtalmie). Also resorption of the foetuses was observed. Tomatidine and diosgenine had no effect (Hänsel *et al*., 1994).

α-chaconine and α-solanine had teratogenic and embryotoxic effect in the frog embryoteratogenesis assay, Xenopus (FETAX), with and without metabolic activation by Aroclor 1254-induced rat liver microsomes. α-chaconine was more active than α-solanine. The aglycones demissidine, solanidine and solasodine were less toxic than the glycosides α-chaconine and α-solanine (Friedman *et al*., 1991).

A dose of 1.7 mg/kg/day of α-chaconine was given i.v. via implanted osmotic minipumps to pregnant rats (n = 17) to maintain a stable blood concentration on days 6-13 of gestation. The foetal body weights and the number of resorbed or dead foetuses per litter in the verum group were not significantly different from that in the control groups. No case of malformation was detected among 143 foetuses observed in the treated group (Hellenäs *et al*., 1992).

The aglycones solanidine, solasodine and tomatidine were evaluated for their effects on liver weight increase (hepatomegaly) in non-pregnant and pregnant mice and on fecundity in pregnant mice. The aglycones were fed for 14 days in the diet containing 2.4 mmol/kg of aglycones. In pregnant and non-pregnant mice, observed ratios of % liver weights to body weights (% LW/BW) were significantly greater than those of the control values. For pregnant mice, (a) body weight gains were less with the aglycones than with the controls, (b) litter weights were less than with the controls, (c) the % LW/BW ratio was less than that of controls and (d) the average weight of the foetuses was less than that of the controls. Abortion of foetuses occurred in 5 of 24 pregnant mice in the solanidine diet and none of the other diets (Friedman *et al*., 2003).

Local tolerance

No information available.

3.4. Overall conclusions on non-clinical data

No studies on the pharmacology of the herbal substance or herbal preparations of *Solanum dulcamara* L., stipites are available. Other plant parts and constituents isolated from the herbal substance such as steroid alkaloid glycosides have shown a variety of activities in different *in vitro* and *in vivo* models. The results of pharmacological studies on other plant parts and constituents are of limited value for the monograph on *Solanum dulcamara* L., stipites.

No toxicological information on the herbal substance or herbal preparations of *Solanum dulcamara* L., stipites is available. The results on other plant parts and constituents are of limited value for the monograph on *Solanum dulcamara* L., stipites.

Most toxicological studies have been performed on solanine and chaconine, steroid alkaloid glycosides present in *Solanum tuberosum* L. (potato) but not in *Solanum dulcamara* L., stipites. The content of solanine in the flowers and in the green fruit of potato is about 1% and in the sprout about 5% (Wolf, 1992). Compared to *Solanum tuberosum* L., the content of steroid alkaloid glycosides in *Solanum dulcamara* L., stipites is low (0.07-0.4%). It should also be taken into account that studies on solanine have showed that the bioavailability after oral administration is poor.

No toxicological information on the saponines has been found, but saponines in general have haemolytic activity and might influence the absorption of other pharmacologically active compounds. On oral administration, they might contribute to the toxicity of the steroid alkaloid glycosides by increasing their absorption.

The only study found on the toxicity of calystegines indicates that their toxicity is low. Their content in the herbal substance is also very low (0.05%).

No information on toxicity on topical application of the herbal substance or herbal preparation or its constituents has been found.

Scientific evidence for the safe use of *Solanum dulcamara* L., stipites during pregnancy or lactation is not available.

In summary, no non-clinical data are available for the herbal substance and the herbal preparation. The results from studies on other plant parts and constituents are of limited value for the monograph on *Solanum dulcamara* L., stipites. Therefore, a Community list entry cannot be recommended from a non-clinical point of view.

4. Clinical Data

4.1. Clinical Pharmacology

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

No information on the clinical pharmacology of the herbal substance or herbal preparation is available. After oral administration of the salt of the aglycone solasodine i.e. solasodine citrate, cardiotonic effects and a desensitising effect were observed in patients with rheumatic arthritis and ankylosing spondylitis (Morbus Bechterew) (Hänsel *et al*., 1994).

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

No information on the herbal substance or the herbal preparation is available.

4.2. Clinical Efficacy

No data from clinical trials of adequate quality are available. Safety information from some open clinical studies is reviewed under section 5. Clinical safety.

4.2.1. Dose response studies

No information on the herbal substance or the herbal preparation is available.

4.2.2. Clinical studies (case studies and clinical trials)

No information on the herbal substance or the herbal preparation is available.

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

No information on the herbal substance or the herbal preparation is available.

4.3. Overall conclusions on clinical pharmacology and efficacy

There are no data on clinical pharmacology or efficacy available for *Solanum dulcamara* L., stipites to support a well-established use indication.

On the basis of documented long-standing medicinal use, the requirement of plausibility for a therapeutic indication as a traditional herbal medicinal product for the relief of symptoms of mild chronic eczema is fulfilled for *Solanum dulcamara* L., stipites.

5. Clinical Safety/Pharmacovigilance

In the literature, *Solanum dulcamara* L. is regarded as a toxic plant and symptoms similar to solanine poisoning, such as abdominal pain, diarrhoea, nausea, vomiting, agitation, hypothermia and headache, have been described following ingestion of the fruit (Wolf, 1992; Bruneton, 1999). Roth *et al*. state that all plant parts are poisonous and that 30-40 unripe fruits of *Solanum dulcamara* L. are considered a deadly dose for a child (Roth *et al*., 1994). Fatal cases after ingestion of 10 fruits have been described in the literature (Roth *et al*., 1994; Frohne & Pfänder, 1987).

Solanum dulcamara L. stem is not recommended by the Council of Europe as a natural source of flavourings due to its inherent toxic potential and ensuing health risks. The stem (preparations and products thereof) is considered to be unfit for human consumption in any amount (Natural sources of flavourings, Rep No 3, Council of Europe, 2008). The Council of Europe report indicates that the FDA also classified the plant as an unsafe poisonous herb.

According to the European Commission database 'CosIng', which provides information on cosmetic substances and ingredients (contained in the Cosmetics Regulation EC No 1223/2009, Cosmetics Directive 76/768/EEC and Inventory of Cosmetic Ingredients), *Solanum dulcamara* L. stem extract can be used without restriction in cosmetics and is classified as a substance used for skin conditioning (i.e. used to maintain the skin in good condition). Information on the nature of the extract (extraction solvent used) is not available in 'CosIng'.

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

No information on toxicological/safety data of the herbal substance or herbal preparation is available. However, there are some open clinical studies on an ethanol extract (30% ethanol m/m) of the herbal substance (Schilcher *et al*., 2010) and one double-blind and controlled study on steroid alkaloid glycosides that may add some information on the clinical safety. The studies are presented below.

Cutaneous use

In an open study, 45 patients (aged 20 to 84 years) with chronic eczema were treated with an ointment containing an extract of the herbal substance (1:5, extraction solvent: ethanol 30% m/m, 10 g/100 g of the final product) 4 times daily for 3 weeks. Pruritus had to be present and at least one of the following symptoms: erythema, vesicles, formation of scabs, lichenification, swelling, weeping, and scalification. Forty patients completed the study and an improvement of the sum score of eight characteristic symptoms was reported. The safety of the product in the study was assessed as very good. One patient experienced a burning sensation in the skin after administration, possibly due to the ethanol content of the ointment (Eberhardt *et al*., 1995).

In an open study, 536 patients were treated with an ointment containing an extract of the herbal substance (1:5, extraction solvent: ethanol 30% m/m, 10 g/100 g of the final product) for 4 weeks. The diagnoses were atopical eczema (380 patients), contact dermatitis (106 patients), and other diagnoses with eczema. The symptoms itching, formation of wheals, erythema, weeping and scalification were generally recorded to improve during the trial. Five hundred and twenty six patients completed the four-week study. Six patients stopped the treatment by themselves (no reason given).

Twenty three patients experienced local side effects such as burning sensation in the skin and erythema and one patient showed urticaria (Oestreich & Stoeter, 1995).

A 0.005% mixture of solasodine glycosides (mainly solasonine and solamargine) was assessed for the safety and efficacy in the treatment of basal cell carcinoma every 12 hours (under occlusive dressing) for 8 weeks. The study included 94 patients (aged 32 to 95 years) and was a double-blind, randomised, placebo-controlled (vehicle), parallel group and multicentre study. Safety data were collected from all patients and the safety endpoint was assessment of the frequency, nature and severity of adverse events and evaluation of laboratory tests. The ITT group (62 patients) reported 286 adverse events compared to 133 adverse events in the vehicle group (32 patients). Ten patients in the treated group did not complete for various reasons; 6 out of 62 patients in the ITT group withdrew due to the severity of local irritation. Laboratory data did not reveal any clinically significant patterns of change for any parameter in the ITT group or the vehicle group. The authors concluded that there were no treatment-related severe adverse events (hospitalisation/death) (Punjabi *et al*., 2008).

Oral use

In an open study, 30 patients (mean age 35 years) with neurodermitis were treated with an extract of the herbal substance (1:5, extraction solvent: ethanol 30%) as oral drops, solution (40 drops, 4 times daily for 6 weeks). The treatment was reported to lead to a general improvement in itching and erythema. No adverse events were reported (Hölzer, 1992).

In an open study, 96 patients with itching dermatoses were treated with an extract of the herbal substance (1:5, extraction solvent: ethanol 30%) as tablets. 1-6 tablets were taken daily for 1-15 weeks. The diagnoses were atopic eczema (64 patients), chronic urticaria (17 patients), and allergic contact eczema (11 patients). At baseline, the symptoms of pruritus, wheals, erythema, weeping and scalification were judged according to a 4-point scale. During treatment, a decrease in the mean scores was observed. Adverse events were recorded in 3 patients. One patient interrupted the treatment because of eyelid oedema (Oestreich, 1993).

5.2. Patient exposure

No information on the herbal substance or herbal preparation is available.

5.3. Adverse events and serious adverse events and deaths

Skin sensitising, burning and erythematic effects have been observed in open clinical trials of the ethanol extract (1:5, extraction solvent: ethanol 30%) of the herbal substance, see section 5.1.

5.4. Laboratory findings

No information available on the herbal substance or herbal preparation is available.

5.5. Safety in special populations and situations

A report on *Solanum dulcamara* L. poisoning describes a 4-year-old girl, who presented to the emergency department in acute anticholinergic crisis from large woody nightshade berries ingestion. The patient responded to physostigmine-treatment. The child had symptoms more suggestive of the deadly nightshade species, *Atropa belladonna* L. A detailed laboratory analysis of the suspect berries revealed neither atropine nor hyoscyamine. Analysis did reveal steroids consistent with solanine (Ceha *et al*., 1997).

Scientific evidence for the safe use of herbal substance or herbal preparation during pregnancy or lactation is not available.

No studies or information on the use in children is available. The ethanol extract of *Solanum dulcamara* L., stipites (1:5, extraction solvent: ethanol 30% m/m, 10 g/100 g of the final product) has been registered in Sweden since 2006 for the relief of mild chronic eczema in adults and adolescents above 12 years of age. There are no safety issues reported from Sweden.

No information on drug interactions, drug abuse or withdrawal or rebound is available.

No effects on ability to drive or operate machinery or impairment of mental ability are anticipated after cutaneous use, although results of studies are not available.

5.6. Overall conclusions on clinical safety

Solanum dulcamara L. contains toxic steroid alkaloid glycosides and is regarded a toxic plant in the literature. The Council of Europe does not recommend *Solanum dulcamara* L., stem as a natural source of flavouring due to its toxicity. Due to a general lack of safety data on the herbal substance, oral use of the herbal substance or the herbal preparation cannot be recommended and the monograph only covers cutaneous use.

According to EU legislation, *Solanum dulcamara* L. stem extract (no information on the extraction solvent) can be used without restriction in cosmetics for skin conditioning within the EU. The substances of primary toxicological concern are steroid alkaloid glycosides and the issue of systemic toxicity can be anticipated to be much less following topical administration than following oral administration. Available documentation (information from handbooks, products available on the market and valid registrations within the EU record a long-standing and ongoing use of the herbal substance/preparation in the EU. No signals of clinical safety concern have been identified in the literature or based on pharmacovigilance systems information.

Because of the results from reproductive and developmental toxicity studies in animals on constituents and other structurally similar substances, the herbal substance and herbal preparation should not be recommended during pregnancy and lactation (see section 3.3.).

The use in children and adolescents under 18 years of age is insufficiently documented and cannot be recommended.

6. Overall conclusions

Well-established use is not accepted for *Solanum dulcamara* L., stipites, due to the lack of data on clinical efficacy.

Traditional medicinal use of *Solanum dulcamara* L., stipites, is well-documented in several handbooks throughout a period of at least 30 years, including at least 15 years within the EU. A traditional use in chronic itching eczema, chronic bronchitis, asthma, rheumatism, gout and obstinate skin eruptions has been described for *Solanum dulcamara* L., stipites. Most references include the treatment of eczema. The other conditions mentioned cannot be considered suitable for safe self-medication within the framework of the traditional use registration scheme.

Eczema is the most common skin disease. There are many different forms of eczema but they all include an inflammatory process in the upper layers of the skin. Eczema may vary in intensity and duration over time. Intense forms of eczema with severe itching, reddening, pustules and skin damage are conditions that require medical supervision. Such acute cases of eczema are clearly not suitable for

self-medication. But often the eczema becomes a more or less chronic condition that remains mild in intensity. It appears reasonable to limit the indication to mild, chronic eczema. This type of mild chronic eczema is often treated with mild corticosteroids within the framework of self-medication today. This indication also seems appropriate considering the rules that apply to traditional herbal medicinal products. At finalisation of the monograph, the HMPC decided to amend the wording of the indication to better reflect the intended use in patients with repeated relapses of mild eczema.

The product information should include a warning text advising the patient to see a doctor or a qualified health care practitioner if the symptoms worsen or persist longer than 2 weeks during the use of the product.

There is very limited clinical toxicological/safety data of the herbal substance and herbal preparations, but the herbal substance contains toxic steroid alkaloid glycosides, and additionally saponines that might facilitate the absorption of the alkaloids. *Solanum dulcamara* L. is regarded a toxic plant in the literature and the stem is not recommended in food by the Council of Europe due to its toxicity. Also, there is no official European Pharmacopoeia monograph on the quality of *Solanum dulcamara* L., stipites, with specifications limiting the amount of toxic constituents. Thus, it is not recommended to include the herbal substance or herbal preparation for oral use in the Community herbal monograph.

According to the current EU legislation, *Solanum dulcamara* L. stem extract (extract not specified) can be used without restrictions in cosmetics for maintenance of the skin in good condition. The formulation of a medicinal product for cutaneous use will limit the possible amount of substances available for systemic toxicity compared to oral administration. Although no toxicological data on the herbal substance or the herbal preparation for cutaneous use are available, an acceptable level of safety could be expected due to the documented long-standing cutaneous use with no serious adverse events reported.

Scientific evidence for the safe use of herbal substance or herbal preparation during pregnancy or lactation is not available. Because of positive results in reproductive and developmental toxicity studies in animals on constituents and structurally similar substances, the herbal substance and herbal preparation are not recommended during pregnancy and lactation (see section 3.3.).

A Community list entry for *Solanum dulcamara* L., stipites for oral or cutaneous use cannot be recommended in the absence of data on potential genotoxicity.

In summary, a monograph on *Solanum dulcamara* L., stipites for cutaneous use is established with the following indication:

‘Traditional herbal medicinal product for the symptomatic relief of mild recurrent eczema.

The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.’

Annex

List of references