28 January 2015
EMA/HMPC/586887/2014
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Hedera helix* L., folium

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

Draft – revision

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Hedera helix* L., folium
Herbal preparation(s)	a) Dry extract (DER 4-8:1), extraction solvent ethanol 24-30% m/m b) Dry extract (DER 6-7:1), extraction solvent ethanol 40% m/m c) Dry extract (DER 3-6:1), extraction solvent ethanol 60% m/m d) Liquid extract (DER 1:1), extraction solvent ethanol 70% V/V e) Soft extract (DER 2.2-2.9:1), extraction solvent ethanol 50% V/V: propylene glycol (98:2)
Pharmaceutical forms	Herbal preparations in solid or liquid dosage forms for oral use.
Rapporteur	J Wiesner
Assessor	M Peikert
Peer-reviewer	W Knöss

Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Hedera helix* L., folium. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Introduction

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

- Herbal substance(s)

Hederae folium (Ivy leaf) (European Pharmacopoeia 2008)

Whole or cut, dried leaves of *Hedera helix* L., collected in spring.

Content: minimum 3.0% of hederacoside C ($C_{59}H_{96}O_{26}$; Mr 1221) (dried herbal substance).

The species *Hedera helix* L., Araliaceae, is known under the synonyms: *Hedera caucasigena* POJARK; *H. chrysocarpa* WALSH; *Hedera helix* ssp. *caucasica* KLEOP.; *Hedera helix* var. *chrysocarpa* TEN.; *Hedera taurica* CARR.; *Hedera helix* var. *taurica* TOBLER (HagerROM, 2006). The species *Hedera helix* L., which is a source of the drug, is subdivided into three botanical varieties, *Hedera helix var. baltica, Hedera helix var. helix* and *Hedera helix* var. *hibernica.* (HagerROM, 2006).

In the European countries *Hedera helix* is designated as follow: German: Efeubätter, Rankenefeu, Mauerefeu, Totenranke, Epig; English: English Ivy, Common Ivy, Woodbind, Bindwood; French: Lierre à cautère, Lierre commun, Lierre des poètes, Lierre grimpant; Italian: Edera, Ellera; Spanish: Hiedra; Danish: Efeu, Vedbend; Dutch: Klimop; Norwegian: Bergflette, Eføi; Polish: Bluszcz; Russian: Pluszcz; Swedish: Murgröna; Czech: Břečtan obecný; Hungarian: Borostyán (HagerROM, 2006).

Constituents:

According to Wichtl (2004) the most important constituents of the plant are:

- About 2.5-6% mostly bidesmosidic triterpene saponins with hederagenin, oleanolic acid and bayogenin (= 2ß-hydroxyhederagenin) as aglycones and acylglycosidic sugar chains at C-28 of the carboxyl group
- Small amounts of monodesmosides such as α-hederin and hederagenin-3-O-ß-D-glucoside, which can develop during the drying process from the bisdesmoside in the fresh leaves by hydrolytic cleavage of the sugar chain at C-28
- The main saponin is the hederasaponin C (hederacoside C) with other hederasaponins (B, D, E, F, G, H and I) present as well. The content ratios of the hederasaponins (C : B : D : E : F : G : H : I) are about 1000 : 70 : 45 : 10 : 40 : 15 : 6 : 5
- Flavonoids such as quercetin and kaempferol including their 3-O-rutinosides and 3-O-glucosides (= isoquercitrin and astragalin)
- Caffeic acid derivates and other phenolics such as caffeic acid and dihydroxy-benzoic acid
- Coumarin glycoside scopolin and the polyacetylenes falcarinone, falcarinol and 11, 12-dihydrofalcarinol
- Phytosterols as stigmasterol, sitosterol, cholesterol, campesterol, α-spinasterol
- The volatile oil (in the fresh leaves 0.1-0.3%) consists of methyl-ethyl ketone, methylisobutyl ketone, trans-hexanal, germacrene D, ß-caryphyllene, sabinene, α- and ß-pinene
- Hamamiletol
- Free amino acids

- The occurrence of the alkaloid emetine could not be confirmed in recent studies (Czygan, 1990). From four varieties grown in Egypt the alkaloid emetine was isolated (Mahran *et al*., 1975). Convincing studies are missing (HagerROM, 2006).

- Herbal preparation(s)

See chapter 1.2.

- 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.

Ivy extracts are also used in combination with other herbal substances/herbal preparations. This monograph refers exclusively to monopreparations.

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

Table 1. Specified products on the market in the European Member State

Member State	Medicinal Product	Regulatory Status
Austria	1) 1 lozenge contains 26 mg dry extract (4-8:1), extraction solvent ethanol 30% (m/m)	MA 2005
	2) 1 capsule contains 26 mg dry extract (4-8:1), extraction solvent ethanol 30% (m/m)	MA 2005
	3) 1 effervescent tablet contains 50 mg dry extract (4-8:1), extraction solvent ethanol 30% (m/m)	MA 2005
	4) 100 g syrup contain 0.792g dry extract (6-7:1), extraction solvent ethanol 40% (m/m)	MA 2005
	5) 100 g oral solution contain 1.98 g dry extract (6-7:1), extraction solvent ethanol 40% (m/m)	MA 2005
	7) 1 effervescent tablet contains 25 mg dry extract (4-8:1), extraction solvent ethanol 30% (m/m)	MA 2007
	8) 1 effervescent tablet contains 50 mg dry extract (4-8:1), extraction solvent ethanol 30% (m/m)	MA 2003
	9) 1 capsule contains 26 mg dry extract (4-8:1), extraction solvent ethanol 30% (m/m)	MA 2002
	10) 100 g syrup contains 0.792 g dry extract (6-7:1), extraction solvent ethanol 40% (m/m)	MA 2002
	11) 100 g oral solution contains 1.98 g dry extract (6-7:1), extraction solvent ethanol 40% (m/m)	MA 2002
	12) 1 effervescent tablet contains 65 mg dry extract (5-7.5:1), extraction solvent ethanol 30% (m/m)	MA 2000
	13) 5 ml oral solution contains 35 mg dry extract (5-7.5:1), extraction solvent ethanol 30% (m/m)	MA 2007
	14) 2.5 mg oral solution contains 17.5 mg dry extract (5-7.5:1), extraction solvent ethanol 30% (m/m)	MA 1998
	15) 1 ml contains 20.0 mg dry extract (no further details)	MA 1989
Belgium	There are no preparations on the market. The herbal substance is available in combination products. The products are multi-ingredient herbal teas “authorised” since longer than 1962.	other

Czech Republic	1) Hederae helicis folii extractum fluidum 1:10 (prepared from Hederae folium 10.0g, Propylenglycolum 2.0 g, Ethanolum 96% 41.2 g, Aqua purificata ad 100.0 g) 100 g/100 g of the finished product	MA 2000
	2) Hederae helicis folii extractum spissum (2.2-2.9:1), extracted with the mixture of ethanol 50% (V/V) and propylenglycol 98:2 (0.8 g/100 ml of the finished product)	MA 1998
	3) Hederae helicis folii extractum siccum (6-7:1), extracted with ethanol 40% (m/m) (2.04 g/100 ml of the finished product)	MA 2007
	4) Hederae helicis folii extractum siccum (6-7:1), extracted with ethanol 40% (m/m) (0.9 g/100 ml of the finished product)	MA 2007
	5) Hederae helicis folii extractum siccum (5-7.5:1), extracted with ethanol 30% (m/m) (0.700 mg/100 ml of the finished product)	MA 2008
Denmark	The herbal substance is only available in combination products. One authorised product contains extracts of 3 combination substances: *Hedera helix* herba, *Thymus vulgaris* L., herba, *Glycyrrhiza glabra* L., radix	MA 1999
Estonia	1) 100 ml syrup contains 2.0 g ivy leaf soft extract (Extr. Hederae helic. Spiss.) (1:1), standardised	MA 2002
	2) 1 ml (=31 drops) contains 0.04 g extract from ivy leaves (2.2-2.9:1), extraction solvent: ethanol 50% by volume, propylene glycol (98:2)	MA 1999
	3) 100 ml solution contains 700 mg of dried ivy leaf extract (5-7.5:1), extraction solvent: ethanol 30% (m/m)	MA 1999
	4) 1 tablet contains 65 mg of dried ivy leaf extract (5-7.5:1), extraction solvent: ethanol 30% (m/m)	MA 2000
	5) 1ml solution contains 20 mg of dried ivy leaf extract (5-7.5:1), extraction solvent: ethanol 30% (m/m)	MA 2004
France	1) dry extract from Hederae helicis folium (5-7:1), extraction solvent: ethanol 30% (m/m)	MA 1997
	2) dry extract from Hederae helicis folium (4-6:1) extraction solvent: ethanol 30% (V/V)	MA 2001
Germany	1) dry extract from Hederae helicis folium (6-7:1), extraction solvent: ethanol 40% (m/m)	MA 1976
	2) dry extract from Hederae helicis folium (4-8:1), extraction solvent: ethanol 30% (m/m)	MA 1976
	3) dry extract from Hederae helicis folium (5-8:1), extraction solvent: ethanol 30% (m/m)	MA 1976
	4) soft extract from Hederae helicis folium (2.2-2.9:1), extraction solvent: ethanol 50% (V/V):propylene glycol (98:2)	MA 1976
	5) dry extract from Hederae helicis folium (5-7.5:1), extraction solvent: ethanol 30% (m/m)	MA 1976
	6) liquid extract from Hederae helicis folium (1:1), extraction solvent: ethanol 70% (V/V)	MA 1976
	7) liquid extract from Hederae helicis folium (1:7-9), extraction solvent: ethanol 50% (V/V):propylene glycol (98:2)	MA 1990
	8) dry extract from Hederae helicis folium (3-6:1), extraction solvent: ethanol 60% (m/m)	MA 1976
	9) dry extract from Hederae helicis folium (4-5:1), extraction	MA 2001

	solvent: ethanol 30% (m/m)	
Greece	100 ml solution contains 700 mg of dried ivy leaf extract (5-7.5:1), extraction solvent: ethanol 30% (m/m)	MA 2002
Hungary	Hederae helicis folii soft extract (2.2-2.9:1), extraction solvent: ethanol 50% (V/V): propyleneglycol (98:2)	MA 1995
Latvia	1) Hederae helicis folii extractum spissum (2.2-2.9:1), extraction solvent: ethanol 50% (V/V), propylenglycol (98:2), pharmaceutical form: syrup 8 mg/ml; oral drops, solution 40 mg/ml 2) Hederae helicis folii extractum siccum (5-7.5:1), extraction solvent: ethanol 30% (m/m), pharmaceutical form: syrup 7 mg/ml; oral drops solution 20 mg/ml; effervescent tablets 65 mg	MA 1995 MA 1999
Lithuania	Hederae helicis folii soft extract (2.2-2.9:1), extraction solvent: ethanol 50% (V/V): propyleneglycol (98:2)	MA 1998
Norway	The herbal substance is only available in one combination product. *Hedera helix* L., herba is in combination with *Thymus vulgaris* L., herba and *Glycyrrhiza glabra* L., radix.	Traditional use
Poland	1) Syrup Hederae helicis folii extractum siccum (5-7.5:1), extraction solvent: ethanol 30% (m/m) 2) Syrup Hederae helicis folii extractum spissum (2.2-2.9:1), extraction solvent: ethanol 50% (V/V) 3) Tablets Hederae helicis folii extractum siccum (4-8:1), extraction solvent: ethanol 30% (m/m) 4) Oral drops Hederae helicis folii extractum siccum (5-7.5:1), extraction solvent: ethanol 30% (m/m) 5) Syrup Hederae helicis folii extractum siccum (4-8:1), extraction solvent: ethanol 30% (m/m)	MA 2000 MA 2000 MA 2001 MA 2000 MA 2000
Slovak Republic	1) Extractum spissum, (1:1), 2.0 g in 100 ml of syrup 2) Extractum spissum, (1:1), 1 ml (31 drops) contains 0.1 g extract 3) Extractum siccum, ethanol 30% (m/m), (5-7.5:1), 700 mg in 100 ml of syrup 4) Extractum siccum, ethanol 30% (m/m) , (5-7.5:1), 65 mg in 1 tablet 5) Hederae helicis folii soft extract (2.2-2.9:1), extraction solvent: ethanol 50% (V/V): propyleneglycol (98:2) There are combination products on the market. The main combination substances are Thymi extractum fluidum and Hederae helicis extractum.	MA 1997 MA 2001 MA 2007 MA 2007 MA 2001
Slovenia	1) 1 ml of syrup contains 7 mg of *Hedera helix* L., folium; extractum siccum) (5-7.5:1), extraction solvent: 30% (V/V) ethanol 2) 1 tablet contains 65 mg of *Hedera helix* L., folium; extractum siccum) (5-7.5:1), extraction solvent: 30% (V/V) ethanol	MA 2001 MA 2001
Spain	Dry extract (4-6:1), extraction solvent ethanol 30% (V/V)	MA 2001
Sweden	Ethanolic extract (5-7.5:1), ethanol 30%. 1 ml corresponding to 35-52.5 mg herbal substance Comment of the Swedish agency: “The product is approved as a so called natural remedy.”	Traditional use 2006

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Combinations
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Denmark	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketing authorisation
France	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketing authorisation
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketing authorisation
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 marketing authorisation
Norway	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Combination
Poland	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketing authorisation
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketing authorisation

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

Other: If known, it should be specified or otherwise add 'Not Known'

This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

A literature search was performed on 21 April 2008 using the DIMDI database information system. The searched databases were "X-med-all": CCOO, CDSR93, DAHTA, GA03, GM03, HG05, KR03, KL97, KP05, CDAR94, INHTA, SM78, SPPP, SP97, TVPP, TV01, CCTR93, ME60, ZT00, MK77, ED93, HN69, CV72, CB85, NHSEED, AZ72, IA70, BA26, EM74, DH64, EA08, DD83, II78, IS74. Further literature search was performed in the BfArM-database "Lidos". The search term was "hedera, ivy". The literature list was examined and 245 articles were ordered. Additional hand searches were performed in books on herbal medicines and plant monographs in the BfArM own library. The bibliographies of included trials and other relevant reviews were searched to identify further potential trials.

In the list of references, the references supporting the assessment report are listed first and secondly references used but not introduced into the assessment report. An additional search in the same databases was performed on 26 January 2009 for the period from April 2008 to January 2009.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Madaus (1938) notes, that ivy leaf is mentioned since Dioskurides and Hippokrates. The phytotherapeutical books of the 16th would describe very different indications as jaundice, lithiasis dysenterie, emenaegogum etc. The oral use of ivy (1/2 teaspoon as infusion as daily dose) at rachitis, lithiasis, bile- and liver dysfunction is recommended.

Steinmetz (1961) resumes that although the plant is decidedly poisonous (in large doses death can occur by respiratory paralysis!), the leaves and berries have some good uses in therapy - provided they are administered in safe doses – as a stimulating medicine for chronic catarrh, bronchitis, and especially whooping cough, for which Leclerc said the leaves deserve a place of honour as a "specific". The use of ivy in whooping cough was the object of clinical tests by Leuret (of Bordeaux), who demonstrated its action. In small doses and taken internally, the leaf is a very active vaso-dilator. However, in large doses, it is a vaso-constrictor which slows the beat of the heart and at the same time increases its tonus. A daily intake of 15 drops (children) to 50 drops (adults) of a tincture of the leaves, in doses of 5 to 15 drops, is said to restore hypertension to normal level within a few days and without recurrence taking place soon after discontinuance. Experience has shown that ivy, applied externally, acts as a very efficacious moderator of the sensitivity of the peripheral nerves, which finds its principal indications in the treatment of rheumatism, neuritis, neuralgia and particular cellulagias. The pounded leaves are also used externally as parasitic and insecticide, e.g., against scabies and lice, including fauves.

According to the monograph *Hedera helix* of the Kommission D (1986), ivy is also used in homeopathic preparations. The homeopathic preparations are indicated in diseases of the respiratory tract, gastrointestinal tract, rheumatic diseases and hyperthyroidism. Due to the lack of clinical studies, those indications are not considered in this assessment report.

Literature on current traditional use of *Hedera helix* leaves (not for marketed preparations)

Chichiricco (1980) collected information about traditional phytotherapy in the Subequana valley Abruzzo, Central Italy. He noted the boiled leaves of *Hedera helix* L., applied to the part of the body afflicted, fight ringworm, scabies and worm. The cataplasm of the leaves would rapidly heal furuncles.

Brussel (2004) focused in his study on plants used for medicinal purposes in the Mt. Pelion area of Greece. He reported the traditional use of a libation made by letting crushed ivy leaves set in a container of red wine for two weeks. It was used to treat depression and was said to have stimulant,

narcotic and hallucinogenic properties that were dependent on the amount that was drunk.
Kültür (2007) collected information on traditional medicinal plants of the region of Kirklareli Province in Turkey. A decoction of the leaves of *Hedera helix* L. was used for diabetes and "blood depurative". The dosage reported was one teacup two times daily for 7-8 days.
De Smet *et al.* (1993), Hausen *et al.* (1987), Hausen (1988) and Facino (1990) reported that ivy leaves were also incorporated into topical cosmetic preparations, e.g., for the treatment of cellulites and shampoos. No marketed topical preparations exist currently in the member states.

The current use of ivy is described in many recent phytotherapeutic textbooks and has been introduced into Pharmacopoeias or accepted collections in the European countries:

- Hederae folium (Ivy leaf). European Pharmacopoeia 01/2008:2148 corrected 6.0
- Hederae helicis folium, Efeublätter, German Kommission E Monograph (1988) Indication: "Catarrh of the respiratory passages and for symptomatic treatment of chronic inflammatory bronchial illnesses."
- Hedera helix L. in Medicaments à base plantes (1998): "Traditional used topically as a soothing and antipruriginous application for dermatological ailments and as a protective treatment for cracks, grazes, chapped skin and insect bites", therapeutic indication 86 "traditionally used as an adjuvant to slimming diets". Hedera helix stem wood therapeutic indication nr. 111 "Traditionally used in the symptomatic treatment of cough", therapeutic indication nr. 113: "traditionally used during benign acute bronchial conditions."
- Hederae helicis folium in HagerROM (2006): "Catarrh of the respiratory passages and for symptomatic treatment of chronic inflammatory bronchial illnesses."
- Hederae helicis folium in ESCOP Monographs (2003): "Coughs, particularly when associated with hypersecretion of viscous mucus; as adjuvant treatment of inflammatory bronchial diseases."
- Hederae folium in Wichtl (2004): "Extracts of ivy leaf have expectorant and spasmolytic actions. They are used primarily as expectorants and antispasmodics for catarrh of the respiratory passages and for symptomatic treatment of chronic inflammatory bronchial illnesses."
- IVY. In Williamson (2003): "Cathartic, febrifuge, diaphoretic, anthelmintic. It is widely used in preparations for bronchitis and catarrh, as an expectorant. Ivy extracts are often used in cosmetic preparations to treat cellulite, with some success."
- Ivy. In: Sweetmann (2007) "Ivy leaf is used for catarrh and chronic inflammation of the respiratory tract. It has also been applied externally."
- Ivy Leaf. In British Pharmacopoeia (2008)
- Lierre grimpant. Valnet (1983): internal use: pertussis, chronical bronchitis, tracheitis, laryngitis, rheumatism, lithiasis, hypertension, external use: cellulites, rheumatism, oedemas, erythema/burn

There are no convincing data demonstrating the traditional oral use of ivy leaf as mono-tea preparation. The German Kommission E Monograph defines 0.3 g herbal substance as daily dosage. Ivy leaf is not included in the German Standardzulassungen, where the most important herbal tea preparations are listed. In Germany, there are only data on older tea preparations (1976) but currently no herbal substance for tea as mono-preparation is on the market. The request of information gives no information on tea preparations and their posology in other European countries. In many phytotherapeutic books or generally accepted phytotherapeutic collections, for example WHO Monographs, British Herbal Compendium, British Herbal Pharmacopoeia 1996, ivy leaf is missing completely. Only Valnet (1979) recommends a daily dosage of 3 cups of an infusion of 3 soup spoons (unclear fresh or dry leaves) per 1000 ml water.

Conclusion: There is neither traditional nor well established use for the herbal tea preparation of ivy leaf. Most preparations from ivy leaf contain hydro-ethanolic dry extracts in ethanol-containing or ethanol-free oral liquids.

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

For the following ivy leaf preparations a period of at least 30 years of medical use, as requested by Directive 2004/24/EC for qualification as a traditional herbal medicinal product, is fulfilled and additionally a marketing authorisation has been granted (see Table 1). This assessment report is discussing which preparations are suitable for well-established and which ones for traditional use:

1. dry extract (4-8:1), extraction solvent: ethanol 30% (m/m)
2. dry extract (5-7.5:1), extraction solvent: ethanol 30% (m/m)
3. dry extract (5-8:1), extraction solvent: ethanol 30% (m/m)
4. dry extract (6-7:1), extraction solvent: ethanol 40% (m/m)
5. dry extract (3-6:1), extraction solvent: ethanol 60% (m/m)
6. soft extract (2.2-2.9:1), extraction solvent: ethanol 50% (V/V):propyleneglycol (98:2)
7. liquid extract (1:1), extraction solvent: ethanol 70% (V/V)

For the following ivy leaf preparation the period of at least 30 years of medicinal use is not fulfilled:

dry extract (4-6:1), extraction solvent: ethanol 30% (V/V).

The analytical comparison of the latter ivy leaf dry extract (4-6:1); extraction solvent: ethanol 30% (V/V) used in commercial syrups with ivy leaf dry extract (5-7.5:1); extraction solvent: ethanol 30% (m/m) showed no significant difference between the chemical composition (similar qualitative and quantitative composition based on the main triterpene saponins and main phenolic compounds) of the two preparations (analytical documentation Arkopharma). The HMPC therefore decided to include the preparation in the WEU-part of the monograph. These two preparations are combined as: dry extract (DER 4-8:1); extraction solvent: ethanol 24-30% (m/m).

The specified products on the market in the European Member States are used orally. The route of administration depends on the pharmaceutical form (coated tablets, capsules, effervescent tablets, drops or oral solution). The preparations are taken with a glass of water. The indications with regard to the respiratory tract are the following:

a) “Catarrh of the respiratory passages”

   “Relief of cough associated with catarrhs of the respiratory tract”

   “Acute catarrhs of the airways with cough”

   “Traditionally used in the symptomatic treatment of coughs”

   They can be summarized in “Medicinal product used in common cold associated with cough”.

b) “Traditionally used during benign acute bronchial conditions”

   “Symptomatic treatment of chronic inflammations in the bronchia.”

   “Symptomatic treatment of chronic inflammatory bronchial disorders”

   “Acute inflammations of the respiratory tract accompanied by coughing”

They can be summarised in “Symptomatic treatment of acute and chronic inflammatory bronchial disorders”.

The duration of use is regulated by a warning in the predominant cases. Patients are asked to consult a doctor if the symptoms persist longer than 4-7 days.

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

1. dry extract (4-8:1), extraction solvent ethanol 30 % (m / m)

Posology of the specified products	Posology of the preparation
1 preparation (Austria): 1 lozenge contains 26 mg dry extract *Adults and adolescents*: 2 x 1 lozenge *Children 4-11 years:* 1 x 1 lozenge (MA 2005)	*Adults:* Single dose: 26 mg dry extract (corresponding to 156 mg herbal substance) Daily dose: 52 mg dry extract (corresponding to 312 mg herbal substance) *Children 4-11 years:* Single dose and daily dose: 26 mg dry extract (corresponding to 156 mg herbal substance)
1 preparation (Austria) 1 capsule contains 26 mg dry extract *Adults and adolescents:* 3 x 1-2 capsules (MA 2005)	*Adults:* Single dose: 26-52 mg dry extract (corresponding to 156-312 mg herbal substance) Daily dose: 78-156 mg dry extract (corresponding to 468-936 mg herbal substance)
1 preparation (Austria) and 4 products (Germany) 1 effervescent tablet contains 50 mg dry extract *Adults and, adolescents:* 1 x 1 effervescent tablet (MA 2005)	*Adults:* Single dose: 50 mg dry extract (corresponding to 300 mg herbal substance) Daily dose: 50 mg dry extract (corresponding to 300 mg herbal substance)
1 preparation (Austria) 1 effervescent tablet contains 25 mg dry extract *Adults and adolescents:* 3 x 2 effervescent tablets *Children 4-11 years:* 3 x 1 effervescent tablet (MA 2007)	*Adults:* Single dose: 50 mg dry extract (corresponding to 300 mg herbal substance) Daily dose: 150 mg dry extract (corresponding to 900 mg herbal substance) *Children 4-11 years:* Single dose: 25 mg dry extract (corresponding to 150 mg herbal substance) Daily dose: 75 mg dry extract (corresponding to 450 mg herbal substance)
1 preparation (Austria) 1 effervescent tablet contains 50 mg dry extract *Adults and adolescents:* 3 x 1 effervescent tablet *Children 4-11 years:* 1-2 x 1 effervescent tablet	*Adults:* Single dose: 50 mg dry extract (corresponding to 300 mg herbal substance) Daily dose: 150 mg dry extract (corresponding to 900 mg herbal substance) *Children 4-11 years:*

Posology of the specified products	Posology of the preparation
(MA 2003)	Single dose: 50 mg dry extract (corresponding to 300 mg herbal substance) Daily dose: 50-100 mg dry extract (corresponding to 300-600 mg herbal substance)
1 preparation (Austria) 1 capsule contains 26 mg dry extract *Adults and adolescents:* 3 x 1-2 capsules *Children 4-11 years:* 3 x 1 capsule (MA 2002)	*Adults:* Single dose: 26-52 mg dry extract (corresponding to 156-312 mg herbal substance) Daily dose: 78-156 mg dry extract (corresponding to 468-936 mg herbal substance) *Children 4-11 years:* Single dose: 26 mg dry extract (corresponding to 156 mg herbal substance) Daily dose: 78 mg dry extract (corresponding to 468 mg dry extract)
3 preparations (Germany) 1 oral gum contains 26 mg dry extract *Adults and adolescents:* 2 x daily 1 gum	*Adults:* Single dose: 26 mg dry extract (corresponding to 156 mg herbal substance) Daily dose: 52 mg dry extract (corresponding to 312 mg herbal substance)
1 preparation (Germany) 15 ml (= 19.125 g) syrup contains 50 mg dry extract *Adults and adolescents:* 3 x daily 5 ml	*Adults:* Single dose: 16.7 mg dry extract (corresponding to 100 mg herbal substance) Daily dose: 50 mg dry extract (corresponding to 300 mg herbal substance)
100 g (= 86.6 ml) oral liquid contains 0.25 g dry extract *Adults and adolescents:* 3 x daily 12 ml *Children 6-11 years:* 3 x daily 8 ml *Children 1-5 years:* 3 x daily 4 ml	*Adults:* Single dose: 34.6 mg dry extract (corresponding to 208 mg herbal substance) Daily dose: 105 mg dry extract (corresponding to 623 mg herbal substance) *Children 6-11 years:* Single dose: 23 mg dry extract (corresponding to 138 mg herbal substance) Daily dose: 69 mg dry extract (corresponding to 415 mg herbal substance) *Children 1-5 years:* Single dose: 11.5 mg dry extract (corresponding to 69 mg herbal substance) Daily dose: 34.5 mg dry extract (corresponding to 208 mg herbal substance)
3 preparations (Germany) 1 effervescent tablet contains 31.5 mg dry extract *Adults and adolescents:* 2 x daily 1 (corresponding to 378 mg herbal substance per day)	*Adults:* Single dose: 31.5 mg dry extract (corresponding to 198 mg herbal substance) Daily dose: 63 mg dry extract (corresponding to 378 mg herbal substance)

Posology of the specified products	Posology of the preparation
1.2 g (= 1 measuring spoon) instant herbal tea contain 16.7 mg dry extract *Adults and adolescents:* 3 x daily 1 measuring spoon with 1.2 g instant herbal tea dissolved in 150 ml of hot water (corresponding to 300 mg herbal substance per day)	*Adults and adolescents:* Single dose: 16.7 mg dry extract (corresponding to 100 mg crude herb) Daily dose: 50 mg dry extract (corresponding to 300 mg crude herb)
3 preparations (Germany) 1 coated tablet contains 25 mg dry extract *Adults and adolescents:* 2 x daily 1 containing 25 mg dry extract (corresponding to 300 mg herbal substance per day)	*Adults and adolescents:* Single dose: 25 mg dry extract (corresponding to 150 mg crude herb) Daily dose: 50 mg dry extract (corresponding to 300 mg crude herb)
	Summary of posology for dry extract (4-8:1), extraction solvent ethanol 30 % (m/m) *Adults and adolescents:* Single dose: 16.7-52 mg dry extract (corresponding to 100-312 mg herbal substance) Daily dose: 50-156 dry extract (corresponding to 300-936 herbal substance) *Children 6-11 years:* Single dose: 23-50 mg dry extract (corresponding to 138-300 mg herbal substance) Daily dose: 50-100 mg dry extract (corresponding to 300-600 mg herbal substance) *Children 1-5 years:* Single dose: 11.5 mg dry extract (corresponding to 69 mg herbal substance) Daily dose: 34.5 mg dry extract (corresponding to 208 mg herbal substance)

2. dry extract (5-7.5:1), extraction solvent: ethanol 30 % (m/m)

Posology of the specified products	Posology of the preparation
1 preparations (Austria) and 1 preparation (Germany) 1 effervescent tablet contains 65 mg dry extract (5-7.5:1), extraction solvent ethanol 30% (m/m) *Adults and adolescents:* 2 x 1 effervescent tablet *Children 4-11 years:* 3 x 1/2 effervescent tablet	*Adults:* Single dose: 65 mg dry extract (corresponding to 406 mg herbal substance) Daily dose: 130 mg dry extract (corresponding to 812 mg herbal substance) *Children 4-11 years:* Single dose: 32.5 mg (corresponding to 203 mg herbal substance) Daily dose: 97.5 mg dry extract (corresponding to 609 mg herbal substance)
1 preparation (Austria)	*Adults:*

Posology of the specified products	Posology of the preparation
5 ml oral solution contains 35 mg dry extract (5-7.5:1), extraction solvent ethanol 30% (m/m) *Adults and adolescents:* 3 x 5 ml	Single dose: 35 mg dry extract (corresponding to 219 mg herbal substance) Daily dose: 105 mg dry extract (corresponding to 656 mg herbal substance)
1 preparation (Austria) 2.5 (100) ml oral solution contains 17.5 mg (0.7 g) dry extract (5-7.5:1), extraction solvent ethanol 30% (m/m) *Adults and adolescents:* 3-5 x 5 ml *Children 4-11 years:* 3-5 x 2.5 ml 1 preparation (Germany) *Adults and adolescents:* 3 x 5 ml *Children 6-11 years:* 2 x 5 ml *Children 0-5 years:* 2 x 2.5 ml	*Adults:* Single dose: 35 mg dry extract (corresponding to 219 mg herbal substance) Daily dose: 105-175 mg dry extract (corresponding to 656-1093 mg herbal substance) *Children 4-11 years:* Single dose: 17.5 mg dry extract (corresponding to 109 mg herbal substance) Daily dose: 52.5-87.5 mg dry extract (corresponding to 328-547 mg herbal substance) *Adults and adolescents:* Single dose: 35 mg dry extract (corresponding to 219 mg herbal substance) Daily dose: 105 mg dry extract (corresponding to 656 mg herbal substance) *Children 6-11 years:* Single dose: 35 mg dry extract (corresponding to 219 mg herbal substance) Daily dose: 70 mg dry extract (corresponding to 438 mg herbal substance) *Children 0-5 years:* Single dose: 17.5 mg dry extract (corresponding to 109 mg herbal substance) Daily dose: 35 mg dry extract (corresponding to 219 mg herbal substance)
3 preparations (Germany) 1 ml (=29 drops) contains 0.02 g dry extract *Adults and adolescents > 10 years:* 3 x daily 24 drops (corresponding to 50.4 mg dry extract per day) *Children 4-10 years:* 3 x daily 16 drops (corresponding to 33.6 mg dry extract per day) *Children 1-4 years:* 3 x daily 12 drops (corresponding to 25.2 mg dry extract per day)	*Adults and adolescents > 10 years:* Single dose: 16.8 mg dry extract (corresponding to 105 mg herbal substance) Daily dose: 50.4 mg dry extract (corresponding to 315 mg herbal substance) *Children 4-10 years:* Single dose: 11.2 mg dry extract (corresponding to 70.3 mg herbal substance) Daily dose: 33.6 mg dry extract (corresponding to 210 mg herbal substance) *Children 1-4 years:* Single dose: 8.4 mg dry extract (corresponding to 52.5 mg herbal substance) Daily dose: 25.2 mg dry extract (corresponding to 157.5 mg herbal substance)
1 preparation (Germany)	*Adults and adolescents:*

Posology of the specified products	Posology of the preparation
Adults and adolescents: 3 x daily 2 tablets containing each 25 mg dry extract (corresponding to 150 mg dry extract per day)	Single dose: 50 mg dry extract (corresponding to 312.5 mg herbal substance) Daily dose: 150 mg dry extract (corresponding to 937.5 mg herbal substance)
Adults and adolescents: 3 x daily 5 ml (1 bag) containing 35 mg dry extract (corresponding to 105 mg dry extract per day)	*Adults and adolescents:* Single dose: 35 mg dry extract (corresponding to 218 mg herbal substance) Daily dose: 105 mg dry extract (corresponding to 656 mg herbal substance)
	Summary of posology for dry extract (5-7.5:1), extraction solvent: ethanol 30 % (m/m) *Adults and adolescents:* Single dose: 16.8-65 mg dry extract (corresponding to 105-406 mg herbal substance) Daily dose: 50.4-175 dry extract (corresponding to 315-1093 mg herbal substance) *Children 6-11 years:* Single dose: 11.2-32.5 mg dry extract (corresponding to 70.3-203 mg herbal substance) Daily dose: 33.6-97.5 mg dry extract (corresponding to 210-609 mg herbal substance) *Children 1-5 years:* Single dose: 8.4-17.5 mg dry extract (corresponding to 52.5-109 mg herbal substance) Daily dose: 25.2-35 mg dry extract (corresponding to 157-219 mg herbal substance

3. dry extract (5-8:1), extraction solvent: ethanol 30 % (m/m)

Posology of the specified products	Posology of the preparation
1 preparation (Germany) 100 ml contains 154 mg dry extract *Adults and adolescents:* 3 x daily 10 ml	*Adults:* Single dose: 15.4 mg dry extract (corresponding to 100 mg herbal substance) Daily dose: 46.2 mg dry extract (corresponding to 300 mg herbal substance)

4. dry extract (6-7:1), extraction solvent: ethanol 40 % (m/m)

Posology of the specified products	**Posology of the preparation**
1 preparation (Austria) 100 g syrup contains 0.792 g dry extract (6-7:1) extraction solvent ethanol 40% (m/m) *Children < 1 year:* 2 x 1 ml *Children 1-3 years:* 3 x 1 ml *Children 4-11 years:* 2 x 2 ml *Adults and adolescents:* 3 x 2 ml	No information about density (mg/ml) was given.

Posology of the specified products	Posology of the preparation
1 preparation (Austria) 100 g oral solution contains 1.98 g dry extract (6-7:1) extraction solvent ethanol 40% (m/m) *Children <1 year:* 3 x 8 drops *Children 1-3 years:* 3 x 12 drops *Children 4-11 years:* 2 x 16 drops *Adults and adolescents:* 3 x 25 drops	No information about density (mg/drop) was given.
1 preparation (Austria) 100 g syrup contains 0.792 g dry extract (6-7:1) extraction solvent ethanol 40% (m/m) *Children 1-3 years:* 3 x 1 ml *Children 4-11 years:* 2 x 2 ml *Adults and adolescents:* 3 x 2 ml	No information about density (mg/ml) was given.
1 preparation (Austria) 100 g oral solution contains 1.98 g dry extract (6-7:1) extraction solvent ethanol 40% (m/m) *Children <1 year:* 3 x 6 drops *Children 1-3 years:* 3 x 9 drops *Children 4-11 years:* 2 x 16 drops *Adults and adolescents:* 3 x 25 drops	No information about density (mg/drop) was given.
4 preparations (Germany) 100 ml (= 110 g) oral liquid contains 0.871 g dry extract *Adults and adolescents:* 3 x daily 1.8 ml *Children 1-4 years:* 2 x daily 1 ml *Children 5-11 years:* 1-2 x daily 1.8 ml	*Adults:* Single dose: 15.6 mg dry extract (corresponding to 102 mg herbal substance) Daily dose: 46.8 mg dry extract (corresponding to 306 mg herbal substance) *Children 5-11 years:* Single dose: 15.6 mg dry extract (corresponding to 102 mg herbal substance) Daily dose: 15.6-31.2 mg dry extract (corresponding to 102-204 mg herbal substance) *Children 1-4 years:* Single dose: 8.7 mg dry extract (corresponding to 56.5 mg herbal substance) Daily dose: 17.4 mg dry extract (corresponding to 113 mg herbal substance)
5 preparations (Germany) 100 g oral liquid contains 1.98 g dry extract 10 drops oral liquid corresponding to 75 mg herbal substance (11.55 mg dry extract) *Adults and adolescents:* 3 x daily 12-15 drops 3 preparation of this 3 preparations contains a	*Adults:* Single dose: 13.8-17.2 mg dry extract (corresponding to 90-112 mg herbal substance) Daily dose: 41.4-51.6 mg dry extract (corresponding to 270-335 mg herbal substance) *Children 4-12 years:* Single dose: 11.55 mg dry extract (corresponding to 75 mg herbal substance) Daily dose: 34.7 mg dry extract

Posology of the specified products	Posology of the preparation
posology for children: *Children 4-11 years:* 3 x 10 drops *Children 1-3 years:* 3 x 7 drops	(corresponding to 225 mg herbal substance) *Children 1-3 years:* Single dose: 8 mg dry extract (corresponding to 53 mg herbal substance) Daily dose: 25 mg dry extract (corresponding to 160 mg herbal substance)
4 preparations (Germany) 100 ml oral liquid contains 0.9 g dry extract *Adults and adolescents:* 3 x daily 2 ml (corresponding to 350 mg herbal substance per day) *Children 4-11 years:* 3 x daily 1.5 ml (corresponding to 260 mg herbal substance per day); one preparation: 2 x daily 2 ml (corresponding to 230 mg herbal substance per day) *Children 1-3 years:* 3 x daily 1 ml (corresponding to 175 mg herbal substance per day)	*Adults:* Single dose: 18 mg dry extract (corresponding to 117 mg herbal substance) Daily dose: 54 mg dry extract (corresponding to 350 mg herbal substance) *Children 4-12 years:* Single dose: 13.5 / 18 mg dry extract (corresponding to 88 / 117 mg herbal substance) Daily dose: 40 / 36 mg dry extract (corresponding to 260 / 230 mg herbal substance) *Children 1-3 years:* Single dose: 9 mg dry extract (corresponding to 58 mg herbal substance) Daily dose: 27 mg dry extract (corresponding to 175 mg herbal substance)
100 ml oral liquid contains 2.08 g dry extract; 1 ml = 29 drops *Adults and adolescents:* 3 x daily 20-25 drops (corresponding to 280-350 mg herbal substance per day)	*Adults:* Single dose: 14-18 mg dry extract (corresponding to 93-117 mg herbal substance) Daily dose: 43-54 mg dry extract (corresponding to 280-350 mg herbal substance)
2 preparations (Germany) 100 ml oral liquid contain 2.040 g dry extract *Adults and adolescents:* 3 x daily 27 drops (corresponding to 318 mg herbal substance per day) *Children 4-11 years:* 3 x daily 21 drops (corresponding to 245 mg herbal substance per day)	*Adults and adolescents* Single dose: 16.3 mg dry extract (corresponding to 106 mg herbal substance) Daily dose: 49 mg dry extract (corresponding to mg crude 318 herbal substance) *Children 4-11 years:* Single dose: 12.5 mg dry extract (corresponding to 82 mg herbal substance) Daily dose: 38 mg dry extract (corresponding to 245 mg herbal substance)
1 preparation (Germany) 50 g (= 47.4 ml) oral liquid contain 0.99 g dry extract *Adults and adolescents:* 3 x daily 21-26 drops (corresponding to 270-338 mg herbal substance per day) *Children 5-11 years:* 3 x daily 14-17 drops (corresponding to 180-	*Adults and adolescents:* Single dose: 13.8-17.3 mg dry extract (corresponding to 90-112 mg herbal substance) Daily dose: 41.5-52 mg dry extract (corresponding to 270-338 mg herbal substance) *Children 5-11 years:* Single dose: 9.2-11.5 mg dry extract (corresponding to 60-75 mg herbal substance) Daily dose: 27.7-34.6 mg dry extract

Posology of the specified products	Posology of the preparation
225 mg herbal substance per day) *Children 1-4 years:* 3 x daily 10-14 drops (corresponding to 135-180 mg herbal substance per day)	(corresponding to 180-225 mg herbal substance) *Children 1-4 years:* Single dose: 6.9-9.2 mg dry extract (corresponding to 45-60 mg herbal substance) Daily dose: 20.7-27.7 mg dry extract (corresponding to 135-180 mg herbal substance)
	Summary for dry extract (6-7:1) extraction solvent: ethanol 40% (m/m) *Adults and adolescents:* Single dose: 13.8-18 mg dry extract (corresponding to 90-117 mg herbal substance) Daily dose: 41.4-54 mg dry extract (corresponding to 270-350 mg herbal substance) *Children 5-11 years:* Single dose: 9.2-18 mg dry extract (corresponding to 60-117 mg herbal substance) Daily dose: 15.6-40 mg dry extract (corresponding to 102-260 mg herbal substance) *Children 1-4 years:* Single dose: 6.9-9 mg dry extract (corresponding to 45- 8 mg herbal substance) Daily dose: 17.4–27.7 mg dry extract (corresponding to 113-180 mg herbal substance)

5. soft extract (2.2-2.9:1) extraction solvent: ethanol 50% (V/V):propylene glycol (98:2)

Posology of the specified products	Posology of the preparation
3 preparations (Germany) 1 ml (= 31 drops) oral liquid contains 0.04 g extract *Adults and adolescents >10 years:* 3 x daily 31 drops *Children 4-10 years:* 3 x daily 21 drops *Children 2-4 years:* 3 x daily 16 drops	*Adults:* Single dose: 40 mg extract (corresponding to 100 mg herbal substance) Daily dose: 120 mg extract (corresponding to 300 mg herbal substance) *Children 5-10 years:* Single dose: 26.6 mg extract (corresponding to 68 mg herbal substance) Daily dose: 80 mg extract (corresponding to 200 mg herbal substance) *Children 2-4 years:* Single dose: 20 mg extract (corresponding to 51 mg herbal substance) Daily dose: 60 mg extract (corresponding to 150 mg herbal substance)

Posology of the specified products	Posology of the preparation
1 preparation (Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Slovakia) 100 ml oral liquid contains 0.8 g extract *Adults and adolescents >10 years:* 3 x daily 5 ml (corresponding to 300 mg herbal substance per day) *Children 4-10 years:* 4 x daily 2.5 ml (corresponding to 200 mg herbal substance per day) *Children 1-4 years:* 3 x daily 2.5 ml (corresponding to 150 mg herbal substance per day) *Children 0-1 year:* 1 x daily 2.5 ml (corresponding to 50 mg herbal substance per day)	*Adults and adolescents > 10 years:* Single dose: 40 mg extract (corresponding to 100 mg herbal substance) Daily dose: 120 mg extract (corresponding to 300 mg herbal substance) *Children 5-10 years:* Single dose: 20 mg extract (corresponding to 50 mg herbal substance) Daily dose: 80 mg extract (corresponding to 200 mg herbal substance) *Children 1-4 years:* Single dose: 20 mg extract (corresponding to 50 mg herbal substance) Daily dose: 60 mg dry extract (corresponding to 150 mg herbal substance) *Children 0-1 year:* Single dose and daily dose: 20 mg extract (corresponding to 50 mg herbal substance)
	Summary of posology for soft extract (2.2-2.9:1), extraction solvent: ethanol 50 % (V/V):propylene glycol (98:2) *Adults and adolescents > 10 years:* Single dose: 40 mg extract (corresponding to 100 mg herbal substance) Daily dose: 120 mg extract (corresponding to 300 herbal substance) *Children 5-10 years:* Single dose: 20-26 mg extract (corresponding to 50-68 mg herbal substance) Daily dose: 80 mg extract (corresponding to 200 mg herbal substance) *Children 1-4 years:* Single dose: 20 mg extract (corresponding to 50 mg herbal substance) Daily dose: 60 mg extract (corresponding to 150 mg herbal substance *Children 0-1 year:* Single dose and daily dose: 20 mg extract (corresponding to 50 mg herbal substance)

6. dry extract (3–6:1), extraction solvent: ethanol 60 % (m/m)

Posology of the specified products	Posology of the preparation

1 preparation (Germany) 100 ml oral liquid contain 330 mg dry extract *Adults and adolescents:* 2 x daily 10 ml (corresponding to 297 mg herbal substance per day) *Children 4-11 years:* 2 x daily 7.5 ml (corresponding to 223 mg herbal substance per day) *Children 1-3 years:* 2 x daily 5 ml (corresponding to 149 mg herbal substance per day)	*Adults and adolescents:* Single dose: 33 mg dry extract (corresponding to 149 mg herbal substance) Daily dose: 66 mg dry extract (corresponding to 297 mg herbal substance) *Children 4-11 years:* Single dose: 25 mg dry extract (corresponding to 112 mg herbal substance) Daily dose: 50 mg dry extract (corresponding to 223 mg herbal substance) *Children 1-3 years:* Single dose: 16.5 mg dry extract (corresponding to 74.5 mg herbal substance) Daily dose: 33 mg dry extract (corresponding to 149 mg herbal substance)

7. liquid extract (1:1), extraction solvent: ethanol 70% (V/V)

Posology of the specified products	Posology of the preparation
1 preparation (Germany) 50 ml (= 47.9 g) oral solution contains 7.5 g liquid extract *Adults and adolescents > 10 years:* 3 x daily 20-25 drops (corresponding to 300 mg herbal substance per day) *Children 4-12 years:* 3 x daily 15-20 drops (corresponding to 225 mg herbal substance per day) *Children 1-4 years:* 3 x daily 10-15 drops (corresponding to and 170 mg herbal substance per day) *Children 0-1 year:* 3 x daily 8-10 drops (corresponding to 120 mg herbal substance per day)	*Adults and adolescents > 10 years:* Single dose: 0.1 g liquid extract (corresponding to 100 mg herbal substance) Daily dose: 0.3 g liquid extract (corresponding to 300 mg herbal substance) *Children 4-12 years:* Single dose: 0.075 g liquid extract (corresponding to 75 mg herbal substance) Daily dose: 0.225 g liquid extract (corresponding to 225 mg herbal substance) *Children 1-4 years:* Single dose: 0.057 g liquid extract (corresponding to 57 mg herbal substance) Daily dose: 0.170 g liquid extract (corresponding to 170 mg herbal substance) *Children 0-1 year:* Single dose: 0.40 ml liquid extract (corresponding to 40 mg herbal substance) Daily dose: 0.120 g liquid extract (corresponding to 120 mg herbal substance)

8. dry extract (4-6:1), extraction solvent: ethanol 30% (V/V)

Posology of the specified products	Posology of the preparation
1 preparation (France) 100 ml syrup contain 1.00 g dry extract	*Adults and adolescents > 15 years*: Single dose: 50 mg dry extract (corresponding to 250 mg herbal substance)

Adults: 3-4 x daily 5 ml *Children 10-15 years*: 2-3 x daily 5 ml *Children 5-10 years*: 3-4 x daily 2.5 ml *Children < 5 years*: 2 x daily 2.5 ml	Daily dose: 150-200 mg dry extract (corresponding to 750-1000 mg herbal substance) *Children 10-15 years*: Single dose: 50 mg dry extract (corresponding to 250 mg herbal substance) Daily dose: 100-150 mg dry extract (corresponding to 500-750 mg herbal substance) *Children 5-10 years*: Single dose: 25 mg dry extract (corresponding to 125 mg herbal substance) Daily dose: 75-100 mg dry extract (corresponding to 375-500 mg herbal substance) *Children < 5 years*: Single dose: 25 mg dry extract (corresponding to 125 mg herbal substance) Daily dose: 50 mg dry extract (corresponding to 250-1000 mg herbal substance)
1 preparation (France) 1 lozenge contains 30 mg dry extract *Adults*: 4-6 lozenges *Children 10-15 years*: 3-4 lozenges *Children 6-10 years*: 2-3 lozenges	*Adults and adolescents > 15 years*: Single dose: 30 mg dry extract (corresponding to 150 mg herbal substance) Daily dose: 120-180 mg dry extract (corresponding to 600-900 mg herbal substance) *Children 10-15 years*: Single dose: 30 mg dry extract (corresponding to 150 mg herbal substance) Daily dose: 90-120 mg dry extract (corresponding to 450-600 mg herbal substance) *Children 5-10 years*: Single dose: 30 mg dry extract (corresponding to 150 mg herbal substance) Daily dose: 60-90 mg dry extract (corresponding to 300-450 mg herbal substance)
1 preparation (Spain) 100 ml oral solution contain 1.00 g dry extract *Adults*: 3-4 x daily 5 ml *Children 10-15 years*: 2-3 x daily 5 ml *Children 5-10 years*: 3-4 x daily 2.5 ml *Children 2-5 years*: 2 x daily 2.5 ml	*Adults and adolescents > 15 years*: Single dose: 50 mg dry extract (corresponding to 250 mg herbal substance) Daily dose: 150-200 mg dry extract (corresponding to 750-1000 mg herbal substance) *Children 10-15 years:* Single dose: 50 mg dry extract (corresponding to 250 mg herbal substance) Daily dose: 100-150 mg dry extract (corresponding to 500-750 mg herbal substance) *Children 5-10 years:*

	Single dose: 25 mg dry extract (corresponding to 125 mg herbal substance) Daily dose: 75-100 mg dry extract (corresponding to 375-500 mg herbal substance) *Children 2-5 years*: Single dose: 25 mg dry extract (corresponding to 125 mg herbal substance) Daily dose: 50 mg dry extract (corresponding to 250 mg herbal substance)
	Summary of posology for dry extract (4-6:1), extraction solvent: ethanol 30 % (V/V): *Adults and adolescents > 15 years*: Single dose: 30-50 mg dry extract (corresponding to 150-250 mg herbal substance) Daily dose: 120-200 mg dry extract (corresponding to 600-1000 mg herbal substance) *Children 10-15 years:* Single dose: 30-50 mg dry extract (corresponding to 150-250 mg herbal substance) Daily dose: 90-150 mg dry extract (corresponding to 450-750 mg herbal substance) *Children 5-10 years:* Single dose: 25-30 mg dry extract (corresponding to 125-150 mg herbal substance) Daily dose: 60-100 mg dry extract (corresponding to 300-500 mg herbal substance) *Children 2-5 years*: Single dose: 25 mg dry extract (corresponding to 125 mg herbal substance) Daily dose: 50 mg dry extract (corresponding to 250 mg herbal substance)

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

Spasmolytic / bronchodilating activity

In-vitro experiments

Spasmolytic activity
Trute *et al.* (1997): The antispasmodic activity of a dry extract of *Hedera helix* (6:1, extraction solvent 30% ethanol) standardised on papaverine (papaverine equivalent value, PE, activity of 1 g test

substance equivalent to the activity of x mg papaverine) was studied in *in-vitro* tests on isolated guinea pig ileum with acetylcholine as spasmogen. A spasmolytic activity equivalent to that of 1 mg papaverine was exerted by 169 mg of hederacoside C, 18 mg of α-hederin and 21 mg of their aglycone hederagenin, 7 mg of kaempferol and 18 mg of quercetin.

In order to determine the phytochemical basis for the antispasmodic activity, a bioassay guided fractionation and subsequent isolation of phenolic compounds (flavonols and caffeoylquinic acids) and saponins (hederacoside C, α-hederin and hederagenin) from a dry extract of ivy leaves was carried out. Fractions and isolates obtained were investigated for antispasmodic activity and their contribution to the activity of the extract was calculated. A significant activity was found for both saponins and phenolic compounds. The PE values were about 55 and 49 for α-hederin and hederagenin, 54 and 143 for quercetin and kaempferol, and 22 for 3.5-dicaffeoylquinic acid. In view of their relative high concentration, the saponins contributed most to the antispasmodic activity, followed by dicaffeoylquinic acids and the flavonol derivatives. It was concluded that the summed PE value of the compounds mentioned is in agreement with the PE value of the whole extract determined biologically.

Capasso *et al.* (1991): Apigenin, quercetin and kaempferol at a concentration of 10 µM (single doses) significantly reduced the contraction of guinea-pig isolated ileum induced by prostaglandin E_2 (PGE_2) and leukotriene D4 (LTD_4). Flavonoids such as quercetin and kaempferol including their 3-O-rutinosides and 3-O-glucosides (=isoquercitrin and astragalin) are constituents of *Hedera helix*.

Ortiz de Urbina *et al.* (1990): Caffeic and protocatechic acids demonstrated a non-specific antispasmodic action of smooth muscle in several isolated organs of the rat.

Becker (2003) and Beyer (2005) reported from *in-vitro* studies with an ivy leaf extract the accumulation of ß-receptors responsible for spasmolytic and secretolytic activity at concentrations of 500 nmol hederin. According to Becker (2003), a resorption and blood concentration of 650 nmol hederin could be shown in clinical studies. The authors concluded that the *in-vitro* experiment could have clinical relevance.

Hegener *et al.* (2004): A preincubation for 24 h with the saponin compound α-hederin (1 µM) inhibited the terbutaline-stimulated internalization of the β_2-AR in alveolar epithelial typ II cell line (A549) by 87% after 20 min, in agreement with the fact that saponins are cholesterol-complex forming agents and that cholesterol depletion is known to inhibit receptor internalization. Also in fluorescence correlation spectroscopy (FCS) experiments α-hederin exhibited an inhibition of β_2-AR internalization in alveolar epithelial type II cell line (A549). α-Hederin did not show any affinity for the β_2-AR in FCS binding studies.
Runkel *et al.* (2005): α-Hederin (0.5 µM) inhibited the terbutaline-stimulated internalization of the β_2-AR by 60% in alveolar epithelial type II cell line (A 549). The author stated that in recent resorption studies α-hederin was found at 0.66 µM blood plasma concentration which was sufficiently bioavailable to explain a β-mimetic and spasmolytic effect.

Sieben *et al.* (2009): Internalization of 2-adrenergic receptor-GFP fusion proteins after stimulation with 1 µM terbutaline was inhibited by preincubation of stably transfected HEK293 cells with 1 µM α-hederin for 24 h, whereas neither hederacoside C nor hederagenin (1 µM each) influenced this receptor regulation. Pre-treatment of HASM cells with α-hederin (1 µM, 24 h) revealed an increased intracellular cAMP level of 13.5±7.0% under stimulating conditions. Remarkably, structure-related saponins like hederacoside C and hederagenin did not influence either the binding behaviour of 2AR or the intracellular cAMP level.

In-vivo experiments
Haen (1996): In the compressed air model in conscious guinea pigs, an orally administered ethanolic extract from ivy leaf at 50 mg/kg body weight dose-dependently inhibited bronchoconstriction induced

by inhalation of ovalbumin (57% inhibition, p=0.01) or platelet activating factor (43% inhibition, p=0.03). The results demonstrated a statistically significant bronchodilating activity of the extract.

Secretolytic effect

Vogel (1963): Considered the hypothesis of the vagal effector mechanism for improvement of expectoration to be unrealistic. He considered the surface activity of the saponins could play a role in the local liquefaction of the mucus in the throat. Additionally, it might be possible that not only saponins but also other substances like e.g. volatile oils contribute to the effect.

Mills and Bone (2000): Saponins are more or less irritating to gastrointestinal mucous membranes (whether this is related to their detergent or haemolytic properties is not understood). This irritant property creates an acrid sensation in the throat when a saponin-containing herb is chewed. One effect, like the emetics, may be by upper gastrointestinal irritation to induce a reflex expectoration.

März and Matthys (1997): Ivy is used as “expectorant”. For the mucus secretory cell the vagal effector mechanism is only one of several trigger mechanism to induce secretion. Stimulation of gastric receptors by emetic agents causes vomiting by vagal reflex acting through the modularly vomiting centres. Subemetic doses of these agents activate a gastropulmonary mucokinetic vagal reflex, which stimulates the bronchial glands to secrete a watery fluid.

A new mode of action was discussed by Stauss-Grabo (2008) based on the results of Hegener *et al.* (2004) and Runkel *et al.* (2005). α-Hederin inhibited the terbutaline-stimulated internalization of the β_2-AR. The stimulation of β_2-AR provides an increased surfactant production. The surfactant leads to the liquefaction of the mucus.

Anti-inflammatory effect

In-vivo experiments

Haen (1996): An orally administered ethanolic extract from ivy leaf at 162 mg/kg body weight inhibited carrageenan-induced rat paw oedema by 39% after 1 h and by 5% after 5 h.

Kim *et al.* (1999): Some steroidal and triterpenoid saponins were isolated and evaluated for their anti-inflammatory activity using *in-vivo* mouse ear oedema test. Ear oedema was provoked by topical application of 2% arachidonic acid or 2.5% croton oil. The oral dose of 100 mg/kg, several steroidal saponins and triterpenoid saponins such as hederagenin glycosides showed significant inhibition of ear oedema (20-37% inhibition). The inhibition of hederagenin was less potent than indometacin or hydrocortisone.

Süleyman *et al.* (2003) tested the possible anti inflammatory effects of a crude saponin extract (CSE) (10:1; extraction solvent ethanol 80% (V/V)) and saponin purified extracts (SPE) of *Hedera helix* in carrageenan- and cotton-pellet-induced acute and chronic inflammation models in rats. The *Hedera helix* extracts in 50, 100 and 200 mg/kg and indometacin in 20 mg/kg body weight doses were given to rats orally once daily for 4 days. Both the CSE and SPE of *Hedera helix* caused anti-inflammatory effects. The most potent drug screened was indometacin (89.2% acute anti inflammatory effect), while the most potent extract screened was *Hedera helix* CSE at 100 and 200 mg/kg body weight with 77% acute anti-inflammatory effects. For testing chronic anti-inflammatory (antiproliferative) effects, the cotton-pellet-granuloma test was conducted. Indometacin appeared as the most potent drug in the chronic phase of inflammation, with 66% effect, while the SPE of *Hedera helix* was more potent than the CSE in its chronic anti-inflammatory effect (60% and 49%, respectively).

Gepdiremen *et al.* (2005): The anti-inflammatory potential of α-hederin and hederasaponin-C from *Hedera helix* was investigated in carrageenan-induced acute paw edema in rats. Saponins were given orally in concentrations of 0.02 mg/kg body weight and the reference product indometacin in 20 mg/kg body weight. For the first phase of acute inflammation, indometacin was found as the most potent

substance. α-Hederin and hederasaponin-C were found ineffective. For the second phase of acute inflammation, indometacin was determined as very potent compound. α-Hederin was found ineffective for the second phase. Despite hederasaponin-C and E were found effective in the second phase of inflammation, they were not as effective as indometacin.

3.1.2. Secondary Pharmacodynamics

Antibacterial effect

In-vitro experiments

Cioaca *et al.* (1978) tested the antibacterial activity of saponins from *Hedera helix* against a large number of microorganisms. The microbiological assay of saponins was made with 23 strains representing 22 bacteria and one yeast species (*Candida albicans*). In a 10 and 5 mg/ml concentration the saponin solution was bactericidal against al the 23 tested strains. The minimal inhibitory concentration for the gram-positive bacteria varied between 0.312 and 1.250 mg/ml and for the gram-negative bacteria between 1.25 and 5.0 mg/ml. Generally, the saponins are more active against the gram-positive than against the gram-negative bacteria. The activity of the saponins could be demonstrated against some of the more resistant bacteria to antibiotics, like *Staphylococcus aureus* (0.312 mg/ml), *Salmonella para A* (0.312 mg/ml), *Shigella flexneri* (0.625 mg/ml), *Bacillus anthracis* (0.625 mg/ml), *Streptococcus mutans* (1.250 mg/ml). Saponin-containing extracts of ivy were active against 23 strains of bacteria (from 22 genera) and against one yeast.

Ieven et al. (1979): An ethanolic extract of ivy leaf completely inhibited the growth of *Staphylococcus aureus* and *Pseudomonas aeroginosa* and partially inhibited the growth of *E. coli*.

Antiviral effect

In-vitro experiments

Rao *et al.* (1974) reported about the *in-vitro* anti-influenza activity of 11 naturally occurring triterpenoid saponins (*Aesculus hippocastanum, Cyclamen europeum, Glycyrrhiza glabra, Hedera helix, Primula veris, Polygala senega, Quillaja saponica, Bupleurum falcatum, Thea sinensis* and *Gymnema sylvestre*). Hederacoside C inhibited influenza virus at 54% in a concentration of 100 µg/ml. The majority of the triterpenoid saponins containing the acylated ß-amyrin skeleton exhibited anti-influenza activity *in-vitro*.

Antimycotic effect

In-vitro experiments

Wolters (1966): The antifungal activity of 30 saponin containing plant extracts (methanol 10%, no further information) was tested against 4 different strains. *Hedera helix* extract had a fungistatic activity on all the tested strains: *Piricuralia oryzae, Trichothecium roseum, Claviceps purpurea* and *Polyporus vesiculosus*.

Favel *et al.* (1992): The antifungal activity of triterpenoid saponins was evaluated *in-vitro* by the agar diffusion assay and experiments were performed against yeast and dermatophyte strains. Hederagenin derivatives exhibited a broad spectrum of activity. All the yeast species (*Candida albicans*, *C. krusei, C. tropicalis, C. pseudotropicalis, C. glabrata*) were inhibited at 50 µg/ml or less. The MICs for the dermatophytes were within the range 5-100 µg/ml.

Favel *et al.* (1994): The antifungal activity of triterpenoid saponins, with hederagenin or oleanolic acid as aglycon, was investigated *in-vitro* by the agar diffusion assay. Monodesmosidic hederagenin derivatives were shown to exhibit a broad spectrum of activity against yeast as well as dermatophyte species. α-Hederin was the most active compound and *Candida glabrata* was the most susceptible strain (MIC 6.7 µM).

Moulin-Traffort *et al.* (1998): α-Hederin isolated from *Hedera helix* L., was tested on *Candida albicans* ultrastructure. The concentrations used were 6.25, 12.5, and 25 µg/ml for an exposure time of 24 h. Transmission electron microscopy observations indicated that compared with untreated control yeasts, α-hederin induced modifications of cellular contents and alterations of cell envelope with degradation and death of the yeasts. After 24 h of treatment, numerous yeasts were dead disregarding the concentration used. The impact of α-hederin on the biomembranes and in particular on the plasmalemma is discussed. The antifungal activity of α-hederin was efficacious with 25 µg/ml, which conforms the minimal inhibitory concentration (MIC) obtained *in-vitro* by Favel *et al.* (1994).

In-vivo experiments

Timon-David *et al.* (1980): Four saponin derivatives, including hederasaponin C and α-hederin, were isolated from ivy leaves (*Hedera helix*) and their fungicidal effects were determined *in-vitro* and *in vivo* in mice parasitized with *Candida albicans*. Results showed that a saponin mixture (60% hederasaponin C) eliminated the infection in 90% of the animals after oral administration at 50 mg/kg body weight within 7 days and in 100% within 10 days. In comparison, α-hederin eliminated the infection at the same dose of level in 90% in 10 day and hederasaponin C in 40% within 10 days. In comparison, the infections were eliminated by oral amphotericin b at 2.5 mg/kg daily within 6 days.

Molluscicidal effect

In-vitro experiments

Balansard *et al.* (1980): In *in-vitro* tests, α-hederin, obtained by hydrolysis of hedera saponin C, showed molluscicidal activity against liver flukes *Fasciola hepatica* and *Dicrocoelium lanceolatum* at concentration of 1 µg/ml and antifungal activity in Sabouraud liquid medium.

Hostettmann (1980) compared the molluscicidal effects of different ivy extracts and found a crude leaf extract was less active than a crude methanolic extract of the berries. He isolated four saponins from the berries, all of which showed a strong molluscicidal action against the bilharziasis-transmitting snail *Biomphalaria glabrata*.

Hostettmann *et al.* (1982) tested a series of 24 different saponins isolated from various medicinal plants against *Biomphalaria glabrata*, one of the snail vectors of schistosomiasis (bilharziasis). In general, monodesmosidic triterpenoid saponins exhibited a strong molluscicidal activity whereas bidesmosidic saponins as well as the aglycones were fully inactive.

In-vitro and *in-vivo* experiments

Julien *et al.* (1985): The *in-vitro* anthelmintic activity of a saponic complex 60% (CS 60), purified saponic complex 90% (CS 90) and α-hederin isolated from leaves of *Hedera helix* L. was investigated on using the trematodes *Fasciola hepatica* and *Dicocoelium* spp. α-Hederin was the most efficient. *In-vivo* assays with sheep naturally infected with *Dicrocoelium* showed that al 3 products are capable to lower or cease the egg production. One dose of 500 mg/kg and two doses of 800 mg/kg given orally brought about total disappearance of eggs in the faces of sheep treated with CS 60 and CS 90. The authors could not prove that α-hederin showed a lowered effectiveness *in-vivo*.

Protozoidal effect

In-vitro experiments

Majester-Savornin *et al.* (1991): The activity of an isolated extract of *Hedera helix* named CS 60 (60% saponic complex), the bidesmosides hederasaponin B, C and D, their corresponding to monodesmosides α-, beta-, and delta-hederin, and hederagenin was tested *in-vitro* against promastigote and amastigote forms of *Leishmania infantum* and *L. tropica*. CS 60 and bidesmosides had shown no effect while monodesmosides were as effective on promastigote forms as the reference compound (pentamidine). Only hederagenin exhibited a significant activity against amastigote forms, which was equivalent to that of the reference compound (N-methylglucamine antimonate).

Tedlaouti *et al.* (1991): Moderate *in-vitro* antitrypanosomal activity for monodesmosides and hederagenin was shown (α-hederin MIC=25 g/ml), while the bisesmosides hederasaponins C and D did not show any effect on *Trypanosoma brucei*.

Delmas *et al.* (2000): The *in-vitro* antileishmanial activity of three saponins, α-hederin and β-hederin isolated from leaves of *Hedera helix* L., and hederacolchiside A1 isolated from *Hedera colchica* was investigated on *Leishmania infantum*. The assessment of possible targets (membrane integrity, membrane potential, DNA synthesis and protein content) was performed in both *Leishmania* promastigotes and human monocytes (THP1 cells). Results observed in *Leishmania* showed that the saponins exhibited a strong antiproliferative activity on al stages of development of the parasite by altering membrane integrity and potential. Hederacolchiside A1 appeared to be the most active compound against both extracellular promastigotes (IC_{50}=1.2 µM) and intracellular amastigotes (IC_{50}=0.053 µM). α-Hederin and β-hederin showed lower activities, IC_{50}=13.6 and 12.0 µM respectively against promastigotes and IC_{50}=0.35 and 0.25 µM respectively against amastigotes. Results observed in THP1 cells demonstrated that the saponins exerted also a potent antiproliferative activity against human monocytes by producing a significant DNA synthesis inhibition. The authors concluded that the ratio between antileishmanial activity on amastigotes and toxicity to human cells suggested that the saponins could be considered as possible antileishmanial drugs.

Ridoux *et al.* (2001): The *in-vitro* antileishmanial activity of three saponins, α- and β-hederin isolated from *Hedera helix* and hederacolchiside A1 from *H. colchica* was investigated on parasites of the species *Leishmania mexicana* in their promastigote and amastigote forms, compared with their toxicity versus human monocytes. The results showed that saponins exhibited a strong antiproliferative activity on al stages of development of the parasite but demonstrated a strong toxicity versus human cells. Combination of subtoxic concentrations of saponins with antileishmanial drugs such as pentamidine and amphotericin B demonstrated that saponins could enhance the efficiency of conventional drugs on both the promastigote and the amastigote stages of development of the parasite. The results demonstrated moreover that the action of saponins on promastigote membrane was cumulative with those of amphotericin B.

Hepatoprotective effect

In-vitro experiments

Hensel *et al.* (2007) and Goetz (2007): Thirty commonly used medicinal plants were screened by a selective and specific LC-MS/MS method for the occurrence of N-phenylpropenoyl-L-amino acid amides, a new homologous class of secondary products. In 15 plants, one or more of the respective derivatives (1 to 12) were found and quantified.
Especially roots from *Angelica archangelica*, fruits of *Cassia angustifolia*, *C. senna*, *Coriandrum sativum*, leaves from *Hedera helix*, flowers from *Lavandula spec*. and from *Sambucus nigra* contained high amounts (1 to 11µg/g) of mixtures of the different amides 1 to 12. For functional investigations on potential activity in cellular physiology, two amides with an aliphatic (N-(E)-Caffeic acid L-aspartic acid amide (8)) and an aromatic amino acid residue (N-(E)-caffeic acid L-tryptophan amide (5)) were used. (8) and (5) stimulated mitochondrial activity as well as the proliferation rate of human liver cells (HepG2) at 10 µg/ml significantly. When monitoring the influence of selected phase I and II metabolizing enzymes, both compounds did not influence CYP3A4 gene expression, but stimulated CYP1A2 gene expression and inhibited GST expression. Also the proliferation of human keratinocytes (NHK) was increased up to 150% by both, the amides 5 and 8. This stimulation was also detectable on the level of gene expression by an up-regulation of the transcription factor STAT6.

In-vivo experiments

Liu *et al.* (1993) examined the protective effect of α-hederin against cadmium (Cd) hepatotoxicity and the mechanism of protection. α-Hederin pre-treatment (100 µM/kg, s.c.) dramatically decreased Cd

(3.7 mg/kg, i.v.) hepatotoxicity as indicated by a reduction of serum alanine aminotransferase and sorbitol dehydrogenase, as well as by histopathological examination. The increased cytosolic Cd was found primarily bound to a low-molecular-weight protein, metallothionein (MT). α-Hederin produced a dose-dependent increase in hepatic MT with a 100-fold increase over controls 24 h after a single injection of 100 µM/kg. The hepatic MT increase produced by α-hederin is relatively long lasting. Six days after a single administration, it was still eight times control values. The induction of MT was also relatively specific for the liver, as little or no increase in MT was observed in other tissues.

Liu *et al.* (1995) determined the protective effects of α-hederin on chemical-induced liver injury in CF-1 mice and evaluated cytochrome P450 suppression by α-hederin as a means of protection. α-Hederin pre-treatment (30 µM/kg, s.c., 3 days) protected mice from acetaminophen-, bromobenzene-, carbon tetrachloride-, furosemide-, and thioacetamide-induced liver injury, without affecting the hepatotoxicity of chloroform and dimethylnitrosamine. These results demonstrate that treatment of mice with α-hederin decreases the levels and activities of several P450 enzymes. The suppression of P450 appears to be one of mechanisms by which α-hederin protects mice from the hepatotoxicity of some chemicals (Sea also chapter “interactions” 3.2.).
According to Shi and Liu (1996), there were the hepatoprotective effects of α-hederin and sapindoside B at least in part, due to its suppressive effect on liver cytochrome P-450.

Liu *et al.* (1997) examined whether α-hederin modulates hepatic detoxyfying systems as a means of hepatoprotection. Mice were injected with α-hederin 10 and 30 µM/kg, s.c. once daily for 3 consecutive days and liver cytosols were prepared 24 h after the last dose to study antioxidant enzymes and nonenzymatic defense components. α-Hederin increased the liver gluthathion (GSH) content (20%) but had no effect on GSH peroxidase, GSH reductase and GSH S-transferase. The activities of superoxide dismutase and quinone reductase were unaffected. At the high dose of α-hederin, catalase activity was decreased by 20%. The hepatic content of metallothionein was dramatically increased (50-fold), along with elevations of hepatic Zn and Cu concentrations (25%-80%) but no effect on α-tocopherol in the liver was observed.
α-Hederin enhanced some nonenzymatic antioxidant components in the liver, which play a partial role in α-hederin protection against hepatotoxicity produced by some chemicals.

Antithrombin activity

In-vitro experiments
de Medeiros *et al.* (2000): A chromogenic bioassay was utilised to determine the antithrombin activity of methylene chloride and methanol extracts (no information about the DER of the extract) prepared from 50 plants of the Azores. Extracts of the six plants: *Hedychium gardneranum*, *Tropaeolum majus*, *Gunnera tinctoria*, *Hedera helix*, *Festuca jubata* and *Laurus azorica* demonstrated an activity of 78% or higher in this bioassay system. The activity of the *Hedera helix* methylene chloride extract (82%) was higher than the activity of methanol extract (30%). It is believed, that hypercoagulability in cancer is related to an increase of “tissue factor” (TF) in the patients. The author concluded that the lower activity of thrombin caused the lower coagulability, and subsequently the possibility of tumour cells to spread or to adhere to any tissue.

Antioxidant effect

In-vitro experiments
Mba Gachou *et al.* (1999): The study was designed to evaluate the protective effect of α-hederin extracted from *Hedera helix* against H_2O_2-mediated DNA damage on HepG2 cell line by the alkaline comet assay. The effect of α-hederin on catalase activity was evaluated after treating the cells with 3.36 mg/ml of 3-amino-1,2,4-triazole (AMT) singly or in combination with α-hederin (1.5 or 3 µg/ml) and H_2O_2 (8.8 µM) during 1 h. The catalase activity was also biochemically measured after treating cells with α-hederin at 1.5, 3, or 15 µg/ml during 1 h. Additionally, the influence of α-hederin on

membrane Redox potential, pool of reduced glutathione and total protein content was evaluated by flow cytometry. In the pre-treatment, the two concentrations of α-hederin (1.5 and 3 µg/ml) decreased the lesions induced by H_2O_2 (8.8 µM) significantly. This decrease was about 57.2% and 66.1%, respectively. Similar results were observed when cells were treated with α-hederin and H_2O_2 simultaneously. The decrease of H_2O_2-induced lesions was about 78.2% and 83.2% (α-hederin 1.5 and 3 µg/ml, respectively). In the post-treatment protocol, this decrease was not significant. The combination of AMT and H_2O_2 induced more DNA damage than H_2O_2 alone (tail moment (TM) means were 31.4% and 21.8%, respectively). When α-hederin was added to this mixture, TM means were reduced significantly (17.4% for α-hederin 1.5 µg/ml and 15.5% for α-hederin 3 µg/ml). Up to 6.9 µg/ml, α-hederin enhanced catalase activity (60.5%), followed by a decrease of the activity. The total protein content and membrane Redox potential were slightly increased up to 11 µg/ml (14% and 3.6%, respectively) followed by a drop and a plateau. The pool of reduced glutathione remained unchanged up to 10 µg/ml, then dropped and reached a plateau. In conclusion, α-hederin could exert its protective effect against H_2O_2 mediated DNA damage by scavenging free radicals or by enhancing the catalase activity.

Gülcin *et al.* (2004): The antioxidant activities of α-hederin and hederasaponin-C from *Hedera helix*, and hederacolchisides-E and F from *Hedera colchica* were investigated *in-vitro*. The antioxidant properties of the saponins were evaluated using different antioxidant tests: 1,1-diphenyl-2-picryl-hydrazyl free radical scavenging, total antioxidant activity, reducing power, superoxide anion radical scavenging, hydrogen peroxide scavenging and metal chelating activities. α-Hederin and hederasaponin-C exhibited a strong total antioxidant activity compared with model antioxidants such as α-tocopherol, butylated hydroxyanisole and butylated hydroxytoluene. At 75 µg/ml, these saponins showed 94% and 86% inhibition on lipid peroxidation of linoleic acid emulsion, respectively.

Hypoglycaemic activity

In-vivo experiments

Ibrar (2000) and Ibrar *et al.* (2003): The study showed that both the aqueous extracts (200 g of powdered leaves in 1 l distilled water, soaking seven days at room temperature, filtrated and concentrated) and methanolic extracts (no information about DER) of *Hedera helix* L. were hypoglycemic, reducing the blood glucose level in normal rabbits. The methanolic and aqueous extracts were administered orally at a dose equivalent to 4 g of powdered leaf per kg body weight in 20 ml of 2% gum traganth solution. In the alloxan-induced diabetic rabbits the aqueous extract showed a hypoglyccemic effect after 8 h and sustained up to 12 h to significant levels. Trace element analysis of the leaves showed that *Hedera helix* L. leaves contain the "hypoglycemic trace elements" (chromium, manganese and zinc) in sufficiently large amounts. The authors concluded that these had played the main role in reducing the blood glucose level.

Anti-hyaluronidase activity

In-vitro experiments

Facino *et al.* (1990): Evaluation of the anti-hyaluronidase activity of the saponin complex isolated from *Hedera helix* L. leaves and of its constituents α-hederin, hederacoside B and hederacoside C showed that these compounds possess anti-enzyme activity. The complex inhibits hyaluronidase in a dose dependent fashion (10% inhibition at 0.1 mM; 50% at 0.25 mM) comparable to aescin. α-Hederin was less effective than hederacosides.

The authors concluded that the recovery of the integrity of hyaluronic acid (and of its functional interactions with proteoglycans) might lead to recovery of the biochemical integrity of the basal amorphous substance in which the periadipocyte microvascular system is embedded, with a sealing effect on the capillary walls.

Facino *et al.* (1995): *In-vitro* experiments have demonstrated inhibition of hyaluronidase activity by hederagenin (IC_{50}=280.4 µM; oleanolic acid IC_{50}=300.2 µM) but not (only very weak activity) by hederacoside C or α-hederin.

Antiadhesive properties on the adhesion of *Helicobacter pylori* to human stomach tissue

In-vitro experiments

Hensel *et al.* (2007) and Goetz (2007): The aliphatic aspartic compound N-(E)-Caffeic acid L-aspartic acid amide isolated from *Hedera helix* L. leaves showed strong anti adhesive properties on the adhesion of *Helicobacter pylori* to human stomach tissue (see also chapter "hepatoprotective effect").

Antiexsudative effect

In-vivo experiments

Vogel and Marek (1962): A saponin mixture isolated from ivy leaf and administered intravenously, inhibited ovalbumin-induced rat paw oedema (100-150 g rats, 2 mg ovalbumin pro rat paw) with an ED_{50} of 0.32 mg/kg. The therapeutical index (LD_{50}:ED_{50}) was 40.0.

Schottek (1972): A lung oedema was induced in mice by inhalation of a methallyl-air mixture at 2000 ppm of 1 h duration. A dose of 200 mg/kg i.p. of an ivy extract ("Hedelix", no further information) reduced the lung oedema considerably. Other ivy extract ("Prospan®", no further information) had no influence on the development of oedema. A polyamid fraction of an ivy water extract (no further information) increased the development of oedema.

3.1.3. Overall conclusion on pharmacology

A spasmolytic/bronchodilatating effect has been documented in *in-vitro* experiments and in *in-vivo* studies in the compressed air model in conscious guinea pigs. An *in-vitro* effect of α-hederin on β_2-adrenergic receptors was demonstrated by Hegener *et al.* (2004) and Runkel *et al.* (2005). Stauss-Grabo (2008) documented the first pharmacokinetic study which indicated a possible systemic resorption, distribution and elimination of α-hederin and analysed the concentration in different organs. The maximum α-hederin concentration found at 24 h in the lung tissue was 0.018 µg α-hederin/g corresponding to 0.024 nmol/kg (α-hederin has a molecular weight of 750.98 g/mol), so the documented concentration was lower than the concentrations used in the *in-vitro* experiments: 1 µM, (Hegener et *al.*, 2004) and 0.5 µM (Runkel *et al.*, 2005). These results indicate an interesting hypothetical mechanism, however, it could not be considered as clinically relevant because the concentration in the lung is far below that used in the experiments.

The secretolytic activity shown in clinical praxis is not yet clarified in experiments. Probably subemetic doses of saponins activate a gastro pulmonary mucokinetic vagal reflex, which stimulates the bronchial glands to secret a watery fluid. No *in-vitro* or *in-vivo* studies referring to the mechanism of the secretolytic effect exist. The mode of action for the secretolytic effect is discussed contradictory in literature (Hänsel and Sticher, 2004). Büechi (2002) considered the hypothesis of vagal reflex mechanism as implausible because a daily dose of 0.5 g drug was well tolerated. The author considered that the surface activity of the saponins could play a role in the local liquefaction of the mucus in the throat thus being more important in clinical praxis. In contrast, Wagner and Wiesenauer (1995) stated that the surface activity was unrealistic in oral administration. The concentration of saponins in the lung would be too low to explain such an activity. The surfactant hypothesis of Hegener *et al.* (2004) and Runkel *et al.*(2005) was also stated by Stauss-Grabo (2008). The pharmacokinetic study by Stauss-Grabo showed too low concentrations in the lung compared with that used in *in-vitro* experiments and indicated no clinical relevance of this mechanism.
The anti-inflammatory effects could be shown in different *in-vivo* models, for example with orally administered ethanolic ivy leaf extract (Haen, 1996), the topical application of isolated saponin

extracts (Kim *et al*., 1999), the cotton-pellet granuloma test with saponin extracts (Süleyman *et al*., 2003) and with orally administered α-hederin in the carragenaan-induced acute paw oedema in rats. The clinical relevance of this mechanism is not clear.

A lot of secondary phamacodynamic studies were performed *in-vitro* and *in-vivo*. Antibacterial, antiviral, antimycotic, mulluscicidal, hepatoprotectiv, cytotoxic and hypoglycemic effects could be demonstrated *in-vitro* and *in-vivo*.
The hypoglycemic effects were shown with methanolic and aqueous extracts administered orally at a dose equivalent to 4 g of powdered leaf per kg body weight. The dosage corresponds to 280 g ivy leaf in a 70 kg patient. This is approximately the 930-fold dosage of a human daily dosage of 0.3 g. The hypoglycaemic effect is therefore considered to be irrelevant for human praxis with low dosages. The results of the *in-vivo* studies on the antiexsudative effects are contradictory and do not provide much more information.
In-vitro molluscicidal, protozoidal, antithrombin, antioxidant, anti-enzyme activity, antiadhesive properties on the adhesion of Heliobacter pylori to human stomach tissue were shown.

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

Absorption, Distribution, Metabolism, Elimination

Vogel and Marek (1962) found more than 7.7-fold difference between the *i.v.* and *p.o.* LD_{50}-values of saponins from *Hedera helix* in rats. They concluded that small quantities of saponin were absorbed in the rats' intestinal tract.

Schmidt (2003): One hour after a single *p.o.* application of 1 g/kg of an ivy dry extract (5-7.5:1; extraction solvent ethanol 30%) in rats, α-hederin was found in blood samples in concentrations exceeding 10 µg/ml. Three hours after application, 3-7% of the applied amount of α-hederin could be detected. After repeated p.o. application over 3 days approximately, 2% p.o. α-hederin in respect of the total applied saponin content calculated as α-hederin was found. No hederacoside C could be found in the blood. The author concluded that hederacoside C was metabolised to α-hederin in the stomach.

Assessor's comment:

Schmidt (2003) could detect 3-7% of the applied amount of α-hederin in blood in an in-vivo study in rats 3 h after p.o. application of an ivy dry extract. The study was conducted with very high dosages, not comparable to human dosages. Lower dosages could not be analysed because of the limit of detection of α-hederin in blood. The one-point measurement did not allow conclusions about the systemic absorption.

Stauss-Grabo (2008): The pharmacokinetics of α-hederin given as oral single doses were investigated in a pilot study on male Wistar rats. Radioactive tritium was used as a tracer. α-Hederin has a specific radioactivity of 1.398 µCi/µg. The results of the pilot study showed absorption and uptake in blood and further passing into liver and lungs. To allow a statement on the pharmacokinetics and tissue distribution, the main study was carried out over 336 h. 335 µg/kg α-hederin (corresponding to a human dosage of 23.4 mg in a 70 kg patient) was administered in oral single doses to male Wistar rats. From the main study it could be shown that the maximal amounts of radioactivity in the blood could be detected at 24 h (t_{max}). At 24 h, the highest concentration of about 5% of the applied total amount of radioactivity was detectable in the blood. The total systemic uptake at 24 h was estimated to be at least 30% of the applied total amount of radioactivity. Absorption and elimination of α-hederin were documented completely over the period of 336 h. The radioactivity of 1 g lung tissue was documented 5.55+05 DPM (α-hederin group) and 5.76+05 DPM (in the α-hederin + ivy extract group). The radioactivity at 24 h of the lung was documented as 0.02 µCi/g tissue (in the α-hederin group) and

0.025 µCi/g tissue (in the α-hederin +ivy extract group). α-Hederin has a specific radioactivity of 1.398 µCi/µg. The following α-hederin concentrations can be calculated (0.02 or 0.025:1.398):

At 24 h: radioactivity in the lung tissue

in the α-hederin group	0.02 µCi/g	α-hederin 0.014 µg/g
in the α-hederin + ivy extract group	0.025 µCi/g	α-hederin 0.018 µg/g

A table shows the radioactivity in blood over 336 h. At 24 h, the highest radioactivity in blood is approximately 0.32µCi/ml (in the α-hederin +ivy extract group). The following α-hederin concentrations can be calculated (0.32:1.398):

At 24 h: radioactivity in blood

in the α-hederin group	0.27 µCi/ml	α-hederin 0.19 µg/ml
in the α-hederin + ivy extract group	0.32 µCi/ml	α-hederin 0.23 µg/ml

Assessor's comment:

Stauss-Grabo (2008) documented the pharmacokinetic data of α-hederin for the first time. They indicated a possible systemic resorption of α-hederin estimated to be maximally 30% of the applied total amount in 24 h. The examined substance was not unambiguously identified. The quantitative measurement of α-hederin wasn't conducted by HPLC. The concentrations were calculated from the measurement of radioactivity, which may be caused by α-hederin or theoretically also by other metabolites.

Jeong and Park (1998): Treatment of mice with α-hederin (s.c.) decreased the expression and had a blood-concentration-time curve and a concentration-time curve of the excretion in the urine and faces and thus was described for the very first time. The one-compartiment model with absorption and elimination of the first order was suitable to describe the kinetics. The binding of α-hederin was evenly distributed to cellular and non cellular blood components. The uptake of the mixture of pure α-hederin and ivy extract increased both, the rate and the extent of absorption (statistically significant). The authors concluded that these results showed that 50% of α-hederin were eliminated per urin and 50% per feces. At 24 h, the following radioactivity was detected in organs: in the lung approximately 0.2%; stomach 11.1%; gastrointestinal tract approximately 9.2% and in the body without organs approximately 24% of the initial doses.

3.2.1. Pharmacokinetic interactions with other medicinal products

Liu *et al.* (1995): Treatment of mice (10 and 30 µM/kg, s.c. or vehicle once daily for 3 consecutive days) with α-hederin produced a dose-dependent suppression of liver cytochrome P450 (30-50%). α-Hederin treatment also decreased the activities of P450 enzymes. The levels of CYP1A, CYP2A and CYP3A enzymes were also suppressed as determined by immunoblotting with antibodies against rat P450 enzymes.

Jeong (1998): The administration of α-hederin (s.c. at 8, 40, 80 mg/kg body weight) to mice significantly decreased the hepatic content of P450 and the activities of microsomal ethoxyresorufin O-deethylase, methoxyresorufin O-demetylase and aniline hydroxylase, representative activities of cytochrome-P4501A1, P4501A2 and P4502E1 in a dose- and time-dependent manner. However, pentoxyresorufin O-dealkylase, a representative activity of cytochrome P4502B1/2, was decreased to a lesser extent. α-Hederin also decreased inducible monooxygenase activities in the same manner. Suppressions of P450 isozyme expression occurred in α-hederin treated hepatic microsomes, as determined by immunoblot analysis in a consistent manner with that of the enzyme activity levels.

Levels of mRNA of P4501A1/2 and P4502B1/2 were also decreased by α-hederin as shown by Northern blot analysis. In contrast, the level of P4502E1 mRNA in the liver of α-hederin treated mice was unchanged. These results suggested that α-hederin might act as a more specific suppressor for P4501A and P4502E1 than P4502B and that the suppression involved decreases in mRNA levels except in the case of P4502E1.

Assessor's comment:

The in-vivo applied s.c. dosage of 7.5 mg α-hederin/kg was approximately 25-fold higher than the therapeutically oral applied dosage. The different administration is to be considered: in both in-vivo experiments α-hederin was administered subcutaneously and not orally. The influence of P 450 was in a dose dependent manner. No clinical relevance is expected from these results. Anyhow, clinical adverse events should be observed critically in the context of possible interactions because of influence on P 450 enzymes.

3.2.2. Overall conclusion on pharmacokinetics

In two *in-vivo* interaction studies (Liu *et al.*, 1995) and (Jeong, 1998), s.c. administered α-hederin influenced P450 enzymes. According to current resorption studies, by oral administration α-hederin is resorbed maximally in approximately 30%. In the worst case scenario (if the human dosage would be resorbed at all), the clinical relevance can be appreciated as follows: the lowest administered dosage of 10 µmol α-hederin/kg corresponds to approximately 7.5 mg α-hederin/kg. The implicated human daily dosage for adults of 300 mg herbal substance (as recommended of Kommission E) contains approximately 6% saponins, corresponding to 18 mg α-hederin. In a patient of 60 kg weight, the applied dosage is approximately 0.3 mg α-hederin/kg. The *in-vivo* applied s.c. dosage of 7.5 mg α-hederin/kg is approximately 25-fold higher as the therapeutically orally applied dosage. The different administration is to be considered. In both *in-vivo* experiments, α-hederin was administered subcutaneously and not orally. The influence of P450 was in a dose dependent manner. No clinical relevance is expected from these results. Anyhow, clinical adverse events should be observed critically in context of possible interactions because of influence in P 450 enzymes.
In the available literature, it is assumed that hederasaponins are poorly absorbed following oral administration. This assumption is supported by experiments by Vogel and Marek (1962), cited in De Smet *et al.* (1993). Mills and Bone (2000) note, that after oral intake, the major part of saponins is not absorbed or is only slowly and partially absorbed as the aglycones.

Schmidt (2003) could detect, in an *in-vivo* study in rats 3 h after p.o. application of an ivy dry extract, 3-7% of the applied amount of α-hederin in the blood. The study was conducted with very high dosages, not comparable to human dosages. Lower dosages could not be analysed because of the limit of detection of α-hederin in the blood. The one-point measurement doesn't allow conclusions about the systemic absorption.

Stauss-Grabo (2008) documented, for the first time, the pharmacokinetic data on α-hederin. They indicated a possible systemic resorption of α-hederin estimated to be at least 30% of the applied total amount in 24 h. The examined substance is not unambiguously identified. The quantitative measurement of α-hederin wasn't conducted with HPLC. The concentrations were deduced by measurement of radioactivity, which can be caused by α-hederin or theoretically by other chemical substances.

The results have to be considered in the assessment of the hypothetic mode of action and in the assessment of toxicology and use in pregnancy. From the results, it can be concluded, that α-hederin may be resorbed, at approximately 30% in 24 h. The oral resorption is still unclear. No published pharmacokinetic data in repeated oral administration exist.

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

3.3.1. Single dose toxicity

Oral administration

Lanza *et al.* (1980): Oral administration of a dry extract of ivy leaf (ethanol 66% (V/V), no DER information) to rats 3.0-4.1 g/kg body weight caused no death within 72 h. Only diarrhoea was observed.

On the other hand, oral administration of dry extracts of ivy berries (ethanol 66% (V/V), no DER information) to rats at doses 2.8-4.7 g/kg body weight induced the death of all examined wistar rats within 48 h (90% in 24 h). Faintness, diarrhoea and hemorrhage were observed. Diarrhoea was also the only symptom when an aqueous extract from the seed (3.0-3.9 g/kg body weight) was given. No effects were observed with an aqueous extract from the berries (3.0 g/kg).

Vogel and Marek (1962) found LD_{50}-values of >100 mg/kg p.o. for saponin from the leaf of *Hedera helix* in rats.

Timon-David *et al.* (1980): Oral LD_{50} in mice of saponin mixtures from ivy leaf containing 60% and 90% of hederacoside C, and of hederasaponin C and α-hederin, were all >4 g/kg body weight.

Intravenous administration

Vogel and Marek (1962) found LD_{50}-values of 13 mg/kg i.v. for saponin from the leaf of *Hedera helix* in rats.

Wulff (1968): LD_{50}-values of 4.5 mg/kg i.v. for hederin and hederasaponin C >50 mg/kg i.v. in rats after 7 days observation period.

Intraperitoneal administration

Timon-David et al. (1980): The intraperitoneal LD_{50} values in mice of α-hederin and the saponin mixtures from ivy leaf containing 60% of hederacoside C were 1.8 g/kg and 2.3 g/kg body weight, respectively.

3.3.2. Repeat dose toxicity

Oral administration

ESCOP (2003): Daily oral administration of an ivy leaf dry extract to rats at 1.5 g/kg body weight for 100 days caused no toxic effects. Haematological and biochemical parameters, histological findings and kidney and liver weights were normal compared to those of control animals.

Haemolytic effects were detected after oral administration of a hydroethanolic dry extract from ivy leaf to rats at 4 g/kg body weight, for 90 days.

3.3.3. Genotoxicity

Elias et al. (1990): α-Hederin, ß-hederin and δ-hederin isolated from ivy leaf showed no mutagenic potential in the Ames test using *Salmonella typhimurium* strain TA 98, with or without S9 activation. Screening of the antimutagenic activity was performed with the known promutagen benzopyrene (BP) and a mutagenic urine concentrate from a smoker (SU). These three saponins showed dose-dependent antimutagenic effects against benz(a)pyrene and SU at levels between 80 and 200 µg/plate in the Ames test.

Amara-Mokrane *et al.* (1996): The influence of α-hederin, chlorophyllin, the sodium-copper salt of chlorophyll and ascorbic acid (vitamin C) on the direct clastogenicity of doxorubicin (Adriamycin) was investigated *in-vitro* in human lymphocytes for the induction of micronuclei. In order to determine a possible mechanism of action responsible for the antimutagenic activity, treatments were performed

for the three substances at different times of the culture (pre-treatment, simultaneous and post-treatment). α-Hederin (1.3 times 10^{-2}, 0.13, 1.3 and 13 nmol/ml) and chlorophyllin (0.14, 1.4 and 14 nmol/ml) were found to exert an antimutagenic effect against the clastogenicity of doxorubicin (1.5 times 10^{-2} nmol/ml) in all treatments at all concentrations. The results suggested a desmutagenic effect for α-hederin, chlorophyllin and ascorbic acid. Chlorophyllin acted also through a bio-antimutagenic mechanism and α-hederin seemed to induce metabolic enzymes, which inactivated doxorubicin. Preliminary studies showed that the effective antimutagenic concentrations of α-hederin, chlorophyllin and ascorbic acid had no clastogenic or aneugenic effects in human lymphocytes. No cytotoxicity was observed for all the three antimutagenic agents.

Villani *et al.* (2001) studied the antimutagenic potential of α-hederin versus a clastogenic agent, doxorubicin and an aneugenic agent, carbendazim. They have applied a protocol of incorporation of α-hederin as pretreatment, simultaneous treatment and post treatment to determine the mechanism of action. According to this protocol, α-hederin induces a significant diminution of the rate of micronuclei. The authors concluded the results demonstrate the antimutagenic activity of α-hederin.

3.3.4. Carcinogenicity

Data on carcinogenicity studies with ivy leaf extracts or its components are not available.

3.3.5. Reproductive and Developmental Toxicity

Daston *et al.* (1994) tested the hypothesis that toxicant-induced changes in Zn disposition in the pregnant rat, which occurs as part of an acute-phase response, can produce adverse developmental effects by making the embryo Zn deficient. Zn deficiency in the embryo was tested by treating pregnant rats during organogenesis with α-hederin. A single dose of α-hederin, injected subcutaneously at dosages of 3 to 300 µM/kg, caused an acute phase response indicated by decreased Fe and Zn, and increased Cu, α1-acid glycoprotein, and ceruloplasmin concentration in plasma, along with a dosage-related increase in maternal hepatic metallothionein (MT) concentration. Plasma Zn concentration decreased after α-hederin treatment to approximately 75% of control at a dosage of 30 µM/kg and 50% of control at 300 µM/kg. Both 30 and 300 µM/kg increased resorption incidence, and 300 µM/kg also decreased foetal weight and increased the incidence of abnormal foetuses. Abnormalities include encephalocele, undescedent testis, umbilical hernia, hydronephrosis/hydrourether, along of several others of unique incidence. There was also evidence of delayed skeletal ossification in the 300 µmol/kg group. Adding Zn to the serum restored normal embyotoxic development. α-Hederin did not appear to be directly embyotoxic. It did not produce any effects when added to rat embryo cultures. The authors concluded that these data are consistent with the hypothesis that systemic changes in Zn status, brought about by a hepatic acute phase response, including a substantial induction of hepatic MT, may be a mechanism for maternally mediated abnormal development.

Duffy et al. (1997) conducted a study to determine whether repeated administration of low dosages of α-hederin throughout organogenesis would produce a lasting response with substained elevation of metallothionein levels and subsequent developmental abnormities. Rats were injected subcutaneously dosage levels of 0 (vehicle only), 20 or 30 µM/kg from gestation day 6-15. Maternal hepatic metallothionein levels were 10-fold higher on gestation day 16 in the treatment groups than in the controls. Consequently, liver zinc concentrations increased by 60% and 54%, whereas plasma levels decreased by 23% and 33% in the 20 and 30 µM/kg treatment groups, respectively. At gestation day 20, mean foetal weights of the treatment litters were 11% less than control litters. The administration of α-hederin resulted in a 3-fold increase in the number of offspring with developmental abnormalities, including visceral and skeletal malformations. In the 30 µmol/kg treatment group, all of the litters

contained pups that exhibited at least one abnormality. The visceral abnormalities observed included hydrocephaly, hydronephrosis and hydroureter. The skeletal abnormalities included scoliosis, fused and missing ribs, and delayed ossification of sternebrae. Repeated dosing throughout organogenesis, as required in regulated safety assessment testing, increased the severity of the effects previously observed with single large dosages in the study Daston *et al.* (1994) of the toxicant administered during midgestation.

3.3.6. Local tolerance

Vogel (1963) tested *in-vivo* the local tolerance of different saponins at the conjunctiva of the rabbit. The concentration of saponins causing local stimulation was 1:1000 - 1:10000 in this model. No correlation between local stimulation and haemolytic activity was found. There is no specific information on the local stimulation of *Hedera* saponins.

Allergenic activity

Ivy has often been reported to cause allergic contact dermatitis. Boll and Hansen (1987) analysed leaves and stems of 10 species. The allergenic polyacetylene falcarinol was present in *Fatshedera lizei*, *Hedera helix*, *Hedera helix* subsp. *canariensis* and *Tupindanthus calyptrata* (*T. calyptratus*). Bruhn *et al.* (1987) isolated falcarinol and didehydrofalcarinol from *Hedera helix*, subspecies helix and subspecies canariensis and identified its structures by mass spectrometry and NMR.

The principal allergens were isolated also by Hausen *et al.* (1987) using sensitized guinea pigs and were identified as falcarinol and dehydro-falcarinol. Multiple examinations of the extract at different seasons showed a remarkable variation in the concentrations of falcarinol and dehydrofalcarinol as well as their ratio, depending on climate, soil and other regional conditions.

3.3.7. Other studies

Haemolytic activity

In-vivo experiments
Vogel and Marek (1962), Vogel (1963): Studied the haemolytic effect *in-vivo* after i.v. administration of different saponins in rats. A correlation between haemolytic index and toxic dose could not be found. He detected signs of massive intravascular haemolysis as the leading symptom in all saponins, especially haemolytic effects in liver and kidney tissue. The heart was dilated and collapse of the cardiovascular system was seen. No toxic signs were found after oral administration. Fatal absorptive effects were not observed after oral administration. They concluded that no quantities of saponin were absorbed by the rats' intestinal tract. The haemolytic index of Hedera saponin found was 1:103000 in blood (diluted 1:50) and 1:262 000 in washed erythrocytes (diluted 1:50).
Hiller (1966): If saponins get into the bloodstream they are toxic. Toxic signs were found primary in kidneys and liver. At oral administration, no toxic activity is to expect because they are not resorbed by an intact intestinal tract. Infections of the throat, stomach or intestinal tract may elevate the risk of resorption.
Wulff (1968): The haemolytic index of *hedera* saponin C and B is given as 1:1000 and of α-hederin 1:150000).
Mills and Bone (2000): Saponins are capable of destroying red blood cells by dissolving their membranes (a process known as haemolysis) and releasing free haemoglobin into the bloodstream. The toxic dose of an injected saponin occurs when sufficient haemoglobin is released to cause renal failure. After an oral intake, much of the saponin is not absorbed or is slowly and partially absorbed as the aglycone. The kidneys are thereby spared the sudden influx of haemoglobin.

Cytotoxic activity

In-vitro experiments

El-Marzabani *et al.* (1979): An ethanolic ivy extract (70% ethanol, 2:1) showed a cytotoxic activity on Ehrlich tumour cells *in-vitro*. After 4 h incubation almost all cells were non-viable. *In-vivo* there was a significant increase in the lifespan of mice treated with *Hedera helix* extract intraperitoneally (T/C=2.26) when the extract corresponding to 5 g dry plant/kg was given every other day over 10 days period (5 doses).

Quetin-Leclercq *et al.* (1992): The possible cytotoxic effects of sixteen saponins were detected *in-vitro* by the use of a semi-quantitative microtest. The biological test was carried out on four cell strains: mouse B16 melanoma cells, mouse 3T3 non cancer fibroblasts, flow 2002 non-cancer human cells and human HeLa tumour cells. The results showed that the hederasaponins B, C, D isolated from ivy and other plants were at least five times less active than the reference compound (strychnopentamine) and that none of them seemed to have any specific action on cancer cells. The most active compounds were the monodesmosides, which showed some degree of cytotoxicity at concentrations of 10 µg/ml and above, while among them, α- and β-hederin were the most potent substances, about ten times more active than the other saponins. The authors concluded, that α- and β-hederin were cytotoxic but also antimutagenic, which was of interest, because substances used in cancer chemotherapy were, on the contrary, mutagenic.

Danloy *et al.* (1994): The effects of α-hederin were analysed on mouse B16 melanoma cells and non-cancer mouse 3T3 fibroblasts cultured *in-vitro*. The results indicated that in a serum-free medium, α-hederin was cytotoxic and inhibited proliferation in both cell lines at rather low concentrations (<5 µg/ml) after only 8 h of treatment.
Its cytotoxicity decreased in the presence of serum in the culture medium, indicating that α-hederin could, like other saponins, bind to proteins present in FCS and particularly bovine serum albumin (BSA). It also induced vacuolization of the cytoplasm and membrane alterations leading to cell death.

Bun *et al.* (2008): α-hederin at subcytotoxic concentrations of 5 or 10µM enhanced 5-FU antitumor activity in human colon adenocarcinoma cells *in-vitro* about 3.3-fold. In this study, α-hederin alone had a modest growth inhibitory effect in HT-29 cells compared to 5-FU.

In-vivo experiments
Ibrar *et al.* (2001): The methanolic leaf extract of *Hedera helix* (500 g powdered leaves in 1250 ml methanol, vacuum evaporation to semi solid extract) was investigated for cytotoxic potential using brine shrimp bioassay. Results showed that the methanolic leaf extract possessed cytotoxicity (LC_{50}=802.73 µg). The saponin fraction has no cytotoxicity (LC_{50} greater than 1000 µg). The fraction left after separation of saponin ("residue") was cytotoxic (LC_{50}=700.54 µg). Further fractionation and subsequent brine shrimp bioassays of the fractions obtained showed that the fraction F4 contained the cytotoxic principle (LC_{50}=161.84 µg). According to infrared, ultraviolet spectroscopic analysis and chemical tests, the F4 fraction was a phenolic compound. The authors concluded that although methanolic extract of *Hedera helix* leaf was cytotoxic, the saponin isolated was not. This fact is also confirmed by the findings of Quetin-Leclercq *et al.* (1992) that the crude extract of *Hedera helix* exerted cytotoxic activity, both *in-vitro* and *in-vivo*, but the saponin isolated from this plant had no cytotoxic effect on cancer cells.

Olariu (2007): The inoculation of cellular B16F10 line melanoma suspension was made subcutaneous on singenic C57B1/6 line mice. Bioactive compounds isolated from *Salvia officinalis* and *Hedera helix* were applied s.c. beginning with the second and the third passage, 24 h from melanoma induction. The melanoma occurrence was delayed with 20-44 days in average, comparing with control lots. Also tumour attachment was affected by these treatments as shown by much smaller number of ill mice in treated lots. Regarding dissemination of tumour cells in lungs there were no differences between treated and untreated mice.

3.3.8. Overall conclusion on toxicological data

Single/repeat dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance or other particular studies have not been performed according to the state of the art and current guidelines. Only few data have been published based on the results from studies with other intention or summarising secondary literature. The cited studies give only limited information on the acute and chronic toxicity since the DER of the extracts is unclear and the route of administration was mostly i.p. and not oral.

According to Lanza *et al.* (1980), the oral administration of a single dose of a dry extract of ivy leaf (ethanol 66% (V/V), no DER information) to rats 3.0-4.0 g/kg body weight caused no death within 72 h. Only diarrhoea was observed. Similar results reported Timon-David *et al.* (1980) from a study in mice. Oral LD_{50} values in mice of saponin mixtures from ivy leaf containing 60% and 90% of hederacoside C, and of hederasaponin C and α-hederin, were all >4 g/kg body weight. Toxicity studies in other animal species are not published, therefore interspecies differences can not be excluded. Results of toxicity studies in i.v. administration of ivy extracts are not published. LD_{50}-values of 4.5 mg/kg i.v. for hederin and hederasaponin C>50 mg/kg i.v. in rats after 7 days observation period was reported by Wulff (1968).
Haemolytic effects were detected after oral administration of a hydroethanolic dry extract from ivy leaf to rats at 4 g/kg body weight for 90 days; (Bucher, 1969; an internal report, cited in ESCOP, 2003). Repeated oral administration of an ivy leaf dry extract (no more information) to rats at daily 1.5 g/kg body weight for 100 days caused no toxic effects (ESCOP, 2003).
No genotoxicity studies have been conducted with ivy leaf extracts. α-Hederin, ß-hederin and δ-hederin isolated from ivy leaf showed no mutagenic potential in the Ames test using Salmonella typhimurium strain TA 98, with or without S9 activation (Elias *et al.*, 1990).
Embryotoxic effects of the monidesmoside α-hederin were reported from experiments in rats following the single subcutaneous injection of 300 µmol/kg body weight (Daston *et al*., 1994) as well as repeated subcutaneous administration of 10 and 30 µmol/kg body weight (Duffy *et al.*, 1997), which were attributed to an α-hederin induced drop in the maternal serum zinc concentration. The human daily dosage for adults of 300 mg herbal substance (as recommended of Kommission E) contains approximately 6% of saponins corresponding to 18 mg of α-hederin. In a patient of 60 kg weight, approximately 0.3 mg α-hederin/kg (corresponding to 0.4 µmol α-hederin/kg) can be appreciated/ calculated as daily oral dose (30 µmol α-hederin/kg corresponds approximately to 22 mg α-hederin/kg).

Subcutaneous repeated daily dose *in-vivo*	10 and 30 µmol/kg body weight
Human daily oral dose of 300 mg herbal substance (Kommission E dosage)/650 mg herbal substance (dosage of many preparations)	0.4/0.9 µmol α-hederin/kg
Human daily oral dose of 1093 mg herbal substance (the greatest dosage in EU)	1.46 µmol α-hederin/kg

The following points support the view that available data have no clinical relevance:

- Subcutaneous administration cannot be compared with oral administration in *in-vivo* experiments.
- The mode of action, as increasing the maternal hepatic metallothionein levels, α-hederin does not have a direct embryotoxic effect and no embryotoxic metabolites of α-hederin occur in the rat.
- In literature (ESCOP, 2003; Müller-Jakic, 1998) the *in-vivo* studies Daston *et al.* (1994) and Duffy *et al.* (1997) are considered not to be of relevance for human therapy with ivy preparations.

- Consumption of different saponins in human alimentation
- Current studies (Stauss-Grabo, 2008) indicate a 30% resorption of a single dose of α-hederin in 24 h, therefore the safety factor could be assumed as ~40. From earlier studies even lower resorption rates were calculated (see chapter 4.1.2.).
- The study of Stauss-Grabo (2008) could not discriminate between α-hederin and/or its metabolites.

The following arguments support that use during pregnancy and lactation is not recommended:

- A greater resorption in case of infectious diseases as gastritis is hypothetically possible.
- The s.c. administered *in-vivo* concentrations with a clinical manifested toxic effect are only approximately 7-75-fold superior compared to the oral human therapeutic dose (100% resorption, the worst case).
- No screening studies about increasing of human maternal hepatic metallothionein levels of oral ivy extracts exist.
- The question, where developmental toxicity occurs only at the maternally toxic dosages is open.
- The saponins are very different in some pharmacological effects (ivy saponins have a great haemolytic effect).
- Different use in tradition: some saponins are used in the human alimentation others are considered to be toxic (beans are eaten, ivy is not eaten and not prepared as tea).
- The observed embryotoxic effect is considered to be an important effect. In the 30 µmol/kg treatment group, all of the litters contained pups that exhibited at least one abnormality.

From the results of the *in-vivo* study with s.c. administered ivy preparations, no influence on the outcome after orally administered ivy preparations can be concluded. The therapeutically recommended doses with a maximal daily oral dosage of approximately 650 mg of herbal substance are 10-fold under the repeated s.c. doses of the *in-vivo* experiment. Safety during pregnancy and lactation has not been established. In view of the pre-clinical safety data, the use during pregnancy and lactation should be avoided.
The results regarding local cutaneous sensitisation with accompanying contact dermatitis, which were reported for fresh parts of Hedera helix only, are of no relevance for the oral route of administration of preparations containing the dried ivy leaf extract.
In-vivo experiments by Vogel and Marek (1962) found signs of massive intravascular haemolysis, especially haemolytic effects in liver and kidney tissue after i.v. administration of different saponins in rats. Haemolytic effects were detected after an oral administration of a hydroethanolic dry extract from ivy leaf to rats at 4 g/kg body weight for 90 days. The effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
For human safety laboratory data see chapter 5.4. No relevant changes occur in human laboratory parameters after administration of therapeutically recommended dosages. Concerning the pharmacokinetic results of the *in vivo* study Stauss-Grabo (2008) with a possible 30% resorption of a single dose of α-hederin in 24 h, the human laboratory tests indicate no relevant oral resorption and contribute to a positive benefit-risk-relation for the recommended dosage ranges.
Some monodesmosides, especially α-hederin and ß-hederin, showed some degree of cytotoxicity on cancer cells at concentrations of 10 µg/ml and above (Quetin-Leclercq *et al.*, 1992). Melanoma occurrence was delayed by 20-40 days in average compared with control lots in an *in vivo* test performed by Olariu (2007) with s.c. administered “bioactive compounds” of Hedera helix. Regarding

dissemination of tumour cells in lung, there were no differences between treated and untreated mice. Due to the s.c administration and unknown dosages of unknown compounds, a clinical relevance for the extract can not be concluded. There are no appropriate *in-vivo* experiments at present on the relevance on this finding.

3.4. Overall conclusions on non-clinical data

Extracts of ivy leaves are used therapeutically in commercially available preparations in Europe for the treatment at common cold associated with cough and symptomatic treatment of acute and chronic inflammatory bronchial disorders.
The spasmolytic/bronchodilatating effect could be documented in *in vitro* experiments and *in vivo* studies in the compressed air model in conscious guinea pigs. The mechanism of the secretolytic activity observed in clinical praxis has not been established experimentally yet. Probably sub-emetic doses of saponins activate a gastro-pulmonary mucokinetic vagal reflex, which stimulates the bronchial glands to secret a watery fluid. An *in-vitro* effect of α-hederin on β2-adrenergic receptors could be demonstrated. Anti-inflammatory effects could be shown in different *in-vivo* models with orally administered ethanolic ivy leaf extracts. The antibacterial activity of saponins from *Hedera helix* against a large number of microorganisms was shown *in-vitro*. The antiviral activity of hederacoside C was demonstrated in *in-vitro* experiments with the influenza virus.

In summary, the pharmacological data of different *in vitro* and *in vivo* experiments, conducted with ivy leaves extract or saponins, support the use of ivy preparations in the context of inflammatory bronchial diseases and cough and colds.
Single/repeat dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance or other special studies do not exist according to the state of the art and the relevant guidelines. Some aspects have been addressed by the following studies:

Lanza *et al.* (1980): The oral administration of a single dose of dry extract of ivy leaf (ethanol 66% (V/V), no DER information) to rats 3.0-4.0 g/kg body weight caused no death within 72 h. Only diarrhoea was observed. Similar results were reported by Timon-David *et al.* (1980) from a study in mice. Oral LD_{50} values in mice of saponin mixtures from ivy leaf containing 60% and 90% of hederacoside C, and of hederasaponin C and α-hederin, were all >4 g/kg body weight.
The haemolytic effects were detected after oral administration of a hydroethanolic dry extract from ivy leaf to rats at 4 g/kg body weight for 90 days (ESCOP, 2003). Repeated oral administration of an ivy leaf dry extract (no more information) to rats at daily 1.5 g/kg body weight for 100 days caused no toxic effects.

No genotoxicity studies have been conducted with ivy leaf extracts. α-Hederin, ß-hederin and δ-hederin isolated from ivy leaf showed no mutagenic potential in the Ames test using *Salmonella typhimurium* strain TA 98, with or without S9 activation.

Embryotoxic effects of the monidesmoside α-hederin were reported from experiments in rats following the single s.c. injection of 300 µmol/kg body weight (Daston *et al*., 1994) as well as repeated s.c. administration of 10 and 30 µmol/kg body weight (Duffy *et al*., 1997), which were attributed to an α-hederin induced drop in the maternal serum zinc concentration. The fact, that α-hederin does not have a direct embryotoxic effect, is considered to support the safety of α-hederin in the cited publication.

Safety during pregnancy and lactation has not been established. In view of the pre-clinical safety data, the use during pregnancy and lactation should be avoided.
The results regarding local cutaneous sensitisation with accompanying contact dermatitis, which were

reported for fresh parts of *Hedera helix* only, are no relevant for the oral route of administration of preparations containing the dried ivy leaf extract.

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

Primary Pharmacodynamics

No data available.

Secondary Pharmacodynamics

No data available.

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

Schmidt (2003): In a pilot study, the bioavailability of α-hederin was evaluated, in human volunteers after oral administration. One volunteer took orally 1 g of ivy dry extract (5-7.5:1; extraction solvent ethanol 30%) with a content of 6.5% Hederacosid C and 4.0% α-hederin. No α-hederin could be detected in the blood. The limit of detection of α-hederin in blood was calculated with 1.0 g/ml.
A repeated dose of 2 times daily 130 mg of the same extract over a period of 7 days was administered to 4 volunteers (cumulative 1820 mg ivy extract with 72.8 mg α-hederin). In 3 humans, a very small peak whithin the limit of detection could be observed. Quantification was not possible due to the low concentration in the whole blood samples. The estimated/calculated concentrations of α-hederin in blood using reference chromatogram were 0.8; 0.6; 0.5 and 0 µg/ml. It corresponds to 4% of the cumulative administered α-hederin.

Landgrebe (2002): A daily dose of 130 mg of ivy dry extract (5-7.5:1; extraction solvent ethanol 30%) was administered to 16 human volunteers. α-Hederin could be detected only in blood of two of volunteers. The detected concentration was 1.39-1.51 nMol/l plasma.

4.2. Clinical Efficacy

Ivy preparations are worldwide marketed for treatment of different diseases of the respiratory tract system (“Catarrh of the respiratory passages”; “symptomatic treatment of chronic inflammatory bronchial illnesses”; “acute inflammations of the respiratory tract accompanied by coughing”). The following list shows the classification of WHO ICD-10 diseases of the respiratory tract system for the currently used ivy indications:

J00-J99: Diseases of the respiratory system
J00-J06: Acute upper respiratory infections

- J00 Acute nasopharyngitis [common cold]
- J01 Acute sinusitis
- J02 Acute pharyngitis
- J03 Acute tonsilitis
- J03 Acute laryngitis and tracheitis

- J05 Acute obstructive lanryngitis [croup] and epiglotitis
- J06 Acute upper respiratory infections of multiple and unspecified site

J20-J22: Other acute lower respiratory infections

- J20 Acute bronchitis (NOS in those under 15 years of age, acute and subacute bronchits (with bronchospasm, fibrinous, membranous, purulent, septic, tracheitis), acute tracheobronchits (excludes: chronic obstructive pulmonary disease with acute exacerbation NOS and lower respiratory infection)
- J21 Acute bronchiolitis (includes with bronchospasm)
- J22 Unspecified acute lower respiratory infection

J40-J47: Chronic lower respiratory diseases

- J40 Bronchitis, not specified as acute or chronic
- J41 Simple and mucopurulent chronic bronchitis (excludes: chronic bronchitis, NOS, obstructive)
  - J41.0 Simple chronic bronchitis
  - J41.1 Mucupurulent chronic bronchitis
  - J41.8 Mixed simple and mucupurulent chronic bronchitis
- J42 Unspecified chronic bronchitis (chronic bronchitis NOS, tracheitis, tracheobronchitis) excludes: chronic asthmatic bronchitis, chronic bronchitis; bronchitis: simple and mucopurulent; bronchits with airways obstuction; emphysematous bronchitis; obstructive pulmonary disease NOS
- J43 Emphysema
- J44 Other chronic obstructive pulmonary disease
- J45 Asthma (excludes: acute severe asthma, chronic asthmatic (obstructive) bronchitis, chronic obstructive asthma, eosinophilic asthma, lung diseases due to external agents, tatus asthmaticus)
- J46 Status asthmaticus
- J47 Bronchiectasis

Definitions

Definitions were searched in current guidelines: WHO GOLD guideline. Global initiative for chronic obstructive lung disease (2006), BTS Guideline: Recommendations for the management of cough in adults (Morice *et al.,* 2006), DEGAM guideline 11 Husten (cough) (2008) and Leitlinie der Deutschen Atemwegsliga (Vogelmeier *et al.,* 2007).

Viral infection (Common cold):

DEGAM guideline 11-cough (2008): Common cold symptoms are failing or mild fever, sore throat, cough, headache, chest pain, running or blocked nose, first clear and after 2-3 days purulent nasal secretion. If the symptoms improve after 3-4 days, the diagnosis “common cold” is attested.

Acute bronchitis

DEGAM guideline 11-cough (2008): The symptoms of acute bronchitis are dry cough, later productive cough, often fever, sore throat, secretion of the nose and sometimes bronchial obstruction. In 80% it is caused by viral infection (Adenovirus, Rhinovirus, Influenza, Parainfluenza, Coronavirus, RSV and Coxackivirus). In the absence of significant co-morbidity, an acute bronchitis is normally benign and self-limiting. Most of the symptoms improve in 2-5 days. The cough can linger several weeks.

Acute cough with fever, malaise, purulent sputum, or history of recent infection should be assessed for possible serious acute lung infection.

Acute exacerbation of COPD (chronic obstructive pulmonary disease)

Only mild cases can be treated ambulant. The majority of cases have to be treated in hospital. For the ambulant treatment ß-sympatomimetics are given. Antibiotics are recommended for bacterial infections.

Chronical bronchitis

DEGAM guideline 11 (2008): Chronic bronchitis is defined clinically by the presence of chronic bronchial secretions, enough to cause expectoration, occurring on most days for a minimum of 3 months of the year for 2 consecutive years. The pathological basis of chronic bronchitis is mucus hypersecretion secondary to hypertrophy of the glandular elements of the bronchial mucosa. Two forms can be distinguished:

a) Simple chronic bronchitis, the “uncomplicated” form is not obstructive
b) Chronic obstructive pulmonary disease COPD (WHO definition)

Chronic obstructive pulmonary disease (COPD) is a lung disease characterised by chronic obstruction of lung airflow that interferes with normal breathing. It is not fully reversible. The more familiar terms 'chronic bronchitis' and 'emphysema' (emphysema has a pathological definition, which is a condition where there is permanent destructive enlargement of the airspaces distal to the terminal bronchioles without obvious fibrosis) are no longer used, but are now included within the COPD diagnosis. A COPD diagnosis is confirmed by a spirometry test, which measures how deeply a person can breathe and how fast air can move in and out of the lungs (forced expiratory volume in one second FEV_1). Clinical symptoms and signs, such as abnormal shortness of breath and increased forced expiratory time, can be used to help with the diagnosis.

According to the WHO (GOLD guideline, 2006), the regular use of mucolytics in COPD has been evaluated in a number of long-term studies with controversial results; although few patients with viscous sputum may benefit from mucolytics. The widespread use of these agents cannot be recommended at present. The treatment is based on bronchodilatators as anticholinergica, ß-sympatomimetica and theophyllin. Glucocorticoides are also used. Mucolytics should be used critically with respect to the subjective therapeutic success.

Asthma bronchiale (WHO definition)

Asthma is a chronic disease characterised by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person. Symptoms may occur several times a day or a week in affected individuals; for some people become worse during physical activity or at night. The treatment depends on the asthma classification and is based on ß-sympathomimetics, glucocorticoides, chromone and montelucast. Mucolytics are not recommended.

Acute cough

The current DEGAM guideline 11 (2008) gives the following definition for acute cough: A cough lasting less than 3 weeks is termed acute.
According to the BTS guideline (Morice *et al*., 2006), the grey area between 3 and 8 weeks of cough is difficult to define aetiologically since all chronic cough will have started as an acute cough, but the clear diagnostic groups of chronic cough are diluted by those patients with post-viral cough. An upper respiratory tract infection (URTI) cough lingering for more than 3 weeks is usually termed ‘‘post-viral

cough''. Symptomatic URTIs occur at rates of 2-5 per adult person per year, with school children suffering from 7-10 episodes per year (Morice *et al*., 2006).
The differential diagnosis of acute cough includes the following respiratory tract infections: viral infection (common cold), acute bronchitis, pneumonie, viral influenza, acute exacerbation of COPD, asthma bronchiale. Diseases in other organ systems (heart system, gastrointestinal tract) or exogenic causes (medicaments) can also cause acute cough.

Chronic cough (>3 weeks/>8 weeks)

The DEGAM guideline 11 (2008) gives the following definition for a chronic cough: "A cough lasting longer than 3 weeks is termed chronic". According the BTS guideline (Morice *et al.,* 2006), a cough lasting longer than 8 weeks is defined as chronic. According to the same guideline, a cut of 2 months for chronic cough has been arbitrarily agreed in both American and European guidelines.
The differential diagnosis of chronic cough includes often diseases as chronic bronchitis, postnasal drip syndrome, bronchial hyperreagibility, COPD, asthma bronchiale and gastrooesophagial reflux.

4.2.1. Dose response studies

No data available.

Dose comparative clinical studies

Gulyas (1997): In a randomized, double-blind, crossover study involving 25 children (aged 10-15 years) with chronic obstructive pulmonary complaints, changes in lung function were examined after treatment over separate 10-day periods with two oral liquid preparations based on the same ivy leaves dry extract: an ethanol-free preparation (3 x 5 ml daily, corresponding to 3 x 35 mg of dry extract (5-7.5:1), ethanol 30% (m/m) or 630 mg of herbal substance daily) and an ethanol-containing preparation (3 x 20 drops daily, corresponding to 3 x 14 mg of dry extract (5-7.5:1), ethanol 30% (m/m) or 252 mg of herbal substance daily).

The parameters of lung function (FEV_1, forced vital capacity, vital capacity, peak flow rate) were measured on the 1st day (before the start of treatment), on the 5th day and on the 10th day (before and 3 h after administration). Body plethysmography was also used before the start of the treatment and on the 10th day, 3 h after the last dose to measure the airway resistance, intrathoracic gas volume and specific airway resistance. As in the first study, $ß_2$-sympathomimetic drugs were not permitted for 6 h before the lung function test.
The change in airway resistance (RAW) was the main criterion of the study to compare the two presentations in the chosen dosage. The comparison of the airway resistance with the baseline level showed more significant improvement in the first study (after 3 days), than in the second study (after 10 days). Comparable improvements in spirometric and bodyplethysmographic parameters were observed after both treatments. The author concluded that it was necessary to give two times higher dosage of the ethanol-free preparation than the ethanol-containing preparation to achieve the same therapeutic effect.

Assessor´s comment:

This assumption cannot be generalised because the low dose of ethanol-free juice was not examined. The statement on the need of higher dosage ranges is controversially discussed because the study was only conducted in 25 children aged from 10 to 15 years.
For a detailed analysis of the study see chapter 4.2.2. For dosage discussion see the point "dosage" in chapter 4.3.

Unkauf and Friderich (2000): In a randomized prospective multicenter, reference controlled study, 52 children (mean 7.9 years) with a clinically confirmed bronchitis (no information acute or chronic) were treated either with Valverde® (200 ml juice contain 660-1000 mg ivy dry extract (3-6:1), extraction solvent ethanol 60% (m/m)) or Prospan® Hustensaft (100 ml contain 700 mg ivy dry extract (5-7.5:1), extraction solvent ethanol 30 (m/m)). The daily dose of Valverde® was: children up to 4 years 2 x 5 ml daily; 4-10 years 2 x 7.5 ml daily; 10-12 years 2 x 10 ml daily. The dosage of Valverde® corresponds up to 4 years: 150-225 mg herbal substance, 4-10 years 253-338 mg herbal substance, 10-12 years 350-450 mg herbal substance. Prospan® cough juice corresponds up to 4 years:
350-490 mg herbal substance, 4-10 years 525-735 mg herbal substance, 10-12 years 700-980 mg herbal substance per day.
The primary objective endpoint was the bronchitis severity score as judged by the impairment of the state of the patient by means of a visual analogy scale at inclusion and at the end of the study on day 10. Secondary variables were severity of illness (CGI items II), the ratio of the therapeutic effect to the adverse drug reactions (CGI items III), frequency and kind of cough, colour and quality of the expectoration and auscultation.
The primary endpoint "bronchitis severity" was reduced in both treatment groups in the course of the study from day zero to day ten. From 52 children, 51 were responders (98%) and showed an improvement of the variables by at least 50%. The comparison of both medical treatment groups concerning the primary criterion showed a statistically significant equivalence of both ivy products after five days (p=0.0022) and after ten days (p=0.0031). The comparison of the laboratory values at the start and the end of the therapy did not show any relevant variations.

Cwientzek U (2011): In a double-blind, randomised study patients with acute bronchitis were randomised to one of two treatment groups: Ivy leaves extract (Hedelix®) or active control (Prospan® Hustentropfen (dry extract of ivy leaves (5–7.5:1) extraction solvent ethanol 30 (m/m)). The main inclusion criteria were, at least 2 years of age, confirmed clinical diagnosis of acute bronchitis with a BSS ≥ 5, duration of complaints not more than 48 hours and non-use of concomitant medication. Patients took one of the medications three times daily over a period of seven days (±1). The test treatment was: Hedelix s.a. (1 ml solution contains 0.04 g Ivy leaves soft extract (DER 2.2-2.9:1), extraction solvent ethanol 50% V/V: propylene glycol (98:2). The tested dosage corresponds the recommended dosages of the authorized Hedelix s.a.®: Three times daily: 31 drops per dose adults and children from an age of 10 years (93 drops= 0.3 g herbal substance); 21 drops for children between 4 and 10 years old, (63 drops = 0.2 g herbal substance); 16 drops for children between 2 and 4 years old (48 drops = 0.15 g herbal substance). After the admission examination, patients returned for further examinations on day 4±1 (V2) and on day 7±1 (V3).

During the admission examination, the patients underwent an anamnesis and examination related to acute bronchitis and investigators and/or patients evaluated the clinical target criteria (Bronchitis Severity Score BSS, five symptoms for acute bronchitis: cough, sputum, rales/rhonchi, chest pain during coughing, dyspnoea. Each symptom was scored by the investigator on a scale from 0–4. The BSS is the sum of the five symptom subscores. Additionally body temperature, hoarseness, headache, pain in limbs, fatigue/exhaustion, ability to return to work or school were evaluated. During the further examinations these target criteria and in addition global efficacy, global satisfaction with therapy, and tolerability were evaluated. The primary efficacy criterion was the change of BSS at Visit 3 (Day 7±1) vs. baseline (Day 0).

590 patients recruited, randomised, and supplied with study medication were included in the safety dataset (Hedelix: n=295; Prospan: n=295; Hedelix: 2-4 years: n=33; 5-10 years n=67; > 10 years n=195; Prospan: 2-4 years: n=33; 5-10 years n=68; > 10 years n=194). ITT: Hedelix: n=293 Prospan: n=295; PP: Hedelix: n=260 Prospan: n=258.

The border of non-inferiority was 32% of the standard deviation of BSS change observed in the active control group, because the expected superiority over placebo would be approximately 64% of the standard deviation. Efficacy was assumed if the two-sided 95% confidence interval (alternatively the one-sided 97.5% confidence interval) of treatment difference of the ivy leaves extract vs. the active control was completely above the lower limit, i.e. -64% of the standard deviation of BSS change observed in the active control group.

In the ITT group the difference between Hedelix and Prospan was 0.046 (point estimate; 95% CI: -0.2303 to 0.3224) and the lower end of the 95% CI was above the non-inferiority margin (-0.6336). The improvement in the PP dataset was only marginally higher (by approximately 0.1 score point) compared to the ITT dataset. The BSS decreased gradually and to a similar extent in both treatments starting from values of 6.2–6.3±1.2, by approximately 4.7–4.9 points until Visit 3, so that patients left the study with a mean BSS of 1.4–1.6.

The BSS subscales cough, sputum, rhales / rhonchi, chest pain during coughing, and dyspnoea improved to a similar extent in both treatment groups and also in both datasets. In all three age groups (≥2 and ≤4 years; >4 and ≤10 years; >10 years) the mean BSS baseline values were within a ±0.2 score points corridor from the overall group mean and in the non-inferiority margin of ≥ 0.62 points.

In the Hedelix group, 77.1% of the ITT dataset (226 of 293 patients) were classified as responders (defined BSS < 3 points at Visit 3) and in the Prospan group 79.7% (235 of 295 patients).

In the Hedelix group, 12.6% of the ITT dataset (37 of 293 patients) were classified as responders (defined as BSS < 3 points at Visit 3 and decrease of BSS ≥ 7 points by Visit 3) and in the Prospan group 13.2% (39 of 295 patients).

Safety evaluation:

Sixteen patients experienced 24 adverse events, eight patients (11 events) in the Hedelix group and eight patients (13 events) in the Prospan group. In each group 2.7% of patients from the safety dataset had one or two adverse events: 6 patients of the Hedelix group (3 diarrhoea, 4 nausea, 1pyrosis) and 7 patients in the Prospan group (3 diarrhoea, 3 nausea, 2 pyrosis, 2 epigastric pain, 2 vomiting). Investigators considered all gastrointestinal adverse events as possibly or probably related to the study medication. 2 patents of the Hedelix group had infections (1 cystitis, 1 urethritis, 1 varicella). There was a not assessable relationship to the study medication.1 patient in the Prospan group developed asthma bronchiale and not recovered at the end of the study.

Fifteen of the 16 patients experiencing adverse events in this study were over ten years old, only one was between four and ten years old. Compared to the age distribution in the study population, patients younger than ten years were underrepresented, i.e. tolerated the study medication even better than the older ones.

Patients rated their impression of global tolerability with a mean (±SD) of 3.98±0.97 for the Hedelix group and with 3.96±0.95 for the Prospan group on a rating scale from 1 – very poor to 5 – very good tolerability. The investigators rated their impression of global tolerability with a mean (±SD) of 4.21±0.78 for the Hedelix group and with 4.19±0.79 for the Prospan group.

Assessor's comment:

The results of the study show, that the tested preparation has comparable efficacy results for the primary efficacy parameter BSS as the comparator product Prospan drops. In the secondary parameters, the BSS subscales cough, sputum, rhales / rhonchi, chest pain during coughing and dyspnoea improved to a similar extent in both treatment groups and also in both datasets. The results

of the safety evaluation give no reasons for unknown side effects. The art and number of side-effects were similar in the groups.

In the evaluated controlled clinical studies in the AR, conducted with the comparator extract, examination of lung parameters showed no convincing efficacy in bronchospasm. The efficacy of the ivy preparation is based on the secretolytic effects. In the study in question, the BSS values in the start of the study was 6.2–6.3±1.2 of maximal 20 possible points. The low BSS at the beginning of the study, indicate that only patients with an uncomplicated acute bronchitis without bronchial obstruction were included/treated. Therefore, no change of the indication "Herbal medicinal product used as an expectorant in case of productive cough" is recommended. As the comparator product is listed in the chapter "well established use", it is recommended, the preparation "Soft extract (DER 2.2-2.9:1), extraction solvent ethanol 50% V/V: propylene glycol (98:2)" should also be added in the chapter "well-established use" of the HMPC-monograph.

4.2.2. Clinical studies (case studies and clinical trials)

Controlled studies

Meyer-Wegener *et al.* (1993): A randomized controlled double-blind comparative study of 99 adult patients (aged from 25-70 years) with mild to moderate, simple or obstructive chronic bronchitis was carried out. They were treated either 3-5 times daily for 4 weeks with 20 drops of ivy leaves extract ((5-7.5-1), ethanol 30% (m/m); 2 g of dry extract pro 100 ml)) and 3 times daily with 1 placebo tablet or 3-5 times daily with ambroxol 30 mg tablet and 3-5 times daily with 20 drops placebo. The daily dosage was 0.25-0.42 g of a herbal substance. Excluded were patients with asthma bronchial, chronic bacterial bronchitis and patient with severe lung diseases. Objective parameters of the study were the spirometric data (vital capacity, 1 sec. capacity, and peak flow), the symptoms and the auscultation results.

Improvements in spirometric and auscultation parameters were observed in both groups with no significant differences between the groups. The vital capacity in the group treated with the ivy preparation increased slightly more (from 2.84 l to 3.11 l) than in the ambroxol group (from 2.89 l to 2.92 l). The FEV_1 remained unchanged in both groups (1.80 l/s ivy leaf extract and 1.88 l/s ambroxol). The global rating for efficacy was "good" in 58.3% of the cases in the ambroxol group and in 55.1% in the ivy group. The patients' diaries were analysed descriptive because the diaries were not fully completed. The results indicated a tendency towards greater decrease in frequency of coughing, sputum production and dyspnoea in the ivy leaf extract group.

Table 1: Vital capacity (l)

	ivy leaf extract		ambroxol	
Study week	Average	Standard deviation	Average	Standard deviation
0	2.84	1.21	2.89	0.93
1	3.09	0.91	2.92	1.17
2	3.01	0.97	3.02	0.78
3	3.07	0.88	2.90	0.94
4	3.11	1.06	2.92	0.93

Patients rated the tolerability as "good" or "very good" in 87.8% (ivy leaf extract) and 87.5% (ambroxol) of cases in the 3th week and 93.4% (ivy leaf extract) and 95.5% (ambroxol) in the 4th week. In the verum group, 7 patients had undesirable effects (not described). Two of them were considered to have a causal relation to the medication. In the ambroxol group, 6 undesirable effects

occured and 3 of them were considered to have a causal relation to ambroxol. One drop out case occured in the ambroxol group.

Assessor's comment:

The study of Meyer-Wegener et al. (1993) analyses both the spirometric parameters and symptomatic benefits as a combined primary outcome. The study was conducted in simple chronic bronchitis (patients without obstruction) and in patients with obstructive chronic bronchitis. There is no information about the number of patients in the subgroups.
According to the current definition, obstructive chronic bronchitis is subsumed under COPD. Physiological changes characteristic of the disease include mucus hypersecretion, airflow limitation and air trapping (leading to hyperinflation), gas exchange abnormalities, and cor pulmonale. Due to airway fibrosis and alveolar destruction, the airflow limitation is not fully reversible.
For the diagnosis and assessment of COPD, spirometry is the gold standard as it is the most reproducible, standardised and objective way of measuring airflow limitation. Spirometry should measure the volume of air forcibly exhaled from the point of maximal inspiration (forced vital capacity, FVC) and the volume of air exhaled during the first second of this manoeuvre (forced expiratory volume in one second, FEV_1). The ratio of these two measurements (FEV_1/FVC) should be calculated. The presence of a post bronchodilator FEV_1/FVC <0.70 and FEV_1 <80% predicted confirms the presence of airflow limitation that is not fully reversible. According the WHO GOLD guideline (2006), an increase in FEV_1 that is both greater than 200 ml and 12% above the pre-bronchodilator FEV_1 is considered significant.
In this study, the FEV_1 remained unchanged in both groups (1.80 l/s ivy leaf extract and 1.88 l/s ambroxol). The vital capacity in the group treated with the ivy preparation increased slightly more (rise from 2.84 l to 3.11 l) than in the ambroxol group (rise from 2.89 l to 2.92 l). Neither ambroxol nor the ivy preparation reduced the FEV_1 in the range of 12%. The results indicate that both preparations are not eligible to act as "bronchodilator" for efficacy in obstructive chronic bronchitis/COPD.
The study results show no significant differences between the groups in auscultation parameters and clinical symptoms. Patients with viscous sputum may benefit from both preparations.
Ambroxol was granted the indication "For secretolytic therapy in acute and chronic bronchopulmonary diseases, concomitant with disturbance in formation and transport of viscous sputum".
The study results are in line with the indication of ambroxol, where only a secretolytic therapy is described. The results indicate that patients with simple chronic bronchitis and patients with obstructive chronic bronchitis may benefit from the ivy preparation for decreases in frequency of coughing, sputum production and dyspnoea, comparable to the secretolytic therapy with ambroxol. The long term use as a secretolytic in chronic bronchitis can not be deduced by the study results. The benefit is shown only for short term use of maximum 4 weeks.

Maidannik *et al.* (2003): In an open and controlled study (in two clinical hospitals in Kiev and Dnepopetrovsk), 72 children (7 months-15 years) suffering from acute inflammatory diseases of the respiratory tract (6 patients acute respiratory viral infection, 19 acute bronchopneumonia, 25 acute bronchitis, 11 acute obstructive bronchitis, 4 recurrent bronchitis, 5 bronchial asthma, 2 mucoviscidose) were treated either with Prospan® (ivy dry extract (5-7.5:1), ethanol 30% (m/m)) (n=53) or with ambroxol (n=19). Prospan® was prescribed in the following dosages: from 1 to 6 years 3 times daily 1 teaspoon, from 7 to 14 years 3 times daily 2 teaspoons. The duration of a treatment was between 7-10 days. In the case of a chronic disease, the treatment duration was 10-14 days. Spirometric and bodyplethysmographic measurements of the lung function were carried out before the beginning and during the medication (VC, FVC, FEV_1 and PEF, MEF_{25}, MEF_{50}). Subjective symptoms were documented within patient's diaries by using a 5-score rating scale. The documented clinical symptoms were duration of fever, cough, ease of expectoration, character of breathlessness,

auscultatory picture of patient's lung. In addition, the blood analyses, including the calculation of leucocytic count, flora identification, virological and bacteriological test were performed.
The authors resumed, after 7 days of Prospan® treatment, that the velocity parameters of external respiration were normalised nearly in all children with obstructive diseases, while in the ambroxol treatment group normalisation could not be documented, but the parameters got even worse. No results referring to the ambroxol group were shown.
Comparing the course of auscultatory picture in lungs, a fast decrease of crepitation was only seen in the group of children treated with Prospan® (Prospan®: 94.3% before treatment, 45.8% in 7 days; ambroxol: 87.6% before treatment, 47.3% in 7 days).
The comparison of the decrease in productive cough in both treatment groups showed no statistical significant differences. After 7 days of the treatment, the cough in both groups was healed in more than half of the patients, and within 14 days disappeared in general. The clinical symptom "short breath" increased a little bit at day 3 of the treatment, the result at day 7 is not shown. Normalization of leukocytic count was documented after 7+1.5 days. The course of external respiration in % of the normal (VC, FVC, FEV_1, PEF, MEF_{25}, MEF_{50}) was shown only for the ivy preparation group. The authors concluded that after 7 days of Prospan® treatment, the velocity parameters of external respiration were normalised nearly in all children with obstructive diseases, while in the ambroxol group normalisation could not be documented.

Assessor's comment:

This study supports the results of the study conducted by Meyer-Wegener et al. (1993). Patients with cough/viscous sputum may benefit from the use of an ivy preparation or ambroxol. The study demonstrated a positive influence on symptoms such as cough in acute inflammatory diseases. The comparison of the decrease in productive cough in both treatment groups showed no statistical significant differences. Comparing the course of auscultatory picture in lungs, a fast decrease of crepitation was only seen in the group of children treated with Prospan®. After 7 days of the treatment, the cough in both groups was cured in more than half of the patients, and within 14 days it disappeared in general.
No conclusion on efficacy for the specific indications is possible. The number of patients for each of the multifaced diagnosis is 2-25. Because of the small number of patients for each diagnosis, the results of spirometry are to be used with caution. The authors' conclusion, that the ivy preparation has a better efficacy as ambroxol, is not convincing because the ambroxol data are often missing. Blood analyses were performed in this study, so the study contributes to safety data of high dosages of ivy leaf preparations in children.

Bolbot *et al.* (2004): In an open and controlled study (in two clinical hospitals in Krivoy Rog and Dnepropetrovsk, Ukraine), 50 children (2-10 years) suffering from acute bronchitis (25 patients with obstructive and 25 patients with non obstructive acute bronchitis) were treated either with Prospan® syrup (ivy dry extract (5-7.5:1), extraction solvent ethanol 30% (m/m)) (n=25) or with acetylcysteine (n=25). Patients with hypersensitive reactions or taking other expectorants were excluded. Prospan® was prescribed in the following dosages: 2-6 years 3 times daily 5 ml, 7-10 years 3 times daily 10 ml; acetylcysteine: 2-6 years 3 times daily 100-200 mg, 7-10 years 3 times daily 300-400 mg. The duration of the treatment was between 7 and 10 days. Spirometric and bodyplethysmographic measurements of the lung function were carried out before the beginning, at day 5 and after full treatment (FVC, FEV_1 and PEF, MEF_{25}, MEF_{50}, MEF_{75}). Documented clinical symptoms were: cough, sputum, short breath and respiratory pain. Along with the tested products, 48% of the Prospan® group and 56% of the acetylcysteine group were taking additional medication as antibiotics, antihistamines, etc.
After 5 days of the treatment, the improvements of parameters concerning the function of upper and middle airways (FVC, FEV_1, PEF, MEF_{25}, MEF_{50}) were greater in the Prospan® group and statistic

different from parameters in the ACC group ($p<0.05$) and from baseline ($p<0.05$). In 10 days, 15% of the Prospan® group and 28.6% of the ACC group still had cough and sputum. All patients with cough had liquid sputum (no viscous, no half-viscous) at the end of the study. After 10 days, no patients had short breath or respiratory pain. The efficacy ratings of Prospan® were in 96% "very good" and "good" comparable with 79.2% for ACC. The tolerability of Prospan® was rated by doctors in 40% as "very good" and 60% as "good".

Table 2: External respiration parameters during the treatment (in % from normal)

Parameter	Prospan group			ACC group		
	before treatment	in 5 days	after treatment	before treatment	in 5 days	after treatment
FVC	60.5±9.9	73.8±5.4	136±19.1	56±4.3	71.7±7.5	89.4±7.5
FEV_1	62±8.4	74.5±5.8	129.6±18.4	63.7±6.9	71.3±7	88.6±8.5

Assessor's comment:

At the end of the study all patients with cough had liquid sputum (no viscous, no half-viscous). In 10 days, 15% of the Prospan® group and 28.6% of the ACC group still had cough and sputum. The comparison suggests that ivy extracts can be therapeutically equivalent or better than ACC in secretolytic therapy and improvement of cough in patients with acute bronchitis. This study supports the results of the study by Meyer-Wegener et al. (1993), refering to the secretolytic activity of ivy preparations in clinical praxis.
The comparison of the change of the spirometric parameter FEV_1 (ivy: 67%; ACC: 25%) suggests better efficacy in spasmolytic activity for the ivy preparation than for ACC. An increase of 67% (62% before treatment to 129% after treatment of 10 days) for the ivy preparation cannot be assessed without a positive control and without placebo. The low number of patients and the concomitant medication of antibiotics (comparable in the groups) affect negatively the level of evidence with regard to efficacy.
The results of the study indicate that the ivy preparation has a benefit for secretolytic therapy in acute bronchitis, concomitant with disturbance in formation and transport of viscous expectoration.

Additional controlled clinical studies with influence on spirometric and bodyplethysmografhic parameters

Assessor's comment:

In the preclinical studies, ivy preparations showed a convincing antispasmodic activity (compared to papaverine). The clinical controlled studies by Gulyas (1997), Mansfeld et al. (1997, 1998) and Gulyas (1999) analysed the influence on spirometric and bodyplethysmographic parameters in clinical use. These studies were only conducted on small sample size (n=maximal 26), for a short time (10 days, 3 days, 3 days and 14-20 days) and no clinical symptoms were tested. Therefore, they cannot proof efficacy in the intended indications (in the context of bronchitis). They have supportive character for information on clinical pharmacology.

Gulyas (1997): description of the study see chapter 4.2.1

Table 3: Spirometric parameters: average parameters of lung function FEV_1 (l), forced vital capacity FVC (l), vital capacity VC (l) and PEV (l/s).

ethanol-free juice					ethanol-containing drops			
	1st day	5th day	10th day of treatment		1st day	5th day	10th day of treatment	
	before	3 h after	before	3 h after	before	3 h after	before	3 h after

	med.		med.		med.		med.	
FEV_1(l)	2.01	2.08	2.14	2.15	2.00	2.09	2.14	2.15
FVC (l)	2.26	2.34	2.40	2.40	2.27	2.34	2.39	2.40
VC (l)	2.37	2.44	2.49	2.49	2.37	2.45	2.50	2.50
PEF (l/s)	4.44	4.64	4.83	4.91	4.44	4.75	4.97	4.91

Table 4: Bodyplethysmographic parameters (ITGW: intrathoracal gas volume; RAW: Airway resistance; SRAW: Specific airway resistance).

	ethanol-free juice (630 mg herbal substance)		ethanol-containing drops (252 mg herbal substance)	
	1st day before medication	10th day 3 h after medication	1st day before medication	10th day 3 h after medication
RAW (kPa/l/sec.)	3.77	3.39	3.74	3.39
ITGV (l)	2.78	2.59	2.76	2.59
SRAW (kPa/l/sec.)	9.93	8.30	9.81	8.29

Comparable improvements in spirometric and bodyplethysmographic parameters were observed after both treatments. The author concludes thay the ethanol-free preparation is necessary to be given in two times higher dosage than the ethanol-containing preparation to achieve the same therapeutic effect.

Assessor's comment:

The author analysed the reversibility of the bronchial obstruction comparing the data with salbutamol. Salbutamol as a positive control showed changes of 22.5% at first day. Before medication the FEV_1 was 2.0 l in both groups. Ten minutes after inhalative application of 200 µg salbutamol medication, the FEV_1 was 2.46 l in the juice group and 2.44 l in the drops group.
The data show that the FEV_1 rises in the 5th day, 3 h after medication only to 2.08 l in the juice group and 2.09 l in the drop group. The change of proximally 4% is not considered as clinical relevant. After 10 days, the FEV_1 was 2.15 l (proximally 8%) in both treatment groups 3 h after medication. After 10 days the FEV_1 in both groups was 2.15 l before treatment and 2.45 l after salbutamol medication. According the WHO GOLD guideline (2006), an increase in FEV_1 that is both greater than 200 ml and 12% above the pre-bronchodilator FEV_1 is considered clinically significant. The change of 8% is under this borderline. The bronchodilating clinical activity is proximally 1/3 of salbutamol. No placebo control was conducted.
For dosage discussion see the point "dosage" in chapter 4.3.

Mansfeld *et al.* (1997): In a randomized, comparative, cross-over study, 26 children (aged 5-11 years) suffering from bronchial asthma were treated for 3 days with preparations containing a dry extract (5-7.5:1), extraction solvent ethanol 30% (m/m) from ivy leaf 2 x 25 drops of an oral liquid preparation (35 mg of the extract daily, corresponding to 218 mg herbal substance) and then, after a 4-day wash-out interval, 2 suppositories daily (=160 mg dry extract daily, corresponding to 1000 mg herbal substance). The peak flow improved in comparison with the initial value by 21.8% after application of the suppositories and by 25.2% after administration of the drops. A reduction of the airway resistance of 0.49 kPa/l/sec (31%) (oral liquid) and 0.44 kPa/l/sec (23%) (suppositories) compared to initial values was observed. The FEV_1 increased on the 3th day, 3 h after medication from 1.37 l to 1.64 l (suppositories) and 1.39 l to 1.61 l (oral liquid). The FEV_1 after inhalation of fenoterol was 1.61/1.64 l.

Assessor's comment:

The results are comparable to the results of the (asthma) study by Mansfeld et al. (1998), with the difference that no placebo control was conducted in this study. Without a placebo control, the relevance of the data is limited. In the study of Mansfeld et al. (1998) the differences in FEV_1 was not statistically significant in comparison to placebo.

Mansfeld *et al.* (1998): In a randomized, double-blind, placebo controlled crossover comparative study 28 (24) children, 13 girls and 15 boys, aged 4-12 years, suffering from bronchial asthma were treated for 3 days each with a dry extract from ivy leaves (5-7.5:1), ethanol 30% (m/m) or placebo, interrupted by a wash-out phase from 3-5 days. The daily dosage of 2 x 25 drops was equivalent to 35 mg dried ivy leaf extract or 218 mg herbal substance. The change of the airway resistance was evaluated as a primary objective criterion. Four children were not evaluated because they were considered as drop-outs.
A statistically significant reduction of 0.14 kPa/l/sec (23.6%) of the airway resistance was proved in comparison to placebo therapy. The verum therapy had a positive effect on bodyplethysmographic and spirometric parameters that was not statistically significant in comparison to placebo. The assessment of the tolerance by the physician and the patients did not show any relevant differences between verum and placebo and was considered as very good.

Table 5: Bodyplethysmographic parameters

	Airway resistance (kPa/l/sec)		Intrathoracal gas volume (ITGV) (l)		Residual volume (l)	
	Verum	Placebo	Verum	Placebo	Verum	Placebo
1 day before medication	0.75	0.70	1.71	1.64	1.11	1.02
3 days after medication	0.61	0.67	1.55	1.66	0.97	1.00
Difference 3 days after medication	-23.6%	-4.9%	-10.1%	+0.7%	-14.3%	-2.4%
difference to placebo	p=0.0361		p=0.0007		p=0.1671	

Table 6: Spirometric parameters

	VC (l)		FVC (l)		FEV_1 (l)	
	Verum	Placebo	Verum	Placebo	Verum	Placebo
1st day before medication	1.93	1.94	1.82	1.84	1.61	1.59
1st day after	2.00	1.98	1.93	1.92	1.73	1.70
3rd day before	1.89	1.93	1.86	1.89	1.62	1.60
3rd day after	2.06	1.99	1.97	1.90	1.80	1.67
Difference in % 3rd day after medication	6.5	2.8	8.4	3.3	11.8	5.0

	Verum		Placebo	
	Control FEV_1 (l)	10 min after inhalation of 2 x 100 µg fenoterol	Control FEV_1 (l)	10 min after inhalation of 2 x 100 µg fenoterol FEV_1 (l)

		FEV_1 (l)		
1st day before medication	1.44	1.75	1.44	1.75
3rd day 3 h after medication	1.80	1.83	1.67	1.79

Assessor's comment:

A statistic significant reduction of 0.14 kPa/l/sec (23.6%) of the airway resistance was proved in comparison to the placebo therapy. The positive control for reversbility of bronchial obstruction was conducted with inhalative fenoterol.
The author's conclusion that the bronchodilalatory effect of the ivy preparation was comparable to fenoterol is not convincing. On the first day, ivy has a difference in FEV_1 of 0.12 l (1.73-1.61) placebo of 0.11 l (1.70-1.59) and fenoterol of 0.31 l (1.75-1.44). The direct bronchodilatory effect of the ivy preparation on the first day is proximally 1/3 of fenoterol and comparabel to placebo. The difference was not statistically significant in comparison to placebo.
The results showed increases in FEV_1 from day 1 to day 3, both in the verum group and the placebo group (verum 0.36 l (1.80-1.44); placebo 0.23 l (1.67-1.44)). This indicated an improvement in the lung function and was in accordance with the results of airway resistance. The increase of FEV_1 on the third day, 3h after inhalation of 2 x 100 µg fenoterol medication was minimal, 1.80 l to 1.83 l in the ivy group and 1.67 l to 1.79 l in the placebo group. All together, the results indicate an improvement of lung function, but no significant better bronchodilatory effect than placebo.

Gulyas (1999): In a controlled pilot study 20 children (9-15 years), with a chronic obstructive pulmonary disease, were treated either with Prospan® Hustensaft (ivy dry extract (5-7.5:1), ethanol 30% (m/m)) (n=10) or with N-acetylcysteine (NAC) (n=10) in the dosages recommended (ivy extract corresponding to 630 mg herbal substance). The duration of the treatment was between 14 and 20 days. Spirometric and bodyplethysmographic measurements of the lung function were carried out before the beginning of the medication and at the end. VC, FEV_1 and PEF in addition were determined after one-week of therapy.
Regarding the vital capacity (VC), a clinically relevant improvement was seen in the two treatment groups. After one-week therapy with ivy extract, the vital capacity of 1.93 l rose to 2.07 l and 2.19 l until the end of the therapy. VC improved in the acetylcysteine group from 1.78 l to 1.94 l after one week and to 2.01 l at the end of the therapy. With regard to the forced expiratory volume (FEV_1), a clear difference was found in favour of the ivy extract: the FEV_1 increased under ivy extract from 1.56 l to 1.90 l after 2 weeks and under acetylcysteine from 1.50 l to 1.72 l. A similar trend was observed at the peak-flow values and the airway resistance.
The authors concluded that the results of this study show a clinically relevant effect of ivy leaves extract and also of acetylcysteine on the bronchial obstruction in children with a chronic obstructive bronchitis with a tendency towards greater efficacy of the herbal preparation. No statistical evaluation was performed.

Assessor's comment:

No information about a positive control for reversibility of bronchialobstuction was given in the study. The FEV_1 increased under ivy extract from 1.56 l to 1.90 l after 2 weeks and under acetylcysteine from 1.50 l to 1.72 l. Without a positive control the relevance of data cannot be evaluated.

Conclusion

Assessor's comment:

The results of the study by Gulyas (1997) indicate that the FEV_1 change is in the range of 8% that corresponds to proximally 1/3 of the FEV_1 after inhalative application of 200 µg salbutamol (in patients with chronic obstructive pulmonary complaints).
In another placebo controlled study in children with bronchial asthma by Mansfeld et al., (1998), a statistically significant reduction of the airway resistance of 0.14 kPa/l/sec (23.6%) was proved in comparison to placebo therapy. The author's conclusion that the bronchodilalatory effect of the ivy preparation was comparable to fenoterol is not convincing. On the first day ivy caused a difference in FEV_1 of 0.12 l (1.7-1.61) placebo of 0.11 l (1.70-1.59) and fenoterol of 0.31 l (1.75-1.44). The direct bronchodilatory effect of the ivy preparation on the first day was proximally 1/3 of fenoterol and comparable to placebo.

All together, the results indicate a statistically significant improvement of lung function in comparison to placebo, but no significant better bronchodilatory effect as placebo. The results on spirometric and bodyplethysmographic parameters in clinical use indicate a benefit for the use as secretolytic. The bronchospasmolytic activity is approximally 1/3 of salbutamol and fenoterol and is concidered to be to low for clinical relevance in severe obstructive diseases.

Controlled clinical studies with only supportive character for the long tradtional use of ivy preparations in the context of cough

Assessor´s comment:

Some early controlled clinical studies by Stöcklin (1959) and Rath (1968) cannot proof efficacy because of their limited methodological quality. Blinding and randomisation are two essential features for minimising bias. These studies are not double blinded. The method of randomisation is not described. Substantial differences between the numbers of patients in test and control groups exist (Rath, 1968). This could suggest that inappropriate methods of randomisation were used. Formal sample size or power calculation were not reported. There is a lack of description of drop-outs. The validity was further limited by failing to report statistical analysis, or inappropriate analyses. The information about the used ivy leaves extract and dosage is missing in the publication by Stöcklin (1959). Rath (1968) includes patients with bronchopneumonia pertussis, malign diseases. In 53 cases, an additional antibacterial treatment was given.

Stöcklin (1959) evaluated the efficacy of ivy extract in 50 children of 1-8 years who suffered from whooping cough (n=40) or spastic bronchitis (n=10). The control group included 50 children who were treated with standard therapy while the verum group received an ivy preparation (no clear information) in addition to the standard therapy. The "standard therapy" is described as one of different preparations (cardiazol-dicodid, codein, romilar, ipedrin, belladenal etc.). The used ivy leaves extract and dosage are missing in the publication. The children treated with ivy leaves extract accomplished the therapy objective (3 coughing fits/day) on the day 14, 10 days earlier than the control group. The children treated with ivy were attack free after 24 days. In the control group the children where attack free only after 34 days. It was observed that the ivy extract was most successful in reducing the intensity in cases of strong coughing.

Assessor's comment:

The study has only supportive character for the long traditional use of ivy preparations in the context of cough. The extraction solvent, DER and dosage used in the study are unknown. The majority of treated children included in the study suffered from whooping cough. Actually, ivy preparations are not used in whooping cough, so the study is not of relevance. Only 10 children suffered from spastic bronchitis. The methodology was not accurate to proof efficacy in chronic bronchitis. There was no use of FEV_1 and no measurement of symptomatic benefit. No statistical analysis was performed.

Rath (1968): A placebo controlled double-blind study was carried out in 100 children of 3 months-13 years. The ivy product (Prospan® drops) used in this study contained additionally 0.5 mg of anise and thyme oil in 1 g solution. Seventy one children were treated with the ivy preparation and 29 children with placebo. Seventy four children suffered from acute bronchitis in the context of feverish infections, 9 under cough in context of malign diseases, 7 under spastic bronchitis, 10 under chronic bronchitis, bronchopneumonia or pertussis. The number of cough attacks and the auscultation results were assessed. Within only three days the verum therapy was successful in 85% and placebo in 61% cases. In 53 cases an additional antibacterial treatment was given. Therapy success in the verum group was 81% compared to 37% in cases used placebo.

Assessor's comment:

The study has only supportive character for the long traditional use of ivy preparations in the context of cough. The extraction solvent, DER and dosage used in the study are unknown. The majority of treated children included in the study suffered from other diseases as the relevant. The number of children suffering from chronic bronchitis is less than 10. The duration of the study was only 3 days and there was no use of FEV_1 and no measurement of symptomatic benefit. In 53% of the cases, an additional antibacterial treatment was given. No statistical analysis was performed.

Table 7: Controlled studies with ivy leaf products

Authors, Year	Study design, Control type	Duration of Treat-ment	Study and Control drugs, Dose	Number of Subjects by Arms, Age	Diagnosis, Inclusion Criteria	Primary Endpoints	Efficacy results	Safety results
Stöcklin, 1959	open, controlled	30 days	verum: standard therapy in addition to ivy extract drops (no clear composition) infants: 3-4 x 20 drops, children: 3-4 x 30 drops, school children 3-4 x 70 drops control: standard therapy alone oral	n=100 n=50 verum n=50 control	whooping cough (n=40) or spastic bronchitis (n=10)	number and intensity of coughing fits	attack free after 24 days in the verum group, in the control group only after 34 days; reduction of the intensity of coughing	no side effects in both groups
Rath, 1968	placebo controlled, double-blind	3 days	verum: Prospan® drops + 0.5 mg of anise and thyme oil in 1 g solution: infant: 8 x 15 drops, children: 8 x 30 drops, school child: 8 x 45 drops/day corresponding to approximately 0.46-1.38 g herbal substance/day oral	n=100 n=71 verum n=29 placebo (47 as a mono therapy, 53 as an addition to antibiotics)	acute bronchitis (of feverish infections) (n=74), cough (of maligne diseases) (n=9), spastic bronchitis (n=7), chronic bronchitis, bronchopneumo-nia or pertussis (n=10)	number of cough attacks and auscultation results	therapy success on the cough ivy: 85% placebo: 61% ivy and antibiotics: 81% placebo and antibiotics: 37%	no side effects in both groups

Meyer-Wegener *et al.*, 1993	controlled, double-blind, monocentric	4 weeks	verum: 3-5 x 20 drops ivy dry extract (5-7.5:1); ethanol 30% (m/m) 0.25-0.42 g herbal substance/day) standard therapy: ambroxol: 3 x 30 mg/day oral	n=97 n=49 verum n=48 ambroxol 40 female, 57 male 25-70 years	simple or obstructive chronic bronchitis	spirometric, bodyplethys-mographic parameters (VC, 1 sec. C, peak flow), patients diaries	no significant difference for spirometric, bodyplethysmogra-phic parameters (VC in the ivy group 2.84 l to 3.11 l, ambroxol group 2.89 l to 2.92 l) in 4 weeks	verum: 7 undesirable effects (not described) ambroxol: 6 undesirable effects and one drop out
Gulyas, 1997	crossover randomized, double-blind	each treatment : 10 days (wash-out phase: 2-4 days)	Prospan® juice: 3 x 5 ml = 105 mg ivy dry extract (5-7.5:1); ethanol 30% (m/m), corresponding to 0.63 g herbal substance/day Prospan® drops: 3 x 20 drops = 42 mg dry extract (5-7.5:1); ethanol 30% (m/m), corresponding to 0.25 g herbal substance/ day oral	n=25 10-16 years	chronic obstructive pulmonary complaints	spirometric and bodyplethys-mographic parameters	ivy drops and juice therapeutically equivalent; improvement in the lung function parameters clinically and statistically significant; reduction in the airway resistance by 0.38 kPa/l/sec for juice and 0.35 kPa/l/sec for drops	no side effects in both groups

Mansfeld *et al.*, 1997	randomized, crossover	each treatment: 3 days (wash-out phase: 2-4 days)	Prospan® drops: 2 x 25 drops = 35 mg ivy dry extract (5-7.5:1); ethanol 30% (m/m), corresponding to 0.21 g herbal substance/day oral Prospan® supp.: 2 x 1 supp. = 160 mg of ivy dry extract (5-7.5:1); ethanol 30% (m/m), corresponding to 1 g herbal substance/ day) rectal	n=26 11 female 15 male 5-11 years	asthma bronchiale with reversible bronchial obstruction	spirometric and bodyplethys-mographic parameters (VC, 1 sec. C, air way resistance (kPa/l/sec), peakflow	Peak flow improved by 21.8% (suppositories) and by 25.2% (drops); reduction of the airway resistance of 0.49 kPa/l/sec (31%) (oral liquid) and 0.44 kPa/l/sec (23%) (suppositories)	no side effects in both groups
Mansfeld *et al.*, 1998	crossover randomized, placebo-controlled double-blind	3 days verum/ placebo, 3-5 days wash-out phase, 3 days verum/ placebo	Prospan® drops: 2 x 25 drops ivy dry extract (5-7.5:1); ethanol 30% (m/m), corresponding to 0.21 g herbal substance/day oral	n=28 13 female, 15 male 7.8±2.5 years PPA=23 or 24	asthma bronchiale with reversible bronchial obstruction	air way resistance (kPa/l/sec)	reduction of airway resistance by 0.14 kPa/l/sec (23.6%) under verum; significant difference between verum and placebo (p=0.036)	tolerance considered as “very good”
Gulyas, 1999	controlled pilot study	14-20 days	ivy dry extract (5-7.5:1); ethanol 30% (m/m), corresponding to 630 mg herbal	n=20 n=10 ivy n=10 ACC 9-15 years	chronic obstructive respiratory disease	spirometric and bodyplethys-mographic parameters	increase of FEV_1: ivy 0.34 l, ACC: 0.22 l increase of VC: ivy: 0.26 l; ACC: 0.23 l peak-flow: ivy: 57	no information

			substance daily ACC: no information oral				l/min; ACC: 39 l/min	
Unkauf and Friderich, 2000	randomized, reference controlled equivalence study	10 days	Valverde®: ivy dry extract (3-6:1); ethanol 60% (m/m) up to 4 years corresponding to 150-225 mg herbal substance , 4-10 years corresponding to 253-338 mg herbal substance, 10-12 years corresponding to 350-450 mg herbal substance Prospan® cough juice: ivy dry extract (5-7.5:1); ethanol 30% (m/m) up to 4 years corresponding to 350-490 mg herbal substance, 4-10 years corresponding to 525-735 mg herbal substance, 10-12 years corresponding to 700-980 mg herbal	n=52 n=25 Valverde® n=27 Prospan® 25 female 27 male mean 7.9 years	bronchitis	improvement of symptoms (VAS scale), CGI items I, II, III cough, expectoration	equivalence between the two therapies; 98% of the children were responder (improvement of the variables by at least 50%)	no relevant changing in laboratory values, no adverse events

			substance/day oral					
Mai-dannik, 2003	open, reference controlled study	7-14 days	ambroxol: no information Prospan® cough juice: ivy dry extract (5-7.5:1); ethanol 30% (m/m) 1-6 years: 3 x 1 teaspoon = 3 x 5 ml corresponding to 0.63 g herbal substance/day 7-14 years: 3 x 2 teaspoons = 3 x 10 ml corresponding to 1.26 g herbal substance/day oral	n=72 n=53 Prospan® n=19 ambroxol 7 month-15 years	acute respiratory viral infection (n=6), acute bronchopneumo-nia (n=19), acute bronchitis (n=25), acute obstructive bronchitis (n=11), recurrent bronchitis (n=4), bronchial asthma (n=5), mucoviscidose (n=2)	spirometric and bodyplethys-mographic parameters, improvement of symptoms (VAS scale)	velocity parameters of external respiration after 7 days: Prospan® = normalized nearly in all children with obstructive diseases; ambroxol = normali-zation could not be documented; auscultatory picture in lungs: Prospan® = fast decrease of crepitation (94.30% before treatment, 45.80% in 7 days); ambroxol: 87.60% before treatment, 47% in 7 days). decrease in productive cough: no statistical significant differences	no adverse events,

Bolbot 2004	open, reference controlled study	7-10 days	Prospan® cough juice: ivy dry extract (5-7.5:1); ethanol 30% (m/m); 2 to 6 years: 3 x 5 ml, corresponding to 0.63 g herbal substance/day 7 to 10 years: 3 x 10 ml, corresponding to 1.26 g herbal substance/day ACC: 2-6 years: 3 x daily 100-200 mg, 7-10 years 3 x daily 300-400 mg	n=50 (25 and 25)	acute bronchitis	spirometric and bodyplethys-mographic parameters, improvement of symptoms	parameters of external respiration: in Prospan® group statistically higher than in the ACC group; efficacy ratings of Prospan® 96% “very good” and “good” comparable with 79.2% for ACC	tolerability of Prospan® was rated by doctors 40% as “very good” and 60% as “good”
Cwientzek 2011	Double-blind, reference controlled	7 days (±1)	Hedelix s.a. (1 ml solution contains 0.04 g soft extract of ivy leaves (2.2-2.9:1), three times daily. Daily dosage of Hedelix s.a.®: adults and children from an age of 10 years, corresponding 0.3 g herbal substance; 4 to 10 years:	590 patients recruited, randomised, and supplied with study medication were included in the safety dataset (Hedelix: n=295; Prospan: n=295;	clinical diagnosis of acute bronchitis with a BSS ≥ 5, duration of complaints not more than 48 hours and non-use of concomitant medication	change of BSS at Visit 3 (Day 7±1) vs. baseline (Day 0)	ITT: The difference between Hedelix and Prospan was 0.046 (point estimate; 95% CI: -0.2303 to 0.3224) and the lower end of the 95% CI was above the non-inferiority margin (-0.6336). PP: The improvement in the PP dataset was only marginally higher	16 patients experienced 24 adverse events, 8 patients (11 events) in the Hedelix group and 8 patients (13 events) in the Prospan group. In each group 2.7% of

			corresponding 0.2 g herbal substance; 2 to 4 years 0.15 g herbal substance). Prospan Hustentropfen (100 ml solution contain 2 g dry extract of ivy leaves (5-7.5-1) ethanol 30% (m/m); Dosage: Three times daily: adults and children >10 years old: 24 drops; children between >4 and ≤10 years old: 16 drops; children between ≥2 and ≤4 years old: 12 drops.	Hedelix: 2-4 years: n=33; 5-10 years n=67; > 10 years n=195; Prospan: 2-4 years: n=33; 5-10 years n=68; > 10 years n=194). ITT: Hedelix: n=293 Prospan: n=295; PP: Hedelix: n=260 Prospan: n=258.			(by approximately 0.1 score point). The BSS decreased gradually and to a similar extent in both treatments starting from values of 6.2–6.3±1.2, by approximately 4.7–4.9 points until Visit 3, so that patients left the study with a mean BSS of 1.4–1.6.	patients from the safety dataset had one or two adverse events: 6 patients of the Hedelix group (3 diarrhoea, 4 nausea, 1pyrosis) and 7 patients in the Prospan group (3 diarrhoea, 3 nausea, 2 pyrosis, 2 epigastric pain, 2 vomiting).

Non-controlled studies

In early non-controlled clinical studies, ivy leaf extract was used in the treatment of children and adults suffering from various respiratory disorders, involving coughing, where reductions were observed in frequency of coughs. The studies, were all conducted in a small number of patients (under 100). In some studies, the preparation was administered per inhalation while the posology is not mentioned and there is no information about additional medication. For example, Arch (1974) examined 30 patients with tuberculosis; Düchtel-Brühl (1976) examined 44 patients, no posology and no endpoint criteria; Böhlau (1977) included 30 patients in aerosol therapy; Rudowski (1979) examined 29 children in aerosoltherapy; Leskow (1985) included 84 patients additional medication to antibiotics and steroids; Gulyas (1992) had only 24 patients, no control. The methodology of these early studies was not considered to be adequate to show efficacy of ivy leaf preparations in the labelled indication of currently marketed products (Loos, 1958; Arch, 1974; Düchtel-Brühl, 1976; Böhlau, 1977; Rudkowski, 1979; Leskow, 1985; Gulyas, 1992). Therefore they are not described in the assessment report in detail.

Non-controlled clinical studies with relevance for clinical safety

The methodology of non-controlled clinical studies is appropriate to draw conclusions about safety. They support the efficacy results of the controlled studies.

Lässig *et al.* (1996): In a multicenter surveillance study, 113 children (aged 6-15 years) suffering from recurrent obstructive respiratory complaints were treated with Prospan® cough juice ((100 ml contains 0.7 g ivy dry extract (5-7.5:1), ethanol 30% (m/m)) for up to 20 days (in some cases up to 30 days). As daily dose 64% of the patients took 3 x 5 ml (15 ml/day), 32% took 8-10 x 2.5 ml (20-25 ml/day) and 4% took only 3-4 x 2.5 ml (7.5-10 ml/day). The lung function parameters (FVC, FEV_1, PEF, MEF_{25}, MEF_{50}) as well as the symptoms cough (frequency, kind) and expectoration (colour, quality) improved significantly in the course of the medical treatment. The physician considered the tolerance of the therapy as very good: 68.7%, good: 29.5%.

Hecker (1999): In an open comparative study 248 children (176 patients (71%) were younger than 15 years) suffering from chronic obstructive bronchitis were treated with two different ivy leaf preparations. 120 patients were treated with Prospan® cough juice (100 ml contains 0.7 g dry ivy extract (5-7.5:1), ethanol 30% (m/m)) and 128 took Prospan® acute effervescent cough Tablets® (one effervescent tablet contains 65 mg evy leaf extract (5-7.5:1), ethanol 30% (m/m)). The duration of use was 7.3+2.4 (juice) and 8.2+2.5 (effervescent tablets) days. The dosage was 76% as recommended in the package leaflet (no specific information). The efficacy on the symptoms of cough, expectoration, dyspnea and respiratory pain was evaluated by the physician with a four-step scale. In the general judgement, the efficacy was documented in 86% of the patients as "very good" or "good". A healing or improvement of the symptoms of cough and expectoration were observed in about 90% of the patients. The authors considered this outcome as meaningful, because all patients, except one, suffered from cough and more than half (63%) had expectoration at the beginning of the study. From 16% of the patients having dyspnoea and 23% having respiratory pain, 60% reached a healing or recovery. The tolerance to the therapy was considered as "very good" or "good" for 98% of the patients. One adverse event (allergic exanthema) was occured.

Jahn and Müller (2000), Müller and Bracher (2002): In an open study 372 children aged from 2 months to over 10 years (mean 5.7 years, 186 male, 178 female, 8 no data) suffering from respiratory tract infections (64.8%) or infections of the lower respiratory tract (22.8%) and both lower and upper respiratory tract (11.6%) were treated for 5-8 days (7.2 days) with an oral liquid preparation containing a dry extract from ivy leaves ((6-7:1), ethanol 40%; 2 ml of a preparation contained 18 mg of extract corresponding to 108-126 mg of herbal substance). Depending on age, the average daily

doses ranged from 2.8 to 6.7 ml, corresponding to 150-420 mg of herbal substance. The patient age groups were:

0-1 year: n=26
1-3 years: n=93
4-9 years: n=189
10-16 years: n=56
≥ 16 years: n=4
no information: n=4

The irritation of the throat improved in the course of the medical treatment for 89.5% of the patients. At the end of the study no cough was observed in 119 patients (32.0%). In the third of the patients (30.3%), the dry cough was solved and changed into a productive one. The frequency of the expectoration was reduced in the course of the medical treatment from 33.6% in the beginning to 19.6% in the end of therapy.

Spirometric data were available from 187 children at least 4 years old. The lung function improved in the course of the ivy treatment, with an increase of the peak-flow rate from 228 l/min to 273 l/min. As expected, a stronger increase in the peak-flow rate could be reached in relation to increasing age. The patients were symptom free on the average after 6.5 days. Almost half of the patients were recovered after one-week therapy and the illness improved by 47.8%. The physicians judged the therapy success as "very good" or "good" for 94.4% of the patients. No adverse reaction occured. Four patients dropped out. The dosages used were in accordance to the dosage recommendations of Dorsch *et al.* (2002).

Roth (2000): In an open study, 1024 children (mean 4.4 ±3.8 years old) suffering from acute infections of the upper respiratory system (52.4%), acute bronchitis/bronchiolitis (26.6%) and bronchitis (not further specified, 22.2%) were treated with the same ivy leaf dry extract in two different alcohol-free preparations. 789 children took Sedotussin® ivy juice (100 g contain 0.79 g ivy dry extract (6-7:1), ethanol 40% (m/m)) and 234 children got Sedotussin® ivy drops (100 g drops contain 1.98 g ivy dry extract (6-7:1), ethanol 40% (m/m)).

The patient groups were the following:

Sedotussin drops:

0-1 year:	3 x 8 drops (0.166 g herbal substance) (n=72)
1-3 years:	3 x 12 drops (0.250 g herbal substance) (n=72)
4-9 years:	3 x 16 drops (0.333 g herbal substance) (n=59)
greater then 10 years:	3 x 25 drops (0.520 g herbal substance) (n=36)

Sedotussin ivy juice:

0-1 year:	2 ml (0.118 g herbal substance) (n=87)
1-3 years:	3 ml (0.177 g herbal substance) (n=332)
4-9 years:	4 ml (0.236 g herbal substance) (n=324)
greater than 10 years:	6 ml (0.354 g herbal substance) (n=36)

A significant decrease ($p<0.01$) of the complaints (cough, expectoration and dyspnoea) could be recorded at the end of the treatment. 72.6% of the children were cough free at the end of the study period; cough was improved at further 24.2%. No expectoration or an improvement was documented in 3.2% of the children. The symptom dyspnoea could be removed or improved in 99.2% of the children. The tolerability was considered as ‘very good’ and ‘good’ in 95.9% of the patients by the physicians, and in 90.8% by patients’ judgment. According to the publication, infants till 1 year received the drug as a middle daily dose of 0.1 g, children (1-4 years) 0.15 g, schoolchildren (4-10

years) 0.2 g as well as teenagers and adults 0.3 g. Depending on the age, average daily doses ranged for Sedotussin® juice (789 patients) from 2 to 6 ml, corresponding to 0.118-0.354 g of herbal substance. The daily dosage for Sedotussin® drops (234 patients) ranged from 24 drops to 75 drops, corresponding to 0.166-0.52 g herbal substance. There was no difference between the efficacy and tolerability of the different dosage regimes. One patient had vomiting and another patient exanthema.

Hecker *et al.* (2002): The changes of clinical symptoms and the tolerability of Prospan® acute effervescent Cough Tablets® (one effervescent tablet contains 65 mg ivy leaf dry extract (5-7.5-1), ethanol 30% (m/m)) were investigated in a multicenter, prospective post-marketing surveillance study (PMS) focusing on patients with chronic bronchitis. The study included 1350 patients (682 male and 667 female) aged 4 years and above who were treated in one of 135 participating medical practices and who suffered from chronic bronchitis (with or without airway obstruction). 1043 patients were upon 25 years old, 128 were 13-24 years old and 165 were 12 years old or younger.
During a scheduled observational period of 4 weeks, the patients had to take 1(1/2) or 2 tablets per day (depending on their age), according to the manufacturer's dosing recommendations, corresponding to 97.5 or 130 mg of dried ivy leaf extract (about 585-780 mg of herbal substance). The treatment success was assessed by observing the changes in the direct symptoms of chronic bronchitis between the baseline examination and the end of treatment. Safety was evaluated by analysing adverse events. In comparison to baseline, the following percentages of patients showed improved symptoms or were cured at treatment end: cough 92.2%; expectoration 94.2%; dyspnoea 83.1%; respiratory pain 86.9%. In each of the four symptoms at least 38% of the initially affected patients were completely free of complaints. Three patients (0.2%) experienced adverse events (2 eructation, 1 nausea), in which a causal relationship to the drug under investigation could not be excluded. The authors concluded that considering the favourable changes in all investigated clinical symptoms as well as the excellent tolerability in children and adults, that the ivy leaf extract preparation Prospan® acute Effervescent Cough Tablets could be considered as a therapeutic option in alleviating the symptoms of chronic bronchitis.

Büechi and Kähler (2003): In a multicenter open drug surveillance study over the period of one week, the efficacy and safety of ivy pastilles (one pastille contains 26 mg ivy leaf extract; 4-8:1, ethanol 30% (m/m)) were tested on 56 patients (7-93 years, average: 49 years) suffering from respiratory system disease with expectoration (14), from acute bronchitis (18) and from cough (30) because of cold. The dosage used was at least 2 pastilles / day (corresponding to 312 mg of herbal substance). Ninenteen patients took the middle dosage of 2-4 pastilles /day (corresponding to 312-624 mg of herbal substance) and 35 took the maximal dosage of 4-6 pastilles /day (corresponding to 624-936 mg of herbal substance). Compared to baseline (symptom scale), improvement of clinical symptoms was observed. The irritation of the throat was reduced from 2.7 on 1.3, the quantity of expectoration from 1.5 on 1.1, the colour of the mucus got clearer or whiter and the consistence of the mucus improved from 2.2 on 1.3. Adverse drug reactions did not occur.

Kraft (2004): A retrospective survey in a great number of children (52,478) between 0 and 12 years from 310 medical practices was conducted to evaluate the tolerability of Prospan® cough juice (100 ml contains 0.7 g dry ivy extract 5-7.5:1, ethanol 30% (m/m)).

0-1 year: 15% (n=7,871)
1-5 years: 51% (n=26,763)
6-9 years: 25% (n=13,119)
≥ 10 years: 9% (n=4,723)

In children under 1 year, the average daily dose corresponded to 227 mg of herbal substance. Children from 1-5 years were administered 364 mg herbal substance daily, from 6-9 years 653 mg and up to 10 years 710 mg herbal substance daily. 115 (0.22%) adverse effects were reported. The most frequent

adverse effects were: diarrhoea (0.1%), enteritis (0.04%), allergic exanthema/urticaria (0.04%) and vomiting (0.02%). In total, gastrointestinal disturbances occurred in 0.17% of children. The incidence of adverse effects was age dependent. In children under 1 year, adverse effects occured in 0.4% and in children upon 9 years in 0.13%.

Assessor's comment:

The study provides substantial information on tolerance and safety, because it included a large number of patients (42,478 patients) and relatively high dosages were administered.

Fazio *et al.* (2009): A total of 10,562 patients were recruited by 3,287 doctors participating in an open multicenter postmarketing study in 11 Latin American countries. Nine hundred and five patients were not eligible for analysis because they did not show up for the follow-up visit. In the study on 9,657 patients consisting of 5,181 children (53.7%) at the age of 0-14 years (median 5.5) and 4,476 (46.3%) adults aged from 15-98 years (median 41.9) with bronchitis (acute or chronic bronchial inflammatory disease, associated with hypersecretion of mucus and productive cough, frequently associated with an infectious agent, and patient with cough alone) were treated with Prospan® cough juice (100 ml contains 0.7 g dry ivy extract (5-7.5:1), ethanol 30% (m/m)) for 7 days. The age range of children was:

<1 year:	188 (3.6%),
1-5 years:	2,822 (54.5%),
6-12 years:	1,843 (35.6%),
13-14 years:	328 (6.3%).

The recommended dosages were: 0-5 years 2.5 ml 3 x day, 6-12 years 5 ml 3 x day, >12 years and adults 5-7.5 ml 3 x day. Concomitant drugs were prescribed in 60.7%, and 39.2% used antibiotics. Adverse events were reported in a total of 2.1% of the patients, while 1.2% were reported in children. Forty six (0.5%) patients discontinued the therapy due to adverse events, mainly to gastrointestinal disorders. The adverse events were: 1.5% gastrointestinal disorders (diarrhoea 0.8%, abdominal and epigastric pain 0.4%, nausea and vomiting 0.3%), 0.1 skin allergy. Other adverse events that occurred in less than 0.1% were: dry mouth and thirst, anorexia, eructation, stomatitis, anxiety, headache, drowsiness, palpitation, sweating and others. The relative risk of adverse events when using *Hedera helix* alone was significantly lower compared to the group receiving *Hedera helix* plus antibiotics (increased by 26%). It was more than twice when other non antibiotic medication was added. A good tolerance was in 96.6% of the patients. Improvement / healing of the symptoms assessed by doctors was achieved in 95.1%. The authors concluded that the analysis of efficacy shows that the application of antibiotics in case of bronchitis has no additional benefit.*Assessor's comment:*

The study provides substantial information on tolerance and safety because it included a large number of patients, and relatively high dosages were administered. The results show a higher event rate than the retrospective study by Kraft (2004). A point for criticism is the high rate of drop outs. Nine hundred and five patients, 8.6% of 10,562 patients, were not analysed because they did not take part in the follow-up visit. This may be attributed to the special situation that the study was performed in South America. 388 Patients (4%) of the analysed patients discontinued the therapy. Considering the drop outs of 8.6%, the adverse events can theoretically be in a higher range compared with the reported 2.1% of the analysed patients. The documented frequency of adverse events is therefore to be considered as a minimum. The results are considered only for safety conclusions. The study is not blinded, so probably the "strong cases" were treated with antibiotics. It can be considered that at the beginning of the study the symptom-score of the antibiotic group was not comparable to that of the ivy group. Therefore, the efficacy results have only supportive character for simple acute bronchitis. The duration of the study was 7 days, so it is not appropriate to draw any conclusions of efficacy in chronic bronchitis.

Schmidt (2012): Two galenical formulations of *Hedera helix* soft extract (DER 2.2-2.9:1), extraction solvent ethanol 50% V/V: propylene glycol (98:2), syrup and drops, were tested for their efficacy and safety in paediatric treatment of cough and bronchitis in two independent open, non-interventional studies with identical design. 133 children aged 0-12 years were treated with syrup and 135 with drops for up to 14 days. Five adverse events classified as mild and non-serious were reported (diarrhoea, nausea, vomiting, dermatitis) and correspond to the known safety profile of ivy leaf preparations. The patients indicated a good or very good tolerability in 98.1 and 94.1% of cases on days 4-7 and 98.2 and 96.9% of cases at final visit for syrup and drops. The global assessment of torelability by the physician yielded “good” or “very good” results for syrup on 98.4% at the visit on day 4-7 and 99.2% at the final visit and 99,2% /100% respectively for drops.

Assessor’s comment:

The two non-interventional studies confirmed a good safety profile in children, as also shown in the controlled study Cwientzek (2011). The safety profile is in accordance with the other well-established use Hedera preparations. From the qualitative aspect it is important to notice, that the ethanol content is removed in the factory process of this soft extract. The tested dosages corresponded the usual dose of the licenced products and were in a low range, compared with corresponding herbal substance of other ivy preparations.

Table 8: Non-controlled studies with ivy leaf products

Authors, Year	Study design, Control type	Duration of Treat-ment	Study and Control drugs, Dose	Number of Subjects by Arms, Age	Diagnosis, Inclusion Criteria	Primary Endpoints	Efficacy results	Safety results
Lässig *et al.*, 1996	open multicenter surveillance study	75% of the cases: 20 days 26% of the cases: 21-30 days	Prospan® cough juice (100 ml contains 0.7 g dry ivy extract (5-7.5:1); ethanol 30% (m/m)): daily dose: 32%: 8-10 x 2.5 ml (20-25 ml/day) 64%: 3 x 5 ml (15 ml/day), 4%: 3-4 x 2.5 ml (7.5-10 ml/day) daily dose corresponding to 0.32-1.09 g herbal substance	n=113 45% female 55% male mean: 8.9 years (6-15 years)	obstructive respiratory disease with cough and expectoration	symptoms, spirometric parameters	Lung function parameters, cough and expectoration significantly improved (concomitant ß-sympatomimetica!)	safety statement of the physician: very good: 68.7%; good: 29.5%; satisfactory: 0%; deteriorate: 0%
Hecker, 1999	open multicenter, comparative surveillance study	7.3-8.2 days	Prospan® cough juice (100 ml contains 0.7 g dry ivy extract (5-7.5:1), ethanol 30% (m/m)) Prospan acute® effervescent tablets (1 tablet contains 65	n=248 n=120 juice n=128 efferescent tablets 138 female 110 male	bronchitis (45%); respiratory system infection (29%)	symptoms (cough, expectoration, dyspnoea, respiratory pains), judgment of the physician	improvement or healing: in cough and expectoration: 90%, in dyspnoea and respiratory pains: 60% efficacy very good or good in 86% of the patients	safety very good and good in 98% of the cases; one adverse drug reaction "allergic exanthema"

			mg ivy dry extract (5-7.5:1); ethanol 30% (m/m)) Dose in accordance with “manufacturer recommendation” (no information) oral					
Jahn and Müller, 2000	open multicenter surveillance study	7 days	dry extract from ivy leaves (6-7:1), ethanol 40% (m/m), 2 ml contained 18 mg of dry extract corresponding to 108-126 mg of herbal substance) dosage: age dependent 3 x 0.5-2 ml corresponding to herbal substance: 0-1 year: 0.15-0.17 g; 1-4 years: 0.22-0.25 g; 4-10 years: 0.29-0.34 g older: 0.36-0.42 g; oral	n=372 186 female 178 male 5.7 years	infection of the respiratory tract upper: 241, lower: 85, both: 43; infection acute: 86.6% recurrent: 10.5% chronic: 2.4%	symptoms (cough, expectoration) peak flow at 187 patients	89.5% improvement of the irritation of the throat; improvement of the quality of the cough; increase in the peak flow from 228 l/min to 273 l/min efficacy “very good” and “good” in 94.4%; 48.7% recovered	safety very good and good in 98.9% of the patients; no adverse drug reactions
Roth, 2000	open multicenter surveillance study	2 weeks	Sedotussin® juice: corresponding to herbal substance/day: 0-1 year: 0.1 g; 1-4 years: 0.15 g; 4-10	n=1024 n=789 juice n=234 drops mean: 4.4	acute infection of the upper respiratory tract: acute bronchitis /bronchiolitis	symptoms (cough, expectoration and dyspnoea) 4 point scale	cough, expectoration and dyspnoea: significant decrease ($p<0.01$); 72.6% of the children cough	safety very good and good in 95.9% of the patients (physicians judgement) and

			years: 0.2 g; 12 years and older: 0.3 g Sedotussin® drops: age dependent: corresponding to 0.166-0.52 g herbal substance/day oral	years	(52.4%), , bronchitis (26.6%); not further specified (22.2%)		free; effectiveness very good or good in 67.4% of the cases	in 90.8% (patients judgment)
Hecker *et al.,* 2002	open multicenter surveillance study	4 weeks	Prospan acute® effervescent tablets (1 tablet contains 65 mg ivy dry extract (5-7.5:1); ethanol 30% (m/m)): 1.5-2 tablets, corresponding to 585-780 mg herbal substance/day oral	n=1350 667 female 682 male up to 12 years: 165 13-24 years: 128, up to 25 years: 1043	chronic bronchitis with or without obstruction	symptoms	improvement of cough: 92.2% expectoration: 94.2% dyspnoea: 83.1% respiratory pains: 86.9%	3 adverse drug reactions (0.2%) (2 x eructation, 1 x nausea)
Büechi and Kähler, 2003	open multicenter surveillance study	1 week	Ivy leaves extract pastilles (1 pastille contains 26 mg ivy leaf dry extract (4-8:1); ethanol 30% (m/m)) 2-6 pastilles corresponding to 312-936 mg herbal substance daily oral	n=56 7-93 years (mean: 49 years)	respiratory system disease (n=14)	symptoms (irritation of the throat, quantity of expectoration, colour of mucus, consistence of mucus)	irritation of throat reduced from 2.7 to 1.3; quantity of expectoration reduced from 1.5 to 1.1; consistence of mucus improved from 2.2 to 1.3	no adverse drug reaction; tolerance of ivy pastilles very good
Kraft,	retro-	no data	Prospan® cough	n=52,478	diseases of the	adverse	115 adverse effects	

2004	spective study		juice (100 ml contains 0.7 g dry ivy extract (5-7.5:1); ethanol 30% (m/m)): 0-1 year: 227 mg herbal substance/ day; 1-5 years: 364 mg herbal substance/day; 6-9 years: 653 mg herbal substance/ day; 10-12 years: 710 mg herbal substance/day oral	(0-12 years) children 1-5 years = 51% of the patients	respiratory tract	effects	(0.22%): diarrhoea (0.1%); enteritis (0.04%), allergic exanthem/ urticaria (0.04%); vomiting (0.02%); gastrointestinal disturbances 0.17% in total: children 0-1 year (0.4%), children 2-9 years (0.13%)	
Schmidt (2012)	open multicenter surveillance study	10-12 days	1 ml Hedelix s.a. drops contains 0.1 g *Hederae helix* soft extract (1:1); ethanol 45% V/V, (preparation is identical with soft extract (DER 2.2-2.9:1); ethanol 50% V/V: propylene glycol (98:2) [other declaration]) 0-1 year: 3 x 5 drops corresponding to 0.05 g herbal substance daily; 1-4	n=136 n=32 (0-1 year) n=36 (1-4 years) n=34 (5-10 years) n=34 (11-12 years)	symptoms of common cold; symptoms of chronic obstructive bronchitis	safety evaluation (additional evaluation: symptom score, statement of efficacy)	improved clinical symptoms at the end of the study efficacy: very good: 27.5%; good: 68.7%; satisfactory: 3.9% (physicians judgement)	safety: very good: 38.7%; good: 60.5%; satisfactory: 0.8% (parents judgment); very good: 47.6%, good: 52.4%, (physicians judgement); 3 adverse drug reactions:2 vomiting, 1 dermatitis, causality was considered as

			years: 3 x 16 drops corresponding to 0.15 g herbal substance daily; 5-10 years: 3 x 21 drops corresponding to 0.2 g herbal substance daily; 11-12 years: 3 x 31 drops corresponding to 0.3 g herbal substance daily					possible
Schmidt (2012)	open multicenter surveillance study	10-12 days (min. 9, max. 18)	100 ml Hedelix Hustensaft contain 2 g *Hederae helix* soft extract (1:1); ethanol 45% V/V, (preparation is identical with soft extract (DER 2.2-2.9:1); ethanol 50% (V/V): propylene glycol (98:2) [other declaration]) 0-1 year: 1 x 2.5 ml corresponding 0.05 g herbal substance daily; 1-4 years: 3 x 2.5 ml corresponding 0.15 g herbal substance daily; 5-	n=133 n=35 (0-1 year) n=32 (1-4 years) n=33 (5-10 years) n=33 (11-12 years)	symptoms of common cold, symptoms of chronic obstructive bronchitis	safety evaluation (additional evaluation: symptom score, statement of efficacy)	improved clinical symptoms at the end of the study Efficacy: very good: 25.4%; good: 71.4%; satisfactory: 3.2% (physicians judgement)	safety: very good: 22.7%; good: 73.1%; satisfactory: 4.2% (parents judgment); very good: 26.9%; good: 72.3%; satisfactory: 0.8%(physicians judgement); 2 adverse drug reactions: 1 diarrhoea and 1 stomach disorder with nausea; causality was considered as

			10 years: 4 x 2.5 ml corresponding 0.2 g herbal substance daily, 11-12 years: 3 x 5ml corresponding 0.3 g herbal substance daily					possible
Fazio *et al.*, 2009	open multicenter surveillance study	7 days	Prospan® cough juice (100 ml contain 0.7 g dry ivy dry extract (5-7.5:1); ethanol 30% (m/m)) 0-5 years: 3 x 2.5 ml/day; 6-12 years 3 x 5 ml/day, >12 years and adults: 3 x 5-7.5 ml/day concomitant drugs: 60.7%, antibiotics: 39.2%	n=9,657 children= 5,181 (53.7%) n= 188 (0-1 year; 3.6%) n=2,822 (1-5 years; 54.5%) n=1,843 (6-12 years; 35.6%) n=328 (13-14 years; 6.3%) n=4,476 (adults; 46.3%)	inflammatory bronchial diseases (acute and chronic bronchitis, cough)	adverse effects	improvement / healing of the symptoms in 95.1% (physicians assessment)	adverse events: 2.1% of the patients (1.2% in children) 1.5% gastro-intestinal disorders (diarrhoea 0.8%, abdominal and epigastric pain 0.4%, nausea and vomiting 0.3%); 0.1 skin allergy; other adverse events <0.1%: dry mouth and thirst, anorexia, eructation, stomatitis, anxiety, head ache, drowsi-ness,

								palpitation, sweating and others 46 (0.5%) patients discontinued therapy due to adverse events

Reviews

Landgrebe *et al.* (1999): A discussion about an extract of *Hedera helix* (ivy) was presented, including the contents of active substances and an examination of pertinent literature on clinical tests of the therapeutic effects as an expectorant in obstructive respiratory system disorders. The authors concluded an alcohol-free preparation prepared of a dry ethanolic extract and water needed a 2.5-fold dosage for the equivalent efficacy as a preparation containing the alcoholic liquid extract. They recommended considering new dosage recommendations.

Hofmann *et al.* (2003): A systematic review of trials documented in the literature with re-analysis of original data was performed to investigate the efficacy of dried ivy leaves in the treatment of chronic airway obstruction in children, suffering from bronchial asthma. Five randomized controlled trials were included investigating the efficacy of ivy leaf extract preparations in chronic bronchitis. Three of these trials were conducted in children and met the selection criteria. One trial compared ivy leaf extract cough drops to placebo (n=24), one compared suppositories to drops (n=26) and one tested syrup against drops (n=25). The main outcome measures were body-plethysmographic and spirometric measures. Drops were significantly superior to placebo in reducing airway resistance (primary outcome measure; p=0.04 two-sided). A major limitation of the analysis was that the only one placebo-controlled trial had a small sample size (n=24 patients evaluable for efficacy). For syrup and suppositories, at least 54%, resp. 35% of the effect against placebo were preserved. Thus, the trial with suppositories showed an ineffective treatment because the margin of 50% for the minimum effect size was not fulfilled. The authors concluded that the trials included in this review indicated that ivy leaf extract preparations had effects with respect to an improvement of respiratory functions of children with chronic bronchial asthma. More far-reaching conclusions could hardly be drawn because of a limited database, including the fact that only one primary trial included a placebo control and no clinical symptoms were tested. Further research, particularly into the long-term efficacy of the herbal extract, is needed.

The CDR (Centre for Reviews and Dissemination) (2008) assessed the results of the review, that ivy leaf preparations may lead to improvement of respiratory functions, as promising but based on limited and low quality evidence.

Guo *et al.* (2006): In a review the authors referred to the effectiveness of different herbal medicines for treating chronic obstructive disease. The authors concluded that currently the evidence from randomised clinical trials was scarce and often methodologically weak. For ivy, only one clinical study meets the criteria stated by EMA for COPD.

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

Children:

Well established use:

Ivy preparations are used commonly in children. In prospective conducted clinical studies more than 7,000 children were involved. More than 52,000 children were analysed in a retrospective study. The safety studies were conducted with a large number of children including groups of low age, for example:

0-1 year:	26 by Jahn and Müller (2000); 159 by Roth (2000); 188 by Fazio (2009); 7,871 by Kraft (2004); (=8,244 children).
1-3 years:	93 by Jahn and Müller (2000); 404 by Roth (2000); (=497 children).
1-5 years:	2,822 by Fazio (2009); 26,763 by Kraft (2004); (=29,585 children).

The tolerability was judged by physicians and patients as “good” and “very good” in ranges of approximately 90-98%. See also chapter “5.5 Safety studies in children”.

The following studies were conducted in children:

Controlled studies:

Authors, Year	**Number of Subjects by Arms, Age**
Stöcklin, 1959	n=100 children (verum: 50, control: 50)
Rath, 1968	n=100 children (verum: 71, placebo: 29) (47 as a monotherapy, 53 as an addition to antibiotics)
Gulyas, 1997	n=25 (10-16 years)
Mansfeld *et al.,* 1998	n=28 (13 female, 15 male, 7.8 ± 2.5 years) PPA=23 or 24
Gulyas, 1999	n=20 (Ivy: 10 /acetylcysteine: 10) 9-15 years
Unkauf and Friderich, 2000	n=52 (25 female, 27 male (25: Valverde, 27: Prospan)) mean 7.9 years
Maidannik *et al.,* 2003	n=72 children (7 month-15 years)
Bolbot *et al.,* 2004	50 children (2-10 years)
Cwientzek *et al.,* 2011 (partially)	Soft extract (DER 2.2-2.9:1), extraction solvent ethanol 50% V/V: propylene glycol (98:2): 2-4 years: n=33; 5-10 years n=67; >10 years n=195 Dry extract (DER 4-8:1), extraction solvent ethanol 24-30% m/m: 2-4 years: n=33; 5-10 years n=68; > 10 years n=194

Uncontrolled studies:

Authors, Year	**Number of Subjects by Arms, Age**
Lässig *et al.,* 1996	n=113 (45% female, 55% male) 8.9 years (6-15 years)
Hecker, 1999	n=248 (138 female, 110 male)
Jahn and Müller 2000	n=372 (186 female, 178 male) 5.7 years 0-1 year: 26 1-3 years: 93 4-9 years: 189 10-16 years: 56 ≥16 years: 4; no information: 4
Roth, 2000	n=1024 (4.4 years) 0-1 year: 159 1-3 years: 404 4-9 years: 383 ≥10 years: 72
Hecker *et al.,* 2002	n=1350 (667 female, 682 male) up to 12 years: 165, 13-24 years: 128, up 25 years: 1043
Büechi and Kähler, 2003	n=56 (7-93 years, mean: 49 years)
Kraft, 2004 (retrospective)	n=52,478 (0-12 years) 0-1 year: 15%=7,871 1-5 years: 51%=26,763 6-9 years: 25%=13,119 ≥10-12 years: 9%=4,723
Fazio, 2009	5,181 (53.7%) children

	<1 year: 188 (3.6%) 1-5 years: 2,822 (54.5%) 6-12 years: 1,843 (35.6%) 13-14 years: 328 (6.3%)
Schmidt 2012	n = 136 (galenic formulation drops) 0-1 year:32 1-4 years:36 5-10 years: 34 11-12 years:34 n = 133 (galenic formulation syrup) 0-1 year:35 1-4 years:32 5-10 years:33 11-12 years:33

The used dosages of the relevant extracts are tabulated in table 7 and 8. The daily dosages used in children are in high ranges. Ethanol-containing ivy preparations are used in daily dosages of maximally 420 mg (over 12 years). Ethanol-free preparations are used in daily dosages of maximally 1 g (over 12 years).

Ethanol-containing ivy preparations:
In accordance with the above listed study results and the literature, for all ethanol-containing ivy preparations, the following maximum daily dosages for children are proposed:

2-5 years: 150 mg
6-12 years: 210 mg

Ethanol-free ivy preparations:
No study indicates that dosages higher than 656 mg herbal substance are necessary for efficacy in adults.

It is proposed that the group of 6-12 years old children should be given maximum 2/3 of daily dosage of the group of children over 12 years and adults. The group of 2-5 year old children should take maximal 1/3 of the daily dosage of children over 12 years and adults. In summary, the best benefit/risk ratio is a low dose administration. The recommended dosages for children are derived from studies. For the safety of the use in children see also chapter 5.5. The following maximum daily dosages are recommended:

2-5 years: 219 mg herbal substance
6-12 years: 437 mg herbal substance

The use in children under 2 years is contraindicated due to possible aggravation of respiratory symptoms. See also chapter 5.5.

4.4. Overall conclusions on clinical pharmacology and efficacy

The comparative study of Meyer-Wegener *et al.* (1993) showed that ivy extracts could be therapeutically equivalent to the secretolytic drug ambroxol in improvement of symtoms of cough in adults, with chronic bronchitis. Bolbot (2004) showed an improvement of symptoms in children with acute bronchits comparable to the secretolytic drug ACC. The results indicated that patients with viscous sputum, benefit from the ivy preparation for secretolytic therapy for short term use, of maximum duration of use for 4 weeks.
Ambroxol has a well established use licence for the indication “For secretolytic therapy in acute and

chronic bronchopulmonary diseases, concomitant with disturbance in formation and transport of viscous sputum". In the ATC classification system of the WHO, ambroxol is classified as R (respiratory system), R05 (cough and cold preparations), R05C (expectorants, excl. combinations with cough suppressants), R05CB (mucolytics).

The study of Meyer-Wegener *et al.* (1993) was performed in 1993 and "COPD" was newly defined in 2006. Therefore, indications examined in these studies would today be evaluated according to the guidance on COPD. There are no studies on ivy reflecting all features of COPD as currently defined. Therefore, an indication "chronic bronchitis" can not be supported because according the current definitions this would stand for COPD. Ivy products are often used in children, where COPD does not exist. An additional argument for restriction of chronic diseases is the fact, that the results are based on clinical studies with duration of maximum 4 weeks. This period is not in line with the definitions of "chronic" forms of bronchitis. The observational studies in children are conducted in acute diseases of the respiratory tract. Also "acute bronchitis" (the symptoms are dry cough, later productive cough, often fever, sore throat, secretion of the nose and sometimes bronchial obstruction) does not exactly reflect the therapeutic benefit proven for ivy.
Symptom scores were analysed in many of non-controlled studies and an impairement on bronchitis symptoms could be shown. The influence on spirometric and bodyplethysmographic parameters was examined in clinical controlled studies. The results indicate a statistically significant improvement of lung function in comparison to placebo, but no significant better bronchodilatory effect.

In summary, the data from numerous clinical trials and the existing medicinal products fulfil the requirements of a well-established medicinal use with recognised efficacy and are eligible for a marketing authorisation with the indication "herbal medicinal product used as an expectorant in case of productive cough". This indication considers as well the data on improvement of symptoms by preparations of ivy as the limitations by current guidance on COPD. It was derived from the discussions during the development of the monograph and the AR on ivy leaf.

The data of the following herbal preparations fulfil the requirements of a well-established medicinal use with recognised efficacy and are eligible for a marketing authorisation in the indication: "herbal medicinal product used as an expectorant in case of productive cough".

dry extract (4-8:1), extraction solvent: ethanol 30% (m/m)
dry extract (5-7.5:1), extraction solvent: ethanol 30% (m/m)
dry extract (5-8:1), extraction solvent: ethanol 30% (m/m)
dry extract (6-7:1), extraction solvent: ethanol 40% (m/m)
dry extract (3-6:1), extraction solvent: ethanol 60% (m/m)

The herbal preparations 1-3 have the same extraction solvent and similar DER. They are combined in the monograph as follow:
Dry extract (4-8:1), extraction solvent: ethanol 30% (m/m)

After the HMPC discussion, it was decided to add the liquid extract (1:1), extraction solvent: ethanol 70% (V/V) in the WEU part of the monograph. It was considered, that the liquid extract (1:1), extraction solvent ethanol 70% (V/V) is comparable to the dry extract (3-6:1), extraction solvent ethanol 60% (m/m). The preparation of both extracts starts with the extraction of the herbal drug with ethanol. The ethanol concentration for the extraction of the ivy leaves is 60% (m/m) in the preparation of the dry extract while 62.4% (m/m) (= 70% (V/V)) in the preparation of the liquid extract. It was considered, that the minimal difference of the ethanol concentrations is unlikely to produce significant changes between the resulting herbal extracts.

The HMPC also decided to add the dry extract (DER 4-6:1), extraction solvent: ethanol 30% (V/V) (ethanol 24, 6% m/m) in the WEU part of the monograph. The analytical documentation comparing ivy leaf dry extract (4-6:1); extraction solvent: ethanol 30% (V/V) and ivy leaf dry extract (5-7, 5:1); extraction solvent: ethanol 30% (m/m) was the basic document for the market products in France and Spain. Considering this fact, the HMPC members decided to accept the documentation also for the monograph. These two preparations are combined as: dry extract (4-8:1), extraction solvent: ethanol 24-30% (m/m).

The HMPC further decided that for the WEU liquid preparation with the extraction solvent ethanol 70% (V/V) the use in children under 6 years of age cannot be recommended due to the content of ethanol per single dosage.

Following the conclusion of the HMPC on the validity of the BSS, the study Cwientzek (2011) shows that the preparation soft extract (DER 2.2-2.9:1), extraction solvent ethanol 50% (V/V): propylene glycol has comparable efficacy results for the primary efficacy parameter BSS and comparable safety results as the comparator product Prospan drops. Therefore it is suggested to be added in the WEU part of the monograph.

Table 9: Posology recommended in the literature

Commission E	corresponding 300 mg herbal substance daily
Dorsch *et al.,* 2002 and Schapowal, 2007	0-1 year: 0.02-0.05 g 1-4 years: 0.05-0.15 g 4-10 years: 0.10-0.20 g 11-16 years: 0.20-0.30 g
ESCOP 2003	Ethanol-containing preparations 0-1 year: 20-50 mg 1-4 years: 50-150 mg 4-12 years: 150-210 mg Adults: 250-420 mg Ethanol-free preparation: 0-1 year: 50-200 mg 1-4 years: 150-300 mg 4-12 years: 200-630 mg Adults: 300-945 mg

Posology of ethanol-free medicinal preparation and ethanol-containing medicinal preparations:

The used dosages of clinical studies are tabulated in table 7 and 8. The daily dosages are in high ranges:
Ethanol-containing ivy preparations are used in clinical studies in daily dosages of maximum 420 mg (over 12 years).
Ethanol-free preparations are used in clinical studies in daily dosages of maximum 1 g (over 12 years). (See also chapter 4.2.3 “Children” and Table 9)

Ethanol-containing preparations

In accordance with the above mentioned study results and the literature for all ethanol-containing ivy preparations maximum daily dosages are proposed because they have been shown to be effective:
2-5 years: 150 mg herbal substance

6-12 years: 210 mg herbal substance
>12 years: 420 mg herbal substance.

Ethanol-free preparations:

From the published data it can be concluded, that the discussion about high dosages started in 1997 with the study of Gulyas (1997). The statement of Gulyas (1997) “the ethanol-free preparation would be necessary to be given in two times higher dosage than the ethanol-containing preparation to achieve the same therapeutic effect” was not proven and controversially discussed in the literature.

The study by Gulyas (1997) was conducted in 25 children (10-16 years) with Prospan® cough juice in a dosage of 3 times 5 ml corresponding to 656 mg of herbal substance. No other study exists which indicates that dosages higher than 656 mg of herbal substance are necessary in adults or children for efficacy. There is no study that indicates that younger children (6-11 years old) should take 630 mg of herbal substance daily.

According to Hecker (1997a, b), the dosage of an ethanolic dry extract which is solved in an alcohol-free preparation is to elevate 2.5-fold compared with the dosage of an ethanolic dry extract administered as ethanolic solution.

The Kooperation Phytopharmaka (2003) concluded, in a statement referring to the dosage of ivy preparations in children, that Gulyas (1997) was wrong. The Kooperation Phytopharmaka was of the opinion that based on the results of surveillance studies with different ivy preparations, it could be concluded that they were well tolerated in a higher range. For example, the open multicenter surveillance study by Jahn and Müller (2000) using both FEV_1 and a measure of symptomatic benefit, included 372 children under 12 years, treated with an ethanol-free preparation in a low dosage of 140-350 mg herbal substance. Improvement of the quality of the cough and increase in the peak flow from 228 l/min to 273 l/min was documented. The study indicated efficacy of low dosages of ethanol-free preparations as well as high dosages.

Assessor’s comment:

Based on the above mentioned data, it is recommend that the maximum dosage of preparations of ivy dry extract (4-8:1) or (5-7.5:1) extraction solvent: ethanol 30% (m/m), without ethanol in the finished product, should correspond to 656 mg herbal substance.
Maximum dose:
2-5 years: 219 mg herbal substance
6-12 years: 437 mg herbal substance
Adults and children over 12 years: 656 mg herbal substance.

The use in children under 2 years of age is contraindicated because of the risk of aggravation of respiratory symptoms (See also chapter 5.5.).

Duration of use:
The duration of use in clinical studies varied from 3 days to 4 weeks. In order to assure safe use in self-medication, the duration of use is limited. The following wording is introduced in the monograph: “If the symptoms persist during the use of the medicinal product longer than a week, a doctor or a qualified health care practitioner should be consulted.”

5. Clinical Safety/Pharmacovigilance

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

Studies referring to allergic reactions

Hausen *et al.* (1987): The principal allergens were isolated by using sensitized guinea pigs, and were identified as falcarinol and dehydro-falcarinol. In addition, 4 patients with ivy allergy, described by case reports, have been patch tested. Even in low concentrations (0.03%), the main allergen falcarinol elicited strong reactions in all of them. Dehydro-falcarinol elicited equal patch test reactions only when concentrated as high as 1%. The authors demonstrate that falcarinol is the main sensitizer, while dehydro-falcarinol is also an allergen but does not elicit reactions in all patients.

Gafner *et al.* (1988): In a human maximization test of 5% falcarinol isolated from *Hedera helix*, 10 of 20 subjects were sensitised. No subjects gave irritant reactions to 5%, 10 became sensitive to 1% and 7 to 0.05%, with 3 of these giving 3+ to 4+ bilious reactions. The authors concluded that the ability of falcarinol to sensitize 10 of 20 subjects at a non-irritating concentration of 5% indicates this substance to be a skin sensitizer of significant potency.

Mahillon *et al.* (2006): A group of 59 patients with allergic rhinitis were submitted to skin prick tests (SPT) using both the leaves of their own indoor plants and commercial extracts of the most frequent airborne allergens. A control group of 15 healthy subjects was tested with the same allergens. While no subject from the control group developed a significant SPT to any of the tested plants, 78% of allergic rhinitis had positive SPT to at least one plant, the most frequent sensitization being *Ficus benjamina*, yucca, ivy and palm tree. The authors concluded, in allergic rhinitis, that indoor plants should be considered as potential allergens. The allergen avoidance of the concerned plant was considered useful.

So far, data on the allergenic potential of falcarinol focus on cutaneous use. Knowledge on quantities of falcarinol and derivatives in herbal preparations of ivy leaf for oral use is limited.

5.2. Patient exposure

Ivy preparations have been marketed worldwide in many countries in large quantities. More than 10,000 patients have been included in open multicenter prospective surveillance studies with a high dosage range. Approximately 7,000 children were included in prospective clinical studies. A retrospective study was conducted with about 52,000 children.

5.3. Adverse events and serious adverse events and deaths

General data

Wichtl (2004) and Wagner and Reger (1986): The occurrence of the alkaloid emetin could not be confirmed in recent studies. Toxic effects due to the presence of emetine and cephaeline were unlikely, in view of the low concentration isolated (Mayer *et al.,* 1987).

Mühlendahl (1995): In a period of 10 years (1972-1991), in a toxicological centre 301 toxicological events referring ivy were documented. Commonly children ate 1-5 ivy fruits, rarely up to 10 fruits or leaves. Vomiting and diarrhoea occurred in 10% of cases. One 8-month old child who had eaten one leaf showed changing colour of lips and marbled skin, while a 2.5 year boy who had eaten 6-8 ivy fruits showed marbled skin at the extremities and no further symptoms.

Czygan (1990): Vomiting and diarrhoea occurred in 9 cases of 65 children who had eaten ivy berries.

Frohne and Pfänder (2004): In a period of 7 years in a toxicological centre in Berlin, 516 toxicological events had been documented. Only a few adverse events with vomiting and diarrhoea referred to ivy poisoning. The authors recommended fluid intake and symptomatic treatment.

Ivy poisoning in humans

Serious cases:

Gaillard *et al.* (2003) reported one fatal case of asphyxia caused by leaves of common ivy. Macroscopic examination of the corpse during the autopsy disclosed an incredible quantity of leaves of *Hedera helix* in the mouth and throat of the decedent. In order to rule out the possibility of poisoning by the toxic saponins contained in the plant, they have developed an efficient LC-EI/MS-MS assay of hederacoside C, α-hederin, and hederagenin in biological fluids and plant material. Sample cleanup involved solid-phase extraction of the toxins on cartridges followed by LC analysis under reversed-phase conditions in the gradient elution mode. Solute identification was performed using full scan MS-MS spectrum of the analyses. Oleandrine was used as internal standard.
Under these conditions, saponins in powdered dried leaves of *Hedera helix* were measured at a concentration of 21.83 mg/g for hederacoside C, 0.41 mg/g for α-hederin and 0.02 mg/g for hederagenin. No toxin was detected in cardiac blood, femoral blood or urine of the deceased, but hederacoside C was quantised at 857 ng/ml in the gastric juice. These findings led the authors to conclude that the man committed suicide and that the death was caused by suffocation by leaves of common ivy.

BfArM-case 06002941: A 3 year old boy was found dead because of aspiration in connection with vomiting. The patient took a codeine juice, ibuprofen juice and Prospan® drops for one week. There was unclear and inconsistent information about dosage and formulation of the ivy product. Analytic data showed very high morphine and codeine concentrations. The twin brother of the dead patient could be reanimated. He also had very high morphine and codeine concentrations in the blood. The physician related the subconsciousness and respiratory depression to codeine.

Assessor's comment:

The causal relationship to codeine, according the physician's comment, is probable. Adverse neurotoxical effects of over dosage of narcotics are known. Ibuprofen is metabolised by the liver and an influence on the codeine/morphine metabolism is therefore considerable. An interaction with the ivy preparation is theoretically also possible. Despite of the unknown formulation and dosages in the case reports an interaction with narcotics as codeine and morphine should be considered as a signal (see chapter 4.4 special warnings and precautions for use in the monograph).

Case reports

There are 63 case reports in the BfArM Database on suspected adverse drug reactions (October 2009). Most of them are related to allergic reactions (urticaria, skin rash, tuberose, dyspnoea) and gastrointestinal reactions (nausea, vomiting and diarrhoea). Beside these reactions, other adverse events occur and are listed below together with the case reports of the literature.

Hyposensitive reactions

A review of older dermatitis cases (1909 up to 1979) is given by Mitchell (1979). The author concluded, based on present evidence, that it is reasonable to conclude that *Hedera helix* is an irritant plant, which may also on occasions induce sensitization. Contact dermatitis has also been reviewed by Hausen *et al.* (1987) and updated by Lovell (1993). In the majority of cases, a direct contact dermatitis occurs after pruning ivy in the garden. According to Frohne and Pfänder (2004), 60 cases of hyposensitive reactions have been published since 1899.

Hausen *et al.* (1987) described 32 cases of irritant and allergic contact dermatitis caused by *Hedera helix* subspecies (1899-1985). The most affected parts are the upper part of the body- face, hands, forearms, head and neck. He noted the difficulties to ascertain which of the described cases of ivy

dermatitis have been allergic. When applying stricter criteria giving a more detailed report on low test concentrations and sufficient controls, the author considered only 6 cases to be relevant.

Murdoch *et al.* (2000) and Machado *et al.* (2002) recommend that patients allergic to falcarinol (present in carrots) should also avoid a number of Araliaceae family plants, such as common ivy, *Schefflera actinophylla* (umbrella tree) and *Schefflera arboricola*.

Published case reports

Roed-Petersen (1975): A 22 year old female with atopic dermatitis from infancy, until the age of 10, developed eczema on the front of the legs, the forearms and the hands after working in a plant nursery. Patch tests gave positive reactions to ivy (fresh plant). Among 138 consecutive patients with contact dermatitis tested, three women had positive reactions.

Mitchell (1981): A 33 year old female developed acute vesicular dermatitis of the hands, wrist, forearms and face after pruning garden ivy. A patch test produced a (+) reaction to leaf of *Hedera helix*.

Boyle (1985): A 31 year old female patient developed an acute weeping eczematous eruption with bulla formation, periorbital oedema and pain. This affected her arms, dorsa of hands, face and neck. The lesions healed under treatment with systemic steroids, antibiotics and wet compresses slowly over 3 weeks. Patch tests to the crushed leaves were positive (++) at 48 and 96 h.

Garcia (1995): A 44 year old non atopic man developed contact dermatitis with erythrema and papules (1-2) mm on his forearms after pruning in the garden. He healed with oral and topical corticosteroid treatment in 5 days. An open patch test with a fresh leaf of *Hedera helix* elicited a positive reaction (++) at D2 and D4.

Sanchez-Perez *et al.* (1998): A 60 year old man with no previous history of contact dermatitis had several outbreaks of itchy erythrematous oedematous lesions on the hand, forearms, neck and face 8-12 h after pruning common ivy. They healed in 5-7 days. An open patch test with fresh leaf and stem of *Hedera helix*, falcarinol 0.03% elicited a ++ reaction at D2 and D4 at 2 and 4 days.

Johnke and Bjarnason (1994): One case of allergic contact dermatitis to common ivy is presented. The patient, a 16 year old female gardener, who developed severe blistering dermatitis of the hands, forearms and face after frequent contact with *Hedera helix*. The authors highlighted the potential of common ivy as a sensitizer.

Yesudian and Franks (2002): A 50 year old man was admitted in April 1999 with severe eczema on the right upper limb and less florid involvement of the trunk (UK). His wife had simultaneously developed eczema on her trunk. 10 days prior to onset, the patient had scratched his right arm while cutting roses. He subsequently spent time pruning common ivy (*H. helix*) and his wife helped him to clear the trimmings. Four days later, the patient's right arm became itchy and exudative at the site of the scratch. A diagnosis of cellulites was made and penicillin and flucloxacillin were prescribed. The patient felt well and 3 days prior to admission he completed pruning the plant and his wife assisted him again. Over the next 3 days, both husband and wife developed extensive eczema. On examination, an acute eczema with confluent erythematous vesicular and bullous lesions was noted on the right forearm, with less severe patchy involvement of the trunk. A linear streak of small vesicles was seen on the dorsum of the right hand. His wife showed less florid vesicular erythematous plaques on the forearm and trunk. Allergic phytodermatitis from common ivy was diagnosed.

Özdemir *et al.* (2003): The authors reported a case of a male hobby gardener with appropriate clinical history (2 days after working in the garden develops an erythrema on hand and neck, and 2 days later an oedema) and positive patch test on *Hedera helix*. The pathogenic mechanism was a type

IV reaction following a sensitization exposure. Contact with common ivy or falcarinol may lead to sensitization and then a delayed hypersensitivity reaction. It was recommended to gardeners and landscape architects with frequent exposure to common ivy and thus a high risk of sensitization to wear appropriate protective clothing.

Hannu (2008): The authors presented the first case of ivy induced occupational asthma. A 40 year old female who had worked in her own flower shop for the past 11 years had symptoms of cough 4 years prior to the current examinations, and one year later dyspnoea. The skin prick test was negative. Peak flow varied between 340-510 l/min during working days, with the lowest values occurring when handling green plant, especially ivy. In the specific test, the handling of ivy caused an immediate asthmatic reaction, with 21% reduction in FEV_1 and with 20-30 reduction in PEF, with simultaneous subjective symptoms of dyspnoea.

Thormann *et al.* (2008) reported a case of contact urticaria to common ivy and rosemary with cross-reactivity to the *Labiatae* family in an atopic gardener handling these plants on a daily basis. The authors concluded heavy exposure in atopic persons carries a risk of sensitization.

Neurotoxicity and psychoactive effects

Turton (1925): A boy aged 3.5 years developed mild delirium after ingestion a considerable quantity of ivy leaves. During the delirious stage clonic convulsions developed. He screamed and cried and could not stay still/upright. He had visionary hallucinations lasting for many hours. An intense scarlatiniform rash most marked on the legs, face and back was present while there was no vomiting. The pupils were widely dilated and the temperature was raised. The pulse was rapid but full and bounding. The symptoms abated after wash out the stomach and in about 3 h he was fairly well. The same case report was also cited by De Smet *et al.,* (1993).

Polizzi *et al.,* (2001): A 3 year girl developed episodic stiffness and abnormal posturing with rigidity after ingestion of a mixture of methyl codeine and an extract from *Hedera* (no information about DER, extraction solvent and dosages). These paroxysmal events persisted for 24 h then promptly disappeared. There was severe painful stimulus sensitive multifocal dystonia, superimposed on voluntary actions and postures each time involving face, eyes, jaw, neck, hands and legs. The patient could neither walk nor stand. The drug was discontinued and the patient was treated with saline solution intravenously. The patient was well thereafter.

Assessor's comment:

Adverse effects and over dosage of narcotics (codeine, dextromethorphane) associated with administration of "cough and cold preparations" (not near explained) in children are reported (Polizzi et al., 2001). Interaction with narcotics as codeine and morphine should be considered as a signal (see chapter 4.4 special warnings and precautions for use in the monograph).

BfArM-case 06062429: A 12 year old patient developed hallucinations 2 h after ingestion of Aerius® (desloratadin) and Prospan® (no information to dosage and formulation). The patient recovered after desloratadin was discontinued. No information was given whether ivy was also discontinued.

Assessor´s comment:

Neurotoxical effects of antihistamine drugs are known and are stronger in children than in adults. Therefore a causal relationship to desloratadin is probable while unlikely to the ivy preparation. Information about the ivy preparation is limited.

Other reactions

BfArM-case 06052045: A 42 year old female patient developed tachycardia after ingestion of Prospan® cough juice. No information to time of reaction, concomitant medications, diseases and outcome exist.

Assessor's comment:

Because of limited information, a causal relationship to the ivy preparation cannot be concluded, but also cannot be completely ruled out. Based on this data, at present no labelling is necessary.

Other adverse drug reactions described in the literature

Hoppe (1981): Ivy has cardiac effects. No near explanations or case reports are given.

According to the monograph *Hedera helix* of the Kommission D (1986) ivy is also used in homeopathic preparations. The homeopathic is indicated among others in hyperthyroidism. Homeopathic preparations up to D4 can increase a hyperthyroidism (*Hedera helix*, monograph of the Kommission D (1986).

Ivy poisoning in animals

Brömel and Zettl (1986) reported ivy poisoning in a roe deer after eating ivy after a fall of snow. It was showing signs of nervous disease; therefore the animal was killed and sent to the laboratory. Ivy leaves were present in the rumen.

On the other side, **Metcalfe (2005)** describes in a bio-geographical study on ivy a lot of animal feeders. Roe deer shows a distinct preference for ivy during autumn and winter, when it may form a significant part of its diet, with mainly foliage but some fruits taken also. However, roe deer shows a distinct avoidance or low consumption in the summer. Fallow deer and red deer also have ivy foliage in winter. Sheep relish ivy, sick beasts accept ivy leaves when refusing other forage. Sheep may severely restrict ivy colonization of grassland areas and woodland under storey.

Mills and Bone (2000): Saponins are toxic to fish and other cold-blooded animals and have been used to kill snails which harbour the bilharzias parasite. Grazing animals which consume large amounts of saponins can develop cholestatic liver damage. While it is unlikely that normal human doses would cause cholestasis, this phenomenon should be considered in unexpected cases of this disorder in patients consuming herbs.

5.4. Laboratory findings

Unkauf and Friderich (2000): In a randomized prospective multicenter, reference controlled study, 52 children (mean 7.9 years) with a clinically proved bronchitis were treated either with Valverde® (200 ml juice contains 660-1000 mg ivy extract (3-6:1), ethanol 60% (V/V) or Prospan Hustensaft (100 ml contains 0.7 g ivy extract (5-7.5:1), ethanol 30% (m/m)). The daily dose of Valverde® was: children up to 4 years 2 x 5 ml daily; 4-10 years 2 x 7.5 ml daily; 10-12 years 2 x 10 ml daily. The duration of the study was 10 days. The comparison of the laboratory values (haemoglobin, haematocrit, erythrocytes, thrombocytes, LDH, GOT, gamma-GT, bilirubin, kreatinin, natrium, kalium) between the therapy beginning and therapy end did not show any relevant variations.

5.5. Safety in special populations and situations

5.5.1. Drug interactions

Van den Bout-van den Beukel *et al.* (2006): Investigation on potential herb-antiretroviral drug interactions was performed on 25 herbal medicines. The authors aimed to provide an overview of the

modulating effects of Western and African herbal medicines on antiretroviral drug-metabolizing and transporting enzymes, focusing on potential herb-antiretroviral drug interactions. The conclusion was that Echinacea, garlic, Ginkgo, milk thistle, and St. John's worth have the potential to cause significant interactions. *Hedera helix* was not on the list of plants, considered / suspected to cause interactions.

Mills and Bone (2000): Saponins readily increase the permeability of the mammalian small intestine *in-vitro*, leading to the increased uptake of otherwise poorly permeable substances and a loss of normal function. The disruptive effect of saponins on the architecture of the cell membrane could lead to impaired absorption of smaller nutrient molecules which are otherwise rapidly absorbed. This appears to be the case for glucose and ethanol, based on *in-vitro* models.

There were two adverse events (Polizzi, 2001; BfArM case nr. 06002941) occurring by administration of narcotics (as antitussives) and ivy preparations. The hepatic glucoronidation pathway is incompletely developed in infants, which places them at particular risk of adverse dose-related effects (ex. from codeine or dextromethorphan). Furthermore, alteration of hepatic enzyme pathways by illness or concurrent drug therapy may further alter metabolism of these drugs and increase the risk of drug toxicity (American Academy of Paediatrics 1997). Adverse effects and over dosage of narcotics (codeine, dextromethorphan) associated with administration of cough and cold preparations in children are reported. Due to the unknown formulation and dosages of the ivy products and less information in the case reports, an interaction of ivy products with narcotics should be considered as signal (see chapter 4.4 special warnings and precautions for use in the monograph).

5.5.2. Safety studies in children

Well established use:

The safety studies were conducted with a large number of children in low age groups as well, for example:

0-1 year:	26 by Jahn and Müller (2000); 159 by Roth (2000); 188 by Fazio (2009); 7,871 by Kraft (2004); (=8,244 children)
1-3 years:	93 by Jahn and Müller (2000); 404 by Roth (2000) (=497 children)
1-5 years:	2,822 by Fazio (2009); 26,763 by Kraft (2004); (=29,585 children) (See chapter 4.2.3)

In prospective conducted clinical studies more than 7,000 children were involved. The tolerability was assessed by physicians and patients as “good” and “very good” in ranges of approximately 90-98%.

Fazio (2009): In the study 5,181 (53.73%) children was treated with Prospan® cough juice (100 ml contains 0.7 g dry ivy extract (5-7.5:1), ethanol 30% (m/m)) for 7 days. The dosages recommended were for 0-5 years: 2.5 ml 3 times/day, for 6-12 years: 5 ml 3 times/day, >12 years and adults: 5-7.5 ml 3 times/day. Adverse events were reported in a total of 2.1% of the patients, while 1.2% of adverse events were reported in children. Forty six (0.5%) patients discontinued therapy due to adverse events, mainly to gastrointestinal disorders. The main adverse events were: 1.5% gastrointestinal disorders (diarrhoea 0.8%, abdominal and epigastric pain 0.4%, nausea and vomiting 0.3%), 0.1 skin allergy. Other adverse events occurring less than 0.1% were: dry mouth and thirst, anorexia, eructation, stomatitis, anxiety, headache, drowsiness.

Kraft (2004): The retrospective study was conducted with approximately 52,478 patients. The most frequent adverse effects were: diarrhoea (0.1%), enteritis (0.04%), allergic exanthema/urticaria (0.04%) and vomiting (0.02%). In total, gastrointestinal disturbances occurred in 0.17% of the

children. The incidence of adverse effects was age dependent. In children under 1 year, adverse effects occurred in 0.4% and in children up to 9 years in 0.13%.

In April 2010, The French Health Agency decided to contraindicate the use of mucolytic agents in children below 2 years of age. This decision was based on a national Pharmacovigilance Survey on mucolytics and agents that fludify bronchial secretions. The investigation revealed a risk of respiratory congestion and rising bronchiolitis in infants due to functional features of their air passages and thoracic cavity (small calibre bronchi, immature bronchial surfaces that limit the lung's capacity to remove mucus flow). The Italian Medicines Agency took the same measure.

The HMPC decided to accept the use in children from 2-4 years of age for the well-established-use preparations giving special warnings for use: “persistent of recurrent cough in children between 2-4 years of age requires medical diagnosed before treatment.” The use in children below 2 years of age was contraindicated due to the concerns from several European countries as a general precautionary measure.

5.5.3. Use in pregnancy and lactation

Mahran *et al.* (1975) isolated emetine alkaloid from an alcoholic extract (90% ethanol) of four varieties of *Hedera helix* L. growing in Egypt. The author concluded, that since ivy possibly contains small amounts of emetine, it should not be recommended during pregnancy, as emetine may increase uterine contractions. According to Wichtl (2004), the occurrence of the alkaloid emetine could not be confirmed in recent studies.

ESCOP (2003): No human data are available. In accordance with general medical practice, the product should not be used during pregnancy and lactation without medical advice.

Conclusion:

Safety during pregnancy and lactation has not been established. In view of the pre-clinical safety data, the use during pregnancy and lactation is not recommended. See also chapter 3.4.

5.5.4. Overdose, drug abuse

Teat and Ellis (1981): Symptoms of poisoning vary among individuals and may include salivation, nausea, vomiting, diarrhoea, abdominal pain, headache, fever, excessive thirst, rash, and mydriasis. Haemolysis has also been reported which is proportional to the amount ingested. Ataxia, muscular weakness and incoordination may also occur. The author recommends that the treatment English Ivy poisoning should be initiated by inducing emesis with syrup of ipecac. Gastric lavage and the administration of activated charcoal should be considered for large ingestions (e.g. four or more berries or two or more leaves). After the ingested plant has been removed from the stomach, the patient should be given demulcents to provide comfort from the local irritation produced by the ivy.

BfArM-case 04900053: a 4 year old girl developed aggressivity and diarrhoea after drinking accidental a bottle of 90 ml of cough juice (15 ml juice (19.125 g) contain 50 mg ivy dry extract (4-8:1), ethanol 30% (m/m) corresponding 0.3 g herbal substance). The accidental dosage corresponds to 1.8 g herbal substance.

Assessor’s comment:

This is a 12-36-fold dosage compared to the recommended dosage by the Kooperation Phytopharmaka (children 1-4 years: corresponding to 0.05-0.15 g herbal substance daily). Compared to the high

dosage recommended by ESCOP 2003 for preparations prepared without ethanol (children 1-4 years: 150-300 mg herbal substance), it is the 6-12-fold dosage. The information is given in the monograph.

ESCOP (2003): Overdosage can provoke nausea, vomiting, diarrhoea and excitation.

Withdrawal and rebound

None reported.

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

No data available.

5.6. Overall conclusions on clinical safety

Ivy fresh plant is known to cause contact dermatitis, which is documented in numerous reports (Mitchell, 1979). Such reactions are attributed to falcarinol and derivatives in relation to skin contact or cutaneous use. With respect to oral administration, neither data from clinical studies nor case reports on adverse events give a clear hint on potential risks. However, the quantities of falcarinol and its derivatives in herbal preparations of ivy leaf are not well documented. Until now, it can not be completely excluded that even low levels could contribute to elicit an allergic response in patients with a pre-existing ivy allergy. Allergic reactions (urticaria, skin rash, tuberoses and dyspnoea) and gastrointestinal reactions (nausea, vomiting and diarrhoea) observed for herbal preparations of ivy leaf after oral administration are considered in the chapter “undesirable effects”.

There are suggestions of an association between ivy and rhinitis symptoms (Mahillon, 2006) and a first case of occupational asthma, related to the fresh plant, is documented (Hannu, 2008). Mild delirium occurred in a 3 year boy after ingestion of a considerable quantity of ivy leaves. During the delirious stage clonic convulsions developed, the boy screamed and cried, and he could not stay still upright. He had visionary hallucinations.

According to Kommission D monograph, (homeopathic) ivy preparations up to D4 can increase a hyperthyroidism. Because no published well documented cases of hyperthyroidism are reported, the effect is not mentioned in the monograph.

The dosage of ivy preparations (preparations intended for well-established use) is discussed contradict in the literature. In a controlled study, the efficacy was shown with low dosages (app. 300 mg herbal substance). There are preparations on the market with daily dosages up to approximately 1000 mg herbal substance. One study with only 25 patients indicated that dosages of approximately 650 mg herbal substance were necessary for efficacy of ethanol free preparations. This statement was later proven to be wrong. Other studies indicated that no higher dosages are necessary for the efficacy. This issue is analysed in chapter 4.3. Taking into account that some ivy preparations prepared without alcohol have been on the market for 10 years, with higher dosages and under consideration of the study result and safety reasons, dosage ranges corresponding to a maximum of 650 mg herbal substance daily are recommended for adults and lower dosages for children (1/3 or 2/3), depending on age. The preparation intended for traditional use is in the low dosage range.
In the chapter “overdosage” the information that overdose of ivy preparations can provoke nausea, vomiting, diarrhoea and excitation should be included. One case of aggressivity occurs. Further neurotoxical reactions observed after consumption of ivy fresh leaves are not reported neither for the medicinal use of normal dosages nor for overdoses of ivy leaf preparations.

Interactions are not expected from the results of non clinical *in-vivo* studies. There were no clinical well-known drug interactions with ivy leaf. The case Polizzi *et al.* (2001) and one BfArM case refer to

neurotoxical events of narcotics given concomitant with ivy preparations. Adverse effects and over dosage of narcotics (codeine, dextromethorphan) associated with administration of cough and cold preparations in children are reported (Polizzi *et al.,* 2001). Due to the unknown formulation and dosages of the ivy products and less information in the case reports, interactions of ivy products with narcotics should be considered as signal (See section 4.4 Special warnings and precautions for use).

From the long traditional use of ivy preparations in children no general safety concerns referring the use in therapeutic dosages can be derived. From the prospective clinical studies with approximately 7,000 children and a retrospective study conducted with about 52,000 children, it can be concluded that ivy preparations are well tolerated in high dosage ranges.

Allergic reactions and gastrointestinal reactions may occur. From the study Fazio *et al.* (2009) which included more than 5,000 children, the frequency of adverse events can be calculated: gastrointestinal reactions in 1.5% (common ≥1/100 to <1/10) and allergic reactions in 0.1% (uncommon ≥1/1000 to ≤1/100). Due to methodological reasons (concomitant medication, drop outs, no placebo control), different extracts of the monograph, in the monograph the frequency of adverse events is given as "not known" The saponins can induce nausea and vomiting that can lead to aspiration in infants. The use for children below 2 years of age is contraindicated because of the risk of aggravation of respiratory symptoms. Because of gastrointestinal reactions caution is recommended in patients with gastritis or gastric ulcer.

Safety during pregnancy and lactation has not been established. In view of the pre-clinical safety data, the use during pregnancy and lactation is not recommended. No data on the use in lactation are available. Because of general reasons it should not be used during lactation.

6. Overall conclusions

Based on the data documented in this Assessment Report, the well-established medicinal use and a traditional use for several preparations from *Herdera helix* are suitable for a Community monograph. The data fulfil the requirements of a well-established medicinal use with recognised efficacy and are eligible for a marketing authorisation in the indication "Herbal medicinal product used as an expectorant in case of productive cough."

Ivy preparations have been marketed worldwide in many countries, in large quantities. Symptom scores were analysed in a lot of studies, which were not blinded. There were more than 10,000 patients included in open multicenter prospective surveillance studies with a high dosage range. Most of the studies were conducted in children. Thus, the safety of the herbal medicine is appropriately analysed and known. The recommended dosages for the preparations correspond to the dosages used in praxis and are up to the maximum dosage used in the Gulyas (1997) study.

Pharmacotherapeutic group: respiratory system / Proposed ATC code: RO5 C / The mechanism of action is not known.

Due to the lack of adequate data on genotoxicity, a Union list entry is not proposed.

Benefit / Risk assessment

The herbal substance is subject of a European Pharmacopoeia monograph. An unambiguous macroscopic, microscopic chemical identification of the herbal substance is possible. Adulteration/contamination of the herbal substance is not reported. There are acceptable side effects concerning gastrointestinal reactions and allergic reactions with a therapeutic posology of the herbal preparations reported in literature or reference sources. No serious adverse events with a therapeutic

posology of the herbal preparations are reported in literature or reference sources with a well documented history.

Genotoxicity investigations are available for some ivy saponines which are constituents of the herbal preparations and the herbal medicinal products. No genotoxic tests are available for the whole plant extracts. Well documented drug-drug interactions of the herbal medicinal ivy preparations with other medicines are not reported in literature or reference sources in general. The herbal substance or preparations thereof are studied in one or more placebo controlled clinical trials. The number of patients involved in the published clinical trials (open controlled) with the herbal substance or preparations thereof exceeds more than 10,000. Ivy preparations are subject of reviews.

The use in children under 2 years is contraindicated because of the risk of aggravation of respiratory symptoms. In the well-established use part of the monograph, the use in children older than 2 years is accepted after medical diagnosis before treatment except for the liquid preparation with the extraction solvent ethanol 70% (V/V). This is due to the high ethanol content. Although there are also data for children of lower age (0-2 years) on ivy, this conclusion takes into account the existing data and the particular requirements with respect to safety for very young children. Safety during pregnancy and lactation has not been established. In view of the pre-clinical safety data, the use during pregnancy and lactation is not recommended.

Therapeutic alternatives for the indication are available including chemical substances such as ambroxol. Ambroxol is known to have side effects concerning gastrointestinal reactions and allergic reactions. For no other herbal preparation a well-established-use exists in this indication. Herbal preparations from ivy leaf have been shown as effective as ambroxol.
Intoxication, due to ivy herbal medicinal preparations, is not reported in literature or reference sources. One case of overdose led to aggressivity and diarrhoea. α-hederin, a metabolite present in the herbal substance and/or preparations, has a well-known acute toxicity to humans. Hovewer, according to the current knowledge it is not resorbed.

It can be concluded that the benefit/risk assessment for ivy preparations is positive for the use as an expectorant in the context of infections of the upper respiratory tract under specific conditions and in therapeutical dosages.

Annex

List of references