EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/HMPC/325715/2017
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Hedera helix* L., folium

Final

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

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 form(s)	Herbal preparations in liquid or solid dosage forms for oral use
Rapporteur(s)	J. Wiesner
Assessor(s)	M. Peikert
Peer-reviewer	I. Chinou

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

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1. Introduction

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

- Herbal substance(s)

Diverse national monographs for Hederae folium have been replaced by the current European Pharmacopoeia 9th edition 2017. Hederae folium are the whole or cut, dried leaves of *Hedera helix* L., collected in spring.

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

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
- main saponin is the hederasaponin C (hederacoside C) with other hederasaponins (B, D, E, F, G, H and I) present as well. Hederasaponin A, described in an earlier publication could no longer be found in subsequent studies. 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
- polyacetylenes falcarinone, falcarinol and 11, 12-dihydrofalcarinol
- phytosterols as stigmasterol, sitosterol, cholesterol, campesterol, α-spinasterol
- volatile oil (in the fresh leaves 0.1-0.3%) consists of methylethyl ketone, methyl isobutyl ketone, trans-hexanal, germacrene D, ß-caryphyllene, sabinene, α- and ß-pinene
- hamamiletol
- free amino acids
- the occurrence of the alkaloid emetine in the leaves could not be confirmed (Jensen *et al*., 1975; Czygan, 1990); from four varieties grown in Egypt the alkaloid emetine was isolated (Mahran *et al*., 1975); convincing studies are missing (Blaschek *et al.*, 2006; 2014).

- Herbal preparation(s)

See chapter 2.1

- 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 mono-preparations.

1.2. Search and assessment methodology

A literature search was performed using the DIMDI database information system on 17.01.2017. The searched scientific, medical, toxicological 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 for references “Lidos”.

Pharmacovigilance resources were the BfArM database for undesirable effects “VigilanceCentral” and information provided by the Member States. All EU member states were asked to give information on products on the market.

Additional hand searches were performed in books, book chapters, articles and letters in Journals, Medical press reviews, Acts of law and regulations in the BfArM owned library. The bibliographies of included trials and other relevant reviews were searched to identify further potential trials.

2. Data on medicinal use

2.1. Information about products on the market

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

Information on medicinal products marketed in the EU/EEA

Historic development of the monograph on *Hedera helix* L. folium:

On 31 March 2011 the European Union herbal monograph on *Hedera helix* L. folium (EMA/HMPC/289430/2009) was established.

In 2015, the monograph was revised only relating to the conclusion of the HMPC on the validity of the Bronchitis Severity Score (BSS) and published (EMA/HMPC/586888/2014).

According the European Union herbal monograph on *Hedera helix* L. folium (EMA/HMPC/586888/2014) of 24 November 2015 the well-established use is fulfilled for the following preparations:

a) Dry extract (DER 4-8:1), extraction solvent ethanol 24-30% m/m

The extract was combined by the four preparations

1. Dry extract (DER 4-8:1), extraction solvent: ethanol 30% (m/m)
2. Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)
3. Dry extract (DER 5-8:1), extraction solvent: ethanol 30% (m/m)
4. Dry extract (DER 4-6:1), extraction solvent: ethanol 30% (V/V) (= ethanol 24.6% (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)

The HMPC decided to add the liquid extract (DER 1:1), extraction solvent ethanol 70% (V/V) in the WEU part of the monograph, as it was considered that it is comparable to the dry extract (DER 3-6:1), extraction solvent: ethanol 60% (m/m). 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)) for the liquid extract.

e) Soft extract (DER 2.2-2.9:1), extraction solvent ethanol 50% (V/V): propylene glycol (98:2)

- **First systematic review**

For the first systematic review of the HMPC-monograph for ivy leaf in November 2015 an overview of marketing status was performed in all the European Countries in order to check the currently marketed products.

In AT, SK, SE, LV, IE, HR and DE the herbal ivy preparations listed in the first HMPC-monograph are still on the market. DK, BE and FI informed that up till now no medicinal products containing *Hedera helix* folium are authorised, however some procedures are currently on-going. From the other European countries no information was available. No herbal ivy preparations with new qualitative and quantitative composition were authorised in the member states. Since the establishment of the HMPC-monograph up to the systematic review of the monograph new approvals were performed with reference to the HMPC-monograph and in accordance with the dosages and indications of the ivy monograph.

In the majority of the marketed products the duration of use is not limited. The indications of the newer approved preparations are in accordance with the HMPC-monograph as an expectorant in case of productive cough. However, the older preparations have broader indications, including the use in chronic inflammatory bronchial disorders. The duration of use for self-medication 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.

Table 1: Overview of data obtained from marketed medicinal products

a) Dry extract (DER 4-8:1), extraction solvent: ethanol 24-30% (m/m)

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
Dry extract (DER 4-8:1), extraction solvent: ethanol 30% (m/m)	Relief of cough in case of catarrhs of the airways.	1 pastille contains 26 mg dry extract adults and adolescents: up to 6 pastilles per day children 4-11 years of age: up to 4 pastilles per day	WEU, 2003, AT
Dry extract (DER 4-8:1), extraction solvent: ethanol 30% (m/m)	Relief of cough in case of catarrhs of the airways.	1 effervescent tablet contains 50 mg dry extract adults and adolescents: 1 effervescent tablet 3 times daily children 4-11 years of age: 1 effervescent tablet 1-2 times daily	WEU, 2003, AT
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Expectorant in case of productive cough.	1 effervescent tablet contains 65 mg dry extract adults and adolescents: 1 effervescent tablet 2 times daily children 4-11 years of age: ½ effervescent tablet 3 times daily	WEU, 2000, AT
Dry extract (DER 4-8:1), extraction solvent: ethanol 30% (m/m)	Relief of cough in case of catarrhs of the airways.	1 capsule contains 26 mg dry extract adults and adolescents: 1-2 capsules 3 times daily children 4-11 years of age: 1 capsule 3 times daily	WEU, 2002, AT
Dry extract (DER 4-8:1), extraction solvent: ethanol 30% (m/m)	Expectorant in case of productive cough.	100 ml syrup contain 825 mg dry extract adults, adolescents, and elderly: 6 ml 2 times daily (99 mg dry extract per day). children 6-11 years of age: 4 ml syrup 2 times daily (66 mg dry extract per day) children 4-5 years of age: 2 ml syrup 2 times daily (33 mg dry extract per day)	WEU, 2015, AT
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Expectorant in case of productive cough.	1 ml syrup contains 7 mg dry extract adults and adolescents: 5-7.5 ml 2 times daily (70-105 mg dry extract daily) children 6-12 years of age: 5 ml 2 times daily (70 mg dry extract daily) children 2-5 years of age: 2.5 ml 2 times daily (35 mg dry extract per day)	WEU, 2012, AT
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Expectorant in case of productive cough.	1 ml contains 20.0 mg dry extract adults and adolescents: 20 drops 3-5 times daily children 6–12 years of age: 15 drops 2-3 times daily children 2-5 years of age: 10 drops 2-3 times daily	WEU, 1989, AT

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Expectorant in case of productive cough.	5 ml oral solution contain 35 mg dry extract adults and adolescents: 5 ml 3 times daily children 6-12 years of age: 5 ml 2 times daily	WEU, 2007, AT
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Expectorant in case of productive cough.	2.5 mg oral solution contain 17.5 mg dry extract adults, adolescents and children from 6 years of age: 5 ml 3-5 times daily children 1-5 years of age: 2.5 ml 3-5 times daily children 1-12 month of age: 2.5 ml syrup 1-2 times daily	WEU, 1998, AT
Dry extract (DER 4-8:1), extraction solvent ethanol 30% (V/V)	Herbal medicinal product used as an expectorant in case of productive cough.	100 ml syrup contain 154 mg extract adults and adolescents: 20 ml 3 times daily children 6-12 years of age: 15 ml 3 times daily children 2-5 years of age: 7.5 ml 3 times daily	WEU, 2014, Croatia
Dry extract (DER 4-8:1), extraction solvent ethanol 30% (V/V)	Herbal medicinal product used as an expectorant in case of productive cough.	1 ml syrup contains 3.675 mg extract adults and adolescents: 9 ml 3 times daily children 6-11 years of age: 6 ml 3 times daily children 2- 5 years of age: 3 ml 3 times daily	WEU, 2015, Croatia
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Herbal medicinal product used as an expectorant in case of productive cough.	1 ml syrup contains 7 mg extract adults and adolescents: 5-7.5 ml 2 times daily children 6-12 years of age: 5 ml 2 times daily children 2-6 years of age: 2.5 ml 2 times daily	WEU, 2012, Croatia
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Herbal medicinal product used as an expectorant in case of productive cough.	1 ml contains 20 mg extract adults and adolescents: 24 drops 3 times daily children 6-12 years of age: 16 drops 3 times daily children 2-6 years of age: 12 drops 3 times daily	WEU, 2012, Croatia
dry extract (DER 4-8:1), extraction solvent ethanol 30% (V/V)	Herbal medicinal product used as an expectorant in case of productive cough.	1 film coated tablet contains 35 mg extract adults and, adolescents: 1 tablet 3 times daily children 6-11 years of age: 1 tablet 2 times daily	WEU, 2015, Croatia
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Herbal medicinal product used as an expectorant in case of productive cough.	1 lozenge contains 26 mg extract adults and adolescents: 1 lozenge 4 times daily children 6-12 years of age: 1 lozenge 4 times daily	WEU, 2012, Croatia
Dry extract (DER 4-8:1),	Symptomatic treatment	1 effervescent tablet contains 50 mg dry extract	WEU, 2001, DE

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
extraction solvent: ethanol 30% (m/m)	of chronic inflammatory bronchial diseases.	>12 years of age: 1 tablet 2 times daily 6-12 years of age: 1/2 tablet 2 times daily	
Dry extract (DER 4-8:1), extraction solvent: ethanol 30% (m/m)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	1 effervescent tablet contains 63 mg dry extract >12 years of age: 1 tablet 1-2 times daily	WEU, 2001, DE
Dry extract (DER 4-8:1), extraction solvent: ethanol 30% (m/m)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	1 effervescent tablet contains 31.5 mg dry extract >12 years of age : 1 tablet 2 times daily 4-12 years of age: 1 tablet 1 time daily	WEU, at least since 1976, DE
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Expectorant in case of productive cough.	1 effervescent tablet contains 65 mg dry extract >12 years of age: in the morning 1 tablet (=65 mg dry extract), in the evening ½ tablet (=32.5 mg dry extract) 6-12 years of age: ½ tablet (=32.5 mg dry extract) 2 times daily generally 1 week	WEU, at least since 1976, DE
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	1 film-coated tablet contains 25 mg dry extract >12 years of age: 2 tablets 2 times daily (daily dose 100 mg dry extract)	WEU, at least since 1976, DE
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	1 oral gum contains 26 mg dry extract >12 years of age: 1 oral gum 4 times daily (daily dose 104 mg dry extract) 6-12 years of age: 1 oral gum 2 times daily (daily dose 52 mg dry extract)	WEU, 2008, DE
Dry extract (DER 4-8:1), extraction solvent: ethanol 30% (m/m)	Expectorant in case of productive cough.	1 bag contains 50 mg dry extract >12 years of age: 1 bag 1-2 times daily	WEU, 2001, DE
Dry extract (DER 5-7.5:1), extraction	Common cold associated with cough; symptomatic	1 bag (5 ml) contains 35 mg dry extract >12 years of age: 1 bag 3 times daily	WEU, 2014, DE

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
solvent: ethanol 30% (m/m)	treatment of chronic inflammatory bronchial diseases.	6-11 years of age: 1 bag 2 times daily generally 1 week	
Dry extract (DER 4-8:1), extraction solvent: ethanol 30% (m/m)	Expectorant in case of productive cough.	100 ml (111 g) syrup contain 154 mg dry extract >12 years of age: 15 ml 3 times daily 6-11 years of age: 15 ml 2 times daily 2-5 years of age: 10 ml 2 times daily	WEU, 2014, DE
Dry extract (DER 4-8:1), extraction solvent: ethanol 30% (m/m)	Expectorant in case of productive cough.	1 ml (=1.18 g) syrup contains 8.25 mg dry extract >12 years of age: 4 ml 2-3 times daily (daily dose 66-99 mg dry extract) 6-12 years of age: 4 ml 2 times daily (daily dose 66 mg dry extract) 2-5 years of age: 2 ml 2 times daily (daily dose 33 mg dry extract)	WEU, 2016, DE
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	100 ml oral liquid contain 2 g dry extract; 1 ml = 29 drops >10 years: 24 drops (=16.8 mg dry extract) 3 times daily 4-10 years: 16 drops (=11.2 mg dry extract) 3 times daily 1-4 years: 12 drops (=8.4 mg dry extract) 3 times daily	WEU, at least since 1976, DE
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	5 ml oral liquid contain 35 mg dry extract >12 years of age: 5 ml (=35 mg dry extract) 3 times daily 6-12 years of age: 5 ml (=35 mg dry extract) 2 times daily	WEU, at least since 1976, DE
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	100 ml oral liquid contain 0.7 g dry extract >12 years of age: 5 ml (=35 mg dry extract) 3 times daily 6-12 years of age: 5 ml (=35 mg dry extract) 2 times daily <6 years of age: 2.5 ml (=17.5 mg dry extract) 2 times daily	WEU, at least since 1976, DE
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Expectorant in case of productive cough.	1 ml syrup contains 7 mg extract adults and adolescents: 5 ml syrup 3 times daily (corr. to 105 mg extract) children 6-12 years of age: 5 ml syrup 2 times daily (corr. to 70 mg extract): children 2-5 years of age: 2.5 ml 2 times daily syrup (corr. to 35 mg extract) 1 ml solution contains 20 mg extract adults, adolescents and children >10 years of age: 24 drops 3 times daily	WEU, 1999, Latvia

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		(50.4 mg extract) children 4-10 years of age: 16 drops 4 times daily (33.6 mg extract) children 1-4 years of age: 12 drops 3 times daily (25.2 mg extract) 1 effervescent tablet contains 65 mg extract adults and adolescents: 1 tablet 2 times daily children 4-12 years of age: ½ tablet 3 times daily	
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Herbal medicinal product used as an expectorant in case of productive cough.	1 ml contains 7 mg dry extract adults, adolescents, and elderly: 5 ml 3 times daily children between 6-11 years of age: 5 ml 2 times daily children between 2-5 years of age: 2.5 ml 2 times daily	WEU, 2010, Sweden
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Therapy of acute respiratory inflammation accompanied by cough and symptomatic therapy of chronic bronchitis.	1 effervescent tablet contains 65 mg dry extract adults and adolescents > 12 years of age: 1 tablet 2 times daily children 6–12 years of age: ½ tablet 3 times daily	WEU, 2007, SK
Dry extract (DER 4-8:1), extraction solvent ethanol 30% (V/V)	Herbal medicinal product used as an expectorant in case of productive cough.	1 effervescent tablet contains 50 mg dry extract adults and adolescents: 1 tablet 2 times daily children 3–12 years of age: ½ tablet 2 times daily	WEU, 2012, SK
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Therapy of acute respiratory inflammation accompanied by cough and symptomatic therapy of chronic bronchitis.	100 ml of syrup contain 700 mg dry extract children ≥ 10 years of age, adolescents and adults: 5 ml 3 times daily; dose for adults can be increased to 7.5 ml 3 times daily, if needed children 6–9 years of age: 5 ml 3 times daily children 1–5 years of age: 2.5 ml 3 times daily Children <1 year of age: 2.5 ml 2 times daily	national authorization; since 2007, SK
Dry extract (DER 5-7.5:1), extraction solvent: ethanol 30% (m/m)	Herbal medicinal product used as an expectorant in case of productive cough.	1 ml syrup contains 7 mg dry extract adults and adolescents: 5-7.5 ml syrup 2 times daily (70-105 mg dry extract daily) children 6-12 years of age: 5 ml syrup 2 times daily (70 mg dry extract daily) children 2-5 years of age: 2.5 ml syrup 2 times daily (35 mg dry extracts daily)	WEU, 2011, SK
Dry extract (DER 4-8:1),	Herbal medicinal product	100 ml of syrup contains 154 mg dry extract	WEU,2015, SK

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
extraction solvent ethanol 30% (V/V)	used as an expectorant in case of productive cough for adults, adolescents and children from 2 years of age.	adults and adolescents: 20 ml 3 times daily (corresponding to 92.40 mg of dry extract daily) children between 6-12 years of age: 15 ml 3 times daily (corresponding to 69.30 mg of dry extract daily) children 2-5 years of age: 7.5 ml 3 times a daily (corresponding to 34.65 mg of dry extract daily)	

Table 2: Overview of data obtained from marketed medicinal products

b) Dry extract (DER 6-7:1), extraction solvent: ethanol 40% (m/m)

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
Dry extract (DER 6-7:1), extraction solvent: ethanol 40% (m/m)	Relief of cough in case of catarrhs of the airways.	100 g syrup contain 0.792 g dry extract (1 ml = 1.14 g corresponding to 9 mg dry extract) children 4-11 years of age: 2 ml 2 times daily children 1-3 years of age: 1 ml 3 times daily children up to 12 months of age: 1 ml 2 times daily	WEU, 2002, AT
Dry extract (DER 6-7:1), extraction solvent: ethanol 40% (m/m)	Relief of cough in case of catarrhs of the airways.	100 g syrup contain 0.792 g dry extract(1 ml = 1.14 g corresponding to 9 mg dry extract) adolescents and adults: 2 ml 3 times daily children 4-11 years of age: 2 ml 2 times daily children 1-3 years of age: 1 ml 3 times daily children <1 year of age: 1 ml 2 times daily	WEU, 2005, AT
Dry extract (DER 6-7:1), extraction solvent: ethanol 40% (m/m)	Relief of cough in case of catarrhs of the airways.	100 g oral solution contain 1.98 g dry extract (1 ml = 17 drops = 1.07 g corresponding to 21 mg dry extract) children 4-11 years of age: 16 drops 2 times daily children 1-3 years of age: 9 drops 3 times daily children <1 year of age: 6 drops 3 times daily	WEU, 2002, AT
Dry extract (DER 6-7:1), extraction solvent:	Relief of cough in case of catarrhs of the airways.	100 g oral solution contain 1.98 g dry extract (1 ml = 17 drops = 1.07 g corresponding to 21 mg dry extract)	WEU, 2005, AT

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
ethanol 40% (m/m)		adolescents and adults: 25 drops 3 times daily children 4-11 years of age: 16 drops 2 times daily children 1-3 years of age: 12 drops 3 times daily children < 1 year of age: 8 drops 3 times daily	
Dry extract (DER 6-7:1), extraction solvent: ethanol 40% (m/m)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	100 ml (=113,14 g) syrup contain 0.895 g dry extract adolescents and adults: 2 ml 3 times daily children 4-12 years of age: 1.5 ml 3 times daily children 1-3 years of age: 1 ml 3 times daily	WEU, at least since 1976, DE
Dry extract (DER 6-7:1), extraction solvent: ethanol 40% (m/m)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	100 ml oral liquid contain 0.87 g dry extract adolescents and adults: 1.8 ml 3 times daily children 5-11 years: 1.8 ml 1-2 times daily children 1-4 years: 1 ml 2 times daily	WEU, 2004, DE
Dry extract (DER 6-7:1), extraction solvent: ethanol 40% (m/m)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	100 ml oral liquid contain 0.87 g dry extract adolescents and adults: 2 ml 3 times daily children 5-11 years: 2 ml 1-2 times daily children 1-4 years: 1 ml 2 times daily	WEU, 2004, DE
Dry extract (DER 6-7:1), extraction solvent: ethanol 40% (m/m)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	100 g oral liquid (=107.8 ml) contain 1.98 g dry extract (10 drops =0.58 g) adolescents and adults: 12-15 drops 3 times daily children 4-12 years: 10 drops 3 times daily children 1-3 years: 7 drops 3 times daily	WEU, at least since 1976, DE
Dry extract (DER 6-7:1), extraction solvent: ethanol 40% (m/m)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	100 g oral liquid (=95.2 ml) contain 1.98 g dry extract adolescents and adults: 0.7-0.9 ml 3 times daily children 5-11 years: 0.45-0.6 ml 3 times daily children 1-4 years: 0.35-0.45 ml 3 times daily	WEU, at least since 1976, DE
Dry extract (DER 6-7:1), extraction solvent: ethanol 40% (m/m)	Common cold associated with cough; symptomatic treatment	100 ml oral liquid contain 2.04 g dry extract adolescents and adults: 27 drops 3 times daily children 4-12 years: 21 drops 3 times daily	WEU, at least since 1976, DE

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
	of chronic inflammatory bronchial diseases.		
Dry extract (DER 6-7:1), extraction solvent: ethanol 40% (m/m)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	100 ml oral liquid contain 0.9 g dry extract adolescents and adults: 2 ml 3 times daily children 4-12 years: 1.5 ml 3 times daily children 1-3 years: 1 ml 3 times daily	WEU, at least since 1976, DE
Dry extract (DER 6-7:1), extraction solvent: ethanol 40% (m/m)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	100 g oral liquid (=95.2 ml) contain 1.98 g dry extract (10 drops =0.39 g) adolescents and adults: 18-22 drops 3 times daily children 5-11 years: 12-15 drops 3 times daily children 1-4 years: 9-12 drops 3 times daily	WEU, at least since 1976, DE
Dry extract (DER 6-7:1), extraction solvent: ethanol 40% (m/m)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	100 ml oral liquid (=104.91 g) contain 2.08 g dry extract (10 drops =0.39 g) adolescents and adults: 20-25 drops 3 times daily children 4-12 years: 16 drops 3 times daily children 1-3 years: 12 drops 3 times daily	WEU, at least since 1976, DE
Dry extract (DER 6-7:1), extraction solvent: ethanol 40% (m/m)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	100 ml oral liquid contain 0.87 g dry extract adolescents and adults: 2 ml 3 times daily children 6-11 years: 2 ml 1-2 times daily children 2-5 years: 1 ml 2 times daily	WEU, 2011, DE

Table 3: Overview of data obtained from marketed medicinal products

c) Dry extract (DER 3-6:1), extraction solvent: ethanol 60% (m/m)

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
Dry extract (DER 3-6:1), extraction solvent: ethanol 60% (m/m)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	100 ml oral liquid contain 330 mg dry extract adolescents and adults: 10 ml 2 times daily children 5-11 years: 7.5 ml 2 times daily children 1-4 years: 5 ml 2 times daily	WEU, at least since 1976, DE

Table 4: Overview of data obtained from marketed medicinal products

d) Liquid extract (DER 1:1), extraction solvent ethanol 70% V/V

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
Liquid extract (DER 1:1), extraction solvent: ethanol 70% (V/V)	Expectorant in case of productive cough.	10 ml (=9.58 g) oral liquid contain 1.5 g liquid extract adolescents and adults: 20-25 drops 3 times daily (daily dose 2 ml = 300 mg herbal substance) children 6-12 years: 15-20 drops 3 times daily (daily dose 1.5 ml) = 230 mg herbal substance) children 2-5 years: 10-15 drops 3 times daily (daily dose 1.13 ml = 170 mg herbal substance)	WEU, at least since 1976, DE

Table 5: Overview of data obtained from marketed medicinal products

e) Soft extract (DER 2.2-2.9:1), extraction solvent: ethanol 50% (V/V):propyleneglycol (98:2)

Active substance	**Indication**	**Pharmaceutical form** **Posology** **Duration of use**	**Regulatory Status**
Extract (DER 2.2-2.9:1), extraction solvent: ethanol 50% (V/V) : propylene glycol (98:2)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	1 ml oral liquid (31 drops) contain 0.04 g extract >10 years of age: 31 drops 3 times daily 4-10 years of age: 21 drops 3 times daily 2-4 years of age: 16 drops 3 times daily	WEU, at least since 1976, DE
Extract (DER 2.2-2.9:1), extraction solvent: ethanol 50% (V/V) : propylene glycol (98:2)	Common cold associated with cough; symptomatic treatment of chronic inflammatory bronchial diseases.	100 ml syrup contain 0.8 g extract >10 years of age: 5 ml 3 times daily 4-10 years of age: 2.5 ml 4 times daily 1-4 years of age: 2.5 ml 3 times daily 0-1 year of age: 2.5 ml 1 time daily	WEU, at least since 1976, DE
Soft extract (DER 2.2-2.9:1), extraction solvent: ethanol 50% (V/V):propylene-glycol (98:2)	Traditional herbal medicinal product used as an expectorant in cough associated with cold.	1 ml solution (31 drops) contains 0.04 g extract adults and adolescents: 31 drops 3 times daily children 5-12 years of age: 21 drops 3 times daily; children >4 years of age: 16 drops 3 times daily	TU, 2015, HR
Soft extract (DER 2.2-2.9:1), extraction solvent: ethanol 50% (V/V):propylene-glycol (98:2)	Traditional herbal medicinal product used as an expectorant in cough associated with cold.	100 ml syrup contains 0.8 g extract adults and adolescents: 5 ml 3 times daily children 5-12 years of age: 2.5 ml 4 times daily children >4 years of age: 2.5 ml 3 times daily	TU, 2015, HR
Soft extract (DER 2.2-2.9:1), extraction solvent: ethanol 50% (V/V):propylene-glycol (98:2)	Acute catarrh (inflammation) of the respiratory tract; symptomatic treatment of chronic inflammatory bronchial diseases.	1 ml syrup contains 8 mg extract: adults, adolescents and children (>10 years of age): 5 ml 3 times daily children 4-10 years of age: 2.5 ml 4 times daily children 1-4 years of age: 2.5 ml 3 times daily children 0-1 years of age: 2.5 ml 1 time daily 1 ml solution contains 40 mg extract adults, adolescents and children (>10 years of age): 31 drops 3 times daily children 4-10 years of age: 21 drops 3 times daily children 2-4 years of age: 16 drops 3 times daily	WEU, 1995, LV

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

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

Not applicable

Information on other products marketed in the EU/EEA (where relevant)

According to the monograph *Hedera helix* of the Kommission D (1986), ivy is also used in homeopathic preparations. 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.

Information on other marketed product is not applicable, however De Smet (1993), Hausen *et al*. (1987), Hausen (1988) and Facino *et al*. (1990) reported that ivy leaves were also incorporated into topical cosmetic preparations, e.g., for the treatment of cellulites and shampoos.

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

Not applicable

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

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

Steinmetz (1961) resumed 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 vasodilator. However, in large doses, it is a vasoconstrictor 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 favus”.

Chichiricco *et al.* (1980) collected information about traditional phototherapy in the Subequana valley Abruzzo, Central Italy. He noted the boiled leaves of *Hedera helix*, 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 in the region of Kirklareli Province in Turkey. A decoction of the leaves of *Hedera helix* was used for diabetes and “blood depurative”. The dosage reported was one teacup two times daily for 7-8 days. Mayer (2010) described the cultural-

historical portrait of ivy leafs. The medical practitioners of the Middle Ages were at variance regarding its effectiveness, although the most widespread indications ranged from head and tooth aches, chronic catarrh, diarrhoea, ulcers, inflammations and burns. Moreover, ivy served as a contraceptive whose abortive effect was also taken into account.

Ivy leaf preparations marketed in Europa contain hydro-ethanolic extracts. The request for information gave no information on tea preparations and their posology in European countries. In most cases the available phytotherapeutic textbooks do not list the tea preparation, inform that making the tea is rarely done and give no clear information to the single and daily dose. All together as no preparations are on the market and the literature data on traditional use are not convincing the use as tea preparation is not recommended for the monograph.

Table 6: Overview of historical data

Herbal preparation	**Documented use / Traditional use**	**Pharmaceutical form**	**Reference**
All herbal preparations	Catarrh of the respiratory passages and for symptomatic treatment of chronic inflammatory bronchial illnesses.	Daily dose for the cut drug is 0.3 g in all appropriate produced preparations.	German Kommission E Monograph (1988); Hänsel *et al*. (1993); Blaschek *et al*. (2006)
All herbal preparations	Catarrh of the respiratory passages and for symptomatic treatment of chronic inflammatory bronchial illnesses.	Corresponding herbal substance 0-1 year of age: 0.02-0.05 g 1-4 years of age: 0.05-0.15 g 4-10 years of age: 0.10-0.20 g 11-16 years of age: 0.20-0.30 g	Dorsch *et al*., 2002; Schapowal, 2007
Herbal preparations	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" Traditionally used as an adjuvant to slimming diets.	No dose recommendation (Note: ivy is not listed in Pharmacopoée Francaise (1965) "tisanes" dose recommendations for herbal teas)	Cahiers de L'Agence N°3 (1998)
Ethanol-containing preparations and ethanol-free preparations	Coughs, particularly when associated with hypersecretion of viscous mucus; as adjuvant treatment of inflammatory bronchial diseases.	Corresponding herbal substance: ethanol-containing preparations 0-1 year of age: 20-50 mg 1-4 years of age: 50-150 mg 4-12 years of age: 150-210 mg adults: 250-420 mg ethanol-free preparations: 0-1 year of age: 50-200 mg 1-4 years of age: 150-300 mg 4-12 years of age: 200-630 mg adults: 300-945 mg	ESCOP Monographs (2003)
Extracts of ivy leaf	Extracts of ivy leaf have expectorant and spasmolytic actions. They are used primarily as expectorants and antispasmodics for catarrh of the respiratory	"Making the tea is rarely done": Pour boiling water (no information on quantity) over 0.5 g of dried leaf (1 teaspoon= about 0.8 g) 1989: drink one cup 1-3 times daily	Wichtl (1989, 2004); Wichtl & Anton 1999

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
	passages and for symptomatic treatment of chronic inflammatory bronchial illnesses.	1999: drink one cup 1-2 times daily the dose is unclear	
(All) herbal preparations	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	Herbal preparations corresponding 0.3 g herbal substance as daily dosage	Williamson (2003)
Herbal preparations	For catarrh and chronic inflammation of the respiratory tract. It has also been applied externally	No information	Sweetmann (2007)
Herbal preparations (unclear fresh or dried leaves)	Internal use: pertussis, chronical bronchitis, tracheitis, laryngitis, rheumatism, lithiasis, hypertension, external use: cellulites, rheumatism, oedema, erythema/burn	3 cups per day of an infusion made by 3 spoons of drug in one liter of water	Valnet (1983)

2.3. Overall conclusions on medicinal use

After the HMPC-monograph for ivy leaf was established all the approvals were done with reference to this monograph. The specified products on the market in the European Member States are used orally. The route of administration depends on the pharmaceutical form (as coated tablets, capsules, effervescent tablets, drops or oral solution). The preparations are taken with a glass of water. No changes result from the new data. The well-established-use is the same as in the earlier version of this EU herbal monograph on *Hedera helix* L., folium; EMA/HMPC/586888/2014 from 24.11.2015.

Table 7: Overview of preparations accepted as well-established-use according EMA/HMPC/586888/2014 from 24.11.2015:

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
a) Dry extract (DER 4-8:1), extraction solvent: ethanol 24-30% (m/m)	Herbal medicinal product used as an expectorant in case of productive cough.	Adolescents, adults and elderly: single dose: 15-65 mg, 1-3 times daily daily dose: 45-105 mg (Note: maximum daily dose for ethanol-containing finished products: 67 mg; corresponding to 420 mg herbal substance) children between 6-11 years of age: single dose: 11-35 mg, 2-3 times daily; daily dose: 33-70 mg.	WEU, since 1976, DE

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
		(Note: maximum daily dose for ethanol-containing finished products: 34 mg; corresponding to 210 mg herbal substance) children2-5 years of age: single dose: 8-18 mg, 2-3 times daily; daily dose: 24-36 mg (Note: maximum daily dose for ethanol-containing finished products: 24 mg; corresponding to 150 mg herbal substance)	
b) Dry extract (DER 6-7:1), extraction solvent: ethanol 40% (m/m)	Herbal medicinal product used as an expectorant in case of productive cough.	Adolescents, adults and elderly: single dose: 14-18 mg 3 times daily children 6-11 years of age: single dose: 9-18 mg, 2-3 times daily; daily dose: 15-40 mg children 2-5 years of age: single dose: 7-9 mg, 2-3 times daily; daily dose: 17-27 mg	WEU, since 1976, DE
c) Dry extract (DER 3-6:1), extraction solvent: ethanol 60% (m/m)	Herbal medicinal product used as an expectorant in case of productive cough.	Adolescents, adults and elderly: single dose: 33 mg 2 times daily children 6-11 years of age: single dose: 25 mg, 2 times daily children 2-5 years of age: single dose: 17 mg, 2 times daily	WEU, since 1976, DE
d) Liquid extract (DER 1:1), extraction solvent: ethanol 70% (V/V)	Herbal medicinal product used as an expectorant in case of productive cough.	Adolescents, adults and elderly: single dose: 100 mg 3 times daily children 6-11 years of age: single dose: 75 mg, 3 times daily	WEU, since 1976, DE
e) Soft extract (DER 2.2-2.9:1), extraction solvent: ethanol 50% (V/V):propylene glycol (98:2)	Herbal medicinal product used as an expectorant in case of productive cough.	Adolescents, adults and elderly: 40 mg 3 times daily children 6-11 years of age: single dose: 20-26 mg, 3-4 times daily daily dose: maximum 80 mg children 2-5 years of age: single dose: 20 mg, three times daily	WEU, since 1976, DE

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

Table 8: Overview of the main non-clinical data/conclusions

Herbal preparation tested	**Posology**	**Experimental model**	**Reference**	**Main non-clinical conclusions**
Comparable / similar preparations to preparations of the monograph				
Dry extract (6:1), extraction solvent 30% ethanol	1.4 papaverine equivalent value	*In-vitro*, isolated guinea pig ileum	Trute *et al*. (1997)	Antispasmodic activity
Ethanolic extract from ivy leaf (no further information)	Oral, 50 mg/kg body weight	*In-vivo*, compressed air model in conscious guinea pigs	Haen (1996)	Inhibition of bronchoconstriction induced by inhalation of ovalbumin
Ethanolic extract from ivy leaf (no further information)	Oral, 162 mg/kg body weight	*In-vivo*, anti-inflammatory effect in rats	Haen (1996)	Inhibition in carrageenan-induced rat paw oedema
Ethanolic extract from ivy leaf (ethanol 30%; DER 6.9:1))	200 mg/kg gastric administration; ambroxol: 250 mg/kg theobromine: 50 mg/kg	*In-vivo*, phenol red secretion in mice trachea in-vivo, citric acid-induced cough measurement in guinea pigs trachea	Song *et al*. (2015)	Antitussive and expectorant activities: ivy: 13.39±4.22 ambroxol: 25.80±2.41 antitussive activities: ivy: 39.89±4.14 theobromine: 53.22±5.66

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
Ethanolic extract (no further information)	IP extract: 2.5, 5 and 7.5 ml/kg diclofenac: 100 mg/kg	*In-vivo*, formalin 2% as oedematogenic agent for induction of paw oedema in mice	Rai (2013)	Anti-inflammatory activity extract (7.5 ml/kg): 88.89% inhibition diclofenac: 94.44% inhibition
Ethanolic extract (no further information)	30 mg/kg bw oral administration	*In-vivo*, antiviral properties against influenza A/PR/8 (PR8) virus in pulmonary inflammation in PR8-infected mice	Hong *et al*. (2015)	Co-administration of ivy extract with oseltamivir decreased pulmonary inflammation
Other preparations				
Crude saponin extract (CSE) (10:1); extraction solvent ethanol 80% (V/V)	CSE: 50, 100 and 200 mg/kg indomethacin: 20 mg/kg; orally once daily for 4 days	*In-vivo*, anti-inflammatory effects in carrageenan- and cotton-pellet-granuloma test in rats	Süleyman *et al*. (2003.	CSE at 100 and 200 mg/kg anti-inflammatory effects

Spasmolytic / bronchodilating activity

Comparable/similar preparations to preparations of the monograph

The antispasmodic activity of fractions and isolated substances from 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 spasmogenic. Main spasmodic activity was found for 3,5-dicaffeoylquinic acid, a-hederin and hederagenin, quercetin and kaempferol, respectively (Trute *et al*., 1997).

Single substances

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* (Capasso *et al.,* 1991).

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

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.

A pre-incubation for 24 hours with the saponin compound α-hederin (1 µM) inhibited the terbutaline-stimulated internalization of the β_2-AR in alveolar epithelial type II cell line (A549) by 87% after 20 minutes, 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 (Hegener *et al.,* 2004).

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 authors 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 (Runkel *et al.,* 2005).

Internalization of β_2-AR -GFP fusion proteins after stimulation with 1 µM terbutaline was inhibited by pre-incubation of stably transfected HEK293 cells with 1 µM α-hederin for 24 hours, 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 β_2-AR or the intracellular cAMP level (Sieben *et al.,* 2009).

In-vivo experiments

Comparable/similar preparations to preparations of the monograph

In the compressed air model in conscious guinea pigs, an orally administered ethanolic extract (no further information) 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 (Haen, 1996).

Mendel *et al*. (2011) examined the effect of two main active constituents extracted from the plant, α-hederin and hederacoside C, and the effect of the whole dry extract of *H. helix* on the gut motility. The obtained results revealed that α-hederin, applied in a concentration that ranged from 25 to 320 μM, significantly changed the spontaneous motoric activity of rat stomach smooth muscle. Hederacoside C did not alter the motility of rat isolated stomach corpus and fundus strips when administered in a concentration up to 100 μM. However, if applied in a concentration of 350 μM, it induced a remarkable contraction of smooth muscles. The whole extract of *H. helix*, in a dose containing 60 μM of hederacoside C, produced a strong contraction with a strength that was comparable to the reaction generated by acetylcholine, as reference molecule.

Mendel *et al.* (2012) evaluated the participation of cholinergic pathways in α-hederin-induced contraction of rat isolated stomach strips (rat isolated fundus and corpus stomach strips) under isotonic conditions. The effect of atropine (1 μM) and hexamethonium (1 μM) on α-hederin-induced contraction of stomach strips was investigated. The obtained results revealed that the administration of atropine neither prevented nor reduced the response of stomach strips to α-hederin. The contraction caused by saponin (100μM) in the presence of atropine amounted to 96.02±23.06% and 102.73±11.01% of the reaction induced by acetylcholine for stomach corpus and fundus strips, respectively, whereas the response to α-hederin without atropine pre-treatment was as big as 94.79±75.91% and 101.57±27.75% of the reaction produced by acetylcholine for stomach corpus and fundus strips, respectively. The application of nicotinic antagonist also did not change the force of α-hederin-induced contraction. If the administration of saponin was preceded by treatment with hexamethonium the strength of stomach fundus strips contraction was 106.68±11.90% of the reaction to acetylcholine and the contraction was comparable with the one caused by α-hederin without prior hexamethonium-treatment. The authors assumed that the cholinergic pathways do not participate in α-hederin-evoked contraction of rat isolated stomach preparations.

Mendel *et al.* (2013) investigated the contractile effect of α-hederin, the main active constituent of an ivy extract on smooth muscles of rats. This study was also performed on rat isolated stomach corpus and fundus strips, under isotonic conditions. The effect of α-hederin (100 μM) on smooth muscle preparations was measured before and after the treatment with verapamil (100 μM) during the incubation in modified Krebs-Henseleit solution. The obtained results revealed that the application of verapamil significantly inhibited the reaction evoked by α-hederin.

In order to identify whether additional compounds near α-hederin also mediate an increased ß2-adrenergic responsiveness, the authors examined the ingredients of an ivy leaves dry extract (EA 575) protocatechuic acid, neochlorogenic acid, chlorogenic acid, cryptochlorogenic acid, rutin, kaempferol-3-O-rutinoside, 3,4-, 3,5- and 4,5-dicaffeoylquinic acid, hederacoside B, and ß-hederin. Within all the tested substances, only ß-hederin inhibited the internalization of GFP-tagged $ß_2$AR in stably transfected HEK293 cells. Using fluorescence correlation spectroscopy ß-hederin (1 μM, 24 h) pretreated HASM cells showed a statistically significant increase in the $ß_2$AR binding from 33.0±8.9% to 44.1±11.5%. The increased binding was selectively found for the receptor-ligand complex with unrestricted lateral mobility, whereas the binding of $ß_2$AR with hindered lateral mobility was not affected. Compared to control cells, a statistically significant increase of 17.5±6.4% (n = 4, $p<0.05$) and 24.2±5.8% (n = 4, $p<0.001$) in the cAMP formation was found for ß-hederin pretreated HASM cells after stimulation with 10 μM of terbutaline and simultaneous stimulation with 10 muM terbutaline and 10 μM forskolin, respectively. Within this systematic study focusing on the influence of the ingredients of an ivy leaves dry extract on HASM cells it was possible to identify ß-hederin as further component presumably responsible for the $ß_2$-mimetic effects (Greunke *et al*., 2015).

Secretolytic effect

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

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 (Mills and Bone, 2000).

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. According to the author, sub-emetic doses of these agents activate a gastropulmonary mucokinetic vagal reflex, which stimulates the bronchial glands to secrete a watery fluid (März and Matthys, 1997).

Single substances

A new mode of action was discussed by Stauss-Grabo *et al.* (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. It was proposed that the surfactant leads to the liquefaction of the mucus.

In-vivo experiments

Ethanolic extract

Song *et al*. (2015) investigated the additive effect of the *Hedera helix* (HH) and *Rhizoma coptidis* (RC) extracts mixture on antitussive and expectorant activities in animals. The expectorant assay was performed with phenol red secretion in mice trachea. After gastric administration of the test extracts in mice, 2.5% phenol red solution (0.2 mL) was intraperitoneally injected. Trachea was dissected and optical density of tracheal secretion was measured. The mixture of HH and RC extracts in a 1:1 concentration at a dose of 200 mg/kg showed a more potent effect on phenol red secretion (25.25±3.14) than the individual use of each extracts [phenol red secretion; HH 13.39±4.22 (p=0.000), RC 20.78±2.50 (p=0.010), ambroxol 25.80±2.41. After gastric administration of the test extracts in guinea pigs, the antitussive activities were assessed using a citric acid-induced cough measurement. The extracts of HH and RC significantly increased cough inhibition (61.25±5.36); HH 9.89±4.14 (p=0.010), RC 30.25±7.69 (p=0.000), theobromine 53.22±5.66.

Anti-inflammatory effect

In-vivo experiments

Comparable/similar preparations to preparations of the monograph

An orally administered ethanolic extract from ivy leaf (no further information) at 162 mg/kg body weight inhibited carrageenan-induced rat paw oedema by 39% after 1 hour and by 5% after 5 hours (Haen, 1996).

Rai (2013) tested an ivy leaf ethanolic extract (no DER information) for its anti-inflammatory properties in Swiss Albino mice. Formalin 2% was used as the oedematogenic agent. Intraperitoneal injections of 7.5 ml/kg body weight ethanol extract showed anti-inflammatory activity with 88.89% inhibition as compared to reference drug diclofenac, which showed 94.44% inhibition at 180 min after induction of inflammation.

Mulkijanyan *et al*. (2013) conducted a comparative phytochemical study of the biologically active water extracts of *H. colchica* and *Hedera helix* (no DER information) and evaluation of their ulcer preventive efficacy in ethanol-induced ulcer model in rats. Water extracts of *H. colchica* and *H. helix* (300 mg/kg, i.p.) significantly ($p<0.01$) decrease the ulcer index (0.50 and 1.38 vs 3.17 in control) and rise macroscopic curative ratio (84.2% and 56.6%, respectively). *H. colchica* produced a greater protection ($p<0.01$) than *Hedera helix*.

Ethanolic extract

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 *H. helix* in carrageenan- and cotton-pellet-induced acute and chronic inflammation models in rats. The *H. 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 *H. 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 *H. helix* CSE at 100 and 200 mg/kg body weight with 77% acute anti-inflammatory effects. For testing chronic anti-inflammatory (anti-proliferative) effects, the cotton-pellet-granuloma test was conducted. Indometacin appeared to be 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).

Single substances

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 doses 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 (Kim *et al.,* 1999).

The anti-inflammatory potential of α-hederin and hederasaponin-C from *Hedera helix* was investigated in carrageenan-induced acute paw oedema 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 was found effective in the second phase of inflammation, they were not as effective as indometacin (Gepdiremen *et al.,* 2005).

Rai (2013) studied the anti-inflammatory effect by using a 2.5 - 7.5 ml/kg weight ethanol extract of *H. helix* in 3 different ranges (2.5 mg/kg; 5 mg/kg; 7 mg/kg, no DER information) and comparing this to a reference drug, diclofenac, and a control group. Freshly prepared 2% formalin was used as the oedematogenic agent. Twenty minutes after injection of various doses of the plant extract and reference drug in mice of both sexes, each animal was injected with 20µl of formalin to create a paw oedema to screen chronic anti-inflammatory agents, as it closely resembles human arthritis. The ethanol *H. helix* plant extract showed 88.89% inhibition as compared to reference drug diclofenac, which showed 94.44% inhibition in formalin-induced paw oedema. The anti-inflammatory response of *H. helix* extract suggested the usefulness in the treatment of inflammation-associated diseases like arthritis.

3.1.2. Secondary pharmacodynamics

Antibacterial effect

In-vitro experiments

Ethanolic extract

An ethanolic extract of ivy leaf (no further information) completely inhibited the growth of *Staphylococcus aureus* and *Pseudomonas aeroginosa* and partially inhibited the growth of *E. coli* (Ieven *et al.*, 1979).

Water extract

Orhan *et al*. (2012) investigated twenty-seven aqueous extracts obtained from 21 plants used in the treatment of respiratory tract infections as folk remedies in Turkey for their relative total phenolic contents and antioxidant, antibacterial, antimycobacterial, and antifungal activities. Antibacterial effects were determined using the microdilution method. Antibacterial activity of all extracts was more pronounced against gram-positive bacteria than against gram-negative bacteria. The minimum inhibition concentration (MIC: µg/ml) for the ivy extract were:
Gram-positive microorganism: *S. pneumonia*: 64; *S. pyogenes*: 64; *S. aureus*: 32; *S. epidermidis*: 32
Gram-negative microorganism: *K. pneumoniae*: 128; *H. influenzae*: 16; *P. aeruginosa*: 128; *A. baumannii*: 64.

Other extracts

Uddin *et al*. (2011) tested a methanol extract of *H. helix* and its fractions on antimicrobial activity. The ethyl acetate and methanol extract were the most active extracts, showing activity against three selected Gram positive (*Staph. aureus, Staph. epidermidis, Bac. subtillis*) and one Gram negative bacterial stain (*E. coli*) and thus displayed highest inhibitory zone of (18:0 mm) at the tested concentration (22 mg/ml). No activity against *Klebsiella pneumonia* was shown.

Saponins

Cioaca *et al.* (1978) tested the antibacterial activity of saponins from *H. 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.

Antiviral effect

In-vitro experiments

Single substances

Rao *et al.* (1974) reported about the *in-vitro* anti-influenza activity of 11 naturally occurring triterpenoid saponins (plant sources - *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*.

The antiviral activity of hederasaponin B from *H. helix* against enterovirus 71 (EV71) subgenotypes C3 and C4a in vero cells has been indicated in a study of Song *et al*. (2014). EV71 is the predominant cause of hand, foot and mouth disease. The results showed that hederasaponin B and 30% ethanol extract of *H. helix* containing hederasaponin B had significant antiviral activity against EV71 subtypes C3 and C4a. Hederasaponin B also inhibited the viral VP2 protein expression, which could lead to inhibition of the viral capsid protein synthesis.

In-vivo experiments

Ethanolic extract

Hong *et al*. (2015) analyzed the therapeutic strategy of enhancing the antiviral efficacy of an existing neuraminidase inhibitor, oseltamivir, by coadministering with the leaf extract from *H. helix*. In the present study the potential antiviral properties against influenza A/PR/8 (PR8) virus in a mouse model with suboptimal oseltamivir that mimics a poor clinical response to antiviral drug treatment was analyzed. Suboptimal oseltamivir resulted in insufficient protection against PR8 infection. Oral administration of 30 mg/kg bw of ivy extract (DER unknown, 30% ethanol) with suboptimal oseltamivir increased the antiviral activity of oseltamivir. Ivy extract and its compounds, particularly hedrasaponin F, significantly reduced the cytopathic effect in PR8-infected A549 cells in the presence of oseltamivir. Compared with oseltamivir treatment alone, coadministration of the fraction of ivy extract that contained the highest proportion of hedrasaponin F with oseltamivir decreased pulmonary inflammation in PR8-infected mice. Inflammatory cytokines and chemokines, including tumor necrosis factor alpha and chemokine (C-C motif) ligand 2, were reduced by treatment with oseltamivir and the fraction of ivy extract. Analysis of inflammatory cell infiltration in the bronchial alveolar of PR8-infected mice revealed that CD11b(+-)Ly6G(+) and CD11b(+)Ly6C(int) cells were recruited after virus infection; coadministration of the ivy extract fraction with oseltamivir reduced infiltration of these inflammatory cells.

Antimycotic effect

In-vitro experiments

Other preparations

Wolters (1966) tested the antifungal activity of 30 saponin containing plant extracts (methanol 10%, no further information) 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*.

Single substances

Favel *et al.* (1992) evaluated the antifungal activity of triterpenoid saponins *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 minimal inhibitory concentrations (MICs) for the dermatophytes were within the range 5-100 µg/ml.

Favel *et al.* (1994) investigated the antifungal activity of triterpenoid saponins, with hederagenin or oleanolic acid as aglycon, *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) tested α-hederin isolated from *Hedera helix*, on *Candida albicans* ultrastructure. The concentrations used were 6.25, 12.5, and 25 µg/ml for an exposure time of 24 hours. 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 hours 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 MIC obtained *in-vitro* by Favel *et al.* (1994).

In-vivo experiments

Single substances

Timon-David *et al.* (1980) isolated four saponin derivatives, including hederasaponin C and α-hederin 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

Single substances

Balansard *et al.* (1980) reported 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) investigated 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 *H. helix* on the trematodes *Fasciola hepatica* and *Dicocoelium* spp. α-Hederin was the most efficient. *In-vivo* assays with sheep naturally infected with *Dicrocoelium* showed that all 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

Single substances

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-, ß-, 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) (Majester-Savornin *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* (Tedlaouti *et al.,* 1991).

The *in-vitro* antileishmanial activity of three saponins, α-hederin and β-hederin isolated from leaves of *H. helix*, 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 all 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 (Delmas *et al.*, 2000).

The *in-vitro* antileishmanial activity of three saponins, α- and β-hederin isolated from *H. 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 all 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 (Ridoux *et al.,* 2001).

In-vivo experiments

Ethanolic extract

Hooshyar *et al*. (2014) evaluated the effects of different concentrations (20% and 70%) of an alcoholic *H. helix* extract on the BALB/c murine model infected by active promastigotes of *Leishmania major*. The results showed that the main lesion size did not decrease significantly, nor did the small lesions completely disappear after treatment by the *H. helix* alcoholic extract. No support was provided on the antileishmanial effect of *H. helix* extract.

Hepatoprotective effect

In-vitro experiments

Single substances

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 (Hensel *et al.,* 2007; Goetz, 2007). 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 (CA)) and an aromatic amino acid residue (N-(E)-caffeic acid L-tryptophan amide (CT)) were used. CA and CT significantly stimulated mitochondrial activity as well as the proliferation rate of human liver cells (HepG2) at 10 µg/ml. When monitoring the influence of selected phase I and II metabolizing enzymes, neither of the compounds influenced 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 amides CT and CA. This stimulation was also detectable on the level of gene expression by an up-regulation of the transcription factor STAT6.

In-vivo experiments

Single substances

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 hours 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 demonstrated that treatment of mice with α-hederin decreased the levels and activities of several P450 enzymes. The suppression of P450 appeared 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 *and Liu* (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 hours 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

Other preparations

De Medeiros *et al.* (2000) utilised a chromogenic bioassay 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 *H. 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

Single substances

Mba Gachou *et al.* (1999) evaluated the protective effect of α-hederin extracted from *H. 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 hour. The catalase activity was also biochemically measured after treating cells with α-hederin at 1.5, 3, or 15 µg/ml during 1 hour. 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. The authors concluded, 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) investigated the antioxidant activities of α-hederin and hederasaponin-C from *Hedera helix*, and hederacolchisides-E and F from *Hedera colchica 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

Other preparations

Ibrar (2000) and Ibrar *et al.* (2003) examined 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 *H. helix* 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 hypoglycemic effect after 8 hours and sustained up to 12 hours to significant levels. Trace element analysis of the leaves showed that *H. helix* leaves contained 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

Single substances

Facino *et al.* (1990) evaluated the anti-hyaluronidase activity of the saponin complex isolated from *H. helix* leaves and of its constituents α-hederin, hederacoside B and hederacoside C and showed that these compounds possessed 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) demonstrated in *in-vitro* experiments 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

Single substances

Hensel *et al.* (2007) and Goetz (2007) examined that the aliphatic aspartic compound N-(E)-caffeic acid L-aspartic acid amide isolated from *H. helix* leaves showed strong antiadhesive properties on the adhesion of *Helicobacter pylori* to human stomach tissue (see also chapter “hepatoprotective effect”).

Antiexsudative effect

In-vivo experiments

Single substances

Vogel and Marek (1962) reported 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) reported a lung oedema was induced in mice by inhalation of a methallyl-air mixture at 2000 ppm of 1 hour duration. A dose of 200 mg/kg i.p. of an ivy extract (no further information)

reduced the lung oedema considerably. Other ivy extract (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.

Induced membrane permeabilization by saponins

In-vitro experiments

Single substances

Lorent *et al*. (2013) showed the effect of α-hederin, δ-hederin and hedaragenin on membrane permeabilization in a human monocytic cell line depleted or not for cholesterol. α-Hederin showed greater ability to induce pore formation, δ-hederin in inducing budding and hederagenin induced intravesicular budding but no pore formation. All these saponins interact with lipid membranes. A curvature-driven permeabilization mechanism dependent on the interaction between saponin and sterols and on the molecular shape of the saponin and its ability to induce local spontaneous curvature was proposed.

Antitumour effect

In-vitro experiments

Methanolic extract

Jamal *et al*. (2013) tested three Libyan plants namely *Ballota pseudodictamnus*, *Hedera helix*, *Thapsia garganica* were for anticancer activity. The plants were shed dried and subjected to Soxhlet extraction by methanol. Phytochemical screening indicated the presence of 2-deoxy sugars, flavonoids, saponins and tannins but absence of alkaloids in all three plants under investigation. Antiproliferative activity was performed breast adenocarcinoma cell line (MCF7). At the concentration of 100 µg/mL, *B. pseudodictamnus*, *T. garganica* and *H. helix* showed 90, 60 and 5% cell death, respectively as compared to the control.

In-vitro experiments

Single substances

Liu (2014) evaluated whether hederagenin could induce apoptosis of human colon cancer LoVo cells and explore the possible mechanism. MTT assay showed that hederagenin could significantly inhibit the viability of LoVo cells in a concentration-dependent and time-dependent manner by IC50 of 1.39 µM at 24 h and 1.17 µM at 48 h. The apoptosis ratio was significantly increased to 32.46% and 81.78% by the induction of hederagenin (1 and 2 µM) in Annexin V-FITC/PI assay. Hederagenin could also induce the nuclear changes characteristic of apoptosis by Hoechst 33342 nuclear staining under fluorescence microscopy. DCFH-DA fluorescence staining and flow cytometry showed that hederagenin could increase significantly ROS generation in LoVo cells. Real-time PCR showed that hederagenin induced the up-regulation of Bax and down-regulation of Bcl-2, Bcl-xL and Survivin. Western blotting analysis showed that hederagenin decreased the expressions of apoptosis-associated proteins Bcl-2, procaspase-9, procaspase-3, and polyADP-ribosepolymerase (PARP) were increased, while the expressions of Bax, caspase-3, caspase-9 were increased. However, there was no significant change on caspase-8. These results indicated that the disruption of mitochondrial membrane potential might contribute to the apoptosis of hederagenin in LoVo cells.

In-vivo experiments

Ethanolic extract

Rai (2011) reported, the alcoholic Hedera extract (no DER information) showed cytotoxic effect against Ehrlich ascitic cells. When 25 µl of the extract was injected in tumour bearing mice, tumour disappeared in 83.3% animals. Further treatment by alcoholic Hedera extract on the 16.7% cases of tumour bearing animals where the tumour did not disappear, the plant extract curbed the growth of the tumours and increased the survivality of the animals compared to control animals. The mice in contro animals all died within 5 weeks whereas mice which had been treated survived till 13 weeks.

Histopathology in Chronic Asthma

In-vivo experiments

Water extract

Hocaoglu *et al*. (2012) aimed to determine the effect of oral administration of *Hedera helix* dryied water extract on lung histopathology in a murine model of chronic asthma. BALB/c mice were divided into four groups; I (Placebo), II (*H. helix*), III (Dexamethasone) and IV (Control). All mice except controls were sensitized and challenged with ovalbumin. Then, mice in group I received saline, group II 100 mg/kg *H.helix* and group III 1 mg/kg dexamethasone via orogastic gavage once daily for one week. Airway histopathology was evaluated by using light and electron microscopy in all groups. Goblet cell numbers and thicknesses of basement membrane were found significantly lower in group II, but there was no statistically significant difference in terms of number of mast cells, thicknesses of epithelium and subepithelial smooth muscle layers between group I and II. When *H. helix* and dexamethasone groups were compared with each other, thickness of epithelium, subepithelial muscle layers, number of mast cells and goblet cells of group III were significantly ameliorated when compared with the group II. Dexamethasone ameliorated all histopathologic parameters except thickness of basement membrane better than *H. helix*.

Cytotoxic activity

In-vitro experiments

An ethanolic ivy extract (70% ethanol, DER 2:1) showed cytotoxic activity on Ehrlich tumour cells *in-vitro*. After 4 hours incubation almost all cells were non-viable (El-Marzabani *et al.*, 1979).

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 (Quetin-Leclercq *et al.,* 1992).

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 hours 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 (Danloy *et al.,* 1994).

α-Hederin at sub-cytotoxic concentrations of 5 or 10 µM 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 (Bun *et al.,* 2008).

In-vivo experiments

The methanolic leaf extract of *H. helix* (500 g powdered leaves in 1250 ml methanol, vacuum evaporation to semi solid extract) was investigated for cytotoxic potential using brine shrimp bioassay (Ibrar *et al.* 2001). Results showed that the methanolic leaf extract possessed cytotoxicity (LC_{50}=802.73 µg). The saponin fraction had 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 the methanolic extract of *H. 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 *H. helix* exerted cytotoxic activity, both *in-vitro* and *in-vivo*, but the saponin isolated from this plant had no cytotoxic effect on cancer cells.

The inoculation of cellular B16F10 line melanoma suspension was made subcutaneous on syngeneic C57B1/6 line mice. Bioactive compounds isolated from *Salvia officinalis* and *H. helix* were applied s.c. beginning with the second and the third passage, 24 hours 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 (Olariu *et al.,* 2007).

There was a significant increase in the lifespan of mice treated with ethanolic ivy extract (70% ethanol, DER 2:1) 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) (El-Marzabani *et al.*, 1979).

3.1.3. Safety pharmacology

No data available.

3.1.4. Pharmacodynamic interactions

No data available

3.1.5. Conclusions

The mechanism of action is not known.

A spasmolytic/bronchodilatating/expectorant activity of the extract and/or isolated substances such as α-hederin has been documented in several *in-vitro* and in *in-vivo* studies. 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 *et al.* (2008). The pharmacokinetic study by Stauss-Grabo (2008) showed too low concentrations in the lung compared with those used in *in-vitro* experiments and indicated no clinical relevance of this mechanism. Also anti-inflammatory effects could be shown in different *in-vivo* models. The clinical relevance of this mechanism is not clear.

A lot of secondary phamacodynamic studies (e.g. antibacterial, antiviral, antimycotic, molluscicidal, hepatoprotective, cytotoxic, hypoglycemic, protozoidal, antithrombinic, antioxidant and anti-adhesive properties) were performed *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.

There are no results of kinetic studies or specific receptor binding studies. Therefore the *in-vivo* data cannot be assessed on their importance to the human/clinical situation. Furthermore there are no human-phamacological studies concerning the clinical relevance of these results.

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 *H. helix* in rats. They concluded that small quantities of saponin were absorbed in the rats' intestinal tract.

One hour after a single p.o. application of 1 g/kg of an ivy dry extract (DER 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 (Schmidt, 2003).

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 hours 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.

The pharmacokinetics of α-hederin given as oral single doses were investigated in a pilot study on male Wistar rats (Stauss-Grabo, 2008). 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 hours. Three hundred thirty-five 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 hours (t_{max}). At 24 hours, the highest concentration of about 5% of the applied total amount of radioactivity was detectable in the blood. The total systemic uptake at 24 hours 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 hours.

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 hours 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 could be calculated (0.02 or 0.025:1.398):

Table 9: Radioactivity in the lung tissue at 24 hours (Stauss-Grabo, 2008)

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 hours. At 24 hours, the highest radioactivity in blood is approximately 0.32 µCi/ml (in the α-hederin +ivy extract group). The following α-hederin concentrations could be calculated (0.32:1.398):

Table 10: Radioactivity in blood at 24 hours (Stauss-Grabo, 2008)

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 hours. The examined substance was not unambiguously identified. The quantitative measurement of α-hederin was not 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.

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 faeces and thus was described for the very first time. The one-compartment 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 urine and 50% per faeces. At 24 hours, 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 (Jeong and Park, 1998).

Pharmacokinetic interactions with other medicinal products

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 (Liu *et al.,* 1995).

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 (Jeong and Park, 1998).

Assessor's comment:
The in-vivo applied s.c. dosage of 10 µM α-hederin/kg (corresponds to 7.5 mg α-hederin/kg) was approximately 25-fold higher than the orally applied therapeutic 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 the context of possible interactions because of influence on P450 enzymes.

Overall conclusion on pharmacokinetics

In two *in-vivo* interaction studies (Liu *et al.*, 1995; Jeong and Park, 1998), s.c. administered α-hederin influenced P450 enzymes. According to current resorption studies, by oral administration α-hederin is resorbed maximally 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 single dosage for adults of maximum 65 mg dry extract (as recommended in the monograph) contains approximately 10% hederacoside C (to be converted into α-hederin) and α-hederin, respectively (Trute *et al*., 1997), corresponding to maximum 6.5 mg α-hederin in the single dose. In a patient of 50 kg weight, the applied dosage is approximately 0.13 mg α-hederin/kg. Taking into consideration the determined content from Gaillard *et al.* (2003) the applied dosage would only be approximately ¼ of the calculated intake (0.033 mg α-hederin/kg). The *in-vivo* applied s.c. dosage of 7.5 mg α-hederin/kg (human equivalence dose = 0.61 mg/kg) is therefore approximately 5-18-fold higher as the therapeutically orally applied dosage. The different administration has to be considered, taking into account different absorption rates. 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 P450 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 (1993). Mills and Bone (2000) noted that after oral intake, the major part of saponins was not absorbed or was only slowly and partially absorbed as the aglycones.

While Schmidt (2003) could detect in an *in-vivo* study in rats only 3-7% of the applied amount of α-hederin in the blood 3 hours after p.o. application of an ivy dry extract, Stauss-Grabo (2008) documented a possible systemic resorption of α-hederin estimated to be at least 30% of the applied total amount in 24 hours. However, the by Strauss-Grabo (2008) examined substance was not unambiguously identified. The quantitative measurement of α-hederin was not 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 study of Schmidt (2003) 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 does not allow conclusions about the systemic absorption and the *concentration* in the liver. Therefore no final conclusion about

the absorption rates of α-hederin can be drawn. These results have to be considered in the assessment of the hypothetic mode of action and in the assessment of toxicology and use in pregnancy. 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

Oral administration of a dry extract (ethanol 66% (V/V), no DER information) of ivy leaf (3.0-4.1 g/kg body weight to rats caused no death within 72 hours. Only diarrhoea was observed (Lanza *et al.,* 1980). 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 hours (90% in 24 hours). 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 a saponin from the leaf of *H. helix* in rats. Timon-David *et al.* (1980) described the 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, with >4 g/kg body weight.

Intravenous administration

Vogel and Marek (1962) found LD_{50}-values of 13 mg/kg i.v. for a saponin from the leaf of *H. helix* in rats. According to Wulff (1968) LD_{50}-values of 4.5 mg/kg i.v. were reported for hederin and hederasaponin C >50 mg/kg i.v. in rats after 7 days observation period.

Intraperitoneal administration

Timon-David *et al.* (1980) described 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

No original publication on repeat dose toxicity is available.

According an internal report of Bucher (1969) for K. Engelhard Fabrik, cited in ESCOP (2003) a daily oral administration of an ivy leaf dry extract (no more information) 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

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 benzopyrene and SU at levels between 80 and 200 µg/plate in the Ames test (Elias *et al.*, 1990).

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 any of the three antimutagenic agents (Amara-Mokrane *et al.* 1996).

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 pre-treatment, simultaneous treatment and post-treatment to determine the mechanism of action. According to this protocol, α-hederin induced a significant diminution of the rate of micronuclei. The authors concluded the results demonstrated 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, undescendend testicles, umbilical hernia, hydronephrosis/hydroureter, 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 embryotoxic development. α-Hederin did not appear to be directly embryotoxic. 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 sustained 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*. 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 dehydrofalcarinol. 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.

Leonti *et al*. (2010) showed that falcarinol exhibits binding affinity to both human CO receptors but selectively alkylates the anandamide binding site in the CB1 receptor (K_i = 594 nM), acting as covalent inverse agonist in CB1 receptor-transfected CHO cells. In human HaCaT keratinocytes falcarinol increased the expression of the pro-allergic chemokines IL-8 and CCL2/MCP-1 in a CB1 receptor-dependent manner. Moreover, falcarinol inhibited the effects of anandamide on TNF-alpha stimulated keratinocytes. *In-vivo*, falcarinol strongly aggravated histamine-induced oedema reactions in skin prick tests. The data suggest that falcarinol-associated dermatitis is due to antagonism of the CB1 receptor in keratinocytes, leading to increased chemokine expression and aggravation of histamine action.

3.3.7. Other special studies

Haemolytic activity

In-vivo experiments

Vogel and Marek (1962) and 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. They 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 *et al.* (1966) reported that 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) reported the haemolytic index of *Hedera* saponin C and B with 1:1000 and of α-hederin with 1:150000.

According to 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.

3.3.8. Conclusions

Single/repeat dose toxicity, genotoxicity, carcinogenicity, local tolerance or other particular studies according to the state of the art and current guidelines are not available for ivy leaf. 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.

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), while 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 such toxic effect (Kramer, 1968; an internal report, cited in 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 monodesmoside α-hederin were reported from experiments in rats following the single subcutaneous injection of 300 µmol/kg body weight (human equivalence dose = 48.4 µmol/kg) as well as repeated subcutaneous administration of 20 and 30 µmol/kg body weight, which were attributed to an α-hederin induced drop in the maternal serum zinc concentration (10 µmol α-hederin/kg corresponds approximately to 7.5 mg α-hederin/kg).

Subcutaneous repeated daily dose of α-hederin *in-vivo*	20 and 30 µmol/kg body weight (converted into human equivalent dose: 2.4 and 3.6 mg/kg body weight)
Human daily oral dose of α-hederin Based on: - a daily dosage of 315 mg dry extract + - a content of hederacoside C and α-hederin in the extract of 10% (Trute *et al.*, 1997) +	0.63 mg/kg body weight

- a complete transformation of hederacoside C into α-hederin + - the administration of the whole daily dosage at once + - a complete and prompt absorption of the daily dose of α-hederin + - a body weight of 50 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 (Müller-Jakic, 1998) the *in-vivo* studies of 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 hours, 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 the 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* concentration with a clinical manifested toxic effect is only approximately 4-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, whether 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 *H. helix* only, are of no relevance for the oral route of administration of preparations containing the dried ivy leaf extract.

3.4. Overall conclusions on non-clinical data

A spasmolytic/bronchodilatating/expectorant activity of the extract and/or isolated substances such as α-hederin has been documented in several *in-vitro* and in *in-vivo* studies. 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. Also anti-inflammatory effects could be shown in different *in-vivo* models with orally administered ethanolic ivy leaf extracts.

In summary, results from relevant experimental studies on ivy leaf to support the proposed indications are very limited. The reported pharmacological effects are not considered contradictory to the clinical uses.

Specific data on pharmacokinetics and interactions are not available.

Non-clinical information on the safety of ivy leaf preparation is scarce. 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.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed 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 monodesmoside α-hederin were reported from experiments in rats following the single s.c. injection as well as repeated s.c. administration, which were attributed to an α-hederin induced drop in the maternal serum zinc concentration. The fact, that α-hederin did not have a direct embryotoxic effect, is considered to support the safety of α-hederin in the cited publication. As there is no information on reproductive and developmental toxicity and in the view the possible indirect embryotoxic effect, the use during pregnancy and lactation should be avoided. Effects in non-clinical studies were observed only at s.c. injections/exposures considered in excess of the maximum human exposure indicating little relevance to clinical oral use.

The results regarding local cutaneous sensitisation with accompanying contact dermatitis, which were reported for fresh parts of *H. helix* only, are not relevant for the oral 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

No data available.

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

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 (DER 5-7.5:1; extraction solvent ethanol 30%) with a content of 6.5% Hederacoside 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 µg/ml (Schmidt, 2003). 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 within 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.

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

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 laryngitis [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 bronchitis (with bronchospasm, fibrinous, membranous, purulent, septic, tracheitis), acute tracheobronchitis (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 Mucopurulent chronic bronchitis

- J41.8 Mixed simple and mucopurulent chronic bronchitis

– J42 Unspecified chronic bronchitis (chronic bronchitis NOS, tracheitis, tracheobronchitis) excludes: chronic asthmatic bronchitis, chronic bronchitis; bronchitis: simple and mucopurulent; bronchitis with airways obstruction; 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, status 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), Guideline of the German respiratory Society for Diagnosis and Treatment of Adult Suffering from Acute or Chronic Cough (Kardos *et al*., 2010), COPD-Clinical Practice Guideline MedStar Health (2016).

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 Coxackievirus). 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-sympathomimetics 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 COPD guideline (2016) the treatment is based on bronchodilators as anticholinergics, ß-sympathomimetics and theophylline. Inhaled corticosteroids) may also be used. Mucolytics should be used critically with respect to the subjective therapeutic success. They are used in high risk patient category (D) with more symptoms and sporometric classification GOLD 3-4.

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, glucocorticoids, 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 Guideline of the German respiratory Society for Diagnosis and Treatment of Adult Suffering from Acute or Chronic Cough (Kardos *et al*. ,2010) cough as a symptom is categorized as either acute (lasting up to 8 weeks) or chronic (lasting more than 8 weeks) and attributed to distinct diseases.

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, pneumonia, viral influenza, acute exacerbation of COPD, bronchial asthma. Diseases in other organ systems (heart system, gastrointestinal tract) or exogenous 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 to 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, post-nasal drip syndrome, bronchial hyperreactivity, COPD, bronchial asthma and gastrooesophageal reflux.

4.2.1. Dose response studies

No data available

4.2.2. Clinical studies (case studies and clinical trials)

Controlled studies

Schaefer *et al*. (2016) conducted a randomized, placebo-controlled, double-blind trial to assess the efficacy and safety of ivy leaves extract in acute cough (dry extract according table 1: Overview of data obtained from marketed medicinal products).
A total of 181 adult patients with acute cough and/or acute bronchitis were treated with either ivy leaves cough liquid (89 patients) containing EA 575® (5 ml contain 35 mg ivy leaves dry extract (DER 5-7.5:1), extraction solvent ethanol 30% (m/m)) or with placebo (92 patients) three times a day for one week. 178 patients completed the clinical trial.
Subjects aged 18 to 75 years of both genders suffering from acute cough with symptoms lasting 2 to 3 days prior to treatment were included in the clinical trial. Subjects could be of any ethnicity and needed to be able to understand and to comply with trial instructions. Health needed to be satisfactory except for the cough as determined by the investigator based on medical history and physical examination. Other inclusion criteria were a cough severity score of at least 50 mm on a 100 mm VAS, an acute BSS of at least 10 points and a VCD score of at least 2 points. Exclusion criteria were allergic bronchial asthma, bronchial hyperreactivity, chronic bronchitis, other chronic or inherited lung disease, urticaria, severe allergic diathesis and known hypersensitivity against any excipient of the applied drugs. Patients with any gastrointestinal complaints within 7 days before inclusion, known chronic and significant diseases, pregnancy, lactation and treatment with drugs which are known to cause cough were excluded. During the clinical trial any medications or treatments that may influence acute bronchitis or mucociliary clearance were prohibited.

The primary efficacy outcome was cough severity (CS) assessed by Visual Analogue Scale (VAS) over the whole treatment period $AUC_{(0\text{-}168\ h)}$ over 7 days (visit V1, V2, V3, V4, and V5). There was a significant difference between the two study groups with regard to the primary variable: the mean $AUC_{(0\text{-}168\ h)}$ was 7902.6 mm in the verum group and 9637.3 mm in the placebo group. The secondary endpoints, the CS assessed by VAS over the whole observation period (V1 – V6) improved from 72.8 mm to 22.4 mm in the active treatment group and from 72.3 mm to 40.3 mm in the placebo group. The Bronchitis Severity Score (BSS) changed from 11.2 to 2.8 score points in the active treatment and from 11.3 to 5.5 in the placebo group. The Verbal Category Descriptive (VCD) score had changed from 3.3 to 1.4 score points in the active group and from 3.4 to 2.1 in the placebo group. The evaluation of the VAS, BSS and VCD score revealed that subjects treated with ivy leaves cough liquid showed statistically significant and clinically relevant reductions in CS, severity of symptoms associated with cough and bronchitis compared to the placebo group. Furthermore, a remarkable early onset of efficacy was observed as significant reductions of cough severity were detected within 48 hours after

the first drug intake. At visit 5 and 7 days after the end of treatment (V6) the treatment efficacy was assessed globally via GEA by the subjects and investigators. A significant treatment advantage was detected in comparison to placebo. At V5 84.1% of the patients in the treatment group rated their conditions as “good” or “very good” versus 42.4% in the placebo group. At V6 the rating was 85.2 in the treatment group vs. 37.0% in the placebo group.

Table 11: Cough severity assessments on BSS – Total Score (FAS) (Schaefer *et al.*, 2016)

			Ivy leaves cough liquid (n=89)	Placebo (n= 92)	p
BSS (total score)	V	M	11.2	11.3	-
		SD	1.5	1.3	
	V	M	9.0	10.2	0.0003
		SD	2.5	2.3	
	V	M	6.9	9.0	< 0.0001
		SD	2.9	3.0	
	V	M	5.4	7.7	< 0.0001
		SD	3.2	3.4	
	V	M	2.8	5.6	< 0.0001
		SD	3.0	3.4	

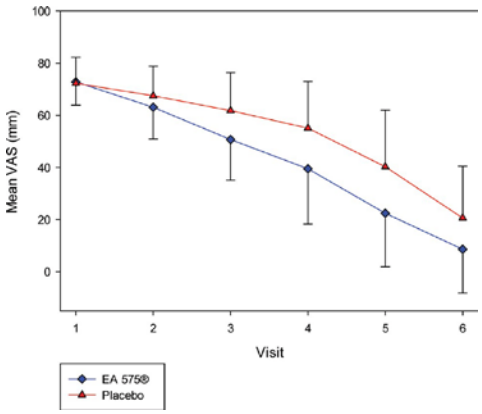

Fig. 1: CS assessed by VAS (Mean + SD) over time (FAS) (Schaefer *et al.*, 2016)

Adverse events occurred in 21 of 181 (11.6%) subjects (active treatment: n=9, placebo: n=12). Of these, 18 subjects had one single adverse event, one subject in the active treatment group and one subject in the placebo group had two adverse events each, another subject in the placebo group had four adverse events. All reported adverse events were relatively well-balanced between the treatment groups and are closely connected to the underlying disease as cough (“worsening of cough”), middle ear effusion, and sinusitis. All adverse events in this clinical trial were non-serious, mild or of moderate severity and not drug-related.

Assessor’s comment:
The placebo-controlled clinical study by Schaefer et al. (2016) shows efficacy and safety of ivy leaves extract in patients with acute cough. The evaluation of the primary endpoint cough severity assessed by Visual Analogue Scale (VAS) over the whole treatment period $AUC_{(0\text{-}168\ h)}$, revealed that subjects treated with ivy leaves cough liquid showed statistically significant and clinically relevant reductions. Severity of symptoms associated with cough and bronchitis assessed as BSS and VCD showed also better improvement in the verum group compared to the placebo group.

A randomised 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 (Meyer-Wegener *et al.*,

1993). They were treated either 3-5 times daily for 4 weeks with 20 drops of ivy leaves extract ((DER 5-7.5-1), ethanol 30% (m/m); 2 g of dry extract per 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 herbal substance. Excluded were patients with asthma bronchial, chronic bacterial bronchitis and patients 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 12: Vital capacity (l) (Meyer-Wegener *et al.*, 1993)

	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 occurred and 3 of them were considered to have a causal relation to ambroxol. One drop out case occurred 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 patients with simple chronic bronchitis (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 cannot be deduced by the study results. The benefit is shown only for short term use of maximum 4 weeks.

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 mucoviscidosis) were treated either with ivy syrup (ivy dry extract (DER 5-7.5:1), ethanol 30% (m/m)) (n=53) or with ambroxol (n=19) (Maidannik *et al.,* 2003). Ivy syrup 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 body plethysmographic 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 and auscultatory picture of patient's lung. In addition, the blood analyses, including the calculation of leucocyte count, flora identification, virological and bacteriological test were performed.
The authors resumed, after 7 days of ivy 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 ivy syrup (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. Normalisation of leukocyte 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 ivy 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 ivy extract. 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 multifaceted 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.

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 ivy syrup (ivy dry extract (DER 5-7.5:1), extraction solvent ethanol 30% (m/m)) (n=25) or with acetylcysteine (n=25) (Bolbot *et al.*, 2004). Patients with hypersensitive reactions or taking other expectorants were excluded. Ivy syrup 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 body plethysmographic 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 verum 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 ivy group and statistically different from parameters in the ACC group ($p<0.05$) and from baseline ($p<0.05$). In 10 days, 15% of the ivy 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 ivy group were in 96% "very good" and "good" comparable with 79.2% for ACC. The tolerability of ivy syrup was rated by doctors in 40% as "very good" and 60% as "good".

Table 13: External respiration parameters during the treatment (in % from normal) (Bolbot *et al.*, 2004)

Parameter	Ivy 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 ivy 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), referring 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 body plethysmographic parameters

Assessor's comment:
The clinical controlled studies by Gulyas et al. (1997), Mansfeld et al. (1997, 1998) and Gulyas (1999) analysed the influence on spirometric and body plethysmographic 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.

Table 14: Spirometric parameters: average parameters of lung function FEV_1 (l), forced vital capacity FVC (l), vital capacity VC (l) and PEV (l/s) (Gulyas et al., 1997)

Ethanol-free juice					Ethanol-containing drops			
	1st day	5th day	10th day of treatment		1st day	5th day	10th day of treatment	
	before medication	3 h after	before medication	3 h after	before medication	3 h after	before medication	3 h after
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 15: Body plethysmographic parameters (ITGW: intrathoracal gas volume; RAW: Airway resistance; SRAW: Specific airway resistance) (Gulyas *et al.* , 1997)

	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 body plethysmographic parameters were observed after both treatments. The author concludes that 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 hours 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 hours 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.

In a randomised, 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 (DER 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-days wash-out interval, 2 suppositories daily (=160 mg dry extract daily, corresponding to 1000 mg herbal substance) (Mansfeld *et al.,* 1997). 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 hours 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.

In a randomised, 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 (DER 5-7.5:1), ethanol 30% (m/m) or placebo, interrupted by a wash-out phase from 3-5 days (Mansfeld *et al.,* 1998). 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 body plethysmographic 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 16: Body plethysmographic parameters (Mansfeld *et al.,* 1998)

	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 17: Spirometric parameters (Mansfeld *et al.,* 1998)

	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 FEV_1 (l)	Control FEV_1 (l)	10 min after inhalation of 2 x 100 µg fenoterol FEV_1 (l)
1st day before medication	1.44	1.75	1.44	1.75
3rd day 3 hours after medication	1.80	1.83	1.67	1.79

Assessor's comment:

A statistically 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 reversibility of bronchial obstruction was conducted with inhalative fenoterol.
The author's conclusion that the bronchodilatory effect of the ivy preparation was comparable to fenoterol is not convincing. On the first day, ivy had 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 comparable 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, 3 hours 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.

In a controlled pilot study 20 children (9-15 years), with a chronic obstructive pulmonary disease, were treated either with ivy juice (ivy dry extract (DER 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) (Gulyas, 1999). The duration of the treatment was between 14 and 20 days. Spirometric and body plethysmographic 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 bronchial obstruction 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.

Dose comparative clinical studies

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-days 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 (DER 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 (DER 5-7.5:1), ethanol 30% (m/m) or 252 mg of herbal substance daily) (Gulyas *et al.*; 1997).
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 hours after administration). Body plethysmography was also used before the start of the treatment and on the 10th day, 3 hours 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 hours 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 body plethysmographic 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.

In a randomised 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 ivy juice 1 (200 ml juice contain 660-1000 mg ivy dry extract (DER 3-6:1), extraction solvent ethanol 60% (m/m)) or ivy juice 2 (100 ml contain 700 mg ivy dry extract (DER 5-7.5:1), extraction solvent ethanol 30% (m/m)) (Unkauf and Friederich, 2000). The daily dose of ivy juice 1 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 ivy juice 1 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. Ivy juice 2 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 5 days (p=0.0022) and after 10 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.

In a double-blind, randomised study patients with acute bronchitis were randomised to one of two treatment groups: Ivy leaves extract test treatment or active control ivy drops (dry extract of ivy leaves (DER 5–7.5:1) extraction solvent ethanol 30% (m/m)) (Cwientzek *et al.*, 2011). The test treatment was ivy drops (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 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 7 days (±1). The tested dosage corresponds the recommended dosages of the authorised product: 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 (test group: n=295; reference n=295; test group: 2-4 years: n=33; 5-10 years n=67; >10 years n=195; reference group: 2-4 years: n=33; 5-10 years n=68; > 10 years n=194). ITT: test group: n=293 reference group: n=295; PP: test group: n=260 reference group®: 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 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 test 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 reference group 79.7% (235 of 295 patients).
In the test 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 reference group 13.2% (39 of 295 patients).

Safety evaluation:
Sixteen patients experienced 24 adverse events, eight patients (11 events) in the test group and eight patients (13 events) in the comparator group. In each group 2.7% of patients from the safety dataset had one or two adverse events: 6 patients of the test group (3 diarrhoea, 4 nausea, 1 pyrosis) and 7 patients in the reference 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. Two patients of the Hedelix® group had infections (1 cystitis, 1 urethritis, 1 varicella). There was a not assessable relationship to the study medication. One patient in the reference group developed bronchial asthma and not recovered at the end of the study.
Fifteen of the 16 patients experiencing adverse events in this study were over 10 years old, only one was between four and 10 years old. Compared to the age distribution in the study population, patients younger than 10 years were under-represented 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 test group and with 3.96±0.95 for the reference 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 test group and with 4.19±0.79 for the reference 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. 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 were 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. 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)" was also included in the chapter "well-established use" of the HMPC-monograph.

Conclusion

Schaefer *et al.* (2016) supported efficacy and safety of ivy leaves extract in acute cough and acute bronchitis in a randomized, placebo-controlled, double-blind trial in 178 patients. The evaluation of the VAS, BSS and VCD score revealed that subjects treated with ivy leaves cough liquid showed statistically significant and clinically relevant reductions in CS, severity of symptoms associated with cough and bronchitis compared to the placebo group.
The results of the study by Gulyas *et al*. (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 direct bronchodilatory effect of the ivy preparation on the first day was proximally 1/3 of fenoterol and comparable to placebo and is considered to be too low for clinical relevance in severe obstructive diseases.

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

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, codeine, Romilar, ipedrine, 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 were 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 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.

Zeil *et al*. (2014) analysed in a double blind, placebo-controlled, randomized cross-over study, 30 children (median age 9.07 years (min-max: 6-11)) suffering from partial or uncontrolled mild persistent allergic asthma despite long-term treatment with 400 µg budesonide equivalent. After a four week run-in period, patients either received ivy leaves dry extract (DER 5-7.5:1); ethanol 30% (m/m) in a cough liquid, in a daily dose of 2 x 5 ml for four weeks in addition to their inhaled corticosteroid therapy or placebo, followed by a wash-out phase before switching to the other treatment arm. Lung function, FeNO, exhaled breath condensate pH and life quality was analysed after each treatment period. There was a significant improvement of MEF(75-25), MEF25 and VC after treatment with ivy leaves dry extract (MEF(75-25) change in the mean 0.115 l/s, p=0.044; MEF25 change in the mean 0.086 l/s, p=0.041; VC change in the mean 0.052 l, p=0.044), but not after treatment with placebo. For the primary outcome parameters (relative change of FEV1 and MEF(75-25) before bronchodilation) no treatment effect could be detected in the cross-over analysis (FEV1 p=0.6763 and MEF(75-25) p=0.6953).

Assessor's comment:
The study cannot proof efficacy in asthmatic patients. An add-on therapy to standard treatment it cannot be recommended for asthmatic patients.

Table 18: Placebo controlled clinical studies on humans, in the therapeutic area of diseases of the respiratory tract

Type	Study	Test Product(s)	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Clinical Relevance
Adults							
Schaefer *et al*., 2016	Double blind, placebo-controlled, randomized Visit1-visit5: 7 days; Follow up visit V6: 7 day later	Ivy dry extract (DER 5-7.5:1); ethanol 30% (m/m) in a cough liquid or placebo	Randomized: 181; verum: n=89 placebo: n=92 completed: verum: n=88 placebo: n=90	Patients suffering from acute productive cough (2.35±0.49 days from onset)	Primary endpoint: mean $AUC_{(0\text{-}168\ h)}$: verum: 7902.6 mm placebo: 9637.3 secondary endpoints: 1. CS assessed by VAS over the whole observation period (V1 – V6): verum: improvement from 72.8 mm to 22.4 placebo: improvement from 72.3 mm to 40.3 2. Bronchitis Severity Score (BSS): verum: from 11.2 to 2.8 score points placebo: from 11.3 to 5.5 score points 3. Verbal Category Descriptive (VCD) score: verum: from 3.3 to 1.4 score points placebo: from 3.4 to 2.1 score points	ANCOVA model, Mann-Whitney test, Cochran-Mantel-Haenszel test	Can be considered as clinical relevant in context of reducing symptoms in acute bronchitis

Type	Study	Test Product(s)	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Clinical Relevance
Children							
Zeil *et al.*, 2014	Double blind, placebo-controlled, randomized cross-over study	Ivy leaves dry extract (DER 5-7.5:1) ethanol 30% (m/m) daily dose: 2 x5 ml corresponding to 70 mg extract four weeks in addition to their inhaled corticosteroid therapy or placebo,	30 children 6-11 years	Partial or uncontrolled mild persistent allergic asthma	Primary outcome parameters: (relative change of FEV1 and MEF(75-25) before bronchodilation: no treatment effect in the cross-over analysis (FEV1 p=0.6763 and MEF(75-25) p=0.6953) significant improvement of MEF(75-25), MEF25 and VC after treatment with ivy leaves dry extract: MEF(75-25): change in the mean 0.115 l/s, p=0.044 MEF25: change in the mean 0.086 l/s, p=0.041 VC: change in the mean 0.052 l, p=0.044)	t-test, U-test, x2-test	The study cannot proof efficacy in asthmatic patients
Mansfeld *et al.,* 1998	Crossover rando-mised, placebo-controlled double-blind	2 x 25 drops ivy dry extract (DER 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	Reduction of airway resistance by 0.14 kPa/l/sec (23.6%) under verum; significant difference between verum and placebo (p=0.036)	Wilcoxon-test, descriptive and exploratory analysis	Not clinical relevant in bronchial asthma; relevant information for clinical

Type	Study	Test Product(s)	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Clinical Relevance
		3 days verum/ placebo, 3-5 days wash-out phase, 3 days verum/ placebo					pharmaco-logic aspects
Rath, 1968	Placebo controlled, double-blind	Verum: ivy drops + 0.5 mg of anise and thyme oil in 1 g solution: infant: 8 x 15 drops/day, children: 8 x 30 drops/day, school children: 8 x 45 drops/day corresponding to approximately 0.46-1.38 g herbal substance/day oral; 3 days	n=100 verum: n=71 placebo: n=29 (47 as a monotherapy, 53 as an addition to antibiotics)	Acute bronchitis (of feverish infections) (n=74), cough (of malign diseases) (n=9), spastic bronchitis (n=7), chronic bronchitis, bronchopneumonia 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 information	Due to method-logical reasons only supportive for efficacy in acute bronchitis

Table 19: Reference controlled clinical studies on humans, in the therapeutic area of diseases of the respiratory tract

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Clinical relevance
Adults							
Meyer-Wegener *et al*., 1993	Crossover randomised, double-blind	Verum: 3-5 x 20 drops ivy dry extract (DER 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; 4 weeks	n=97 verum: n=49 ambroxol: n=48 40 female, 57 male 25-70 years	Simple or obstructive chronic bronchitis	No significant difference for spirometric, bodyplethysmographic 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	t-test, Chi^2-test, Mann-Whitney-U-test, Wilcoxon-test, descriptive analyses	Clinical relevant
Adults and children							
Cwientzek *et al*., 2011	Double-blind, reference controlled	Preparation 1: 1 ml solution contains 0.04 g soft extract of ivy leaves (DER 2.2-2.9:1), 3 times daily daily dosage: adults and children >10 years: corresponding to 0.3 g herbal substance; children 4 to 10 years: corresponding to 0.2 g herbal substance; children 2 to 4 years:	590 patients recruited, randomised, and supplied preparation 1: n=295 2-4 years: n=33 5-10 years n=67 >10 years n=195 preparation 2: n=295 2-4 years:	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: difference between preparation 1 and 2 = 0.046 (point estimate; 95% CI: -0.2303 to 0.3224); lower end of the 95% CI was above the non-inferiority margin (-0.6336) PP: improvement in the PP dataset only marginally higher (by approximately 0.1 score point) BSS decreased gradually and to a similar extent in both	Treatment difference: ANCOVA model, Secondary endpoints: t-test, Mann-Whitney test, Fishers exact test	Clinical relevant showing reduction of symptoms in acute bronchitis

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Clinical relevance
		0.15 g herbal substance preparation 2: 1 ml solution contains 0.02 g dry extract of ivy leaves (5-7.5:1) ethanol 30% (m/m); 3 times daily daily dosage: adults and children >10 years: 24 drops; children 4 to 10 years: 16 drops; children 2 to 4 years: 12 drops calculated drug intake of the recommended daily dose was comparable in both medicinal products	n=33 5-10 years n=68 >10 years n=194) ITT: preparation 1: n=293 preparation 2: n=295 mean age (±SD): 23±20 years, (range: 2-86 years) median age: 17 years		treatments (starting from 6.2–6.3±1.2 to 1.4–1.6 (mean) at end of study		
Children							
Brattström *et al.*, 2006	Open, reference controlled study 10 days	Preparation 1: ivy leaves dry extract (DER 3-6:1); extraction solvent ethanol 60% (m/m) preparation 2:	n=52	Acute bronchitis	Therapeutically equivalent in VAS intention to treat on day 10 improvement of symptoms of bronchitis	Non-inferiority test (no further information)	As open, reference controlled study it can be considered as supportive

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Clinical relevance
		ivy leaves dry extract (DER 5-7.5:1), extraction solvent ethanol 30% (m/m) same dose children <4 years: 2 x 5 ml children 4-10 years: 2 x 7.5 ml children > 10 years: 2 x 10 ml					for clinical relevance
Bolbot, 2004	Open, reference controlled study	Ivy dry extract (DER 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 to 6 years: 3 x 100-200 mg/day 7 to 10 years: 3 x	n=50	Acute bronchitis	Spirometric and bodyplethys-mographic parameters,improvement of symptoms efficacy ratings of ivy “very good” and “good” comparable with 79.2% for ACC	No information; descriptive and exploratory analysis, treatment difference corresponding to a significance level of $p<0.05$	Can be considered as supportive for clinical relevance

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Clinical relevance
		300-400 mg/day 7-10 days					
Maidannik, 2003	Open, reference controlled study	Ivy dry extract (DER 5-7.5:1); ethanol 30% (m/m) 1-6 years: 3 x 5 ml corresponding to 0.63 g herbal substance/day 7-14 years: 3 x 10 ml corresponding to 1.26 g herbal substance/day ambroxol: no information oral, 7-14 days	n=72 ivy: n=53 ambroxol: n=19 7 month-15 years	Acute respiratory viral infection (n=6), acute bronchopneumonia (n=19), acute bronchitis (n=25), acute obstructive bronchitis (n=11), recurrent bronchitis (n=4), bronchial asthma (n=5), mucoviscidosis (n=2)	Velocity parameters of external respiration after 7 days ivy = normalised nearly in all children with obstructive diseases ambroxol = normalisation could not be documented; auscultatory picture in lungs ivy = 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 statistically significant differences	No information; descriptive and exploratory analysis, treatment difference	Can be considered as supportive for clinical relevance
Unkauf and Friederich, 2000	Randomised reference controlled equivalence study	Preparation 1: ivy dry extract (3-6:1); ethanol 60% (m/m) <4 years:	n=52 preparation 1: n=25 preparation 2:	Bronchitis	Improvement of symptoms (VAS scale), CGI items I, II, III cough, expectoration: equivalence between the two	Confirmatory analyses, Mann-Whitney-Rank-test,	Can be considered as clinical relevant

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Clinical relevance
		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 preparation 2: ivy dry extract (DER 5-7.5:1); ethanol 30% (m/m) <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 substance/day oral	n=27 25 female 27 male mean: 7.9 years		therapies; 98% of the children were responder (improvement of the variables by at least 50%)	descriptive analyses	

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Clinical relevance
Gulyas, 1999	Controlled pilot study	Ivy dry extract (DER 5-7.5:1); ethanol 30% (m/m), corresponding to 630 mg herbal substance daily ACC: no information oral; 14-20 days	n=20 ivy: n=10 ACC: n=10 9-15 years	Chronic obstructive respiratory disease	Increase of FEV1: ivy 0.34 l ACC: 0.22 l increase of VC: ivy: 0.26 l ACC: 0.23 l peak-flow: ivy: 57 l/minutes ACC: 39 l/minutes equivalence between the two therapies 98% of the children were responder (improvement of the variables by at least 50%)	No information	No clinical relevance for efficacy in chronic bronchitis, information on clinical pharmaco-logy
Gulyas *et al*., 1997	Crossover randomi-sed, double-blind	Preparation 1: 3 x 5 ml = 105 mg ivy dry extract (DER 5-7.5:1); ethanol 30% (m/m), corresponding to 0.63 g herbal substance/day preparation 2: 3 x 20 drops = 42 mg dry extract (DER 5-7.5:1); ethanol 30% (m/m), corresponding	n=25 10-16 years	Chronic obstructive pulmonary complaints	Both preparations therapeutically equivalent improvement in the lung function parameters clinically and statistically significant reduction in the airway resistance by 0.38 kPa/l/sec for preparation 1 and 0.35 kPa/l/sec for preparation 2	No information	No clinical relevance for efficacy in chronic bronchitis, information on clinical pharmaco-logic aspects

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Clinical relevance
		to 0.25 g herbal substance/day oral each treatment: 10 days; wash-out phase: 2-4 days					
Mansfeld *et al.,* 1997	Randomised, crossover	Preparation 1: 2 x 25 drops = 35 mg ivy dry extract (DER 5-7.5:1); ethanol 30% (m/m), corresponding to 0.21 g herbal substance/day; oral preparation 2: 2 x 1 supp. = 160 mg of ivy dry extract (DER 5-7.5:1); ethanol 30% (m/m), corresponding to 1 g herbal substance/day; rectal each treatment: 3 days; wash-out phase: 2-4 days	n=26 female: n=11 male: n=15 5-11 years	*Asthma bronchiale* with reversible bronchial obstruction	Peak flow improved by by 25.2% (drops) and 21.8% (suppositories) reduction of the airway resistance of 0.49 kPa/l/sec (31%) (drops) and 0.44 kPa/l/sec (23%) (suppositories)	No information	Not clinical relevant for efficacy in bronchial asthma; information pharmaco-logical aspects
Stöcklin, 1959	Open, controlled; 30 days	Verum: standard therapy in addition to ivy extract drops (no	n=100 verum: n=50 control: n=50	Whooping cough (n=40) or spastic	Attack free after 24 days in the verum group, in the control group only after	No information	Due to method-logical reasons only

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis	Clinical relevance
		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		bronchitis (n=10)	34 days; reduction of the intensity of coughing		supportive

Reviews

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 (Landgrebe *et al.,* 1999).

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 (Hofmann *et al.,* 2003). Five randomised 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 an improvement of respiratory functions, as promising but based on limited and low quality evidence.

In a review Guo *et al*. (2006) 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 (EMA, 1999).

Holzinger and Chenot (2011) performed a systematic review of the effectiveness and tolerability of ivy for acute upper respiratory tract infections (URTIs) and bronchitis in adults and children. Results of 10 eligible clinical studies on 17463 subjects were analysed. Studies were heterogeneous in design and conduct; 2 were RCTs. Three studies evaluated a combination of ivy and thyme, 7 studies investigated mono-preparations of ivy. Only one RCT (n=360) investigating an ivy/thyme combination used a placebo control and showed statistically significant superiority in reducing the frequency and duration of cough. All other studies lack a placebo control and show serious methodological flaws. They all conclude that ivy extracts are effective for reducing symptoms of URTI. The authors concluded although all studies report that ivy extracts are effective to reduce symptoms of URTI, there is no convincing evidence due to serious methodological flaws and lack of placebo controls.

Vila and Cañigueral (2011) reported that clinical studies show both the efficacy as well as the tolerability of the ivy extract (DER: 5-7.5:1; ethanol 30% (m/m)) in the treatment of acute respiratory tract infections accompanied by cough and chronic inflammatory bronchial conditions in children and adults.

Lang *et al*. (2015a) provided information on clinical studies with the ivy leaves dry extract (DER 5–7.5:1), extraction solvent: ethanol 30% (m/m). They conclude overall, 18 publications covering clinical trials and non-interventional studies are available and in total, 65,383 patients suffering from acute as well as chronic respiratory diseases were included in this studies. The authors concluded the use of the extract is well established in the treatment of different respiratory diseases.

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

Children

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 *et al*. (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 *et al*. (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”.

Table 20: Controlled studies in children

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 *et al.*, 1997	n=25 children (10-16 years)
Mansfeld *et al.,* 1998	n=28 children (13 female, 15 male) 7.8±2.5 years PPA=23 or 24
Gulyas, 1999	n=20 children (ivy: 10; acetylcysteine: 10) 9-15 years
Unkauf and Friederich, 2000	n=52 children (25 female, 27 male) mean 7.9 years
Maidannik *et al.,* 2003	n=72 children (7 month-15 years)
Bolbot *et al.,* 2004	n=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

Table 21: Uncontrolled studies in children

Authors, Year	**Number of Subjects by Arms, Age**
Lässig *et al.,* 1996	n=113 children (45% female, 55% male) 8.9 years (6-15 years)
Hecker, 1999	n=248 children (138 female, 110 male)
Jahn and Müller, 2000	n=372 children (186 female, 178 male) 5.7 years 0-1 year: n=26 children; 1-3 years: n=93 children; 4-9 years: n=189

	children; 10-16 years: n=56 children/adolescents; ≥16 years: n=4 adolescents; no information: 4
Roth, 2000	n=1024 children (4.4 years) 0-1 year: 159 children; 1-3 years: 404 children; 4-9 years: 383 children; ≥10 years: 72 children
Hecker *et al.,* 2002	n=1350 children (667 female, 682 male) up to 12 years: 165 children, 13-24 years: 128 adolescents/adults, up 25 years: 1043 adults
Büechi and Kähler, 2003	n=56 children/adults (7-93 years, mean: 49 years)
Kraft, 2004 (retrospective)	n=52,478 children (0-12 years) 0-1 year: 15%=7,871 children; 1-5 years: 51%=26,763 children; 6-9 years: 25%=13,119 children; ≥10-12 years: 9%=4,723 children
Fazio *et al*., 2009	5,181 (53.7%) children <1 year: 188 children (3.6%), 1-5 years: 2,822 children (54.5%), 6-12 years: 1,843 children (35.6%); 13-14 years: 328 adolescents (6.3%)
Schmidt *et al*., 2012	n=136 children (galenic formulation drops) 0-1 year: 32 children; 1-4 years: 36 children; 5-10 years: 34 children; 11-12 years: 34 children n=133 children (galenic formulation syrup) 0-1 year: 35 children; 1-4 years: 32 children; 5-10 years: 33 children; 11-12 years: 33 children
Lang *et al*., 2015b	n=1088 children (525 female, 537 male) 6-12 years

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 years 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.

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.

4.4. Overall conclusions on clinical pharmacology and efficacy

Schaefer *et al.* (2016) examined the efficacy and safety of ivy leaves extract in acute cough and acute bronchitis in a randomized, placebo-controlled, double-blind trial. The evaluation of the VAS, BSS and VCD score revealed that subjects treated with ivy leaves cough liquid showed statistically significant and clinically relevant reductions in CS, severity of symptoms associated with cough and acute bronchitis compared to the placebo group.

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 symptoms of cough in adults, with chronic bronchitis. Bolbot (2004) showed an improvement of symptoms in children with acute bronchitis 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” cannot be supported because according to 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 the impairment on bronchitis symptoms could be shown. The influence on spirometric and body-plethysmographic 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 associated with acute respiratory infection. This indication considers as well the data on improvement of symptoms by preparations of ivy as the limitations by current guidance on COPD. 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:

Dry extract (DER 4-8:1), extraction solvent: ethanol 24-30% (m/m)

Dry extract (DER 6-7:1), extraction solvent: ethanol 40% (m/m)

Dry extract (DER 3-6:1), extraction solvent: ethanol 60% (m/m)

Liquid extract (DER 1:1), extraction solvent ethanol 70% V/V

Soft extract (DER 2.2-2.9:1), extraction solvent ethanol 50% V/V: propylene glycol (98:2)

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

Table 22: Posology recommended in the literature

Commission E	**corresponding 300 mg herbal substance daily**
Dorsch *et al.,* 2002; 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 preparations: 0-1 year: 50-200 mg 1-4 years: 150-300 mg 4-12 years: 200-630 mg Adults: 300-945 mg

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).

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 *et al.* (1997). The study by Gulyas *et al*. (1997) was conducted in 25 children (10-16 years) with ivy cough juice in a dosage of 3 times 5 ml corresponding to 656 mg of herbal substance. The statement of Gulyas *et al.* (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. 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 *et al.* (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/minutes to 273 l/minutes 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 (DER 4-8:1 or DER 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, 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

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 problems, 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 and Latos (1979) examined 29 children in aerosol therapy; Leskow (1985) included 84 patients additional medication to antibiotics and steroids; Gulyas and Lämmlein (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 and Latos, 1979; Leskow, 1985; Gulyas and Lämmlein, 1992). Therefore they are not described in this 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.

In a multicenter surveillance study, 113 children (aged 6-15 years) suffering from recurrent obstructive respiratory complaints were treated with ivy cough juice (100 ml contain 0.7 g ivy dry extract (DER 5-7.5:1), ethanol 30% (m/m)) for up to 20 days (in some cases up to 30 days) (Lässig *et al.,* 1996). 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%.

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 (Hecker, 1999). 120 patients were treated with ivy cough juice (100 ml contain 0.7 g dry ivy extract (DER 5-7.5:1), ethanol 30% (m/m)) and 128 took ivy effervescent cough tablets (one effervescent tablet contains 65 mg ivy leaf extract (DER 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. In the 76% of the patients the dosage was as recommended in the package leaflet (no specific information). The efficacy on the symptoms of cough, expectoration, dyspnoea 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 author 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) occurred.

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 ((DER 6-7:1), ethanol 40%; 2 ml of a preparation contained 18 mg of extract corresponding to 108-126 mg of herbal substance) (Jahn and Müller, 2000; Müller and Bracher, 2002). 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 a 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/minutes to 273 l/minutes. 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 occurred. Four patients dropped out. The dosages used were in accordance to the dosage recommendations of Dorsch *et al.* (2002).

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 ivy juice (100 g contain 0.79 g ivy dry extract (DER 6-7:1), ethanol 40% (m/m)) and 234 children got ivy drops (100 g drops contained 1.98 g ivy dry extract (DER 6-7:1), ethanol 40% (m/m)) (Roth, 2000).

The patient groups were the following:

Ivy 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 than 10 years:	3 x 25 drops (0.520 g herbal substance) (n=36)
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. At the end of the study period 72.6% of the children were cough free; 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 ivy juice (789 patients) from 2 to 6 ml, corresponding to 0.118-0.354 g of herbal substance. The daily dosage for ivy 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.

The changes of clinical symptoms and the tolerability of ivy effervescent tablets (one effervescent tablet contained 65 mg ivy leaf dry extract (DER 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 (Hecker *et al.,* 2002). 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). One thousand forty-three 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. In view of the favourable changes in all investigated clinical symptoms as well as the excellent tolerability in children and adults, the authors concluded that the ivy leaf extract preparation ivy effervescent tablets could be considered as a therapeutic option in alleviating the symptoms of chronic bronchitis.

In a multicenter open drug surveillance study over the period of one week, the efficacy and safety of ivy pastilles (one pastille contained 26 mg ivy leaf extract; DER 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 (Büechi and Kähler, 2003). The dosage used was at least 2 pastilles/day (corresponding to 312 mg of herbal substance). Nineteen 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.

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 ivy juice (100 ml contain 0.7 g dry ivy extract DER 5-7.5:1, ethanol 30% (m/m)) (Kraft, 2004).

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 from 10 years up 710 mg herbal substance daily. One hundred fifty (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 occurred 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.

A total of 10,562 patients were recruited by 3,287 doctors participating in an open multicenter post-marketing study in 11 Latin American countries (Fazio *et al.,* 2009). 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 patients with cough alone) were treated with an ivy leaf preparation (100 ml contain 0.7 g dry ivy extract (DER 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 were 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. Three hundred eighty-eight 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. However, as also other medication was used by the patients the causality cannot be cleared definitely. 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.

Two galenic 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 (Schmidt, 2012). One hundred thirty-three 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 tolerability 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 from Cwientzek et al. (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 to the usual dose of the licenced products and were in a low range, compared with the corresponding herbal substance of other ivy preparations.

Stauss-Grabo *et al*. (2011) investigated in a post-marketing surveillance study the tolerability and safety of film-coated tablets containing ivy leaves dry extract (DER 5-7.5:1), extraction solvent ethanol

30% (m/m) under practice conditions. Adults and children aged 11-85 years of both genders were included. A total of 330 patients suffering from colds accompanied by coughing or from chronic, inflammatory bronchial diseases were scheduled to undergo treatment for a period of at least seven days. The tolerability of the tablets was rated by means of questionnaires. In the global assessment by the practitioner (98.5%) and by the patient (96.4%) the tolerability of the tablets was assed as good or very good.

Lang *et al*. (2015b) analysed the efficacy and tolerability of five different administration forms containing the dry ivy extract (DER 5-7.5:1), extraction solvent ethanol 30% (m/m) in a non-interventional study involving 1088 (525 girls, 537 boys) schoolchildren (aged 6 to 12) suffering from acute bronchitis. Efficacy was recorded by means of an assessment of the findings on the part of the physicians, an assessment of the patients involving questioning of their typical symptoms as well as by means of a diary. There was an improvement in all findings and symptoms over the course of the 7-day treatment. The BSS changed from 6.23 points to 1.29 points (79.3%) There was no difference in patients with co-medication (77.9%) and without co-medication (80.2%). The administration forms proved to be well tolerated and the patients exhibited a high level of compliance.

The aim of the post-marketing study was to confirm the safety of ivy leaf extract in Slovenian children with acute inflammatory airway disease and to investigate the course of treatment (Beden *et al*., 2011). 193 children with clinical signs of acute airway disease, aged 2 to 14 years were included in a prospective post-marketing study. At the beginning of the study, 7-day treatment with syrup of ivy leaf extract (no further information) was started. The treatment was effective in 93.7% of children, who showed an improvement of clinical symptoms. Skin allergy as a side effect was reported in one child. The quality of sputum and frequency of cough changed during the treatment, and the majority of physicians and patients estimated that the treatment was more effective than in previous episodes of the disease when they had not received this drug.

Table 23: Clinical safety data from clinical trials

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Adverse reactions	Comments
Lässig *et al.*, 1996	Open multicenter surveillance study; 75% of the cases: 20 days 26% of the cases: 21-30 days	Juice (100 ml contain 0.7 g dry ivy extract (DER 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)	n=113 45% female 55% male mean: 8.9 years (6-15 years)	Obstructive respiratory disease with cough and expectoration	Safety statement of the physician: very good: 68.7%; good: 29.5%; satisfactory: 0%; deteriorate: 0%	Safety statements, supportive for clinical safety relevance
Hecker, 1999	Open multicenter comparative surveillance study; 7.3-8.2 days	Juice (100 ml contain 0.7 g dry ivy extract (DER 5-7.5:1), ethanol 30% (m/m)) effervescent tablets (1 tablet contains 65 mg ivy dry extract (DER 5-7.5:1); ethanol 30% (m/m)) dose in accordance with "manufacturer recommendation" oral	n=248 n=120 juice n=128 effervescent tablets female n=138 male n=110 male	Bronchitis (45%); respiratory system infection (29%)	Safety very good and good in 98% of the cases; one adverse drug reaction "allergic exanthema"	Safety statements, supportive for clinical safety relevance
Jahn and Müller, 2000	Open multi-center surve-illance study; 7 days	Dry extract from ivy leaves (6-7:1), ethanol 40% (m/m), 2 ml contain 18 mg of dry extract; dosage: age dependent: 3 x 0.5-2 ml	n=372 female n=186 male n=178 5.7 years	Infection of the respiratory tract upper: 241, lower: 85, both: 43; infection acute: 86.6% recurrent: 10.5% chronic: 2.4%	Safety very good and good in 98.9% of the patients; no adverse drug reactions	Safety statements, supportive for clinical safety relevance

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Adverse reactions	Comments
Roth, 2000	Open multi-center surveillance study; 2 weeks	Juice and drops dry extract from ivy leaves (6-7:1), ethanol 40% (m/m), 100 ml contain 1.98 g of dry extract; dosage: age dependent oral	n=1024 n=789 juice n=234 drops mean: 4.4 years	Acute infection of the upper respiratory tract: acute bronchitis / bronchiolitis (52.4%), bronchitis (26.6%); not further specified (22.2%)	Safety very good and good in 95.9% of the patients (physicians judgement) and in 90.8% (patients judgment)	Safety statements, supportive for clinical safety relevance
Hecker *et al.,* 2002	Open multi-center surveillance study; 4 weeks	Effervescent tablets (1 tablet contains 65 mg ivy dry extract (DER 5-7.5:1); ethanol 30% (m/m)): 1.5-2 tablets, oral	n=1350 female n=667 male n=682 up to 12 years: n=165 13-24 years: n=128 up to 25 years: n=1043	Chronic bronchitis with or without obstruction	3 adverse drug reactions (0.2%) (2 x eructation, 1 x nausea)	Supportive for clinical safety relevance
Büechi and Kähler, 2003	Open multi-center surveillance study; one week	Pastilles (1 pastille contains 26 mg ivy leaf dry extract (4-8:1); ethanol 30% (m/m)); 2-6 pastilles daily oral	n=56 7-93 years (mean: 49 years)	Respiratory system disease (n=14)	No adverse drug reaction; tolerance of ivy pastilles very good	Supportive for clinical safety relevance
Kraft, 2004	Retro-spective study	Juice (100 ml contain 0.7 g dry ivy extract (DER 5-7.5:1); ethanol 30% (m/m)): 0-1 year: 227 mg herbal substance/day 1-5 years: 364 mg herbal substance/day	n=52,478 (0-12 years) children 1-5 years = 51% of the patients	Diseases of the respiratory tract	115 adverse effects (0.22%): diarrhoea (0.1%); enteritis (0.04%), allergic exanthema/ urticaria (0.04%); vomiting (0.02%); gastrointestinal	Clinical relevant for safety because of the high number of patients due to

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Adverse reactions	Comments
		6-9 years: 653 mg herbal substance/day 10-12 years: 710 mg herbal substance/day oral			disturbances 0.17% in total: children 0-1 year (0.4%), children 2-9 years (0.13%)	methodological aspects, no frequency of adverse events can be concluded from the results (concomitant medication, retrospective study)
Fazio *et al.*, 2009	Open multi-center surveillance study; 7 days	Ivy juice (100 ml contain 0.7 g dry ivy dry extract (DER 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 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, dizziness, palpitation, sweating and others 46 (0.5%) patients	Supportive for clinical safety relevance

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Adverse reactions	Comments
					discontinued therapy due to adverse events	
Stauss-Grabo *et al*., 2011	Open multi-center surveillance study; minimum 7 days (9-10 days on average)	Ivy leaves dry extract (DER 5-7.5:1), ethanol 30% (m/m) [tablets]	n=330 aged from 12-85 years (one patient 11 years), mean=42 years	Patients suffering from colds accompanied by coughing or from chronic, inflammatory bronchial diseases	Tolerability of the tablets in the global assessment: good to very good by both, the practitioner (98.5%) and by the patient (96.4%)	Open multi-centre surveillance study, supportive for clinical safety relevance
Schmidt, 2012	Open multi-center surveillance study; 10-12 days	1 ml ivy drops contain 0.1 g 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 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	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: 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 possible	Open, multi-centre surveillance study, supportive for clinical safety relevance

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Adverse reactions	Comments
Schmidt, 2012	Open multi-center surveillance study; 10-12 days (minimum 9, maximum 18)	100 ml ivy syrup contains 2 g 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 to 0.05 g herbal substance daily 1-4 years: 3 x 2.5 ml corresponding to 0.15 g herbal substance daily 5-10 years: 4 x 2.5 ml corresponding to 0.2 g herbal substance daily 11-12 years:3 x 5 ml corresponding to 0.3 g herbal substance daily	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: 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 possible	Open, multi-centre surveillance study, supportive for clinical safety relevance
Beden *et al*., 2011	Open multi-center surveillance study	Ivy leaf syrup (no further information) 7 day treatment	193 children aged 2 to 14 years	Acute airway disease,	1 x skin allergy	Open, multi-centre surveillance study, supportive for clinical safety relevance
Schaefer *et al*., 2016	Double blind, placebo-controlled, randomized	Ivy dry extract (DER 5-7.5:1); ethanol 30% (m/m) in a cough liquid or placebo	Randomized: 181; verum: n=89 placebo: n=92	Patients with acute productive cough	Adverse events occurred in 21 of 181 subjects: verum: 9; placebo: 12	Clinical relevant for safety

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Adverse reactions	Comments
	Visit1-visit5: 7 days; follow up visit V6: 7 day later		completed: verum: n=88 placebo: n=90		closely connected to the underlying disease	
Lang *et al*., 2015b	Open multi-center surveillance study; 7s	Ivy dry extract (DER 5-7.5:1); ethanol 30% (m/m) in: n=719 syrup n=197 liquid n=64 drops n=49 pastilles n= 38 effervescent tablet	1088 patients from 6 to 12 years (8.5±0.6 years) 527 girls 537 boys	Patients with acute diseases of the upper respiratory system (since 2.29±0.05 days)	Tolerability good to very good in the global assessment by both, the practitioner (96.7%) and by the patient (95.4%); Ten adverse events occurred: 7 gastrointestinal, 2 allergic, one otherwise	Open, multi-centre surveillance study, supportive for clinical safety relevance

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. Schaefer *et al*. (2016) obtained data from more than 65,000 patients, showing that adults and children profit from ivy preparations.

Aside from market presence and data from studies, there are no concrete data concerning patient exposure.

5.3. Adverse events, serious adverse events and deaths

General data

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

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 years boy who had eaten 6-8 ivy fruits showed marbled skin at the extremities and no further symptoms (Mühlendahl *et al*., 1995).

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

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 (Frohne and Pfänder, 2004).

Morfin-Maciel *et al*. (2012) reported two cases of anaphylaxis related to common ivy syrup (dry ivy extract 7 mg/ml, no further information) ingestion. The causal relationship was confirmed by a skin prick test with the syrup and with the pollen extract, which were positive in both patients.

Paulsen *et al*. (2010) present the results of aimed patch testing with the main common ivy allergen, falcarinol, during a 16-year period and review the newer literature. Consecutive patients tested with falcarinol 0.03% petrolatum from May 1993 to May 2009. One hundred and twenty-seven Danish patients were tested with falcarinol and 10 (7.9%) were tested positive. Seven were occupationally sensitized. Between 1994 and 2009, 28 new cases of contact dermatitis from ivy were reported, 2 of which were occupational. Only 11 of the 28 patients were tested with pure allergens.

Tabali *et al*. (2012) characterized ADRs detected by primary care physicians in the field of complementary and alternative medicine (CAM) in Germany with regard to demographics of patients affected, severity, outcome, management, causality and the ADR causing drugs. The study period lasted from January 2004 until June 2009. From a total of 38 physicians only a subgroup of seven physicians agreed to report all non-serious ADRs in addition to serious ones. All 14 serious ADRs were associated with conventional drugs. In the subgroup of 7 physicians who recorded all non-serious and serious ADRs, 25,966 patients (median age 11 [4-38-] years received a total of 392,243 drugs. Of these 1.2% experienced at least 1 ADR. The rates of ADRs were approximately 4.4 per 10,000 in CAM prescriptions and 13.0 in conventional drug prescriptions. The ADR frequency for Pelargonium root was 0.21%, for ivy leaves 0.17% and for the drug combination of Primula root and Thyme herb 0.09%.

Vasconcelos Pinela *et al*. (2010) report the clinical case of a 80-year-old female, housekeeping with acute eczema with severe erythematous and vesiculobulluous eruption, on the right forearm, hands and lateral side of the neck with 48 h evolution. Epicutaneous testing elicited a positive reaction (++) at 48 h to balsam of Peru, Compositae – Asteraceae (daisy family) mixture, chamomile extract (*Matricaria recutita* ext.) 2.5% in petrolatum (pet), yarrow (*Achillea millefolia* mil wool) ext 1% in pet., tansy (*Tanacetum vulgare*) ext 1% in pet and ivy leaf. At 96 h it also showed positive reaction to cedar oil 10% in pet, eucalyptus oil 2% in pet, matricaria ext 1% pet and worsening of the previous positivity for composite mixture (+++), Ivy leaf (+++) and chamomile ext (+++). The authors describe the existence of co-sensitization/multi-allergy in patients.

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 clean-up 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 years 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 neurotoxic 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.

Case reports of the BfArM Database and other pharmacovigilance databases

There are 129 case reports in the BfArM Database on suspected adverse drug reactions referring to ivy preparations (September 2016). Most of them are related to allergic reactions and gastrointestinal reactions as nausea, vomiting and diarrhoea, stomach pain, cramps in lower abdomen. Allergic reactions occur as well local like urticaria, skin rash, and exanthema as systemic allergic reactions like dyspnoea, swelling of nose and lips, and anaphylactic reaction. Beside these reactions, other adverse events occur and are listed below together with the case reports of the literature.

Pokladnikova *et al*. (2016) analysed immediate allergy-like ADRs to herbals documented in VigiBase®, the WHO international pharmacovigilance database. The documentation of all suspected ADRs in

association with herbal exposure reported to VigiBase® from 1969 to August 2014 was retrieved. Among all reports in which WHO-ART reaction terms were indicative of acute allergic reactions, those classified as 'suspect' with a documented causality assessment and latency time of ≤1 day were selected. They identified 757 reports out of 1039 ADRs. Products with mixed herbals (36.0%) as well as those administered orally (63.2%) were predominant. The most frequent reactions were urticaria and rash (49.2%). Anaphylactic reactions accounted for 9.5%. *Hedera helix* was among the suspected herbals.

Meincke *et al*. (2016) analysed also acute hypersensitivity reactions to herbal remedies in children. The VigiBase® contained 2,646 ICSRs with 14,860 distinct adverse reactions reported in association with herbal medicine in children. Among those, 150 cases with 222 allergic reactions met the inclusion criteria. The most commonly reported WHO-ART terms were urticaria or rash (41.4%), anaphylactic or anaphylactoid reaction (16.2%), asthma, stridor or bronchospasm (9.0%), Anaphylactic shock (5.4%), allergic reaction (5.4%), and oedema mouth (5.4%). The most frequently reported suspect herbals were mixed herbal products (31.2%), herbal pollen (29.7%), *Phleum pratense* (13.1%), and *Hedera helix* (7.2%).

Hyposensitive reactions published in literature

A review of older dermatitis cases (1909 up to 1979) is given by Mitchell and Rook (1979). The authors deduced, based on present evidence that it is reasonable to conclude that *Hedera helix* is an irritant plant, which may also on occasions induce sensitisation. 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. They 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 authors considered only 6 cases to be relevant.

Four 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. Dehydrofalcarinol elicited equal patch test reactions only when concentrated as high as 1%. The authors demonstrated that falcarinol is the main sensitizer, while dehydrofalcarinol is also an allergen but does not elicit reactions in all patients.

Murdoch and Dempster (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*.

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 (Gafner *et al.,* 1988).

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 (Mahillon *et al.,* 2006).

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.

A 22-years-old female with atopic dermatitis 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 (Roed-Petersen, 1975).

A 33-years-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* (Mitchell, 1981).

A 31-years-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 hours (Boyle and Harman, 1985).

A 44-years-old non-atopic man developed contact dermatitis with erythema 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 (García *et al*., 1995).

A 60–years-old man with no previous history of contact dermatitis had several outbreaks of itchy erythematous oedematous lesions on the hand, forearms, neck and face 8-12 hours 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 (Sánchez-Pérez *et al.,* 1998).

One case of allergic contact dermatitis to common ivy is presented. The patient, a 16-years-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 (Jø hnke and Bjarnason, 1994).

A 50-years-old man was admitted in April 1999 with severe eczema on the right upper limb and less florid involvement of the trunk (Yesudian and Franks, 2002). His wife had simultaneously developed eczema on her trunk. Ten 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.

A case of a male hobby gardener with appropriate clinical history (two days after working in the garden he develops an erythema on hand and neck, and 2 days later an oedema) and positive patch test on *Hedera helix* was reported. 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 sensitisation to wear appropriate protective clothing (Özdemir *et al.,* 2003).

Hannu *et al.* (2008) presented the first case of ivy induced occupational asthma. A 40-years-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/minutes 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 and Paulsen (2008) reported a case of contact urticaria to common ivy and rosemary with cross-reactivity to the Labiatae (Lamiaceae) 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.

Jones *et al*. (2009) reported case series on allergic contact dermatitis. Between 1980 and 2007 in UK, a total of 37,065 patients attended St John's Institute of Dermatology for patch testing. Over this 27-year period, 11 patients presented having developed a rash within days of suspected contact with garden ivy (*H. helix*). All patients were amateur gardeners and none were atopic. In only five cases, predominant sites affected were the hands, three described a rash on the arms, two on the face, and one had a more extensive rash. Where it was stated in the history, the rash developed 1-3 days post-exposure. In all but one case, patients described previous episodes. All patients showed a ++ reaction (International Contact Dermatitis Research Group criteria) to the leaf at D4 apart from two who showed a + reaction. A ++ reaction was seen in the patient tested to the ivy stalk at D4.

Bregnbak (2015) reported a case (21-year-old male gardener in Denmark) of allergic contact dermatitis caused by common ivy as a result of airborne exposure. On the basis of the patch test, the morphology of the dermatitis, and the patient's occupational history, he was initially diagnosed with occupational allergic contact dermatitis caused by common ivy. This is thought to be the first report of airborne elicitation of allergic contact dermatitis caused by this plant.

Neurotoxicity and psychoactive effects

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 hours he was fairly well (Turton, 1925). The same case report was also cited by De Smet (1993).

A 3-years-old 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 hours 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 (Polizzi *et al.,* 2001).

Assessor's comment:
Adverse effects and over dosage of narcotics (codeine, dextromethorphan) 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.

Concomitant use with opiate antitussives such as codeine or dextromethorphan is not recommended without medical advice.

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

Assessor´s comment:
Neurotoxic effects of antihistamine drugs are known and are stronger in children than in adults. Therefore a causal relationship to desloratadine is probable while unlikely to the ivy preparation. Information about the ivy preparation is limited.

Other reported adverse reactions

BfArM-case 06052045: A 42-years-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.

Hoppe (1981) reported that ivy has cardiac effects. No near explanations or case reports were 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).

Fuchs *et al*. (2011) conducted a study to identify which plants may lead to severe poisoning, and to define the clinical relevance of plant toxicity for humans in Switzerland. They analyzed 42,193 cases of human plant exposure and 255 acute moderate, severe, and lethal poisonings, which were reported to the Swiss Toxicological Information Centre between January 1995 and December 2009. Plant contact was rarely responsible for serious poisonings. Lethal intoxications were extremely rare and were caused by plants with cardiotoxic (*Taxus baccata*) or mitosis-inhibiting (*Colchicum autumnale*) properties. From the 42,193 cases 628 were related to *Hedera*.

Ivy poisoning in animals

Brömel and Zettl (1986) reported ivy poisoning in 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.

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 (Mills and Bone, 2000).

5.4. Laboratory findings

In a randomized prospective multicenter, reference controlled study, 52 children (mean 7.9 years) with a clinically proved bronchitis were treated either with ivy juice (200 ml juice contain 660-1000 mg ivy extract (3-6:1), ethanol 60% (V/V) or ivy fluid (100 ml contain 0.7 g ivy extract (DER 5-7.5:1), ethanol 30% (m/m)). The daily dose of the juice 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, creatinine, sodium, potassium) between the therapy beginning and therapy end did not show any relevant variations (Unkauf and Friederich, 2000).

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

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

0-1 year: 26 (Jahn and Müller, 2000); 159 (Roth, 2000); 188 (Fazio *et al*., 2009); 7,871 (Kraft, 2004) (n=8,244 children)

1-3 years: 93 (Jahn and Müller, 2000); 404 (Roth, 2000) (n=497 children)

1-5 years: 2,822 (Fazio *et al*., 2009); 26,763 (Kraft, 2004); (n=29,585 children)

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%.

Detailed information on clinical safety is available from two studies with a high number of patients:

In the study of Fazio *et al*. (2009) 5,181 (53.73%) children were treated with ivy juice (100 ml contains 0.7 g dry ivy extract (DER 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.

The retrospective study of Kraft (2004) 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 (ANSM 2009, ANSM 2010a, ANSM 2010b). This decision was based on a national pharmacovigilance survey on mucolytics and agents that fluidify 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 (AIFA 2010a, AIFA 2010b).

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, because of the risk of aggravation of respiratory symptoms.

Use in elder population

In the placebo controlled clinical study Schaefer *et al*. (2016) 8 subjects (of 181) included had an age of 65-75 years. The safety profile in this subgroup did not show any difference to the profile observed in the younger study population.

5.5.2. Contraindications

Ivy preparations are contraindicated in patients with hypersensitivity to the active substance or to plants of the Araliaceae family. The use in children below 2 years of age was contraindicated because of the risk of aggravation of respiratory symptoms.

5.5.3. Special Warnings and precautions for use

Persistent or recurrent cough in children between 2-4 years of age requires medical diagnosis before treatment. Caution is recommended in patients with gastritis or gastric ulcer. When dyspnoea, fever or purulent sputum occurs, a doctor or a pharmacist should be consulted.

5.5.4. Drug interactions and other forms of interaction

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. *Hedera helix* was not on the list of plants, considered / suspected to cause interactions (Van den Bout-van den Beukel *et al*., 2006).

Mills and Bone (2000) reported saponins readily increased 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 appeared to be the case for glucose and ethanol, based on *in-vitro* models.

There were two adverse events (Polizzi *et al*., 2001; BfArM case nr. 06002941) occurring by concomitant 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 is not clear and should be considered as signal. The Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) has

agreed by consensus (CHMP, 2015) new measures to minimise the risk of serious side effects, including breathing problems, with codeine-containing medicines when used for cough and cold in children. As a result the use of codeine for cough and cold was contraindicated in children below 12 years. As conclusion the precaution of use for this signal is not yet mentioned in the monograph.

5.5.5. Fertility, pregnancy and lactation

Mahran *et al*. (1975) isolated the alkaloid emetine from an alcoholic extract (90% ethanol) of four varieties of *Hedera helix* L. growing in Egypt. The authors 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 two animal studies, α-hederin altered maternal zinc distribution, which was associated with adverse developmental outcome in rats. In view of the pre-clinical safety data, the use during pregnancy and lactation is not recommended. No fertility data are available. See also chapter 3.4.

5.5.6. Overdose

According to 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.

BfArM-case 04900053: A 4-years-old child developed aggressivity and diarrhoea after drinking accidentally 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 to 0.3 g herbal substance). The accidental dosage corresponds to 1.8 g herbal substance.

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

Assessor's comment:
For the monograph the information is recommended that overdose can provoke nausea, vomiting, diarrhoea and agitation and one case of a 4 years old child who developed aggressivity and diarrhoea after accidental intake of ivy extract corresponding to 1.8 g herbal substance has been reported.

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

No studies on the effect on the ability to drive and use machines have been performed.

5.5.8. Safety in other special situations

Neither data on intrinsic factors (e.g. patients' characteristics such as gender, race, polymorphic metabolism) nor on extrinsic factors, drug abuse, withdrawal, and rebound are available.

5.6. Overall conclusions on clinical safety

Ivy preparations are considered as safe for the use under the conditions specified in the monograph. A long clinical use has shown that ivy preparations are well tolerated without serious unwanted pharmacodynamic actions on any organ system.

Hedera helix leaves contain triterpenoid saponins as hederacoside C, hederacoside B and α- and ß-hederin. The major saponin is hederasaponin C. Ivy leaves contain also the allergic substances falcarinol and didehydrofalcarinol. Ivy preparations are contraindicated in patients with hypersensitivity to the active substance or to plants of the Araliaceae family. There are suggestions of an association between ivy and rhinitis symptoms (Mahillon *et al*., 2006) and a first case of occupational asthma, related to the fresh plant, is documented (Hannu *et al*., 2008). Ivy fresh plant is known to cause contact dermatitis, which is documented in numerous reports (Mitchell and Rook, 1979). Such reactions are attributed to falcarinol and its 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. Until now, it cannot 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, and dyspnoea, anaphylactic reaction) and gastrointestinal reactions (nausea, vomiting and diarrhoea) observed for herbal preparations of ivy leaf after oral administration. From the study of Fazio *et al*. (2009) which included more than 5,000 children, the frequency of adverse events can be calculated as 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 general methodological reasons of open multicenter surveillance studies (concomitant medication, drop outs, no placebo control) the causality is not clear for the adverse events reported. Therefore in the monograph the frequency of adverse events is given as “not known”. Because of gastrointestinal reactions caution is recommended in patients with gastritis or gastric ulcer.

Overdose of ivy preparations can provoke nausea, vomiting, diarrhoea and excitation. One case of aggressivity occurs. Further neurotoxic 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.

From the long traditional use of ivy preparations in children no general safety concerns referring to 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. Hypothetically, the saponins can induce nausea and vomiting that can lead to aspiration in infants. Because of general safety reasons of expectorants for this age group, the use for children below 2 years of age is contraindicated because of the risk of aggravation of respiratory symptoms. Persistent or recurrent cough in children between 2-4 years of age requires medical diagnosis before treatment.

Available clinical data do not indicate abuse, withdrawal or rebound potential.

Adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed. Safety during pregnancy and lactation has not been established. Studies in animals have shown reproductive toxicity. In two animal studies, α-hederin altered maternal zinc distribution, which was associated with adverse developmental outcome in rats. However, effects in non-clinical studies were observed only at s.c. injection/exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. 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 (benefit-risk assessment)

In summary all the requirements for well-established use (period of medicinal use, acceptable level of safety, recognised efficacy, quantitative aspects of the use of the substance and the degree of scientific interest in its use) are met for the following ivy preparations in liquid or solid dosage forms for oral use:

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).

The well-established use is recommended by the Rapporteur for the indication “Herbal medicinal product used as an expectorant in case of productive cough associated with acute respiratory infection.”

The HMPC adopted on 21 November 2017 the indication “Herbal medicinal product used as an expectorant in case of productive cough. ”

Efficacy and safety of ivy leaves extract used as an expectorant in case of productive cough associated with acute respiratory infection was shown in a randomized, placebo-controlled, double-blind trial. The evaluation of the VAS, BSS and VCD score revealed that subjects treated with ivy leaves cough liquid showed statistically significant and clinically relevant reductions in CS, severity of symptoms associated with cough and acute bronchitis compared to the placebo group. In other reference controlled studies ivy leaf extract was found to be equivalent or superior to ambroxol or acetylcysteine concerning efficacy as expectorant in productive cough. The influence on spirometric and body-plethysmographic 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.

From the long standing clinical use and literature data ivy preparations have shown to be well tolerated in all of its oral formulations without serious unwanted pharmacodynamic actions on any organ system. According to data reported from controlled and not controlled clinical studies gastrointestinal reactions (nausea, vomiting, diarrhoea) as well as allergic skin reactions (urticaria, skin rash) and systemic allergic reactions as dyspnoea were reported. Pharmacovigilance data show also cases of anaphylactic reactions. Because of gastrointestinal reactions caution is recommended in patients with gastritis or gastric ulcer. Overdose can provoke nausea, vomiting, diarrhoea, and agitation. Because of general safety consideration, ivy preparations are contraindicated in patients with hypersensitivity to the active substance or to plants of the Araliaceae family. Children under 2 years of age should not use any secretolytic drugs as ivy preparations because of the general risk of aggravation of respiratory symptoms.

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. Persistent or recurrent cough in children between 2-4 years of age requires medical diagnosis before treatment.

There were no clinical well-known drug interactions with ivy leaf.

Safety during pregnancy and lactation has not been established. In the absence of sufficient human data, the use during pregnancy and lactation is not recommended. No fertility data are available. In two animal studies, α-hederin altered maternal zinc distribution, which was associated with adverse developmental outcome in rats. Effects in non-clinical studies were observed only at s.c. injection/exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

The mechanism of action is not known.

The proposed pharmacotherapeutic group is: respiratory system, the proposed ATC code: R05C.

No constituent with known therapeutic activity or active marker can be recognised by the HMPC.

Annex

List of references