and up to 10 years 710 mg herbal substance daily. 115 (0.22%) adverse effects were reported. The most frequent adverse effects were: diarrhoea (0.1%), enteritis (0.04%), allergic exanthema/urticaria (0.04%) and vomiting (0.02%). In total, gastrointestinal disturbances occurred in 0.17% of children. The incidence of adverse effects was age dependent. In children under 1 year, adverse effects occured in 0.4% and in children upon 9 years in 0.13%.

Assessor's comment:

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

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

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

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

Assessor's comment:

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

antibiotic group was not comparable to that of the ivy group. Therefore, the efficacy results have only supportive character for simple acute bronchitis. The duration of the study was 7 days, so it is not appropriate to draw any conclusions of efficacy in chronic bronchitis.

Table 8: Non-controlled studies with ivy leaf products

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

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

			1-4 years: 0.15 g 4-10 years: 0.2 g 12 years and older: 0.3 g Sedotussin® drops: age dependent: corresponding to 0.166-0.52 g herbal substance/day oral	mean: 4.4 years	/bronchiolitis (52.4%), , bronchitis (26.6%); not further specified (22.2%)	4 point scale	the children cough free; effectiveness very good or good in 67.4% of the cases	judgement) and in 90.8% (patients judgment)
Hecker *et al.*, 2002	open multicenter surveillance study	4 weeks	Prospan acute® effervescent tablets (1 tablet contains 65 mg ivy dry extract (5-7.5:1); ethanol 30% (m/m)): 1.5-2 tablets, corresponding to 585-780 mg herbal substance/day oral	n=1350 667 female 682 male up to 12 years: 165 13-24 years: 128, up to 25 years: 1043	chronic bronchitis with or without obstruction	symptoms	improvement of cough: 92.2% expectoration: 94.2% dyspnoea: 83.1% respiratory pains: 86.9%	3 adverse drug reactions (0.2%) (2 x eructation, 1 x nausea)
Büechi and Kähler, 2003	open multicenter surveillance study	1 week	Ivy leaves extract pastilles (1 pastille contains 26 mg ivy leaf dry extract (4-8:1); ethanol 30% (m/m)) 2-6 pastilles corresponding to 312-936 mg herbal substance daily oral	n=56 7-93 years (mean: 49 years)	respiratory system disease (n=14)	symptoms (irritation of the throat, quantity of expectoration, colour of mucus, consistence of mucus)	irritation of throat reduced from 2.7 to 1.3; quantity of expectoration reduced from 1.5 to 1.1; consistence of mucus improved from 2.2 to 1.3	no adverse drug reaction; tolerance of ivy pastilles very good

Kraft, 2004	retro-spective study	no data	Prospan® cough juice (100 ml contains 0.7 g dry ivy extract (5-7.5:1); ethanol 30% (m/m)): 0-1 year: 227 mg herbal substance/day 1-5 years: 364 mg herbal substance/day 6-9 years: 653 mg herbal substance/day 10-12 years: 710 mg herbal substance/day oral	n=52,478 (0-12 years) children 1-5 years = 51% of the patients	diseases of the respiratory tract	adverse effects	115 adverse effects (0.22%): diarrhoea (0.1%); enteritis (0.04%), allergic exanthem/ urticaria (0.04%); vomiting (0.02%); gastrointestinal disturbances 0.17% in total: children 0-1 year (0.4%), children 2-9 years (0.13%)	
unpub-lished report: 28.01. 2002	open multicenter surveillance study	10-12 days	1 ml Hedelix s.a. drops contains 0.1 g *Hederae helix* soft extract (1:1); ethanol 45% V/V, (preparation is identical with soft extract (DER 2.2-2.9:1); ethanol 50% V/V: propylene glycol (98:2) [other declaration]) 0-1 year: 3 x 5	n=136 n=32 (0-1 year) n=36 (1-4 years) n=34 (5-10 years) n=34 (11-12 years)	symptoms of common cold; symptoms of chronic obstructive bronchitis	safety evaluation (additional evaluation: symptom score, statement of efficacy)	improved clinical symptoms at the end of the study efficacy: very good: 27.5%; good: 68.7%; satisfactory: 3.9% (physicians judgement)	safety: very good: 38.7%; good: 60.5%; satisfactory: 0.8% (parents judgment); very good: 47.6%, good: 52.4%, (physicians judgement); 3 adverse drug reactions:2 vomiting, 1

			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					dermatitis, causality was considered as possible
unpub-lished report: 30.01. 2002	open multicenter surveillance study	10-12 days (min. 9, max. 18)	100 ml Hedelix Hustensaft contain 2 g *Hederae helix* soft extract (1:1); ethanol 45% V/V, (preparation is identical with soft extract (DER 2.2-2.9:1); ethanol 50% (V/V): propylene glycol (98:2) [other declaration]) 0-1 year: 1x2.5 ml corresponding 0.05 g herbal substance daily; 1-4 years: 3x2.5 ml	n=133 n=35 (0-1 year) n=32 (1-4 years) n=33 (5-10 years) n=33 (11-12 years)	symptoms of common cold, symptoms of chronic obstructive bronchitis	safety evaluation (additional evaluation: symptom score, statement of efficacy)	improved clinical symptoms at the end of the study Efficacy: very good: 25.4%; good: 71.4%; satisfactory: 3.2% (physicians judgement)	safety: very good: 22.7%; good: 73.1%; satisfactory: 4.2% (parents judgment); very good: 26.9%; good: 72.3%; satisfactory: 0.8%(physicians judgement); 2 adverse drug reactions: 1 diarrhoea and 1 stomach disorder with

			corresponding 0.15 g herbal substance daily; 5-10 years: 4x2.5 ml corresponding 0.2 g herbal substance daily, 11-12 years: 3x5ml corresponding 0.3 g herbal substance daily					nausea; causality was considered as possible
Fazio *et al.*, 2009	open multicenter surveillance study	7 days	Prospan® cough juice (100 ml contain 0.7 g dry ivy dry extract (5-7.5:1); ethanol 30% (m/m)) 0-5 years: 3x2.5 ml/day; 6-12 years 3x5 ml/day, >12 years and adults: 3x5-7.5 mlday concomitant drugs: 60.7%, antibiotics: 39.2%	n=9,657 children= 5,181 (53.7%) n= 188 (0-1 year; 3.6%) n=2,822 (1-5 years; 54.5%) n=1,843 (6-12 years; 35.6%) n=328 (13-14 years; 6.3%) n=4,476 (adults; 46.3%)	inflammatory bronchial diseases (acute and chronic bronchitis, cough)	adverse effects	improvement / healing of the symptoms in 95.1% (physicians assessment)	adverse events: 2.1% of the patients (1.2% in children) 1.5% gastro-intestinal disorders (diarrhoea 0.8%, abdominal and epigastric pain 0.4%, nausea and vomiting 0.3%); 0.1 skin allergy; other adverse events <0.1%: dry mouth and thirst, anorexia, eructation, stomatitis, anxiety, head

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

Reviews

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

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

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

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

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

Children:

Well established use:

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

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

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

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

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

The following studies were conducted in children:

Controlled studies:

Authors, Year	**Number of Subjects by Arms, Age**
Stöcklin, 1959	n=100 children (verum: 50, control: 50)
Rath, 1968	n=100 children (verum: 71, placebo: 29) (47 as a monotherapy, 53 as an addition to antibiotics)
Gulyas, 1997	n=25 (10-16 years)
Mansfeld *et al.,* 1998	n=28 (13 female, 15 male, 7.8 ± 2.5 years) PPA=23 or 24
Gulyas, 1999	n=20 (Ivy: 10 /acetylcysteine: 10) 9-15 years
Unkauf and Friderich, 2000	n=52 (25 female, 27 male (25: Valverde, 27: Prospan)) mean 7.9 years
Maidannik *et al.,* 2003	n=72 children (7 month-15 years)
Bolbot *et al.,* 2004	50 children (2-10 years)

Uncontrolled studies:

Authors, Year	**Number of Subjects by Arms, Age**
Lässig *et al.,* 1996	n=113 (45% female, 55% male) 8.9 years (6-15 years)
Hecker, 1999	n=248 (138 female, 110 male)
Jahn and Müller 2000	n=372 (186 female, 178 male) 5.7 years 0-1 year: 26 1-3 years: 93 4-9 years: 189 10-16 years: 56 ≥16 years: 4; no information: 4
Roth, 2000	n=1024 (4.4 years) 0-1 year: 159 1-3 years: 404 4-9 years: 383 ≥10 years: 72
Hecker *et al.,* 2002	n=1350 (667 female, 682 male) up to 12 years: 165, 13-24 years: 128, up 25 years: 1043
Büechi and Kähler, 2003	n=56 (7-93 years, mean: 49 years)
Kraft, 2004 (retrospective)	n=52,478 (0-12 years) 0-1 year: 15%=7,871 1-5 years: 51%=26,763 6-9 years: 25%=13,119 ≥10-12 years: 9%=4,723
Fazio, 2009	5,181 (53.7%) children <1 year: 188 (3.6%), 1-5 years: 2,822 (54.5%), 6-12 years: 1,843 (35.6%) 13-14 years: 328 (6.3%).

The used dosages of the relevant extracts are tabulated in table 7 and 8. The daily dosages used in children are in high ranges. Ethanol-containing ivy preparations are used in daily dosages of

maximally 420 mg (over 12 years). Ethanol-free preparations are used in daily dosages of maximally 1 g (over 12 years).

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

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

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

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

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

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

Traditional use:

For the herbal preparation in the traditional use part usage in children has been documented. The use in children under 4 years is not recommended because medical advice should be sought.

4.3. Overall conclusions on clinical pharmacology and efficacy

The comparative study of Meyer-Wegener *et al.* (1993) showed that ivy extracts could be therapeutically equivalent to the secretolytic drug ambroxol in improvement of symtoms of cough in adults with chronic bronchitis. Bolbot (2004) showed an improvement of symptoms in children with acute bronchits comparable to the secretolytic drug ACC. The results indicated that patients with viscous sputum benefit from the ivy preparation for secretolytic therapy for short term use of maximum 4 weeks.
Ambroxol has a well established use licence for the indication “For secretolytic therapy in acute and chronic bronchopulmonary diseases, concomitant with disturbance in formation and transport of viscous sputum”. In the ATC classification system of the WHO, ambroxol is classified as R (respiratory system), R05 (cough and cold preparations), R05C (expectorants, excl. combinations with cough suppressants), R05CB (mucolytics).

The study of Meyer-Wegener *et al.* (1993) was performed in 1993 and “COPD” was newly defined in 2006. Therefore, indications examined in these studies would today be evaluated according to the guidance on COPD. There are no studies on ivy reflecting all features of COPD as currently defined. Therefore, an indication “chronic bronchitis” can not be supported because according the current definitions this would stand for COPD. Ivy products are often used in children, where COPD does not exist. An additional argument for restriction of chronic diseases is the fact, that the results are based on clinical studies with duration of maximum 4 weeks. This period is not in line with the definitions of “chronic” forms of bronchitis. The observational studies in children are conducted in acute diseases of the respiratory tract. Also “acute bronchitis” (the symptoms are dry cough, later

productive cough, often fever, sore throat, secretion of the nose and sometimes bronchial obstruction) does not exactly reflect the therapeutic benefit proven for ivy.
Symptom scores were analysed in many of non-controlled studies and an impairement on bronchitis symptoms could be shown. The influence on spirometric and bodyplethysmographic parameters was examined in clinical controlled studies. The results indicate a statistically significant improvement of lung function in comparison to placebo, but no significant better bronchodilatory effect.

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

Based on the clinical data the monograph has a WEU part and a traditional part:

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

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

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

After the HMPC discussion, it was decided to add the liquid extract (1:1), extraction solvent: ethanol 70% (V/V) in the WEU part of the monograph. It was considered, that the liquid extract (1:1), extraction solvent ethanol 70% (V/V) is comparable to the dry extract (3-6:1), extraction solvent ethanol 60% (m/m). The preparation of both extracts starts with the extraction of the herbal drug with ethanol. The ethanol concentration for the extraction of the ivy leaves is 60% (m/m) in the preparation of the dry extract while 62.4% (m/m) (= 70% (V/V)) in the preparation of the liquid extract. It was considered, that the minimal difference of the ethanol concentrations is unlikely to produce significant changes between the resulting herbal extracts.
The HMPC also decided to add the dry extract (DER 4-6:1), extraction solvent: ethanol 30% (V/V) (ethanol 24, 6% m/m) in the WEU part of the monograph. The analytical documentation comparing ivy leaf dry extract (4-6:1); extraction solvent: ethanol 30% (V/V) and ivy leaf dry extract (5-7, 5:1); extraction solvent: ethanol 30% (m/m) was the basic document for the market products in France and Spain. Considering this fact, the HMPC members decided to accept the documentation also for the monograph. These two preparations are combined as: dry extract (4-8:1), extraction solvent: ethanol 24-30% (m/m).
The HMPC further decided that for the WEU liquid preparation with the extraction solvent ethanol 70% (V/V) the use in children under 6 years of age cannot be recommended due to the content of ethanol per single dosage.

b) For the preparation soft extract (DER 2.2-2.9:1), extraction solvent ethanol 50% (V/V): propylene glycol the data do not fulfil the requirements of a well-established medicinal use with recognised efficacy and are not eligible for a marketing authorisation. The safety and plausibility of efficacy of this preparation is based on long standing use and experience for the indication as

secretolytic in common cold. The following indication is displayed in the traditional use part of the monograph: “Traditional herbal medicinal product used as an expectorant in cough associated with cold. The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use”.

Table 9: Posology recommended in the literature

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

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

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

Ethanol-containing preparations

In accordance with the above mentioned study results and the literature for all ethanol-containing ivy preparations maximum daily dosages are proposed because they have been shown to be effective:
2-5 years: 150 mg herbal substance
6-12 years: 210 mg herbal substance
>12 years: 420 mg herbal substance.

Ethanol-free preparations:

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

The study by Gulyas (1997) was conducted in 25 children (10-16 years) with Prospan® cough juice in a dosage of 3 times 5 ml corresponding to 656 mg of herbal substance. No other study exists which indicates that dosages higher than 656 mg of herbal substance are necessary in adults or

children for efficacy. There is no study that indicates that younger children (6-11 years old) should take 630 mg of herbal substance daily.

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

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

Assessor's comment:

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

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

Traditional use:
Soft extract (2.2-2.9:1), extraction solvent: ethanol 50% (V/V):propylene glycol (98:2)
One preparation has been marketed in Germany for more than 33 years, where it has been used for the treatment of symptoms of the common cold.
There is a comprehensive bibliographic revision to show the evidence of traditional use.
The safety and plausibility of efficacy of this preparation is based on the long-standing use and experience for the indication "Traditional herbal medicinal product used as an expectorant in cough associated with cold. The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use".

The traditionally used dosages are in "lower" ranges, in comparison with the ethanol-containing preparations.

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

5. Clinical Safety/Pharmacovigilance

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

Studies referring to allergic reactions

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

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

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

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

5.2. Patient exposure

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

5.3. Adverse events and serious adverse events and deaths

General data

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

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

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

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

Ivy poisoning in humans

Serious cases:

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

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

Assessor's comment:

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

Case reports

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

Hyposensitive reactions

A review of older dermatitis cases (1909 up to 1979) is given by Mitchell (1979). The author concluded, based on present evidence, that it is reasonable to conclude that *Hedera helix* is an irritant plant, which may also on occasions induce sensitization. Contact dermatitis has also been

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

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

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

Annex

List of references