EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 March 2011
EMA/HMPC/570419/2010
Committee on Herbal Medicinal Products (HMPC)

This document was valid from March 2011 until November 2015.

# Overview of comments received on Community herbal monograph on *Hedera helix* L., folium (EMA/HMPC/289430/2009)

Table 1: Organisations and/or individuals that commented on the draft Community herbal monograph on *Hedera helix* L., folium as released for public consultation on 8 March 2010 until 15 June 2010.

| | Organisations and/or individuals |
|---|---|
| 1 | Association of the European Self-Medication Industry (AESGP) |
| 2 | ARKOPHARMA Laboratories |
| 3 | European Scientific Cooperative on Phytotherapy (ESCOP) |
| 4 | Kooperation Phytopharmaka |



7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
**Telephone** +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
**E-mail** info@ema.europa.eu **Website** www.ema.europa.eu

Table 2: Discussion of comments

## General comments to draft document

| Interested party | Comment and Rationale | Outcome |
|---|---|---|
| AESGP | AESGP welcomes the preparation of the above-mentioned Community herbal monograph which should facilitate mutual recognition in Europe by harmonising the assessment criteria. | |
| ARKOPHARMA | ARKOPHARMA welcomes the preparation of the above-mentioned Community herbal monograph which should facilitate mutual recognition in Europe by harmonising the assessment criteria. | |
| ESCOP | The European Scientific Cooperative on Phytotherapy (ESCOP) appreciates the opportunity to comment on this draft Community Herbal Monograph prepared by the Committee on Herbal Medicinal Products (HMPC). The principle of having a harmonized monograph for the well-established use and the traditional use is welcomed. The draft assessment report gives a comprehensive overview of the accumulated scientific knowledge on Hedera helix L. folium over the last decades. Nevertheless, the following specific comments should be taken into consideration before finalising the community herbal monograph and the assessment report. | |
| Kooperation Phytopharmaka | Kooperation Phytopharmaka, a German scientific organisation, would like to comment on this HMPC draft Community herbal monograph of Hedera helix as follows. | |

## SPECIFIC COMMENTS ON TEXT

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| 2.<br>Qualitative and quantitative composition | AESGP | **Comments:**<br>Studies on Herbal preparations containing *Hedera helix* soft extract (DER 2.2-2.9:1) as well as the long use of authorised medicinal products confirm the well-established medicinal use. Two non-interventional studies have been submitted for re-registration in Germany and one randomised clinical trial was recently conducted in 2008/2009. These unpublished studies should be included in the assessment:<br><br>In 2008/2009, 590 patients were included in a randomised clinical trial comparing the *Hedera helix* soft extract containing medicinal product Hedelix s.a. drops versus Prospan drops with *Hedera helix* dry extract (DER 5-7.5:1) extracted with ethanol 30%. One hundred children aged up to 10 years were included. For the primary endpoint the mean improvement of the Bronchitis Severity Score was compared between test product and comparator. Non-inferiority of Hedelix concerning Prospan was statistically confirmed. These findings confirm the well-established medicinal use of the *Hedera helix* soft extract.<br><br>In 2001, in two non-interventional studies, 266 children up to 12 years were included. Primarily the safety of medicinal products with *Hedera helix* soft extract (DER 2.2-2.9:1) was assessed but efficacy was also assessed with descriptive parameters. The two non-interventional studies confirmed the good safety profile and the described bronchitis symptoms decreased during treatment. Together with alleviation of symptoms during treatment, assessment by physicians and | The enclosed document “list of products containing preparation A which are in the market in member states of the European Union” is included in the draft assessment report.<br>The proposed changes are not endorsed.<br><br>The confidential studies, for only internal HMPC use, are assessed in an enclosure document (at the end of this document) and not integrated in the assessment report. 590 patients were included in a randomised clinical trial comparing the *Hedera helix* soft extract containing medicinal product Hedelix s.a. drops versus Prospan drops with *Hedera helix* dry extract (DER 5-7.5:1) extracted with ethanol 30%. For the primary endpoint the mean improvement of the Bronchitis Severity Score was compared between test product and comparator. (Bronchitis Severity Score BSS is the sum of the 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 results of the randomised clinical trial do not confirm the WEU of the *Hedera helix* soft extract. The study can not prove efficacy in acute bronchitis.<br><br>The inclusion criteria of BSS ≥ 5 is too low for confirming a diagnosis of acute bronchitis (e.g. 4 |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | patients showed a good efficacy of the studied *Hedera helix* soft extract.<br><br>Further information is presented in the confidential study results submitted as unpublished data (see attached confidential Hedelix study reports – **for internal HMPC use only**!).<br>**Proposed change:**<br>We suggest to move preparation A) from the traditional use to the "well-established use":<br><br>**Preparation D) (new):**<br>Soft extract (DER 2.2-2.9:1), extraction solvent ethanol 50% V/V: propylene glycol (98:2)<br>New (unpublished) confidential studies (see attached).<br><br>Enclosure documents<br>**1. Abschlussbericht zur Anwendungsbeobachtung mit Hedelix® Hustentropfen s.a. bei Kindern bis einschließlich 12 Jahren mit Katarrh der Luftwege und zur symptomatischen Behandlung chronisch entzündlich rezidivierender Bronchialerkrankungen (Report 28.01.2002)**<br><br>**2. Abschlussbericht zur Anwendungsbeobachtung mit Hedelix® Hustensaft bei Kindern bis einschließlich 12 Jahren mit Katarrh der Luftwege und zur symptomatischen Behandlung chronisch entzündlich rezidivierender Bronchialerkrankungen (Report 30.01.2002)** | point for rhonchi and 1 point for cough= 5 points) The BSS values at the start of the study was of 6.2–6.3±1.2. These low values show, that only patients with minimal symptoms were treated. No placebo control was conducted, so no efficacy statement can be concluded in this self-limiting disease in "few ill" patients.<br><br>Referring to the secondary efficacy parameters, decrease of BSS ≥ 7 points by Visit 3 and BSS < 3 points at Visit 3, in the Hedelix group only 12.6% of the ITT dataset (37 of 293 patients) were classified as responders and 13.2% (39 of 295 patients) in the Prospan group. These results underline the fact, that the included patients had minimal symptoms at the start of the study.<br><br>The well-established-use indication of the draft monograph is "Herbal medicinal product used as an expectorant in case of productive cough". The study contains no data to the mean value of the symptoms "sputum" and "cough" at the beginning and the end of the study. No efficacy in the target indication can be concluded.<br><br>Positive aspects:<br>The results confirm a good safety profile and did not show unknown adverse effects. The study included children under 12 years (Hedelix: 2-4 years: n=33; 5-10 years n=67). These data supplement the data of the two non controlled surveillance studies. See |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | **3. Hedelix® Ability: Acute bronchitis therapy with ivy leaves extracts in a two-arm study. A double-blind, randomised study vs. active comparator (Report 28.10.2009**)<br><br>**4. An amended list of products containing preparation A which are in the market in Member States of the European Union.** | section 4.2. |
| 2.<br>Qualitative and quantitative composition | AESGP | **Comments:**<br><br>According to the Draft Assessment Report on *Hedera helix L., folium* the dry extract (DER 3-6:1), extraction solvent ethanol 60% m/m "fulfils the requirements of a well-established medicinal use with recognised efficacy" and is "eligible for a marketing authorisation in the indication 'herbal medicinal product used as an expectorant in case of productive cough' ". According to the general monograph *Extracts* of the Ph.Eur., dry extracts are prepared by extracting the herbal drug with a solvent of a suitable concentration and then by evaporating the solvent. Liquid extracts may be prepared either by direct extraction of the herbal drug by ethanol at a suitable concentration (1st method) or by preparing a soft (spissum) or dry extract (siccum) and dissolving it in ethanol or water (2nd method). The ethanol concentration used in the preparation of the soft or dry extract should be the same as the ethanol concentration used for the direct extraction.<br>The preparation of both extracts – dry extract (DER 3-6:1), extraction solvent ethanol 60% m/m and liquid extract (DER 1:1), extraction solvent ethanol 70% V/V - starts with the extraction of the herbal drug (ivy leaves) with ethanol. The | The HMPC decided to accept the suggestion and argumentation of AESGP.<br><br>According to the HMPC, the extract with ethanol 70% (V/V) as extraction solvent is not suitable for children below the age of 6 years due to the amount of ethanol. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | ethanol concentration for the extraction of the ivy leaves is 60% m/m in the preparation of the dry extract and 62.4% m/m (= 70% V/V) in the preparation of the liquid extract. The minimal difference of the ethanol concentrations is unlikely to produce significant changes between the resulting herbal extracts. The subsequent processing steps in the preparation of the liquid extract according to the 2nd method and in the preparation of the dry extract are also quite similar. In both processes the solvent is evaporated from the herbal extract (soft extract). The soft extract is then either dissolved in ethanol (liquid extract) or carefully dried (dry extract).<br>In consideration of the above, the liquid extract of ivy leaves (DER 1:1), extraction solvent ethanol 70% V/V should be considered equivalent to the dry extract of ivy leaves (DER 3-6:1), extraction solvent ethanol 60% m/m and should therefore be added to the list of preparations with well-established medicinal use as well.<br>**Proposed change:**<br>We suggest adding as **Preparation E) (new):**<br>"Liquid extract (DER 1:1), extraction solvent ethanol 70% V/V" (currently listed as Preparation B under "traditional use") to the herbal preparations listed under well-established use. | |
| 2. Qualitative and quantitative composition | ARKOPHARMA | Well established use<br>**Comments:**<br>Amongst products on the market in the European Member States, three additional medicinal products should be added to the list of specified products on the market (draft assessment report), two in **France (Activox Lierre®, Sirop and Activox Expectorant®, Pastille) and one in Spain (Arkotux** | 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 marketed products in France and Spain. Considering this fact, the HMPC members decided to accept the |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | **Jarabe®).** They were registered as traditional herbal medicinal products in France and with a well-established use status in Spain.<br><br>They contain as herbal preparation a **dry extract (4-6:1), extraction solvent: ethanol 30% V/V.**<br>**Activox Lierre®, Sirop (France):**<br>100 ml contains 1.00 g dry extract<br><br>Posology of the specified products<br>Adults : 3-4 x daily 5 ml<br>Children 10-15 years : 2-3 x daily 5 ml<br>Children 5-10 years : 3-4 x daily 2.5 ml<br>Children < 5 years : 2 x daily 2.5 ml<br>(MA 2001)<br><br>Posology of the preparation<br>Adults:<br>Single dose: 50 mg dry extract (corresponding to 250 mg herbal substance)<br>Daily dose: 150-200 mg dry extract (corresponding to 750-1000 mg herbal substance)<br>Children 10-15 years:<br>Single dose: 50 mg dry extract (corresponding to 250 mg herbal substance)<br>Daily dose: 100-150 mg dry extract (corresponding to 500-750 mg herbal substance)<br>Children 5-10 years:<br>Single dose: 25 mg dry extract (corresponding to 125 mg herbal substance)<br>Daily dose: 75-100 mg dry extract (corresponding to 375-500 | documentation also for EMA monograph.<br><br>The solvent strength difference between ethanol 30% V/V (ethanol 24.6% m/m) and ethanol 30% m/m has to be considered. The preparation is added into the WEU-part of the monograph as: dry extract (DER 4-8:1), extraction solvent ethanol 24-30% (m/m). The preparations are included in the assessment report in chapters “Information on period of medicinal use in the community” and “Specified strength/posology/route of administration/duration of use for relevant preparations and indication”. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | mg herbal substance)<br>Children <5 years:<br>Single dose: 25 mg dry extract (corresponding to 125 mg herbal substance)<br>Daily dose: 50 mg dry extract (corresponding to 250-1000 mg herbal substance)<br><br>**Activox Expectorant, Pastille (France)**<br>1 lozenge contains 30 mg dry extract<br><br>Posology of the specified products<br>Adults : 4-6 lozenges<br>Children 10-15 years : 3-4 lozenges<br>Children 6-10 years : 2-3 lozenges<br>(MA 2007)<br><br>Posology of the preparation<br>Adults:<br>Single dose: 30 mg dry extract (corresponding to 150 mg herbal substance)<br>Daily dose: 120-180 mg dry extract (corresponding to 600-900 mg herbal substance)<br>Children 10-15 years:<br>Single dose: 30 mg dry extract (corresponding to 150 mg herbal substance)<br>Daily dose: 90-120 mg dry extract (corresponding to 450-600 mg herbal substance)<br>Children 5-10 years:<br>Single dose: 30 mg dry extract (corresponding to 150 mg herbal substance)<br>Daily dose: 60-90 mg dry extract (corresponding to 300-450 | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | mg herbal substance)<br><br>**Arkotux Jarabe® (Spain):**<br>100 ml contains 1.00 g dry extract<br><br>Posology of the specified products<br>Adults : 3-4 x daily 5 ml<br>Children 10-15 years : 2-3 x daily 5 ml<br>Children 5-10 years : 3-4 x daily 2.5 ml<br>Children 2-5 years : 2 x daily 2.5 ml<br>(MA 2001)<br><br>Posology of the preparation<br>Adults:<br>Single dose: 50 mg dry extract (corresponding to 250 mg herbal substance)<br>Daily dose: 150-200 mg dry extract (corresponding to 750-1000 mg herbal substance)<br>Children 10-15 years:<br>Single dose: 50 mg dry extract (corresponding to 250 mg herbal substance)<br>Daily dose: 100-150 mg dry extract (corresponding to 500-750 mg herbal substance)<br>Children 5-10 years:<br>Single dose: 25 mg dry extract (corresponding to 125 mg herbal substance)<br>Daily dose: 75-100 mg dry extract (corresponding to 375-500 mg herbal substance)<br>Children 2-5 years:<br>Single dose: 25 mg dry extract (corresponding to 125 mg herbal substance) | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | Daily dose: 50 mg dry extract (corresponding to 250 mg herbal substance)<br><br>Remark: in order to grant a marketing authorisation to these herbal medicinal products, French and Spanish authorities asked for supporting data justifying that the chemical composition of the ivy leaf dry extract (4-6:1), ethanol 30% V/V was similar to the one of the ivy leaf dry extract (5-7.5:1), ethanol 30% m/m. The comparative study included:<br><br>• TLC and HPLC fingerprints of bidesmosidic (hederacosides B, C and D) and monodesmosidic (α-hederin) saponins;<br>• TLC and HPLC-UV fingerprints of polyphenolic compounds (flavonoids and phenolic acids) including rutin, chlorogenic acid, 3,5- and 4,5-dicaffeoylquinic acids;<br>• quantitative analysis of the main triterpene saponin, hederacoside C, and other bidesmosidic saponins (hederacoside B, hederacoside D) plus the monodesmosidic saponin α-hederin (3 batches for each drug substance) by liquid chromatography;<br>• quantitative analysis of rutin and chlorogenic acid (3 batches for each drug substance) by liquid chromatography.<br><br>The comparative study supported an appropriate phytoequivalence of the two active substances (similar qualitative and quantitative composition based on the main triterpene saponins and main phenolic compounds). Conformance of the active marker (hederacoside C) content of the ivy leaf dry extract (5-7.5:1), ethanol 30% m/m with specification established for the ivy leaf dry extract (4-6:1), | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | ethanol 30% V/V was checked. The solvent strength difference between ethanol 30% V/V (ethanol 24.6% m/m) and ethanol 30% m/m has no significant effect on the chemical composition of the two ivy leaf dry extracts which can support same efficacy.<br>Further information is presented in the confidential analytical documentation comparing ivy leaf dry extract (4-6:1), ethanol 30% V/V and ivy leaf dry extract (5-7.5:1), ethanol 30% m/m **(see attachment for internal HMPC use).**<br>In this condition, ivy leaf dry extract (4-6:1), ethanol 30% V/V, as an active substance of ivy preparations marketed in 2 EU countries for 10 years, should be considered equivalent to the dry extract of ivy leaf (5-7.5:1), ethanol 30% m/m and added to the list of herbal preparations with well-established medicinal use.<br>In the context of the addition of this herbal preparation, it is recommended to take into account the same DER as the one defined for herbal preparation A, i.e. 4-8:1, in order to cover the range of DER which can be observed for this preparation.<br><br>**Proposed change:**<br>Under ii) Herbal preparation, add:<br>We recommend adding the following traditional use indication:<br>D) Dry extract (DER 4-8:1), extraction solvent: ethanol 30% V/V<br><br>**Enclosure: "Analytical comparison of ivy leaf dry extracts contained in commercial syrups"** | |
| 4.1 Therapeutic | ESCOP | **Traditional use** | The suggestion is partially endorsed. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| indications | | **Comments:**<br>The traditional use of Ivy leaf in coughs has been reported in different handbooks. So, the traditional use indication should also mention it.<br>**Proposed change:**<br>Herbal medicinal product traditionally used for coughs and in common cold. | The use in self medication should cover only "cough" associated with common cold, and not the use in cough associated with other diseases (e.g. COPD).<br>The indication is changed in: "*Traditional herbal medicinal product used as an expectorant in cough associated with cold"*. The new formulation is in accordance with the formulation of other traditionally used plants in the same indication (e.g. HMPC monograph Foeniculum vulgare). |
| 4.2 Posology and method of administration Posology | AESGP | **Comments:**<br>**General considerations on the use in children below 5 years of age**<br>In Germany, since decades, most *hedera helix*-containing preparations include approved dosage regimen over decades for children of 0-5 years and 1-5 years (well-established medicinal use). *Hedera helix* is one of the few herbal meds which have been particularly well investigated in small children. Elimination of the posology for small children (0-)1-5 years of age (decision by MLWP, see page 77 of the draft Assessment Report) is not justified taking into account the clinical studies showing that the *Hedera helix* (ethanolic) extract is both efficacious and safe in children.<br>Regulation (EC) No 1901/2006 aims to facilitate the development and accessibility of medicinal products for use in the paediatric population and to improve information available on the use of medicinal products in various paediatric populations.<br>For this reason the demonstrated safe and effective long-term | **Well-established-use:**<br>The proposed changes are partially rejected. The use in children under two years of age is contraindicated because of the risk of aggravation of respiratory symptoms.<br>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 or recurrent cough in children between 2-4 years of age requires medical diagnosis before treatment." In several European countries mucolytic drugs are not used to treat acute cough or acute upper and lower respiratory tract infections in children younger than 2 years.<br>**Traditional use:** Preparation A)<br>Soft extract (DER 2.2.-2.9:1); extraction solvent ethanol 50% (V/V): propylene glycol (98:2).<br>The proposed changes referring to the traditional use |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | use of ethanolic ivy extracts (ethanol 30% and/or 40% m/m) in Europe and the results of clinical studies where more than 38326 children from 0-5 years of age are involved (page 72 of the draft assessment report: 8244 children aged 0-1 year, 497 children aged 1-3 years, and 29585 children aged 1-5 years) must be taken into consideration. Especially the use in small children (0-5 years) has shown to be effective and the tolerability was judged by physicians as "good" and "very good" in ranges of 90-98 % (positive risk-benefit-ratio!; see also page 73 of the draft assessment report).<br>Additionally, the ESCOP monograph (2003) on Ivy leaf includes on the basis of available data the following doses of drug for the respective age groups:<br>Ethanol-containing preparations:<br>0-1 year: 20-50 mg<br>1-4 years: 50-150 mg<br>4-12 years: 150-210 mg<br>Adults: 250-420 mg<br>Ethanol-free preparations:<br>0-1 year: 50-200 mg<br>1-4 years: 150-300 mg<br>4-12 years: 200-630 mg<br>Adults: 300-945 mg<br>The ESCOP monograph thus also supports a positive risk-benefit ratio for the use of Ivy leaf preparations already in small children.<br><br>**Specific comments on the posology of the different preparations**<br><br>**Preparation A** | in children under 12 years of age are rejected partially.<br><br>New clinical studies – for internal HMPC use only – were submitted. The confidential studies are assessed but not fully disclosed in the assessment report.<br><br>Based on the new data, in the monograph the following posology is added:<br><br>*"Children between 5-12 years of age:*<br>*Single dose: 20-26 mg*<br>*Daily dose: 80 mg*<br><br>*Children of 4 years of age*<br>*Single dose: 20 mg*<br>*Daily dose: 60 mg*<br><br>*The use in children under 4 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').*<br><br>(See also section 2-AESGP).<br><br>Preparation B:<br>Liquid extract (DER 1:1); extraction solvent ethanol 70% (V/V): The preparation was moved from traditional use to the well-established-use chapter (preparation D). (See also section 2) |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | The dosage recommendation of children younger than 4 years of age is mentioned in the Assessment Report (page 72). According to the Assessment Report the dosage has been proven in children from 0 to 4 years in various safety studies (page 72).<br>Ivy preparations are commonly used in children. In prospective clinical studies more than 7,000 children were involved and more than 52,000 children were analyzed in a retrospective study. The safety studies were conducted with a large number of children including groups of low age, for example:<br>0-1 year: 188 Fazio, (2006); 7,871 by Kraft, (2004); (= over 8.000 children).<br>1-5 years: 2,822 Fazio, (2006); 26,763 by Kraft, (2004); (= 29,585 children).<br><br>The tolerability was assessed by physicians and patients as "good" and "very good" in ranges of approximately 90-98%. In the study of Fazio, (2006) 5,181 (53.7%) children were treated 7 days with Prospan Cough Syrup (100 ml contain 0.7 g ivy dry extract 5-7.5:1, ethanol 30% m/m) for 7 days. The dosages recommended 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. Adverse events were reported in a total of 2.1% of the patients, while 1.2% were reported in children. 46 (0.5%) patients discontinued therapy due to adverse events, mainly 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% | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | were: dry mouth and thirst, anorexia, eructation, stomatitis, anxiety, headache, drowsiness.<br>The largest available safety study is the retrospective study published by Kraft (2004) which was conducted in 52,478 children. 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 of age, adverse effects occurred in 0.4% and in children over 9 years of age in 0.13%. However, the percentage of gastro-intestinal disturbances in children below 1 year of age was still only 0.27% and thus according to the definition of adverse event frequency is only to be rated as “uncommon”. This speaks in favour of a positive benefit-risk ratio of preparation A. We thus consider the general exclusion of children below 4 years of age as being a hasty and wrong conclusion which do not reflect the proven safety of preparation A.<br>The posology proposed above for children under 4 years of age is justified by the available scientific documentation and marketing experience with this products and should thus be accepted.<br><br>**Preparation B**<br>The efficacy has been proven in children from 1-5 years in various clinical studies. Safety has also been established. Therefore we strongly recommend to add the dosage recommendations for children 1-5 years of age as proposed above. | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | Preparation B is comparable with other preparations for which efficacy has also been proven in clinical studies. Especially preparation A) DER 4-8:1, extraction solvent ethanol 30% m/m and preparation B) DER 6-7:1, extraction solvent ethanol 40% m/m are comparable because the elution rate of both solvents is almost the same and the narrow DER 6-7:1 of extract B (40% m/m) lies within the wider range of extract A) 4-8:1 (30% m/m). This means that the natural range of constituents and/or the parameters of the extracts within two charges e.g. of preparation A) can be higher than between the preparations A) and B).<br>Additionally **Unkauf and Friderich, (2000)** demonstrated in a randomized prospective multicenter study (including 52 children) a statistically significant equivalence between the preparation C) DER 3-6:1, extraction solvent ethanol 60% m/m and the preparation A) DER 4-8:1, ethanol 30% m/m regarding bronchitis. The comparison of the laboratory values between the two preparations at the beginning of therapy and the end did not show any relevant variations. Thus the hydrophilic extract prepared with 30% m/m ethanol and the more lipophilic extract prepared with ethanol 60% m/m are both effective in the treatment of bronchitis in small children, indicating that the important active ingredients (not yet known) are present in all these ethanolic extracts in comparable extent.<br>Conclusion:<br>If the more hydrophilic preparation A) (DER 4-8:1, ethanol 30% m/m) and even the more lipophilic extract prepared with ethanol 60% m/m are both effective in the treatment of bronchitis, the preparation B) (DER 6-7:1, ethanol 40% m/m) | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | - in between, or close to the extract A) - has to be effective and safe in small children too if used in comparable dosage regimes (calculated to the same amount of *Hedera helix* herbal drug/day). This was concluded by the two clinical studies of Jahn and Müller, (2000) and Roth, (2000) (see below).<br>Furthermore, two clinical trials were conducted using preparation B (DER 6-7:1; ethanol 40% m/m). Both open studies support the safe and effective use of the preparation B in children 0-5 years of age suffering from various respiratory tract infections. These studies are discussed in the draft Assessment Report on page 62 ff:<br>***Jahn and Müller,*** *(2000)/Müller and Bracher, (2001): In an open study 372 children aged from 2 months to over 10 years suffering from respiratory tract infections were treated for 5-8 days. Depending on age, average daily doses ranged from 2.8 to 6.7 ml, corresponding to 150-420 mg of herbal substance. The patient age groups were:*<br>*0-1 year: n = 26*<br>*1-3 years: n = 93*<br>*4-9 years: n = 189*<br>*10-16 years: n = 56*<br>*≥ 16 years: n = 4; no information: n = 4*<br>***Roth, (2000)****: In an open study 1024 children suffering from acute infections of the upper respiratory system/bronchitis were treated with the same ivy leaf dry extract in two different alcohol free preparations (DER both (6-7:1), ethanol 40% (m/m)). The patient groups were the following:*<br>*Sedotussin drops:* | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | *0-1 year: 3x8 drops (0.166 g herbal substance) (n = 72)*<br>*1-3 years: 3x12 drops (0.250 g herbal substance)(n = 72)*<br>*4-9 years: 3x16 drops (0.333 g herbal substance)(n = 59)*<br>*greater 10 years: 3x25 drops (0.520 g herbal substance) (n = 36)*<br>*Sedotussin ivy juice:*<br>*0-1 year: 2 ml (0.118 g herbal substance) (n = 87)*<br>*1-3 years: 3 ml (0.177 g herbal substance) (n = 332)*<br>*4-9 years: 4 ml ( 0.236 g herbal substance) (n = 324)*<br>*greater 10 years: 6 ml (0.354 g herbal substance) (n = 36)*<br>*A significant decrease (p <0.01) of the complaints (cough, expectoration and dyspnoea) could be recorded at the end of the treatment. 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.*<br><br>Together with the other studies conducted with comparable ethanolic ivy preparations (especially preparation A) the proposed dosage regimen for children 1-5 years of age is justified.<br><br>Safety in children 0-5 years of age has also been established. The most frequent adverse effects in clinical studies are gastrointestinal disturbances, the incidence of adverse effects being age-dependent. In children under 1 year adverse effects occur in 0.4% and in children upon 9 years in 0.13%.<br><br>**Preparation D**<br>Children younger than 4 years of age have been included in one randomised clinical trial (2 years and older) and in non-interventional studies (1 month of age and older). The | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | resulting data confirm the safety and efficacy of *Hedera helix* soft extract in children (see comment for preparation D in section 2). In general, *Hedera helix* soft extract is authorised in medicinal products without restriction of age. Dependent on the composition of the other substances (e.g. menthol) restriction of age is possible.<br>As a consequence for all above mentioned preparations, the sentence "The use in children under 4 years of age is not recommended." should be adapted to the above-mentioned specific dosage regimen of the preparations.<br><br>**Traditional use**<br>The Assessment Report states that no clinical studies exist in children under 12 years of age. According to the European Directive 2004/24/EC, clinical studies are not required to justify the traditional use. The 30-years period of medicinal use of Ivy leaf preparations includes the use in children under 12 years of age. For this reason the use in children under 12 years of age is justified although no clinical studies exist.<br>As a consequence, the sentence "The use in children under 12 years of age is not recommended." should be adapted to the specific dosage regimen of the traditional preparation.<br><br>**Proposed change:**<br><br>**Well-established use:**<br><br>Herbal preparation A:<br>We suggest to add the following dosage recommendations for children of 0-4 years of age:<br>Single dose: 8-18 mg | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | Average daily dose: 25-35 mg<br>~~The use in children under 4 years of age is not recommended.~~<br><br><u>Herbal preparation B:</u><br>We suggest to add the following dosage recommendations for children of 1-5 years of age (instead of 4-5 years of age):<br>Single dose: 7-9 mg<br>Average daily dose: 17-27 mg<br>~~The use in children under 4 years of age is not recommended.~~<br><br><u>Herbal preparation D:</u><br>In accordance with the inclusion of preparation D under well-established use, we propose:<br>Adolescents, adults and elderly:<br>Single dose: 40 mg<br>Average daily dose: 120 mg<br>Children between 4-12 years of age:<br>Single dose: 20 mg<br>Average daily dose: 80 mg<br>Children between 1-4 years of age:<br>Single dose: 20 mg<br>Average daily dose: 60 mg<br>Children between 1 month and 1 year of age:<br>Single dose: 20 mg<br>Average daily dose: 20 mg<br>~~The use in children under 4 years of age is not recommended.~~<br><u>Herbal preparation E:</u><br>The text should move from “traditional use” to “well-established use”. | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | Traditional use<br>~~The use in children under 12 years of age is not recommended.~~ | |
| 4.2. Posology and method of administration | ARKOPHARMA | Well established use<br>**Comments:**<br>Based on the comparability of the ivy leaf dry extract (4-6:1), ethanol 30% V/V with the ivy leaf dry extract (5-7.5:1), ethanol 30% m/m, daily doses of herbal preparation D) would be the same as the one of herbal preparation A). | The proposal is accepted. |
| 4.2<br>Posology and method of administation | ESCOP | **Well established use**<br>**Comments:**<br>The draft community herbal monograph on Hedera helix L. folium includes range proposals of average daily doses for preparations of ivy dry extract (DER 4-8:1), extraction solvent ethanol 30% m/m (herbal preparation A) which are as follows:<br>Adolescents, adults and elderly: **45-105** mg<br>Children between 6-12 years of age: **33-70** mg<br>Children between 4-5 years of age: **25-35** mg.<br>Based on comments included in the "Draft Assessment Report on Hedera helix L. folium", it can be deduced that the lowest and the highest values of each range for the three age groups correspond to daily dosages for ethanol-containing ivy preparations having shown to be clinically effective and to the HMPC assessor's recommended maximum dosage of preparations without ethanol in the finished product (based on a DER of 6.25) respectively.<br>For example, in the case of ethanol-free preparations, it is recommended that the dosage for adults and children over 12 years of age should correspond to a maximum of 656 mg herbal substance daily, dosages for children 6-12 years and 4- | Higher dosages:<br>The proposed changes are not accepted.<br><br>There is no study which indicates that dosages higher than 656 mg 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 656 mg herbal substance daily.<br>In a randomised controlled double-blind comparative study (Meyer-Wegener *et al.*, 1993) 99 adult patients (aged from 25-70 years) with mild to moderate, simple or obstructive, chronic bronchitis were treated either 3-5 times daily with 20 drops of ivy leaves extract (5-7.5:1, ethanol 30% (m/m); 2 g of dry extract pro 100 ml) and 3 times daily 1 placebo tablet or 3-5 times daily with ambroxol 30 mg tablet and 3-5 times daily 20 drops placebo. The daily dosage was 0.25-0.42 g herbal substance. No higher dosages are needed for efficacy. In view of the pre-clinical safety data (hemolytic saponins), it was recommended, that the maximum dosage of preparations of ivy dry |

<table>
<tr><th>Section number and heading</th><th>Interested party</th><th>Comment and Rationale</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>5 years being 2/3 and 1/3 respectively. That means:<br>Adults and children over 12 years: 656 mg herbal substance (i.e. 105 mg preparation A)<br>6-12 years: 437 mg herbal substance (i.e. 70 mg preparation A)<br>4-5 years: 219 mg herbal substance (i.e. 35 mg preparation A).<br>However, these proposals of average daily dose ranges for ‘herbal preparation A’ do not cover adequately published data of controlled and non controlled clinical trials for ethanol-free preparations, ESCOP recommendations and daily dosages corresponding to the wide-spread medicinal use of the substance as a medicinal product in the Community in the form of ethanol-free medicinal preparations.<br><u>Published data of controlled and non controlled clinical trials:</u><br>The two tables below summarize the daily dosages which were used during clinical studies performed with ethanol-free and ethanol-containing finished products respectively, according to the different age groups (active substance: ivy dry extract (DER 5-7.5:1), extraction solvent ethanol 30% m/m). Daily dosages which are higher than the ones proposed for the corresponding age group of the HMPC draft recommendation (preparation A) are underlined and bold.<br>Table I. Ivy leaf dry extract daily dose according to the HMPC draft monograph versus dosages corresponding to clinical studies performed with ethanol-free finished products (active substance: ivy dry extract (DER 5-7.5:1), extraction solvent ethanol 30% m/m).<br><table><tr><th>HMPC draft monograph</th><td>Clinical studies</td></tr></table></td><td>extract (4-8:1) or (5-7.5:1) extraction solvent: ethanol 30% (m/m), without ethanol in the finished product, should correspond to a maximum of 656 mg herbal substance.<br>Distinct dosages for ethanolic-containing/ethanol-free finished products.<br>We agree to the fact, that distinct daily doses have been established for ethanolic-containing/ethanol-free finished products. The information for maximum dosages for alcohol-containing finished products is already included in the assessment report in chapter 4.3. The point was discussed in the MLWP but for formal aspects not accepted as proposed for the monograph. For transparency we add the information. In the monograph the following information is added:<br>Posology for preparation A (Adolescents, adults and elderly/6-12 years/2-5 years):<br>Note: Maximum dose for ethanol-containing finished products 67mg (corresponding to 420 mg herbal substance.<br>Note: Maximum dose for ethanol-containing finished products 34 mg (corresponding to 210 mg herbal substance.<br>Note: Maximum dose for ethanol-containing finished products 24 mg (corresponding to 150 mg herbal substance.)”</td></tr>
</table>

| Section number and heading | Interested party | Comment and Rationale | | Outcome |
|---|---|---|---|---|
| | | **recommendation (average daily dose)** | | **Use in children under 4 years of age:**<br>See comments above. |
| | | Adults<br>(preparation A: 45-105 mg) | Non controlled clinical studies:<br>***Hecker, 2002*: 97.5-<u>**130 mg**</u> (*effervescent tablets*)<br>***Büechi, 2003***: 52-<u>**156 mg**</u> (*pastilles*)<br>***Fazio, 2009*: 105-<u>**157.5 mg**</u> (*ethanol free juice*) | |
| | | **Children 6-12 years**<br>(preparation A: **33-70 mg** | Controlled clinical studies:<br>***Gulyas, 1997*: <u>**105 mg**</u> (*ethanol free juice*) / 10-15 years<br>***Mansfeld, 1997*: <u>**160 mg**</u> (suppositories) / 5-11 years<br>***Gulyas, 2000*: <u>**100 mg**</u> (*ethanol free syrup*) / 9-15 years<br>***Unkauf, 2000*: <u>**84-117 mg**</u> (4-10 years), <u>**112-156 mg**</u> (10-12 years) (*ethanol free juice*)<br>***Bolbot, 2004*: <u>**210 mg**</u> (*ethanol free juice*) / 7-10 years<br>***Maidannik, 2003*: <u>**210 mg**</u> (*ethanol free juice*) / 7-14 years | |

| Section number and heading | Interested party | Comment and Rationale | | Outcome |
|---|---|---|---|---|
| | | | Non controlled clinical studies:<br>***Lässig, 1996***: 52.5-**175 mg** (*ethanol free juice*) / 6-15 years<br>***Kraft, 2004***: **105 mg** (6-9 years), **115 mg** (up to 10 years) (*ethanol free juice*)<br>***Fazio, 2009***: **105 mg** (6-12 years) (*ethanol free juice*) | |
| | | Children **4-5 years** (preparation A: **25-35 mg** | Controlled clinical studies:<br>***Unkauf, 2000***: **55-80 mg** (up to 4 years) (*ethanol free juice*)<br>***Maidannik, 2003***: **105 mg** (*ethanol free juice*) / 1-6 years<br>***Bolbot, 2004***: **105 mg** (*ethanol free juice*) / 2-6 years<br>Non controlled clinical studies:<br>***Kraft, 2004***: **35 mg** (< 1 years), **60 mg** (1-5 years) (*ethanol free juice*)<br>***Fazio, 2009***: **52.5 mg** (0-5 years) (*ethanol free juice*) | |
| | | *Table II*. Ivy leaf dry extract daily dose according to the HMPC draft monograph versus dosages corresponding to clinical | | |

<table>
<tr><th>Section number and heading</th><th>Interested party</th><th>Comment and Rationale</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>studies performed with ethanol-containing finished products (active substance: ivy dry extract (DER 5-7.5:1), extraction solvent ethanol 30% m/m).<br><br><table><tr><td>HMPC draft monograph recommendation (average daily dose)</td><td>Clinical studies</td></tr><tr><td>Adults<br>(preparation A: 45-105 mg)</td><td><u>Controlled clinical studies</u>:<br>Meyer-Wegener, 1993: 42-70 mg (drops containing ethanol)</td></tr><tr><td>Children 6-12 years<br>(preparation A: 33-70 mg)</td><td><u>Controlled clinical studies</u>:<br>Gulyas, 1997: 42 mg (drops containing ethanol) / 10-15 years<br>Mansfeld, 1997: 35 mg (drops containing ethanol) / 5-11 years<br>Mansfeld, 1998: 35 mg (drops containing ethanol) / 4-12 years</td></tr></table><br>Ethanol-containing ivy preparations were clinically tested in daily dosages corresponding with the recommended average daily dose range of the HMPC draft monograph (Meyer-Wegener, 1993; Gulyas, 1997; Mansfeld, 1997; Mansfeld, 1998). Nevertheless, all clinical studies performed with ethanol-free preparations were based on higher daily dosages than proposed average daily dose range of the</td><td></td></tr>
</table>

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | **corresponding age group**. For example, beside the study of Gulyas (1997), other studies support a higher daily dosage than the proposed range of 33-70 mg for children aged between 6 and 12 years which were controlled (Gulyas, 2000; Unkauf, 2000; Bolbot, 2004; Maidannik, 2003) and uncontrolled studies (Lässig, 1996; Kraft, 2004; Fazio, 2006). Same observation can be made about the two other age groups. It is to be noticed that the dosage used in the Gulyas (1997) study (105 mg herbal preparation corresponding to 630 mg herbal substance) corresponded much more to the age group of children 6-12 years than the age group of adults and children over 12 years of age (study population aged 10-15 years).<br><br>ESCOP recommendations:<br>Dosage recommendations for ivy in ESCOP monograph (2004) are given with reference to the dried drug. In line with literature data distinct daily doses have been established for ethanolic preparations and ethanol-free preparations. They both reflect clinically tested dosages. Based on an average DER of 6.25 for dry extract (5-7.5:1) ethanol 30%, the ESCOP dosage recommendations are as follows:<br>*Adults*: 40-67 mg (ethanolic preparations), 48-150 mg (ethanol free preparations)<br>*Children 4-12 years*: 24-34 mg (ethanolic preparations), 32-100 mg (ethanol free preparations)<br>*Children 1-4 years*: 8-24 mg (ethanolic preparations), 24-48 mg (ethanol free preparations)<br>*Children 0-1 year*: 3-8 mg (ethanolic preparations), 8-32 mg (ethanol free preparations). | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | Daily dosages corresponding to the wide-spread medicinal use of the substance as a medicinal product in the Community: Products on the market in the European member states correspond to a consistent use over a long period of time of ivy drug products (details given in the draft assessment report). Posologies of these specified products are in line with ranges of clinically tested daily dosages according to each age group.<br><br>For example, the summary of posologies for dry extract (5-7.5:1) ethanol 30% for ethanol-free ivy preparations is as follows:<br>*Adults and adolescents more than 12 years*:<br>Single dose: 35-65 mg dry extract<br>Daily dose: 105-175 mg dry extract.<br>*Children 6-12 years*:<br>Single dose: 17.5-32.5 mg dry extract<br>Daily dose: 52.5-97.5 mg dry extract.<br>*Children 1-5 years*:<br>Single dose: 17.5 mg dry extract<br>Daily dose: 35 mg dry extract.<br>Conclusion:<br>based on documented clinical evidence, former ESCOP recommendations and posologies of herbal medicinal products containing ivy preparation A with a wide-spread medicinal use, it is justified to reconsider daily dosages in line with the recommendations of the "Guideline on the assessment of clinical safety and efficacy in the preparation of community herbal monographs for well-established and of community herbal monographs / entries to the community list for | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | traditional herbal medicinal products / substances / preparations" (EMEA/HMPC/104613/2005), to clearly separate posology of ethanol-free ivy preparations and ethanol containing ivy preparations, and to take into account a specific dosage which includes children between 1-4 years of age.<br><br>**Proposed change:**<br>*Adolescents, adults and elderly*<br>Herbal preparation A:<br>Single dose: **15-65 mg** (ethanol-free or ethanolic preparations)<br>Average daily dose: **40-70 mg** (ethanolic preparations), 50-**156 mg** (ethanol-free preparations)<br>*Children between 6-12 years of age*<br>Herbal preparation A:<br>Single dose: **11-35 mg** (ethanol-free or ethanolic preparations)<br>Average daily dose: **24-34 mg** (ethanolic preparations), **32-100 mg** (ethanol-free preparations)<br>*Children between 1-5 years of age*<br>Herbal preparation A:<br>Single dose: **8-18 mg** (ethanol-free or ethanolic preparations)<br>Average daily dose: **8-25 mg** (ethanolic preparations), **16-50 mg** (ethanol-free preparations) | |
| 4.2. Posology and method of administration | Kooperation Phytopharmaka | **Comments**<br>The decision of the MLWP as referenced in the Assessment Report to the monograph, page 83/86 ("decision by MLWP due to general considerations concerning clinical safety for this age group)" cannot be followed. | **Use in children from 2-3 years (under 4 years) of age (well-established use):**<br>See comments above. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | Especially ivy preparations are used since decades in numerous herbal medicinal products world-wide. This may be depicted at least from the referenced studies, which had been submitted and evaluated by the assessor of the monograph.<br>As highlighted in the list on page 83/86 of the assessment report, several thousands of children below 4 year of age had been treated with ivy preparations in prospective and controlled studies (studies by Jahn and Müller, 2000, Roth, 2000, Fazio, 2006, Kraft, 2004). Moreover, the study by Unkauf and Friedrich (2000) as well included children below 4 year of age (see assessment report page 45/87).<br>In our opinion it should be accepted that the proof of tolerability of herbal medicinal products in children may be shown with prospective studies of such design and quality, as it is not justified to conduct controlled clinical trials in these age group(s).<br>The results of these studies, covering a total of roughly 38,300 children (8244 children <1 year, 497 children 1-3 years, 29585 children 1-5 years) showed a rather low frequency of adverse effects with a incidence of 1.2% at maximum in children in the study of Fazio 2006. It has to be acknowledged, that the nature of the reported reactions is of minor clinical relevance, serious adverse events had never been reported.<br>If there are general safety concerns the exclusion of children below 1 year of age might be justified (but not supported by precise clinical adverse actions, but only by a somewhat higher incidence of adverse reactions as shown by Kraft 2004, see figure 2). But the available data from clinical observations of such a high number of children of 1-4 years of age has to | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | be accepted.<br>Further, under respect of such a high number of roughly 38,300 children the term "…although there are some clinical studies in children below 4 years of age" on page 77/87 in the assessment report is not understandable.<br>From such a database the frequency of minor adverse events of up to 1.2% at maximum (and of 0.15% at maximum for gastrointestinal reactions as shown by Kraft 2004, see figure 2) should be considered as scientific sufficient verified and for the considered age groups as acceptable.<br>Moreover, the pediatrician interrogation of Kooperation Phytopharmaka (referenced in the document: Kooperation Phytopharmaka. Stellungnahme zu „Efeu" - Kinderdosierungen vom 15.01.2003) revealed, that it is common in daily practice to prescribe ivy preparations to children below 4 years of age. This interrogation revealed, that the recommended dosages of preparations without ethanol are in the range of 233 ± 139 mg in children <1 year of age and 270 ± 154 mg in children of 1-4 years of age of equivalent drug amounts.<br>In summary, we consider the database as sufficient to support the use of preparations A, B, and C in children from 1-4 years of age.<br>**Proposed change**<br>We suggest to add the following under the "<u>well-established medicinal use</u>":<br>*Children between 1-5 years of age*<br>Herbal preparation A:<br>Single dose: 8-18 mg<br>Average daily dose: 25-35 mg | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | Herbal preparation B:<br>Single dose: 7-9 mg<br>Average daily dose: 17-27<br><br>Herbal preparation C:<br>Single dose: 17 mg<br>Average daily dose: 33 mg<br><br>The use in children under 1 year of age is not recommended (see section 4.4 'Special warnings and precautions for use'). | |
| 4.2 Posology and method of administration<br><u>Duration of use</u> | AESGP | **Comments:**<br>The wording should be consistent with the traditional use. Furthermore, the normal duration of cough is longer than 4-5 days. Additional information on the need to consult a doctor or pharmacist in case of dyspnoea, fever or purulent sputum is already covered by paragraph 4.4.<br><br>**Proposed change:**<br><br>**Well-established use:**<br>~~The medicinal product should not be used longer than 4-5 days without medical advice.~~<br>~~If the symptoms do not improve during the use of the medicinal product, a doctor or a pharmacist should be consulted.~~<br><br>If symptoms do not improve after 7 days, a doctor or a pharmacist should be consulted. | The proposed change is partly endorsed.<br><br>Well-established use:<br>"If the symptoms persist longer than one week during the use of the medicinal product, a doctor or a pharmacist should be consulted."<br><br>Traditional use:<br>"If the symptoms persist longer than one week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted." |
| 4.2<br>Posology and method of administration | AESGP | **Comments:**<br>The second sentence states that if symptoms persist longer than one week, a doctor should be consulted. Therefore the first sentence can be left out because the patient has to | See comments above. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| Duration of use | | consult a doctor who decides about the continuation of use. Furthermore the duration should be consistent with the well-established use.<br><br>**Proposed change:**<br><br>**Traditional use:**<br>~~Not to be used for more than 2 weeks~~ | |
| 4.2<br>Posology and method of administration<br>Duration of use | ESCOP | Well established use<br><br>**Duration of use**<br><br>**Comments:**<br>The proposed sentence "the medicinal product should not be used longer than 4-5 days without medical advice" is not adequate considering that ivy leaf preparations are used to treat common productive coughs due to benign catarrhal inflammation of the upper respiratory tract caused by a viral infection. So, it is recommended to combine and to replace the two sentences included under 'Duration of use' by the standard sentence included in different HMPC Community Herbal Monographs which recommends to consult a doctor or a pharmacist if symptoms persist.<br><br>**Proposed change:**<br>Replace "the medicinal product should not be used longer than 4-5 days without medical advice" and "If the symptoms do not improve during the use of the medicinal product, a doctor or a pharmacist should be consulted" by:<br>"If the symptoms persist for more than 4-5 days, a doctor or a pharmacist should be consulted". | See comments above (AESGP). |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| 4.3 Contra-indications | AESGP | **Comments:**<br>A general inclusion of the family of the Araliaceae (43 genera, approx. 1450 species) seems too wide and hardly comprehensible for both patients and medical professionals.<br><br>**Proposed change:**<br><br>We therefore propose the following modification:<br>"Hypersensitivity to the active substance ~~or to plants of the Araliaceae family~~." | The proposed change is rejected. Hypersensitivity to the plants of the family is well known and the information is given generally in HMPC monographs. |
| 4.4 Special warnings and precautions for use | AESGP | **Comments:**<br>The sentences "The use is not recommended in children below 4 years or 12 years" should be deleted for the reasons mentioned above under 4.2.<br>In case children below one year are excluded from the use, the second sentence under well-established use (vomiting and diarrhoea) should be deleted. In case such a warning is required (in case of inclusion of children under 1 year) the wording of the Assessment Report (page 77) "can occur" should be used because a causal relationship is not proven.<br><br>**Proposed change:**<br><br>~~The use is not recommended in children below 4 (WEU)/ 12 (Trad. use) years of age due to insufficient data~~<br><br>~~The use in children below one year of age may cause vomiting and diarrhoea~~ | The proposed changes are rejected partially. See also comments to 4.4 Kooperation Phytopharmaka.<br><br>The MLWP decided the preparations should not be used in children below 2 years of age, because they can cause vomiting and diarrhoea and because mucolytic drugs are in general not used in several European countries to treat acute cough and upper and lower respiratory tract infections in this age group. The information is added in chapter 4.3 "Contraindications" both for well-established and traditional use.<br><br>Well-established use: The MLWP decided to accept the use in children from 2-4 years under special conditions.<br><br>The following special warning is given: "Persistent or recurrent cough in children between 2-4 years of age requires medical diagnosis before treatment."<br><br>According to the HMPC decision, the fluid extract with ethanol 70% (V/V) as extraction solvent is not |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | | suitable for children below the age of 6 years due to the amount of ethanol.<br><br>Traditional use: The special warning for the use in children under 4 years of ages is not changed. The use in children under 4 years of age is not recommended because medical advice should be sought. |
| 4.4. Special warnings and precautions for use | Kooperation Phytopharmaka | See comments above (4.2).<br><br>**Proposed change:**<br>We suggest to add the following under the "<u>well-established medicinal use</u>":<br>Not recommended in children below 1 year of age, as the use may cause vomiting and diarrhoea. | See comments above. |
| 4.9 Overdose | AESGP | **Comments:**<br>We propose to leave out the description of the isolated case report regarding the 4 year old girl because it does not lead to additional information and relates to one defined product only. As no isolated case reports are mentioned e.g. under 4.8., it should consequently be left out here.<br><br>Under "traditional use" the statement should be left out as well because the case report was related to the well-established use.<br><br>**Proposed change:**<br><br>~~A 4 year old child developed aggressivity and diarrhoea after accidental intake of an ivy extract corresponding 1.8 g herbal substance.~~ | The proposed change is rejected. The chapter 4.9 should include information about overdoses. Cases of overdoses are usually isolated. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| 5.1 Pharmaco-dynamic properties | AESGP | **Comments:**<br><br>**Well-established use**<br><br>We suggest adding the main pharmacodynamic action "expectorant". Furthermore R05 CA (according to WHO) is specific for expectorants and should be added.<br><br>**Proposed change:**<br><br>Underlined part should be added:<br>Pharmacotherapeutic group: respiratory system<br>ATC code: RO5CA<br><br>Ivy extracts working as an expectorant. Additional anti-inflammatory actions have been reported. | The proposed change is rejected because no *in-vivo* studies referring to the pharmacodynamic action as "expectorant" exist. The formulation is changed in: «The mechanism of action is not known ». |
| 5.3 Preclinical safety data | AESGP | **Comments:**<br>We suggest to add: "…reproductive toxicity for Ivy leaf preparations is not available." because results of an Ames test are given for isolated substances.<br>Data on acute toxicity ($LD_{50}$) could be taken over from the ESCOP monograph: "The oral $LD_{50}$ of several Ivy leaf extracts in mice was determined as >3 g/kg b.w."<br>Existing data as mentioned under well-established should also be included under traditional use.<br><br>**Proposed change:**<br><br>**The oral $LD_{50}$ of several Ivy leaf extracts in mice was determined as >3 g/kg b.w.**<br>…<br>Data on carcinogenicity, genotoxicity and reproductive toxicity **for Ivy leaf preparations** testing are not available. | The suggestion, referring to acute toxicity is not adopted. No information about the tested extracts is given and only secondary literature is available.<br>The other suggestions are adopted. The formulation "Data on carcinogenicity, genotoxicity and reproductive toxicity testing are not available" is changed in "Data on carcinogenicity, genotoxicity and reproductive toxicity testing for ivy leaf preparations are not available."<br>The information on existing data is included also under "traditional use". |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| Other comments | AESGP | Some of the references mentioned in the draft Assessment Report (and therefore quoted in these comments) are not yet included in the HMPC List of References. They should be added to the list of references for Hedera helix.<br><br>Enclosure document : Additional Information about products on the EU Market (December 2009) | The information about products on the EU Market is added in the Assessment Report. |