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EMA/HMPC/680373/2013
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Hieracium pilosella* L., herba cum radice

Final

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Hieracium pilosella* L. , herba cum radice
Herbal preparation(s)	a) Comminuted herbal substance b) Powdered herbal substance
Pharmaceutical forms	Herbal preparation in solid or liquid dosage forms for oral use.
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1. Introduction

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

- Herbal substance(s)

Hieracium pilosella herba (Fam. Asteraceae) is part of the French and the British Herbal Pharmacopoeia. The following monographs exist:

- "Piloselle" published in the French Pharmacopoeia **(Ph. Fr., 1996)**: Whole or fragmented dry plant of *Hieracium pilosella* L. Content: minimum 2.5% of ortho-dihydroxycinnamic derivatives, expressed as chlorogenic acid ($C_{16}H_{18}O_9$; M_r 354.3) (dried drug).

  "Pilosella" **(BHP, 1979)**: Pilosella consists of the dried plant of *Pilosella officinarum* C.H. & F.W. Schultz (Fam. Compositae), a stoloniferous, scapigerous herb up to 30 cm in height, indigenous to the British Isles, Europe and Western Asia. Pilosella consists largely of leaf and contains the coumarin umbelliferone present predominantly as the 7-glucoside, the flavone luteolin and its 7-glucoside and other flavonoids, caffeic acid and chlorogenic acid.

A new monograph in the European Pharmacopoeia is being developed on *Hieracium pilosella*, with the following definition: Whole or fragmented, dried flowering aerial parts with parts of root of *Hieracium pilosella* L. Due to the small size and the shape of the herb, the herbal substance (collected during flowering) on the market always contains a part of the root, either the plant is collected manually or harvested mechanically.

The plant is small, 10-30 cm long. Widely polymorphic, where the stump emits creeping stolons. The flowering stem is lonely, erect, hairy and it ends in a white capitule where the involucre is covered by glandular dark hair. The leaves are lanceolate, about 3 cm long, greyish above with scattered slender hairs and whitish underneath due to the dense covering of branched hairs. Flowers solitary, pale yellow, composite, about 2-3 cm diameter, outer flowers often reddish underneath. The fruit is cylindrical and has simple, brittle tuft of hair (Paris and Moyse, 1971). Taste, bitter, slightly aromatic; odour, faint (Wren, 1998).

Synonyms: Mouse-ear; mouse-ear Hawkweed

Constituents: **(Bézanger-Beauquesne *et al*., 1980 ; Bruneton, 1998; Fournier, 1948; Garnier *et al*., 1961; Gruenwald, 2007; Paris and Moyse, 1971 ; Stanojević *et al*., 2009; Van Hellemont, 1986; Wren, 1998)**

Hydroxycoumarins: umbelliferone (mainly as 7-glucoside; about 0.60% of the dry plant material), skimmine

Flavonoids: luteolin, luteolin-7-*O*-glucoside, apigenin-7-*O*-glucoside (about 0.25% of the dry plant material), isoetin 4'-*O*-β-D-glucopyranoside (Gawrońska-Grzywacz *et al*., 2011)

Tannins

Triterpenoids: alpha- and beta-amyrin, taraxerol, taraxasterol and fern-7-en-3-beta-ol (Gawrońska - Grzywacz and Krzaczek, 2007)

Organic acids: caffeic acid, chlorogenic acid (about 20% of the dry plant material)

Ascorbic acid

According to Stanojević *et al*. (2009) the content of total phenolic compounds is about 240 mg gallic acid equivalents/g of dry extract, while total flavonoids content is close to 80 mg equivalents rutin/g of dry extract.

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

Not applicable.

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

France: Traditional use

1. Powdered drug

Since when on the market?	Pharmaceutical form	Posology / daily dosage
1986	Hard capsules	2 capsules (260 mg/capsule) two times daily. Up to 5 capsules daily, if necessary

Indications:
Traditionally used to promote urinary and digestive elimination functions.
Herbal preparation is currently on the market as an authorised product with a traditional therapeutic indication according to the French regulation before implementation of Directive 2004/24/EC.

Spain: Traditional use

1. Powdered drug

Since when on the market?	Pharmaceutical form	Posology / daily dosage
1. 1987	hard capsules	4 capsules daily/560mg
2. 1992	hard capsules	3-4 capsules daily (600-800 mg), up to 6 capsules daily (1200 mg)

Indications:
For all products: To promote urinary elimination function.
The herbal substance is also available in one combination product (capsules).

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products in the market
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Food Supplements (81 products)
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information available
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information available
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products in the market
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products in the market
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products in the market
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products in the market
France	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	Authorised product with a traditional therapeutic indication according to the French regulation before implementation of Directive 2004/24/EC
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products in the market
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products in the market
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information available
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information available
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products in the market
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products in the market
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information available
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information available
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information available
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information available
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information available
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information available
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information available
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information available
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products in the market
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products in the market
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information available
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information available
Spain	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products in the market
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products in the market

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

Available literature on *Hieracium pilosella* at the electronic databases PubMed, Toxline and The Cochraine Library and the incoming information during the "call for scientific data for use in HMPC assessment work on *Hieracium pilosella* L., herba cum flore", were used for search and assessment. Articles were filtered by using the following terms: *Hieracium pilosella*, Hawkweed. No restrictions to language were applied. The search was performed twice: March 2012 and July 2013.

Results in PubMed

Search term "*Hieracium pilosella*": 37 references obtained in 2013, most of them referring botanical or agricultural items (77.1%).
Search term "Hawkweed": 13 results.

Results in Toxline

Search term "*Hieracium pilosella*": 12 references.
Search term "Hawkweed": No results.

The Cochrane Library

No references were obtained for both search terms (*Hieracium pilosella* and Hawkweed)
Only articles found to be relevant for assessment are included in the list of references.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the European Union

According to the information provided by the National Competent Authorities, no medicinal products with a "well-established use" containing *Hieracium pilosella* herba cum radice or its preparation can be found in the European Union.

Based on the literature data and information provided by the National Competent Authorities, two herbal preparations, comminuted or powdered dried *Hieracium pilosella* herba cum radice have a "traditional use".

The comminuted or powdered dried herbal substance is mentioned in several monographs and handbooks and can be found in the European market since 1986.

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

Le Livre des Plantes Médicinales et Vénénouses de France (Fournier, 1948) describes the following plant properties: diuretic and in consequence aperitif and depurative, astringent, vulnerary, and bactericide. It also includes the reference from Laemmer (1922) as a strong uropoietic, with an increase in chlorure and urea elimination and it is also reporting the internal use of preparations from this specie since Early Middle Ages and Modern ages.

The **Resources Médicinales de la Flore FranÇaise (Garnier *et al*., 1961)** includes *Hieracium pilosella* as a dechlorurant and azoturic diuretic. It is reported, that it was used for influenza (grippe), brucellosis (as an infusion) and to increase diuresis. It was also used in combination with other herbs for rheumatism, gout and urinary lithiasis.

The reference in the **Précis de Matière Médicale (Paris and Moyse, 1971)** for *Hieracium pilosella* includes its strong diuretic activity; the whole plant is used as an infusion or decoction. It is useful against brucellosis.

The **British Herbal Pharmacopoeia (1979)** listed several therapeutic actions for Pilosellae herba: orally spasmolytic, expectorant, anticatarrhal, diuretic, sialagogue, topically vulnerary. The following indications are included: bronchitis, bronchitic asthma, whooping cough, heamoptysis, oedema. Topically applied for herniae and fractures as lotion or compress. Specific indications are: whooping cough, pulmonary affections with excessive sputum, doreness and haemoptysia.

The **Avis aux fabricants concernant les demandes d'autorisation de mise sur le marché de spécialités pharmaceutiques a base de plantes (Ministry of Health and Family, France, 1986)** includes the therapeutic indication « traditionally used to promote water elimination » for Pilosella; this is the same indication included in the **Précis de Phytothérapie by Leclerc (1994)** for the aerial parts from *Hieracium pilosella*.

The monograph in the **Potter's New Cyclopaedia of Botanical Drugs and Preparations (Wren, 1988)** listed the following medicinal uses: expectorant, diuretic, spasmolytic, sialagoge, vulnerary. It is used mainly for whooping cough, bronchitis and asthma as an infusion, and for wounds as a compress.

The monograph included in the **PDR for Herbal Medicines (2007)** describes the internal use of aerial part of Mouse Ear in the treatment of asthma, bronchitis, coughs and whooping cough, and externally in the treatment of wounds. The plant has shown to have diuretic, spasmolytic and diaphoretic effects. Also the reference by **Bishop and Davy (1994)** cited the use of the species against respiratory infections in the British Isles.

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

See section 1.2.

Several posologies for different preparations are available in the literature:

Preparation	Posology	Bibliographic reference
Infusion	100 g fresh plant/ 1 L water 2-4 g dried plant in water, 3 times daily	Font-Quer, 1983 Fournier, 1948 BHP, 1979
Fluid extract (No further specification)	2-4 g daily in 500 ml aromatised water 2-5 g daily of the stabilised fluid extract preparation, as follows: 4 g fluid extract, 100 g lemon syrup, water until 500 g	Fournier, 1948 Garnier et al., 1961
Liquid extract (no further specification)	2-4 ml 1:1 in 25% alcohol: 2-4 ml three times daily	Wren, 1988 BHP, 1979
Syrup (no further specification)	6% in simple syrup: 10-20 ml three times daily	BHP, 1979

Products in the market

Strength (name)	Posology	Route of administration / duration of use
260 mg powdered dried herbal substance	Adults and adolescents > 18 years: 2 capsules 2 times daily. Up to 5 capsules daily	Oral administration
140 mg powdered dried herbal substance	Adults and adolescents > 18 years: 2 capsules 2 times daily	Oral administration

The traditional use of the following *Hieracium pilosella* preparations is well documented, on the basis of the information on the availability of products in the market since 1986, together with the information on the use of such preparations, throughout a period of at least 30 years, as reflected in the bibliographic references and handbooks: comminuted herbal substance as herbal tea and herbal preparations in solid dosage forms, both for oral use.

Accordingly, these preparations are included in the *Hieracium pilosella*, herba cum radice monograph.

3. Non-Clinical Data

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

In general, polyphenolic compounds have shown antioxidant, antimutagenic, antiproliferative, cardioprotective, antiinflammatory and antimicrobial activities **(Stanojević *et al*. 2009)**.

There are limited non-clinical data on *Hieracium pilosella*. Recent studies reported the antioxidant, antiproliferative and antibacterial effects of a new flavonoid isolated from *Hieracium pilosella* (isoetin 4'-*O*-β-D-glucopyranoside) **(Gawrońska-Grzywacz *et al*., 2011)**.

It is well known, that tannins are a group of chemical compounds with tanning properties due to their ability to bond collagen fibers in the skin and so endorsing them with a better resistance to water, heat or abrasion **(Bruneton, 1998).**

3.1.1. Primary pharmacodynamic

No studies for the comminuted or powdered herbal substance could be found.

In vivo studies

The hydroalcoholic extract of *Hieracium pilosella*, aerial parts (dose of 50 mg/kg, i.p. administration), was tested for its diuretic activity in rats. Results showed a significant increase in diuresis from 2-24 h when compared with the control group, with a sizeable rise in Na^+ and K^+ excretion with respect to the control at 8 h. The pH remained unchanged (pH 8.4-8.8). Authors concluded that these results justify the use of this plant as diuretic agent in both traditional medicine and modern phytomedicine **(Beaux *et al*., 1999).**

3.1.2. Secondary pharmacodynamic

In vitro studies

Herbal preparations

Antimicrobial activity

Frey and Meyers (2010) studied the antibacterial activity of *Hieracium pilosella* against mostly avirulent (*Escherichia coli, Streptococcus lactis*) and moderately virulent (*Salmonella typhimurium*, *Staphylocuccus aureus*) microbes at the dose of 100 mg fresh material/ml water using the disk diffusion technique within 48 h preparation and tested using the 96-well plate assay. The extract was particularly effective against *Salmonella typhimurium* (MIC: 3.125 mg/ml).

Antioxidant activity

The antioxidant activity of the aqueous, ethanolic and methanolic extracts of *Hieracium pilosella* whole plant was tested and related to the total phenolic and flavonoid content **(Stanojević *et al*., 2009).** Results showed that it has significant free scavenging activity and is a potential source of natural antioxidants, chlorogenic acid being the most abundant phenolic compound in every extract.

Isolated substances

Antimicrobial activity

A flavonoid isolated from the methanolic extract of aerial parts of *Hieracium pilosella*, isoetin 4'-*O*-β-D-glucopyranoside, inhibited the growth of *Pseudomonas aeruginosa* ATCC 9027 with a MIC=125 µg/ml **(Gawrońska-Grzywacz *et al*., 2011).**

Antiproliferative activity

The antiproliferative effect of isoetin 4'-*O*-β-Dglucopyranoside, a flavonoid isolated from aerial parts of *Hieracium pilosella*, was assessed in two human tumor cell lines derived from lung (A549) and colon (HT-29) carcinomas. Cells were exposed to either culture medium (control) or tested flavonoid compound (1-100 µM) for 96 hours. Proliferation of A549 cells was not affected by up to 25 µM, however, at the highest concentrations (50 and 100 µM) a significant stimulatory effect was observed. In the case of HT-29 cell culture, the proliferation was significantly decreased (10-100 µM) in a non-dose dependent manner. Authors concluded that the flavonoid isoetin 4'-*O*-β-D-glucopyranoside showed a significant antiproliferative activity against colon (HT-29) carcinoma cell line **(Gawrońska-Grzywacz *et al*., 2011).**

Antioxidant activity

Gawrońska-Grzywacz *et al.* (2011) also tested the antioxidant activity of an isolated flavonoid from the methanolic extract of the aerial parts of *Hieracium pilosella* (isoetin 4'-*O*-β-D-glucopyranoside) and showed a strong scavenging activity through the reduction of DPPH (2,2-diphenyl-1-picrylhydrazyl) with EC_{50} 7.9 µM (3.7 µg/ml).

In vivo studies

No data available.

3.1.3. Safety pharmacology

No data available.

3.1.4. Pharmacodynamic interactions

No data available.

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

No data available.

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

3.3.1. Single dose toxicity

No data available.

3.3.2. Repeated dose toxicity

No data available.

3.3.3. Genotoxicity

No data available.

3.3.4. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

No data on developmental toxicity are available from the literature.

3.3.6. Local tolerance

No data are available from the literature.

3.3.7. Other special studies

Not available.

3.4. Overall conclusions on non-clinical data

The scientific information available on the pharmacological activity of *Hieracium pilosella* L., herba cum radice is limited. One study was performed with a dosage which was 7-fold higher than the one recommended for humans, but it was administered intraperitoneally to rats, hence it has limited relevance. However, the reported pharmacological effects are consistent with the traditional use.

There is no non-clinical information on the safety of *Hieracium pilosella* L., herba cum radice available.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

4. Clinical Data

4.1. Clinical Pharmacology

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

No data available.

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

No data available.

4.2. Clinical Efficacy

No clinical studies testing the efficacy of *Hieracium pilosella* L., herba cum radice have been published.

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

No data available.

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

No data available.

4.4. Overall conclusions on clinical pharmacology and efficacy

No clinical studies are available on the effects of *Hieracium pilosella*, herba cum radice on any disease.

Overall, the existing data do not meet the criteria for "well established medicinal use" in accordance with Directive 2001/83/EC.

The plausibilitiy of efficacy of the medicinal product is based on long-standing use and experience and allows the development of a European Union herbal monograph on the traditional use of *Hieracium pilosella* L., herba cum radice.

5. Clinical Safety/Pharmacovigilance

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

No data available.

5.2. Patient exposure

No data available.

5.3. Adverse events and serious adverse events and deaths

No data available.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

No data available.

5.6. Overall conclusions on clinical safety

No clinical data on safety is available.

On the basis of the information on traditional use, comminuted or powdered *Hieracium pilosella* L., herba cum radice is not considered harmful in the specified condition of use.

6. Overall conclusions

Well-established use cannot be accepted for *Hieracium pilosella* L., herba cum radice, due to the absence of authorised products according to Article 10a of Directive 2001/83/EC in the European Union and the lack of data to recognise efficacy.

Traditional medicinal use of *Hieracium pilosella* L., herba cum radice, is well documented in several handbooks and it is substantiated by the presence of medicinal products on the European market throughout a period of at least 30 years (15 years in the European Union), according to the requirements laid down in the Directive 2004/24/EC, for the following preparations and indication: comminuted herbal substance as a herbal tea and powdered herbal substance in solid pharmaceutical form for oral use as a traditional herbal medicinal product used to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary tract complaints.

The scientific information available on the pharmacological activity is limited. One study was performed with a dosage which was 7-fold higher than the one recommended for humans, but it was administered intraperitoneally to rats, hence it has limited relevance. However, the reported pharmacological effects are consistent with the traditional use.

There is neither non-clinical nor clinical information available on the safety of *Hieracium pilosella* L., herba cum radice, but the long-standing traditional medicinal use within the European Union supports the safe use of *Hieracium pilosella* L., herba cum radice in the recommended dosages under the conditions specified in the HMPC monograph.

No fertility data are available on the use of *Hieracium pilosella* L., herba cum radice.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

Therefore the use of *Hieracium pilosella* L., herba cum radice in pregnancy and lactation is not recommended and a list entry is not supported. In conclusion, *Hieracium pilosella* L., herba cum radice, for oral use is recommended with the following indication:

'*Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints".*

Annex

List of references