EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Hieracium pilosella* L., herba

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

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Hieracium pilosella* L. , herba
Herbal preparation(s)	a) Comminuted herbal substance b) Powdered herbal substance
Pharmaceutical forms	Comminuted herbal substance as herbal tea for oral use. Herbal preparation in solid or liquid dosage forms for oral use.
Rapporteur	Olga Palomino
Assessor(s)	Olga Palomino

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

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

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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 a component part of the French and the British Herbal Pharmacopoeia. The following monographs exists:

- Piloselle published in the French Pharmacopoeia **(Fr.Ph. 1996)**: Whole plant or fragmented plant of *Hieracium pilosella* L. Content: minimum 2.5 per cent of ortho-dihydroxycinnamic derivatives, expressed as chlorogenic acid ($C_{16}H_{18}O_9$; M_T 354.3) (dried drug)
- Pilosella **(BHP)**: Pilosella consists of the dried plant of *Pilosella officinarum* C.H. & F.W. Schultz (Fam. Compositae), a stoloniferous, scapigerous herb up to 30cm 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.

The plant is small, 10-30cm 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 3cm long, greyish above with scattered slender hairs and whitish underneath due to the dense covering of branched hairs. Flowers solitary, pale yellow, composite, about 2-3cm diameter, outer flowers often reddish underneath. The fruit is cylindrical and has simple, brittle tuft of hair **(Paris, 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 ; Stanojevic 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-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 (Gawronska-Grzywacz and Krzaczek, 2007)
Organic acids: caffeic acid, chlorogenic acid (about 20% of the dry plant material)
Ascorbic acid

According to Stanojevic 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
1. 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 substance is on the market as Authorised product

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 (1200mg)

Indications:

For all products: To promote urinary elimination function.

Herbal substance is on the market.

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:	
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

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

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

1.3. Search and assessment methodology

Available literature on *Hieracium pilosella* at the electronic databases PubMed, Toxline and The Cochraine Library and the incoming, on the "call for scientific data for use in HMPC assessment work on *Hieracium pilosella* L., herba", was used for a literature search. 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 (*H. 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 Community

According to the information provided by the National Competent Authorities, no preparations within *Hieracium pilosella* herb with a "well-established use" can be found in the European Community.

Based on the data provided by the NationalCompetent Authorities, some *Hieracium pilosella* herb products have a "traditional use".

1. Powdered dry herb

This product is recognized as a traditional product 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* activity as a dechlorurant and azoturic diuretic. It is also used for influenza (grippe), to increase diuresis, to relieve Malta and swaying fevers, as an infusion. 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 brucelloses.

The **British Herbal Pharmacopoeia (1979)** listed several therapeutic actions for Pilosella herba: 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 *H. 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. An extract shows weak antifungal activity.

The *a* as a diuretic

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 et Davy (1994)** cited the use of the specie 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.

Insert table with different extracts

Several posologies for different preparations are available in the literature:

Preparation	Posology	Bibliographic reference
Infusion	100g fresh plant/ 1L water 2-4g dried plant in water, 3 times daily	Font-Quer, 1983 Fournier, 1948 BHP, 1979
Fluid extract	2-4 g daily in 500ml aromatized water 2-5g daily of the stabilised fluid extract preparation, as follows: 4g fluid extract, 100g lemon syrup, water until 500g	Fournier, 1948 Garnier et al., 1961
Liquid extract	2-4ml 1:1 in 25% alcohol: 2-4ml three times daily	Wren, 1988 BHP, 1979
Syrup	6% in simple syrup: 10-20ml three times daily	BHP, 1979

Products in the market

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

The traditional use of the following *H. pilosella* preparations: comminuted herbal substance as herbal tea and herbal preparations in solid or liquid dosage forms, both for oral use, is well documented, on the basis of the information on the availability of products in the market since 1986, provided by the Member States, 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. Accordingly, these preparations have been included in the *H. pilosella,* herba monograph.

3. Non-Clinical Data

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

Polyphenolic compounds have shown antioxidant, antimutagenic, antiproliferative, cardioprotective, antiinflammatory and antimicrobial activities **(Stanojević *et al.* 2008; 2009).** Recent studies proved the antioxidant and antibacterial effects of a new flavonoid isolated from *H. pilosella* (isoetin 4'-O-β-D-glucopyranoside) **(Gawrońska-Grzywacz *et al*., 2011).**

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 powdered material could be found.

In vivo studies

The hydroalcoholic extract of *Hieracium pilosella,* aerial parts (dose of 50mg/kg, i.p. administration), was tested for its diuretic activity in rats. Results showed a significant increase in diuresis from 2-24h when compared with the control group, with a sizeable rise in Na^+ and K^+ excretion with respect to the control at 8h. The pH remained unchanged (pH 8.4-8.8). Authors conclude 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 et 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 100mg fresh material/ml water using the disk diffusion technique within 48h preparation and tested using the 96-well plate assay. The extract was particularly effective against *S. typhimurium* (MIC: 3.125 mg/ml).

Antioxidant activity

The antioxidant activity of the aqueous, ethanol and methanol extracts of *Hieracium pilosella* whole plant was tested and related to the total phenolic and flavonoid content **(Stanojevic *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.

Gawrońska-Grzywacz *et al*. (2011) also tested the antioxidant activity of an isolated flavonoid from the methanolic extract of the aerial parts of *H. pilosella* (isoetin 4'-O-β-D-glucopyranoside) and proved its strong scavenging activity.

Isolated substances

Antimicrobial activity

A flavonoid isolated from the methanolic extract of aerial parts of *H. pilosella*, isoetin 4'-O-β-D-glucopyranoside, inhibits growth of *Pseudomonas aeruginosa* ATCC 9027 with 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 *H. 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 *H. pilosella* (isoetin 4'-O-β-D-glucopyranoside) and proved its strong scavenging activity through the reduction of DPPH with EC50 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 *Hieracium pilosella* herba pharmacological activity is limited to one work that is performed with a dosage which is 7fold higher than the one recommended for humans, and so it's scarce to support the proposed indication. Nonetheless, the reported pharmacological effects agree with the traditional use.

There is no non-clinical information on the safety of *Hieracium pilosella* herba available. As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended. Due to the lack of genotoxicity studies, the list entry cannot be recommended.

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 *Hieracium pilosella* herba efficacy have been published.

4.2.1. Clinical studies (case studies and clinical trials)

No data available.

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

Not found.

4.3. Overall conclusions on clinical pharmacology and efficacy

No clinical studies have been found on the effects of *Hieracium pilosella* 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 Community herbal monograph on the traditional use of *Hieracium pilosella* herba.

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

The medicinal product proves not to be harmful in the specified conditions of use on the basis of the information on its traditional use.

6. Overall conclusions

Well-established use can not accepted for *Hieracium pilosella* L., herba, due to the lack of data on clinical efficacy, in accordance with Directive 2001/83/EC.

There exist no data in relation to reproductive and developmental safety, so the use of Hawkweed in pregnancy is not recommended. Also, because of the lack of data on genotoxicity a list entry is not suggested.

Traditional medicinal use of *Hieracium pilosella* L., herba, is well documented in several handbooks throughout a period of at least 30 years (15 years in the European Community) under Directive 2004/24/EC. Traditional use has shown that *H. pilosella* herba can be recognized as safe when used in recommended dosages under the conditions specified in the monograph.

Several preparations and posologies for *H. pilosella* are included in handbooks. Those including relevant information regarding preparation and dosage have been included in the monograph, together with the existing marketing preparations.

In conclusion, a monograph *Hieracium pilosella* L., herba, 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