EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Pilosella officinarum* Vall. *(*syn *Hieracium pilosella* L.), herba cum radice

Draft – Revision 1

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

Herbal substance (binomial scientific name of the plant, including plant part)		*Pilosella officinarum* Vall. (syn *Hieracium pilosella* L.) , herba cum radice
Herbal preparations		a) Comminuted herbal substance b) Powdered herbal substance
Pharmaceutical form		Herbal preparation in solid or liquid dosage forms for oral use
First assessment	Rapporteur	O. Palomino
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Note: This draft assessment report is published to support the public consultation of the draft revised European Union herbal monograph on *Pilosella officinarum* Vall. (syn *Hieracium pilosella* L.), herba cum radice. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on 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 revised monograph. During the revision, the name of the monograph was changed because *Hieracium pilosella* L. is now classified as a synonym *of Pilosella officinarum* Vall**.**

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1. Introduction

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

- Herbal substance(s)

Pilosella officinarum Vall. (syn *Hieracium pilosella* L.) 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 *Pilosella officinarum* Vall. 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.

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

- Herbal preparation(s)

Powdered herbal substance. For constituents see herbal substance.

- 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. Search and assessment methodology

In 2013, available literature on *Hieracium pilosella* L. in 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.

For the revision of the monograph

Data from EU and non-EU regulatory authorities: No new herbal medicinal products containing *Pilosella officinarum* Vall. (syn *Hieracium pilosella* L.) herba cum radice as single active ingredient were reported and no scientific data were submitted by interested parties during the call for scientific data from 15 March 2022 to 14 June 2022.

Other resources: For the review of the monograph, Scopus and Embase were searched on 18 February 2023 with the search key "Hieracium and Pilosella" and on 12 February 2024 with "Pilosella and Officinarum" in the time period from the year 2013 onwards. No other restrictions were made. With the search key "Hieracium and Pilosella" 109 new references not yet available during the first/previous assessment were identified via Scopus and 40 via Embase. Using "Pilosella and Officinarum" as search key, 35 references were found in Scopus and 5 in Embase. None of these were considered to be relevant for the monograph.

A search in Pharmacovigilance resources resulted in 8 hits; 5 cases in Vigibase and 3 cases in Eudravigilance. In all reported cases there was concomitant use with other herbal products and/or medicinal products.

2. Data on medicinal use

2.1. Information about products on the market

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

According to the information provided by the National Competent Authorities, no medicinal products with a "well-established use" containing *Pilosella officinarum* Vall. (syn *Hieracium pilosella* L.), 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 *Pilosella officinarum* Vall. (sym *Hieracium pilosella* L.), 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.

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form	Regulatory Status
Powdered drug	Traditionally used to promote urinary and digestive elimination functions.	2 capsules (260 mg/capsule) two times daily. Up to 5 capsules daily, if necessary	1986, France
Powdered drug	To promote urinary elimination function	280 mg two times daily	1987, Spain
Powdered drug	To promote urinary elimination function	3-4 capsules daily (600-800 mg), up to 6 capsules daily (1200 mg)	1992, Spain

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

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

Not applicable.

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

Not applicable.

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

Not applicable.

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

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 L. 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 L.* 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* L..

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.

Table 2.1: Overview of historical data

Herbal preparation	**Documented use / Traditional use**	**Posology**	**Reference**
Infusion	Diuretic and in consequence aperitif and depurative, astringent, vulnerary, and bactericide	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)	used for influenza, brucellosis (and to increase diuresis	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)	bronchitis, bronchitic asthma, whooping cough, heamoptysis, oedema	2-4 ml 1:1 in 25% alcohol: 2-4 ml three times daily	Wren, 1988 BHP, 1979
Syrup (no further specification)	bronchitis, bronchitic asthma, whooping cough, heamoptysis, oedema	6% in simple syrup: 10-20 ml three times daily	BHP, 1979

2.3. Overall conclusions on medicinal use

Table 2.3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	**Indication**	**Posology, Strength**	**Period of medicinal use**
Infusion	As a diuretic	2-4 g dried plant in water, 3 times daily	Fournier, 1948 BHP, 1979
powdered dried herbal substance	To promote urinary elimination function	280 mg 2 times daily.	Spain, 1987
powdered dried herbal substance	Traditionally used to promote urinary and digestive elimination functions.	2x 260 mg (=520 mg) two times daily. Up to 5 capsules daily, if necessary	France 1986
powdered dried herbal substance	To promote urinary elimination function	600-800 mg. Up to 1200 mg daily	Spain, 1992

The traditional use of the following *Pilosella officinarum* Vall. 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 *Pilosella officinarum* Vall. (syn *Hieracium pilosella* L.), herba cum radice monograph.

3. Non-Clinical Data

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

There are limited non-clinical data on *Pilosella officinarum* Vall.. Recent studies reported the antioxidant, antiproliferative and antibacterial effects of a new flavonoid isolated from *Pilosella officinarum* Vall. (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. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

3.1.1. Primary pharmacodynamics

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

In vivo studies

The hydroalcoholic extract of *Pilosella officinarum* Vall., 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 pharmacodynamics

In vitro studies

Herbal preparations

Antimicrobial activity

Frey and Meyers (2010) studied the antibacterial activity of *Pilosella officinarum* Vall. 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 *Pilosella officinarum* Vall. 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 *Pilosella officinarum* Vall., 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 *Pilosella officinarum* Vall. was assessed in two human tumour 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 *Pilosella officinarum* Vall. (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.

3.1.5. Conclusions

The scientific information available on the pharmacological activity of *Pilosella officinarum* Vall. (syn *Hieracium pilosella* L.), herba cum radice is limited. Only one *in vivo* study was performed in rats using a hydroalcoholic extract of the arial parts of *Pilosella officinarum* Vall. (dose of 50 mg/kg, i.p. administration). In view of the method of administration and the type of extract used, the study has limited relevance for the monograph. However, the reported pharmacological effects are consistent with the traditional use.

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

No data available.

3.3.1. Single dose toxicity

No data available.

3.3.2. Repeat 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 available.

3.3.6. Local tolerance

No data available.

3.3.7. Other special studies

No data available.

3.3.8. Conclusions

No non-clinical information on the safety of *Pilosella officinarum* Vall. (syn *Hieracium pilosella* L.), herba cum radice available. Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

3.4. Overall conclusions on non-clinical data

Results from relevant experimental studies on *Pilosella officinarum* Vall. (syn *Hieracium pilosella* L.), herba cum radice to support the proposed indication are very limited. A diuretic activity is reported for a hydroalcoholic extract. This extract is not included in the monograph. Nonetheless, the reported pharmacological effect is consistent with the traditional use.

Non-clinical information on the safety of *Pilosella officinarum* Vall. (syn *Hieracium pilosella* L.), herba cum radice is not available.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed. As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

Based on the longstanding use, oral administration of *Pilosella officinarum* Vall. (syn *Hieracium pilosella* L.), herba cum radice can be regarded as safe at traditionally used doses. However, adequate fluid intake is required during treatment *Pilosella officinarum* Vall. (syn *Hieracium pilosella* L.), herba cum radice is not recommended for patients with conditions where reduced fluid intake is advised.

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 data available.

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 *Pilosella officinarum* Vall. (syn *Hieracium pilosella* L.), 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 *Pilosella officinarum* Vall. (syn *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, serious adverse events and deaths

A search in Pharmacovigilance resources resulted in 8 hits; 5 cases in Vigibase and 3 cases in Eudravigilance. Two serious cases, one with hepatitis were reported. In all reported cases there was concomitant use of other herbs and other medicines (paracetamol). Therefore, these reports do not trigger a change in the monograph that was adopted in 2015.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

No data available.

5.5.1. Use in children and adolescents

No data available.

5.5.2. Contraindications

No data available.

5.5.3. Special warnings and precautions for use

No data available.

5.5.4. Drug interactions and other forms of interaction

No data available.

5.5.5. Fertility, pregnancy and lactation

No data available.

5.5.6. Overdose

No data available.

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

No data available.

5.5.8. Safety in other special 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 *Pilosella officinarum* Vall. (syn *Hieracium pilosella* L.), herba cum radice is not considered harmful in the specified condition of use.

6. Overall conclusions (benefit-risk assessment)

Due to the absence of an authorised products according to Article 10a of Directive 2001/83/EC in the European Union and the lack of data to recognise efficacy, well-established use cannot be accepted for *Pilosella officinarum* Vall. (syn *Hieracium pilosella* L.), herba cum radice.

Traditional medicinal use of *Pilosella officinarum* Vall. (syn *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. A diuretic activity was observed in rats with a intraperitoneally administered hydroalcoholic extract. This extract is not included in the monograph, but the observed diuretic effect is consistent with the traditional use.

There is neither non-clinical nor clinical information available on the safety of *Pilosella officinarum* Vall. (syn *Hieracium pilosella* L.), herba cum radice, but the long-standing traditional medicinal use within the European Union supports the safe use of *Pilosella officinarum* Vall. (syn *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 *Pilosella officinarum* Vall. (syn *Hieracium pilosella* L.), herba cum radice.

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

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

'Traditional herbal medicinal product used for the relief of symptoms associated with minor urinary tract complaints in addition to the general recommendation of a sufficient fluid intake to increase the amount of urine".

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

A European Union list entry is not supported due to lack of data on genotoxicity.

Annex

List of references