15 January 2014
EMA/HMPC/280194/2013
Committee on Herbal Medicinal Products (HMPC)

# Assessment report on *Sisymbrium officinale* (L.) Scop., 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) | *Sisymbrium officinale* (L.) Scop., herba |
| Herbal preparation(s) | Dry extract (DER 3.5-5.5:1), extraction solvent water<br>Dry extract (DER 6-8:1), extraction solvent water |
| Pharmaceutical form(s) | Herbal preparation in liquid dosage form for oral use<br>Herbal preparations in solid dosage form for oromucosal use |
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| Assessor(s) | Dr. Zsuzsanna Biró-Sándor |

Note: This draft assessment report is published to support the release for public consultation of the draft Community herbal monograph on *Sisymbrium officinale* (L.) Scop., herba. It should be noted that this document is a working document, not yet fully 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.

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# 1. Introduction

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

- Herbal substance(s)

Dried flowering aerial parts of *Sisymbrium officinale* (L.) Scopoli (= *Erysimum officinale* L.) contain a minimum of 0.3% of total glucosinolates expressed as sinigrin ($C_{10}H_{16}KNO_9S_2$; $M_r$397,5) (calculated for the dried herbal substance) (Ph. Fr. 1998).

**Main active compounds**

Van Hellemont 1986, Hagers Handbuch (Kern *et al.* 1979):
Essential oil; glucosinolates; thiocyanic glycoside; cardenolide glycosides in the semen

Hagers Handbuch (Hänsel *et al.* 1994):

Glycosinolates: in the fresh plant chiefly sinigrin (allylglucosinalates) and gluconapin (3-butenylglucosinolates)

Vitamins: ascorbic acid (216.5 mg/100 g in fresh foliage)

Cardioactive steroid glucosides: in the tips of the foliage including among others corchorosid A (18.5 mg/100 g) and helveticosid (4.5 mg/100 g)

The chemical markers of *Sisymbrium officinale* are sulphated compounds, particularly glucosinolates, isothiocyanates and sulphated lactones, are also found in mustard oil (Gruenwald *et al.* 2004); the main glucosinolate is glucoputranjivine (Carnat *et al.* 1998).

The therapeutic activity of *Sisymbrium officinale* is attributed to the sulphated components (Paris & Moyse 1981). Historically, the sulphated compounds are reputed to stimulate the mucosal secretion in the upper respiratory tract, so increasing expectoration (Leclerc 1983).

Dried flowering aerial parts contain: total glucosinolates 0.63 and 0.94%, mucilages 13.5 and 10.9%, total itols 8.9 and 10.2%, total flavonoids 0.50 and 0.56%, respectively (Carnat *et al.* 1998).

The chemical composition of an aqueous dry extract (DER: 4:1) of the aerial parts of *Sisymbrium officinale* was analysed by TLC and HPLC. The TLC performed in isopropanol/ethylacetate/water, stated the absence of sinigrin and presence of putranjivine and proline. HPLC confirmed these findings and allowed the quantitative determination of putranjivine that resulted to be 0.5 mg/g (Di Sotto *et al.* 2010).

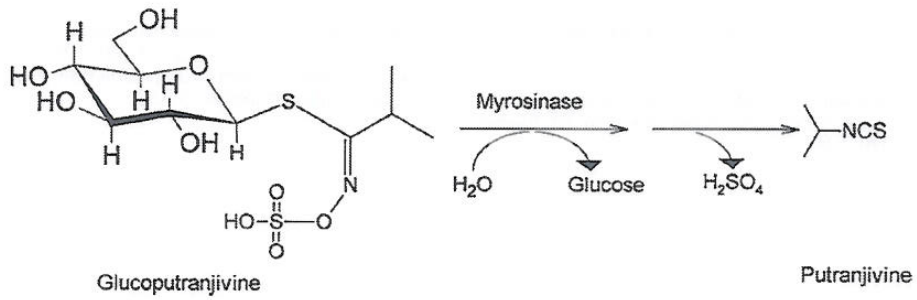


Figure 1: Molecular structure and biosynthesis of putrajivine.

Glucoputranjivin and isopropyl isothiocyanate were isolated from an aqueous dry extract of *Sisymbrium officinale* and were identified by spectroscopic analysis (Di Sotto *et al*. 2012)

Analytical HPLC-UV/PDA comparison between the crude methanol extracts of the fresh and the dried flowering aerial parts of *Sisymbrium officinale* showed the occurrence of some biochemical reactions during the drying process as indicated with different peaks in the chromatographs.

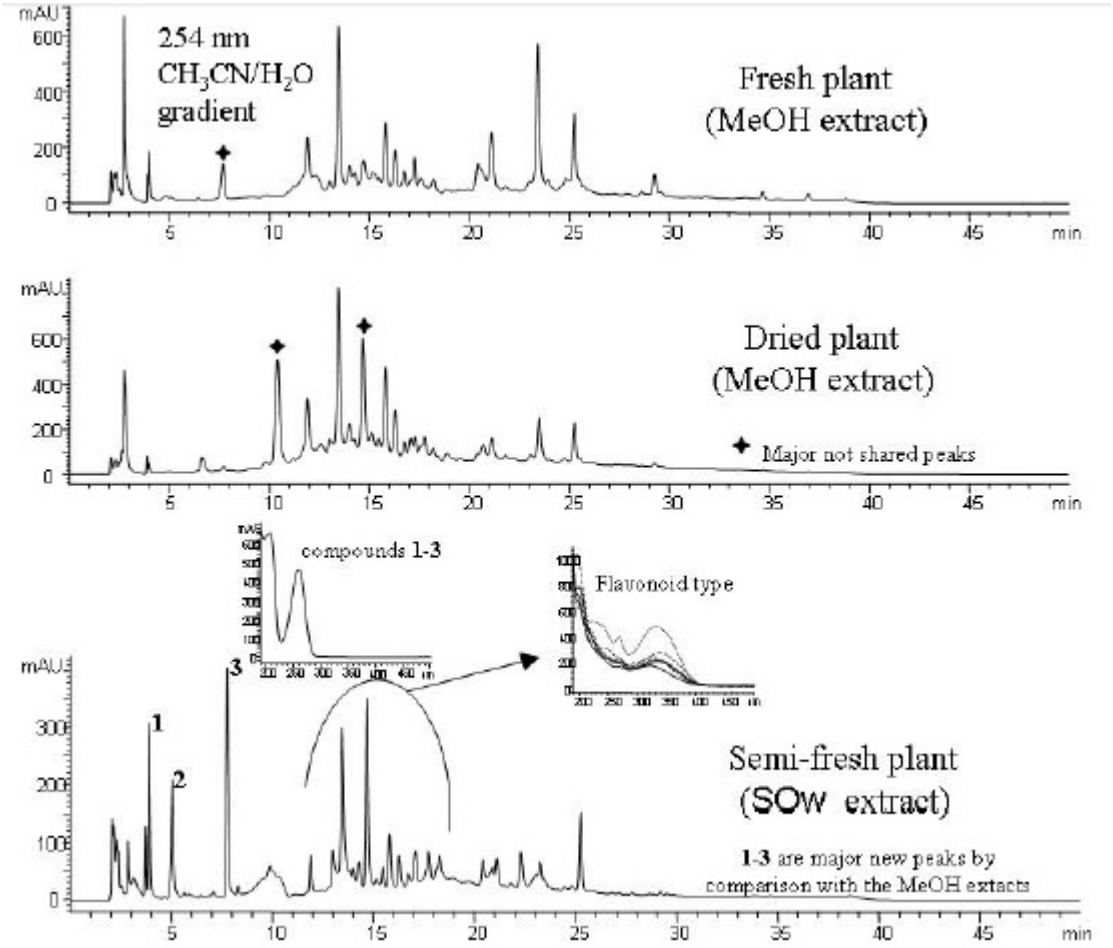


Figure 2 (Politi *et al*. 2008).

The freeze-dried residue of the infusion (SOw) prepared according to the traditional recipe, was re-dissolved in methanol obtaining a soluble fraction (SOw_s) and a precipitate (SOw_p). Further fractionation of SOw_s allowed the identification of adenine, adenosine, and guanosine that were present in significant quantities only in the traditionally prepared aqueous extract. Polysaccharides were detected in the SOw_p fraction and their molecular weight evaluated by DOSY experiments (Politi *et al*. 2008).

Volatile compounds of hedge mustard (*Sysimbrium officinale*) have been investigated. Forty-two compounds were identified after hydrodistillation (without or upon autolysis) with gas chromatography/mass spectrometry analyses. In addition, after decoction and hydrolysis of O-glycosides, 18 volatile O-aglycones were identified. The main volatiles found in hydrodistillates were: isopropyl isothiocyanate (27.6-48.9%), 2-methylpropanenitrile (0.5-18.8%), (Z)-hex-3-en-1-ol (0.5-18.0%), sec-butyl isothiocyanate (4.9-9.4%), (E)-hex-2-enal (3.5-8.6%), (Z)-hex-2-en-1-ol (0.3-8.4%), octanoic (0.5-8.6%) and dodecanoic acid (0-5.0%), 2-methylbutanenitrile (0-4.6%), dibutyl phthalate (0-4.5%), and ethyl linolenate (0-3.6%). The main volatile O-aglycones were: 2-phenylethyl alcohol (21.5%), 6,7-dehydro-7,8-dihydro-3-oxo-alpha-ionol (9.3%), eugenol (8.3%), benzyl alcohol (7.0%), ethyl vanillate (5.2%), 6-(tert-butyl)-5-methylphenol (5.1%), vanillin acetone (4.7%), ethyl 4-hydroxybenzoate (4.3%), and 2-hydroxy-beta-ionone (3.8%).

In general, isothiocyanates were the main hydrolytic products isolated from fresh plant material (58.3% vs. 0.5% nitriles) and from fresh plant material after autolysis (32.5% vs. 1.4% nitriles). The nitrile content of dried plant material isolate was significantly higher (24.4%), although isothiocyanates were still the main degradation products (33.7%). The content of aliphatic alcohols and aldehydes was higher in fresh plant isolates (28.9% and 33.6%, resp.) than in the isolate from dried plant material (15.3%). The highest content of fatty acids and esters (23%) was identified from freshly autolyzed plant material (Blazević *et al.* 2010).

- Herbal preparation(s)

Flos: Comminuted herbal substance

Herba: Dry extract, extraction solvent: ethanol 50% (V/V)
Dry extract, extraction solvent: water

The Community herbal monograph refers only to two herbal preparations from Sisymbrii officinalis herba.

- 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.

Flos: In the past, several combination cough products were on the market in Spain which included Erysimum combined with Liquiritiae radix, Althaea radix, Marrubii herba, Anisi fructus and/or Thymi herba.

Herba: The herbal substance is also available in combination products with other herbals or chemical substances (mainly codeine).
Erysimum was combined with codeine or sulfogajacol and with other herbal substances, for example in Euphon® syrup and pastille (Belgium) until 2004.

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

### Regulatory status overview

| Member State | Regulatory Status | | | | Comments |
|---|---|---|---|---|---|
| Austria | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No authorised herbal medicinal products. |
| Belgium | ☒ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | Three products |
| Bulgaria | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No authorised herbal medicinal products. |
| Croatia | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Cyprus | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Czech Republic | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No authorised herbal medicinal products. |
| Denmark | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No authorised herbal medicinal products. |
| Estonia | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No authorised herbal medicinal products. |
| Finland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No authorised herbal medicinal products. |
| France | ☐ MA | ☒ TRAD | ☐ Other TRAD | ☐ Other Specify: | Five products |
| Germany | ☐ MA | ☒ TRAD | ☐ Other TRAD | ☐ Other Specify: | One product |
| Greece | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No authorised herbal medicinal products. |
| Hungary | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No authorised herbal medicinal products. |
| Iceland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Ireland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No authorised herbal medicinal products. |
| Italy | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No authorised herbal medicinal products. |
| Latvia | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Liechtenstein | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Lithuania | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Luxemburg | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Malta | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| The Netherlands | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No authorised herbal medicinal products. |
| Norway | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Poland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No authorised herbal medicinal products. |
| Portugal | ☒ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | One product |

| Member State | Regulatory Status | | | | Comments |
|---|---|---|---|---|---|
| Romania | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Slovak Republic | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Slovenia | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No authorised herbal medicinal products. |
| Spain | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | In 1978, a combination product was registered by the former registration scheme. The register was revoked in April 2011 because no application was submitted to the Spanish Agency. |
| Sweden | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| United Kingdom | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No authorised herbal medicinal products. |

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.

**Table 1: Products on the market containing Sisymbrii officinalis herba (dried flowered aerial part) as active herbal substance**

| Active substance / pharmaceutical form | Indication | Posology | Legal status / since when on the market |
|---|---|---|---|
| dry extract: extraction solvent: ethanol 50% (V/V); DER: 6-10:1<br>1 lozenge contains 15 mg of extract | Traditionally used locally as an analgesic in conditions of the oral cavity and/or pharynx. | adults: 4 to 6 lozenges/day<br>children over 6 years of age: 2 to 3 lozenges/day<br>due to the pharmaceutical form (solid dosage form) all the products are not to be used for children under 6 years of age | THMP in France 1998, 2006 |
| dry extract:<br>extraction solvent: water; DER: 3.5-5.5:1<br>1 lozenge contains 10 mg of extract | Traditionally used locally as an analgesic in conditions of the oral cavity and/or pharynx.<br>Symptomatic treatment of aphonia, hoarseness and irritating coughs.<br>Laryngeal disorders. | adults: 10 to 12 lozenges/day<br>children over 6 years of age: 5 to 6 lozenges/day<br><br>adults: 10 to 12 tablets/day;<br>children from 6 years old: 5 to 6 tablets/day<br>Let the tablet dissolve in your mouth without chewing. | THMP in France 1959, 1980, 2000<br>WEU: in Portugal 1999 |
| dry extract:<br>extraction solvent: water; DER: 6-8:1<br>1 pastille contains 7.5 mg dry extract | Traditional herbal medicinal product for relief of hoarseness and to support secretion of mucus in the respiratory tract. | adults and adolescents >12 years: 10 to 12 pastilles/day,<br>children 5-11 years: 5 to 6 pastilles/day<br>for oromucosal use<br>duration of use: no limit | THMP in Germany at least since 1976 |
| dry extract:<br>extraction solvent: water; DER 6:1<br>syrup: 5.50 mg dry extract/ml<br>1 pastille contains 10 mg dry extract | Cough reliever.<br>It has local analgesic effect in the oro-pharyngeal area as well. | Oral use:<br>adults: 3 to 4 times 15 ml,<br>children: 3 to 4 times 5ml<br>The use in children under 3 years of age is not permitted.<br><br>Oro-pharyngeal use:<br>adults: 10 to 12 pastilles/day<br>children from 6 years on: 5 to 6 pastilles/day | WEU in Belgium 1962 2004*<br><br>*new formula for Euphon®: the old formula was marketed since 1962 and was a combination product |

### 1.3. Search and assessment methodology

Literature search was conducted using Pubmed/MEDLINE, TOXNET until the end January 2013 with the search terms “hedge mustard”, “*Sisymbrium officinale* (L.) Scop.”, “*Erysimum officinale* L.”.
Literature references of the identified scientific publications and a search in www.google.com were used to look for articles.
Some old references were provided by interested parties during the call for scientific data.

## 2. Historical data on medicinal use

### 2.1. Information on period of medicinal use in the Community

Sisymbrium also known as Erysimum, *Sisymbrium officinale* [Syn. *Erysimum officinale* (L.) Scopoli, family *Cruciferae*]. It is an annual which grows in Europe and in waste grounds in the United States. It is native of North Africa. It is said to be diuretic and expectorant, and has been recommended in chronic coughs, hoarseness and ulceration of the mouth and faces. The juice of the plant is used mixed with honey or sugar, or the seeds may be taken in substance (Remington *et al*. 1918).

Herba Erisimi is already mentioned in the second edition of the Hagers Handbuch (Frerichs *et al.* 1949) and it is recommended for laryngeal catarrh, hoarseness and slime (so called the “singer herb”). In the fourth edition (1979) of this book, asthma, lung diseases, jaundice, bladder problems and kidney stones are mentioned as well. Braun, in his herbal substances’ lexicon, recommends it as chest-tea (1981).

According to the Materia Medica Vegatabilis by Steinmetz (1954), Sisymbrium is an expectorant and diuretic, and is recommended for chronic coughs and hoarseness. The sweetened juice is used.

Potter’s New Cyclopedia of Botanical Drugs and Preparations (Wren 1975) recommends the herb as a remedy for hoarseness and weak lungs.

According to the Précis de Matière Médicale by Paris & Moyse (1981), it is as popular remedy against hoarseness and cough as an expectorant; it is mentioned as the ‘Herbe aux Chantres’.

In his Compendium de Phytothérapie (1986), Van Hellemont mentions that the aerial parts of hedge mustard are traditionally used as a remedy for airway ailments such as laryngitis, pharyngitis, coughs and hoarseness including loss of voice, chronic bronchitis and asthma.

This medicinal use can be found in more recent literature as well (Berdonces 1998, Gruenwald *et al*. 2004). Bruneton (1999) recommends Sisymbrium for local use as an antalgic in buccal or pharynx conditions.

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

**Products that fulfil the requirement of thirty years traditional use**:

Products in the literature:

- Comminuted herbal substance (Frerichs *et al.* 1949, Wolf 1992, Steinmetz 1954, Wren 1975, Braun 1981, Paris & Moyse 1981, Gruenwald *et al*. 2004).
  Indication: (see above).
- Liquid extract (Wren 1975) (1:1) extraction solvent 25% ethanol (based on the current practice at that time in the British Herbal Pharmacopoeia)
  Indication: (see above)

Products from the market overview made by Member States:

1. Dry extract (DER: 3.5-5.5:1), extraction solvent: water; on the French market since 1959. Traditionally used locally as an analgesic in conditions of the oral cavity and/or pharynx. This preparation has a marketing authorisation based on well-established use in Portugal since 1999. Indication: symptomatic treatment of aphonia, hoarseness and irritating coughs. Laryngeal disorders.
2. Dry extract (DER: 6:1), extraction solvent: water; on the Belgian market since 1962 as a combination product, since 2004 as a mono-component product. Cough reliever and as a local analgesic in conditions of the oral cavity and/or pharynx.
3. Dry extract (DER: 6-8:1), extraction solvent: water; on the German market at least since 1976. Traditional herbal medicinal product for relief of hoarseness and to support secretion of mucus in the respiratory tract.
4. Dry extract (DER 6-10:1), extraction solvent: ethanol 50% (V/V) on the French market since 1998, 2006. Traditionally used locally as an analgesic in conditions of the oral cavity and/or pharynx.

Based on the data provided by Member States, the following herbal preparations are included in the monograph:

a) Dry extract (DER 3.5-5.5:1), extraction solvent water

b) Dry extract (DER: 6-8:1), extraction solvent water.

The dry extract (DER: 6:1), extraction solvent water is covered by the herbal preparation b).

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

**Literature**

Potter's New Cyclopedia of Botanical Drugs and Preparations (Wren 1975) recommends:

Liquid extract dose: 0.5-1 fl dr. ("fl dr."= fluid drachm = 3.5 ml)

Gran Enciclopedia de las Plantas Medicinales (Berdonces 1998) recommends:

Powder: 0.3-2 g per dose

Decoction: 50-100 g in 1 litre for topical application

Mother tincture: 25 drops three times daily

Fluid extract: 40-80 drops three times daily

Hagers Handbuch (Hänsel *et al.* 1994) recommends:

Oral use: 0.5-1.0 g herbal substance; as an infusion 3-4 cups daily.

Oromucosal: the infusion is used as a gargle or mouthwash, several times daily.

**Products that fulfil the requirement of thirty years traditional use:**

1. Dry extract (DER 3.5-5.5:1), extraction solvent: water

This herbal preparation is on the French market since 1959 and in Portugal since 1999.

Oromucosal use: a lozenge contains 10 mg of extract

Adults: 10 to 12 lozenges daily (corresponding to 350-660 mg of the herbal substance per day)

Children over 6 years of age: 5 to 6 lozenges daily (corresponding to 175-330 mg of the herbal substance per day)

2. Dry extract (6:1), extraction solvent: water

On the Belgian market since 1962 as combination product, since 2004 as mono-component preparation.

Oral use: syrup which contains 5.50 mg extract/ml;

Adults: 82.5 mg 3 - 4 times daily (corresponding to 1,485-1,980 mg of the herbal substance per day)

Children: 27.5 mg 3 - 4 times daily (corresponding to 495-660 mg of the herbal substance per day)

Oro-pharyngeal use: a pastille contains 10 mg of the extract

Adults: 10 mg 10-12 times daily (corresponding to 600-720 mg of the herbal substance per day)

Children from 6 years of age: 10 mg 5 -6 times daily (corresponding to 300-360mg of the herbal substance per day)

3. Dry extract (6-8:1), extraction solvent: water

On the German market at least since 1976

Oromucosal use: a pastille contains 7.5 mg dry extract

Adults and adolescents over 12 years of age: 10 to 12 pastilles daily, 7.5 mg 10 – 12 times daily (corresponding to 450-720 mg of the herbal substance per day)

Children 5 to 11 years of age: 5 to 6 pastilles daily, 7.5 mg 5 - 6 times daily (corresponding to 225-360 mg of the herbal substance per day)

Duration of use: no limit

**Products that do not meet the requirements of traditional use for thirty years:**

Dry extract (DER 6-10:1), extraction solvent: ethanol 50% (V/V) on the French market since 1998

Oromucosal use: a lozenge contains 15 mg of extract

Adults: 4 to 6 lozenges daily

Children over 6 years of age: 2 to 3 lozenges daily

Based on the data provided by Member States, the following information on the two herbal preparations are included in the monograph:

**Oromucosal use**

*Adolescents, adults and elderly*
a) Dry extract (DER 3.5-5.5:1), extraction solvent water: 10 mg, 10 – 12 times daily
b) Dry extract (DER 6-8:1), extraction solvent water: 7.5 – 10 mg, 10 – 12 times daily

*Children 6 - 11 years of age*
a) Dry extract (DER 3.5-5.5:1), extraction solvent water: 10 mg, 5 - 6 times daily
b) Dry extract (DER 6-8:1), extraction solvent water: 7.5 - 10 mg, 5 - 6 times daily

The oromucosal use in children under 6 years of age is not recommended.

The tablet/lozenge will dissolve in the mouth without chewing.

**Oral use**

*Adolescents, adults and elderly*
b) Dry extract (DER 6-8:1), extraction solvent water: 82.5 mg, 3 - 4 times daily

*Children 3 - 11 years of age*
b) Dry extract (DER 6-8:1), extraction solvent water: 27.5 mg, 3 - 4 times daily

The oral use in children under 3 years of age is not recommended.

**Duration of use**

If the symptoms persist longer than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

**Method of administration**

Oral use.

Oromucosal use.

# 3. Non-Clinical Data

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

**Primary pharmacodynamics**

***Antimicrobial/antifungal activity***

The antimicrobial activity of an aqueous dry extract (DER: 4:1) of the aerial parts of *Sisymbrium officinale* was tested in the range of 7.8-1,000 µg/ml against six bacteria and one yeast: *Gram*-positive bacteria: *Staphylococcus aurius*, *Bacillus subtilis*; *Gram*-negative bacteria: *Escherichia coli*, *Pseudomonas cepacea*, *Shigella flexneri* and *Salmonella enteridis*; yeast: *Candida albicans.* The extract did not show any antibacterial/antifungal activity (Di Sotto *et al*. 2010).

Hedge mustard (*Sysimbrium officinale)* volatiles were isolated from fresh and dried material by different methods i.e. hydrodistillation (without and upon autolysis) and decoction. Autolysis was

performed prior to hydrodistillation in order to allow natural plants enzymes to liberate bound volatiles from non-volatile precursors (Blazević *et al*. 2010).

All hydrodistillates exhibited antibacterial activity against five *Gram*-positive bacteria, nine ampicillin-resistant *Gram*-negative bacteria, and four fungi, at a concentration of 500 µg/ml using the disc diffusion method. The most susceptible organisms were *Gram*-positive bacteria *Clostridium perfringens, Enterococcus faecalis* and *Micrococcus luteus* (20 - 30, 23 - 34 and 20 - 29 mm resp.*)*. Testing for susceptibility to ampicillin was also carried out using commercial discs containing 10 µg ampicillin.

Volatiles isolated from fresh plant material (without and upon autolysis) showed higher antimicrobial activity than dried plant material against all bacterial and fungal strains (see Table below).

Table 3. *Antimicrobial Activity of Volatiles Obtained by Hydrodistillation*

| Microorganisms | No. strains | Diameters of the inhibition zones [mm] | | | |
|---|---|---|---|---|---|
| | | I[a]) | II[b]) | III[c]) | Standard antibiotic |
| ***Gram*-positive bacteria** | | | | | Ampicillin |
| *Staphylococcus aureus* | ATCC 25923 | 18 | 16 | 12 | 26 |
| *Bacillus cereus* | ATTC 11778 | 12 | 14 | 10 | 28 |
| *Clostridium perfrigens* | FNSST 4999 | 20 | 34 | 30 | 25 |
| *Enterococcus faecalis* | ATCC 29212 | 23 | 34 | 30 | 23 |
| *Micrococcus luteus* | ATCC 49732 | 20 | 29 | 24 | 27 |
| ***Gram*-negative bacteria** | | | | | Ampicillin |
| *Aeromonas hydrophila* | FNSST 050 | 27 | 14 | 22 | 6 |
| *Enterobacter sakazakii* | FNSST 021 | 24 | 24 | 11 | 8 |
| *Klebsiella pneumoniae* | FNSST 011 | 25 | 20 | 16 | 6 |
| *Escherichia coli* | FNSST 982 | 26 | 28 | 19 | 6 |
| *Enterobacter cloacae* | FNSST 111 | 19 | 20 | 13 | 6 |
| *Pseudomonas aeruginosa* | FNSST 014 | 16 | 21 | 18 | 6 |
| *Vibrio alginolyticus* | FNSST 985 | 29 | 12 | 14 | 6 |
| *Vibrio vulnificus* | FNSST 983 | 22 | 15 | 24 | 6 |
| *Chryseobacterium indologenes* | FNSST 721 | 32 | 30 | 22 | 6 |
| **Fungi** | | | | | Amphotericin B |
| *Candida albicans* | ATCC 6275 | 17 | 20 | 15 | 21 |
| *Aspergillus niger* | ATCC 10231 | 30 | 28 | 29 | 23 |
| *Saccharomyces cerevisiae* | FNSST 3728 | 24 | 23 | 22 | 20 |
| *Penicillium sp.* | FNSST 3724 | 20 | 30 | 29 | 17 |

[a]) I = Fresh plant material – hydrodistillation. [b]) II = Fresh plant material – hydrodistillation upon autolysis. [c]) III = Dried plant material – hydrodistillation.

According to Blazević *et al.* (2010), the observed antimicrobial activity is due to the isothiocyanates and nitrils content of the plant. In addition alcohols and aldehydes, fatty acids and corresponding esters also can contribute to this activity. These components are present in different percentage in the fresh and the dried plant material.

***Anti-inflammatory activity***

The freeze-dried residue of the infusion (SOw) of the semi-fresh (2 hours after collection) flowering aerial parts of *Sisymbrium officinale*, prepared according to a traditional recipe, was re-dissolved in methanol obtaining a soluble fraction (SOw_s) and a precipitate (SOw_p). Further fractionation of

Sow_s allowed the identification of adenine, adenosine, and guanosine that were present in significant quantities only in the traditionally prepared aqueous extract. Polysaccharides were detected in the Sow_p fraction. They all were tested for the topical anti-inflammatory activity in the murine Croton oil-induced ear oedema model, only a modest effect inhibition was observed at high concentrations (SOw: 25% oedema inhibition at 2,000 µg/cm$^2$, SOw_s 26% at 1,000 µg/cm$^2$ and SOw_p 14% at 1,000 µg/cm$^2$) (Politi *et al*. 2008).

**Secondary pharmacodynamics**

***Myorelaxant activity***

In isolated guinea-pig trachea, an aqueous dry extract (DER: 4:1) of the aerial parts of *Sisymbrium officinale*, tested in the range of the concentrations 0.1-3,000 µg/ml, reduced the contractions induced by carbachol (CAR 1.0 x $10^{-7}$), leukotriene ($LTC_4$ 1.0 x $10^{-9}$) and histamine (HIS 1.0 x $10^{-5}$). The response was concentration-dependent: the regression correlation coefficients ($R^2$) were 0.91, 0.93 and 0.90 in the presence of CAR, HIS and $LTC_4$, respectively. The $IC_{50}$ values were: 335 µg/ml to CAR, 92.6 µg/ml to HIS and 79.3 µg/ml to $LTC_4$. The $IC_{50}$ value of the reference substance, isoproterenol against the CAR-induced concentration was 2.89 x $10^{-2}$ µg/ml corresponding to 0.137 nM (Di Sotto *et al.* 2010).

***Antimutagenic activity***

In preliminary experiments the extract mentioned above *Sisymbrium officinale* showed lack of mutagenic effects in the range of concentrations tested (4.6-17 mg/plate). Based on this results the Ames test, performed by the preincubation method, was used to study the antimutagenic activity of the extract by its capability to inhibit the mutagenic effect of 2-nitrofluorene, sodium azide, methyl methanesulfonate and 2-aminoanthracene, in *Salmonella typhimurium* TA98, *Salmonella typhimurium* TA100 and *Escherichia coli* WP2*uvr*A strains. The higher inhibiting effect was exhibited against 2-aminoanthracene: the inhibition was concentration-dependent and reached values of 60% and 44% in *Escherichia coli* WP2*uvr*A and in *Salmonella typhimurium* TA98 respectively (Di Sotto *et al*. 2010).

Glucoputranjivin and isopropyl isothiocyanate were isolated from an aqueous dry extract of *Sisymbrium officinale* and were identified by spectroscopic analysis. The antimutagenic activity of these compounds was evaluated in a bacterial reverse mutation assay using *E. coli* WP2, WP2uvrA, and WP2uvrA/pKM101 strains, in comparison with the extract. In the absence of the exogenous metabolic activation system S9, the thio compounds exerted antimutagenic activity against the direct-acting mutagen methyl methanesulfonate, in all strains. In the presence of S9, both thio compounds were active against the indirect mutagens 2-aminoanthracene, in WP2uvrA, and 2-aminofluorene, in WP2. The antimutagenicity seems to be due to specific mechanisms, such as the induction of the adaptive response or the excision repair system. Conversely, the inhibition of the CYP450-mediated activation of mutagens was not supported by the results. An antimutagenic effect was also observed for the *Sisymbrium officinale* aqueous extract against the arylamines 2AA and 2AF, but not against MMS. The authors concluded that these results suggest that both thio compounds are involved in the antimutagenicity of *Sisymbrium officinale*. The antimutagenicity of glucosinolate 1 is reported for the first time (Di Sotto *et al*. 2012).

**Safety pharmacology**

No data are available.

**Pharmacodynamic interactions**

No data are available.

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

No data are available.

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

No toxicological data have been found.

### *3.4. Overall conclusions on non-clinical data*

Results from relevant experimental studies on *Sisymbrium officinale* to support the proposed indication are very limited. The reported pharmacological effects are not considered contradictory to the traditional uses.

Specific data on pharmacokinetics and interactions are not available.

Non-clinical information on the safety of *Sisymbrium officinale* could not be retrieved. However, during the long-standing use in the Member States, no adverse effects or incidences were reported. Based on this it is concluded that there are no safety concerns relating to the use of the preparations in the given indication at the traditionally used doses.

As there is no information on reproductive and developmental toxicity the use during pregnancy and lactation cannot be recommended.

Tests on genotoxicity and carcinogenicity have not been performed. The requirements for the establishment of a Community list entry are not fulfilled.

## 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 are available.

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

No data are available.

### *4.2. Clinical Efficacy*

#### 4.2.1. Dose response studies

No data are available.

### 4.2.2. Clinical studies (case studies and clinical trials)

Clinical studies with products containing hedge mustard have not been found in the literature.

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

No data are available.

## *4.3. Overall conclusions on clinical pharmacology and efficacy*

Clinical studies with products containing hedge mustard have not been found in the literature.

# 5. Clinical Safety / Pharmacovigilance

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

No data are available.

## *5.2. Patient exposure*

Clinical studies with products containing hedge mustard have not been found in the literature.

## *5.3. Adverse events and serious adverse events and deaths*

No side effects have been reported (Wolf 1992).

No adverse effects were reported from the Belgian, French and Portuguese market overview.

Information from the package leaflet of a German product:

"Queasiness, vomiting, diarrhoea, headache and cardiac rhythm disorders have been reported."

*Rapporteur's comment: These are the symptoms of overdose.*

**Wording in the Community herbal monograph:**

Not known.

## *5.4. Laboratory findings*

No data are available.

## *5.5 Safety in special populations and situations*

***Contraindications***

Information from the package leaflet of a Belgian product: Hypersensitivity

***Warnings***

Information from the package leaflet of a German product:

The use in children under 5 years of age is not recommended due to lack of adequate data.

Information from the package leaflet Belgian product:

Pastille should not be used under 6 years of age
Syrup should not be used by children under 3 years of age

Information from the package leaflet of a French product:

Due to the pharmaceutical form (solid dosage form) all the products are not to be used for children under 6 years of age.

**Wording in the Community herbal monograph:**

The oromucosal use in children under 6 years of age is not recommended because of the pharmaceutical form (solid dosage form) and due to the lack of adequate data.

The oral use in children under 3 years of age is not recommended due to lack of adequate data and because medical advice should be sought.

***Fertility, pregnancy and lactation***

Information from the package leaflet of Belgian product:

The use of the syrup is not contraindicated during pregnancy and lactation.

Information from the package leaflet of a German product:

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, use during pregnancy and lactation is not recommended.

**Wording in the Community herbal monograph:**

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.
No fertility data available.

***Warnings***

Information from the package leaflet of a German product:
The drug contains <1 ppm cardioactive steroid glycosides. Caution by heart drug digitalis or digoxin, in potassium deficiency or in chronic inflammation in the mouth and pharynx.

*Rapporteur's comment: Interaction with digitalis or digoxin or potassium deficiency is only a theoretical assumption.*

**Wording in the Community herbal monograph:**

If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. If dyspnoea, fever or purulent sputum occurs, a doctor or a qualified health care practitioner should be consulted immediately.

***Interactions***

Information from the package leaflet of a German product:
Potassium deficiency.
Intake of cardiac glycosides.

*Rapporteur's comment: This is only a theoretical assumption; no report is mentioned in the market overview.*

**Wording in the Community herbal monograph:**

Not known.

***Overdose***

Information from the package leaflet of a German product:
Over dosage would have digitalis-like effects. These include queasiness, vomiting, diarrhoea, headache and cardiac rhythm disorders.

Hagers Handbuch (Wolf 1992), PDR for Herbal Medicines (Gruenwald *et al*. 2004):
It is conceivable that over dosage would have digitalis-like effects. These include queasiness, vomiting, diarrhoea, headache and cardiac rhythm disorders.
Cases of poisonings, however, have not been recorded.

**Wording in the Community herbal monograph:**

No case of overdose has been reported.

### *5.5. Overall conclusions on clinical safety*

The medicinal use of hedge mustard preparation is considered safe because no adverse effects have been reported during the long-standing use as a medicinal product in Belgium and Germany.

The known toxic cardioactive steroid glycosides have been documented as a minor component and their concentrations are too low to present any risk to human health.

The oromucosal use in children under 6 years of age is not recommended because of the solid dosage form and due to lack of adequate data.

The oral use in children under 3 years of age is not recommended due to lack of adequate data and because, for the proposed indication, medical advice should be sought for this age group.

Since there are insufficient data, the use during pregnancy and lactation is not recommended.

## 6. Overall conclusions

Sisymbrii officinalis herba has been in medicinal use for a period of at least 30 years as requested by Directive 2004/24/EC, thus the requirement for the qualification as a traditional herbal medicinal product is fulfilled (long-standing use) in the following indication:

Traditional herbal medicinal product for the relief of throat irritation such as hoarseness and dry cough.

Since clinical studies with products containing hedge mustard have not been found in the literature well-established use cannot be recommended.

The pharmacological studies on the anti-inflammatory and antimicrobial effects of hedge mustard might contribute to the proposed traditional indication, however, these effects were only observed at high concentration of the preparations or their components.

The mitigating effect of the herbal substance on the pharyngeal irritation might be due to the high mucilage's content (10.9%-13.5%) (Carnat *et al.* 1998).

The benefit-risk balance can be considered positive.

The oromucosal use in children under 6 years of age is not recommended because of the pharmaceutical form (solid dosage form) and due to lack of adequate data.

The oral use in children under 3 years of age is not recommended due to lack of adequate data and because medical advice should be sought.

In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

Due to the lack of data on genotoxicity, the inclusion of Sisymbrii officinalis herba in the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products cannot be recommended.

# Annex

## *List of references*