EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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)

**Final**

| | |
|---|---|
| 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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# 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.) Scop. (= *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).

According to the Hagers Handbuch (Hänsel *et al*. 1994) in traditional medicine, mainly the fresh flowering plants of *Sisymbrium officinale* (hedge mustard) are used. The dried herb is used only in special cases.

**Main active compounds**

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

**Sulphated compounds**

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). According to the Hagers Handbuch, in the fresh plant mainly sinigrin (an allylglucosinolate) and gluconapin (3-butenylglucosinolate) are present (Hänsel *et al*. 1994). The main glucosinolate is glucoputranjivine (Carnat *et al*. 1998).

Apart from glucoputranjivin an isopropyl isothiocyanate was also isolated from an aqueous dry extract (4:1) of dry aerial parts of *Sisymbrium officinale*. The chemical analysis of this extract revealed the absence of sinigrin and presence of putranjivine, the glucosinolate marker of *Sisymbrium officinale* (in a concentration of 0.5 mg/g) and proline (Di Sotto *et al*. 2010 and 2012).

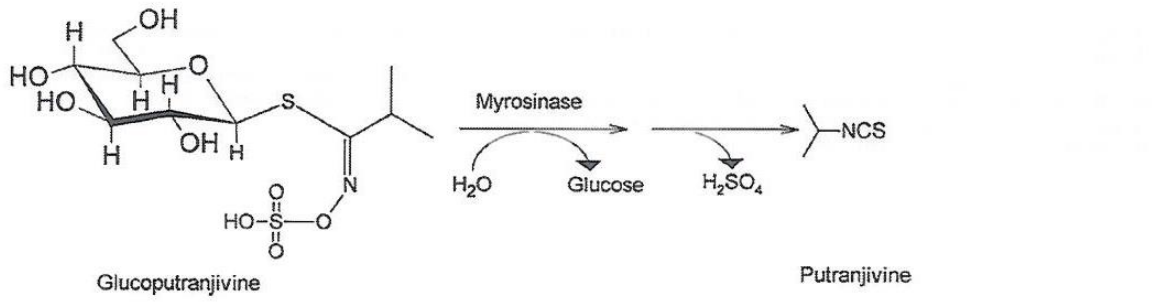



Figure 1: Molecular structure and biosynthesis of putrajivine (Di Sotto *et al.* 2010.)

Isothiocyanates were the main hydrolytic products of glucosinolates 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%) (Blazević *et al.* 2010).

The fresh herb contains thiocyanic acid (Kern *et al.* 1979).

***Cardiac steroid glucosides (cardenolide glycosides)***

Latowski *et al.* 1979 has attempted a chemotaxonomical classification of 12 species of three genera Cruciferae (*Erysium, Cheirantus* and *Sisymbrium*) containing cardenolide glycosides. The raw material was the flowering tops of shoots (10 cm), collected in Pharmacognostical Garden of Medical Academy in Poznań. The raw material was extracted with ethanol, then treated with ethyl acetate (debalasted) and the cardenolide fraction was extracted with chloroform. The dry residue was analysed for cardenolides. Determination of cardenolides was performed according to the method Soos and Baumgarten (1963). Measurement of extinction at 500 nm after chromatographic separation ($R^f$ 0.43) was carried according to Kowalewski method. The content of cardenolides in *Sisymbrium officinale* (L.) Scop was 49.8 mg%, considering Baljet reagent and 42.2 mg% as sum of 2-deoxysugars. 4.5 % cardenolides of *Sisymbrium officinale* was helveticoside and 18.3% corchoroside (**Table 1, 2**).

**Table 1.** (Latowski *et al*. 1979)

Zawartość kardenolidów w badanych gatunkach
Content of cardenolides in the species investigated

| Gatunek Species | Zawartość kardenolidów w mg % Content of cardenolides in mg % | |
|---|---|---|
| | suma z 2-dezoksycukrem sum with 2-desoxysugar | ogólna wobec odczynnika Baljeta considering Baljet regent |
| 1. *Erysimum crepidifolium* Rchb. | 714,9 | 1522,0 |
| 2. *Erysimum cheiranthoides* L. | 142,0 | 310,0 |
| 3. *Erysimum pieninicum* (Zap.) Pawł. | 114,3 | 186,1 |
| 4. *Erysimum linifolium* (Pers.) Gay | 125,0 | 168,0 |
| 5. *Erysimum hieraciifolium* L. | 85,0 | 162,5 |
| 6. *Erysimum wahlenbergii* (Asch. et Eng.) Borb. | 76,4 | 150,8 |
| 7. *Erysimum hungaricum* Zap. | 118,0 | 148,6 |
| 8. *Cheiranthus cheiri* L. | 69,9 | 99,8 |
| 9. *Erysimum cuspidatum* (M. B.) DC. | 29,8 | 52,5 |
| 10. *Sisymbrium officinale* (L.) Scop. | 42,2 | 49,8 |
| 11. *Erysimum aureum* M. B. | 24,4 | 44,4 |
| 12. *Sisymbrium loeselii* L. | 9,5 | 23,9 |

*The analysis of monoglycosides, and particularly of helveticoside and corchoroside, permitted the isolation of 5 groups which suggest change in the systemic rank of some taxons.*

**Table 2**. (Larowski *et al.* 1979)

Podział badanych gatunków na podstawie składników kardenolidowych
Graduation of the species investigated on the basis of the ingredients of cardenolides

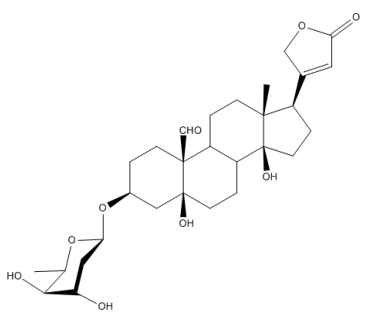
| Grupa chemiczna / Chemical group | | Gatunek / Species | Monoglikozydy kardenolidowe w mg % / Cardenolide monoglycosides in mg % | | |
|---|---|---|---|---|---|
| | | | helwetykozyd / helveticoside | korchorozyd A / corchoroside A | kardenolid o Rf 0,43 / cardenolide Rf 0,43 value |
| I | A | *Erysimum crepidifolium* Rchb. | 158,3 | 5,6 | — |
| | B | *Cheiranthus cheiri* L. | 33,0 | — | — |
| | C | *Sisymbrium loeselii* L. | 9,4 | — | — |
| II | A | *Erysimum cheiranthoides* L. | 42,0 | 31,0 | — |
| | | *Erysimum hieraciifolium* L. | 13,0 | 9,5 | — |
| | | *Erysimum pieninnicum* (Zap.) Pawł. | 16,3 | 31,0 | — |
| | B | *Erysimum wahlenbergii* (Asch. et Engl.) Borb. | 11,8 | 19,2 | — |
| | | *Erysimum hungaricum* Zap. | 14,5 | 19,9 | — |
| | | *Erysimum linifolium* (Pers.) Gay | 17,4 | 19,7 | — |
| III | | *Sisymbrium officinale* (L.) Scop. | 4,5 | 18,3 | — |
| IV | | *Erysimum aureum* M. B. | 2,6 | 2,9 | 1,9 |
| V | | *Erysimum cuspidatum* (M. B.) DC. | 4,2 | — | 3,7 |

*Rapporteur's comment:*

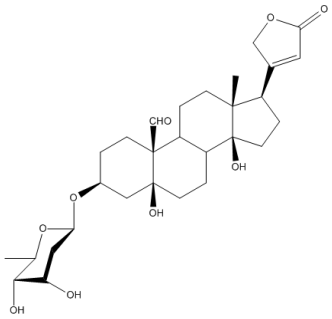
*The tables above show that Sisymbrium officinale has a special composition considering the rate of the two main cardenolide monoglycosides.*

*The chemical structure of cardenolide glycosides found in Sisymbrium officinale is very similar to the structure of strophantin K (see **Figure 2**) which was used in the form of i.v. preparation as a heart tonic in the 1980-90 years.*

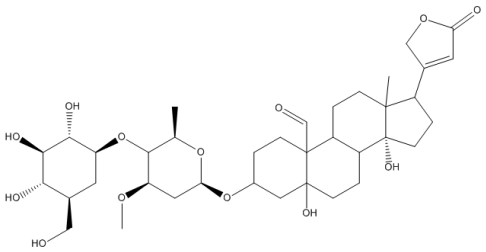
**Figure 2.** The chemical structure of cardenolide glycosides




corchoroside A




helveticoside



strophanthin K

**Volatile compounds**

Blazevits *et al*. (2010) investigated the volatile compounds of hedge mustard (leaves and flowers) (*Sisymbrium officinale*) isolated from fresh (with or upon autolysis) and from the dried plant material. Forty-two compounds were identified after gas chromatography and gas chromatography/mass spectrometry. In addition, after decoction with boiling water for 20 minutes and hydrolysis of *O*-glycosides, 18 volatile 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 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%) (Blazevic *et al.* 2010).

**Other compounds**

The freeze-dried residue of an infusion (SOw) prepared according to a traditional recipe (the plant was extracted with hot water 2 hours after its collection), 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 (Politi *et al*. 2008). The fresh foliage contains ascorbic acid (216.5 mg/100 g) (Hänsel *et al.* 1994).

- Herbal preparation(s)

Flos: Comminuted herbal substance

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

The European Union herbal monograph refers only to two herbal preparations from Sisymbrii officinalis herba. The justification for proposing only two herbal presentations is presented below.

- 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 officinale 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 officinale was combined with codeine or with sulfoguajacol and with other herbal substances for example in a syrup and in a pastille until 2004 (Belgium).

## *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. |

| Member State | Regulatory Status | | | | Comments |
|---|---|---|---|---|---|
| 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 |
| 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
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

**Table 3.** Products on the market containing Sisymbrii officinalis herba (dried flowering aerial part) as active herbal substance

| **Active substance/ pharmaceutical form** | **Indication** | **Posology** | **Legal status/ since when on the market** |
|---|---|---|---|
| Dry extract:<br>extraction solvent:<br>ethanol 50% (V/V);<br>DER: 6-10:1<br>1 lozenge contains<br>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:<br>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 |
| Dry extract:<br>extraction solvent:<br>water; DER: 3.5-5.5:1<br>1 lozenge contains<br>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:<br>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,<br>WEU: in Portugal 1999 |
| Dry extract:<br>extraction solvent:<br>water; DER: 6-8:1<br>1 pastille contains<br>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:<br>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:<br>water; DER 6:1<br>syrup: 5.50 mg dry extract/ml<br>1 pastille contains<br>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>a new formula, 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 European Union*

*Sisymbrium officinale* [syn. *Erysimum officinale* (L.) Scop., *Erysimum officinarum* Crantz, *Erysimum runcinatum* Gilib, *Chamaeplium officinale* Weber) belongs to the *Brassicaceae* (*Cruciferae*) family (Hänsel *et al*. 1994). It is an annual plant of Eurasian origin, which grows in Europe, Asia north-America and Northwest-Africa. It is said to be diuretic and expectorant, and has been recommended for chronic coughs, hoarseness and ulceration of the mouth and faces. The juice of the plant is used mixed with honey or sugar (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. It is drunk by singers before performances as a tea, and it is known as Singer's plant. 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.

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'.

The therapeutic activity of *Sisymbrium officinale* was 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).

Braun (1981), in his herbal substances' lexicon, recommends it as chest-tea.

Potter's New Cyclopedia of Botanical Drugs and Preparations (Wren 1982) recommends the herb as a remedy for hoarseness and weak lungs.

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 the flower and fresh or dried flowering tops of *Sisymbrium* for the symptomatic treatment of cough, during acute benign bronchial disease, and locally (collutorium or lozenges) 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**

*Literature:*

- Comminuted herbal substance (Frerichs *et al.* 1949, Steinmetz 1954, Wren 1982, Braun 1981, Paris & Moyse 1981).
  Indication: As a diuretic and expectorant, and for chronic coughs, hoarseness and ulceration of the mouth and faces
- Liquid extract (Wren 1975, 1982) (1:1) extraction solvent 25% ethanol (based on the current practice at that time in the British Herbal Pharmacopoeia)
  Indication: For hoarseness and weak lungs and to recover the voice.

*Products on the market according to information 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.

**Product that does not meet the requirements of traditional use for thirty years**

1. 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.

*Rapporteur's comment: This product has been registered in France as traditional herbal medicine product. Since the proof for the 30 year traditional use is not available in the public domain, this preparation (hydro-alcoholic extract) is not included into the European Union Monograph.*

Based on the data mentioned above and taking into account the indication accepted by HMPC for other herbal substances with the same properties the following indication is included in the monograph:

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

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.

*Assessor's comment: 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**

*Preparation that fulfils the requirement of thirty years of traditional use:*

Potter's New Cyclopedia of Botanical Drugs and Preparations (Wren 1982):

Liquid extract 1:1) extraction solvent 25% ethanol (based on the current practice at that time in the British Herbal Pharmacopoeia)

dosage: 0.5-1 fl dr. ("fl dr."= fluid drachm = 3.5 ml)

*Rapporteur's comment: It is not known from the provided posology whether this is a daily dose or a single dose, thus this preparation has not been included in the monograph.*

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

Gran Enciclopedia de las Plantas Medicinales (Berdonces 1998):

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):

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.

**Market overview provided by Member States**

*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 has been 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

This herbal preparation has been on the Belgian market as a combination product since 1962 and as a mono-component preparation since 2004.

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)

*Rapporteur's comment: this product is covered by the following preparation (dry extract (6-8:1), extraction solvent: water) thus it is not mentioned separately in the monograph but its posology is taken into account.*

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

The preparation which is made from the dried herbal substance has been 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) has been 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 the 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 healthcare practitioner should be consulted.

**Method of administration**

Oromucosal use

Oral 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 dry 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 volatiles were isolated from fresh and dried material by different methods i.e. hydrodistillation (without and upon autolysis). 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 respectively). 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 4**).

**Table 4**. (Blazević *et al.,* 2010)
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*, 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/cm2, SOw_s 26% at 1,000 µg/cm2 and SOw_p 14% at 1,000 µg/cm2) (Politi *et al*. 2008).

**Secondary pharmacodynamics**

***Myorelaxant activity***

In isolated guinea-pig trachea, an aqueous dry extract (DER: 4:1) of the dry 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 above mentioned extract of *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 (4:1) of the dry aerial parts of *Sisymbrium officinale*. 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* (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 on the herbal substance.

Only some toxicological data can be found for the cardiac glycoside, Helveticosid (=k-strophanthidin-D –digitoxosid)(Hänsel *et al* 1993):

$LD_{L0}$ i.v.: pigeon 0.285 mg/kg, guinea pig 0.867 mg/kg, cat 0.106 mg/kg, monkey 0.103 mg/kg

$LD_{50}$ i.v.: rat 54 mg/kg, i.p. mice 7.8 mg/kg.

*Rapporteur's comment: $LD_{L0}$: Lethal Dose Low: Lowest dose of a substance reported to have caused death in humans or animals.*

## *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.

Content of cardiac steroid glycosides (cardenolides) in the tips of the flowering plant of *Sisymbrium* officinale was measured to be 49.8 mg/100 g after extraction with chloroform (Larowski *et al.* 1979).

The recovery of cardenolides is low after extraction with water. If the cardenolides content of the aqueous extract is ≤1ppm, a lozenge containing 10 mg extract would contain less than 10 ng cardenolides. The daily amount of lozenges is up to 12 that means maximum 120 ng cardenolides. In various publications it is assumed that the oral resorption of strophantin is poor (~20%). That would mean that the daily dosage would be around 24 ng cardenolides. For the oral use, the maximum daily dose of cardenolides would be (82.5x4)/0.2 is 66 ng. This is substantially lower than the minimum therapeutic *i.v.* dose of K-strophantin of 0.125 mg (Knoll 1983). A limit of ≤1ppm for the cardenolides content is included into the monograph.

Based on this calculation it can be concluded that there are no safety concerns relating to the use of the preparations in the given indication at the traditionally used doses. During the long-standing use in the Member States, no adverse effects or incidences were reported.

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 European Union 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 (Hänsel et al. 1994).

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

**Wording in the European Union 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 European Union 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 on liquid preparations.

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 European Union 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 cardiac 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.

According to the literature (Hänsel *et al.* 1994) adverse effects have not been reported.

**Wording in the European Union herbal monograph**

If the symptoms worsen during the use of the medicinal product, a doctor or a qualified healthcare practitioner should be consulted. If dyspnoea, fever or purulent sputum occurs, a doctor or a qualified healthcare 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 or pharmacoviligance case is known according to information provided by the Member States.*

**Wording in the European Union herbal monograph**

Not reported.

***Overdose***

Information from the package leaflet of a *German* product:
There is no information about overdose.

Hagers Handbuch (Hänsel 1994), 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 European Union 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 content of cardiac steroid glycosides measured in the aqueous extract is too low to present any risk to human health. A limit of ≤1ppm for the cardenolides content is included into the monograph.

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 for the liquid pharmaceutical forms.

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 plausible effect of the herbal substance on the pharyngeal irritation might be due to the high mucilage's content (10.9%-13.5%).

For the water extracts and their corresponding posology, there are no safety concerns due to the low cardenolide (cardiac steroid glycosides) recovery with the aqueous extraction. A limit of ≤1ppm for the cardenolides content is included into the 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 lack of adequate data for the liquid pharmaceutical forms.

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 European Union list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products cannot be recommended.

# Annex

## *List of references*