EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Plantago lanceolata* L., folium

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)	*Plantago lanceolata* L., whole or fragmented, dried leaf and scape of the plant
Herbal preparation(s)	Traditional use: a) Herbal substance, comminuted b) Herbal substance, powdered c) Dry extract (3-6:1); extraction solvent: water d) Liquid extract (1:0.8-1.2); extraction solvent: ethanol 20%-40% (V/V) e) Soft extract (1.5-1.7:1); extraction solvent ethanol 20% (m/m) f) Expressed juice (1:0.5-0.9) from the fresh herb g) Liquid extract (1:11); extraction solvent water
Pharmaceutical forms	Traditional use: Comminuted herbal substance as herbal tea, powdered herbal substance in a solid dosage form and other herbal preparations in liquid or solid dosage forms for oral and/or oromucosal use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.
Rapporteur	
Assessor(s)	

Note: This Assessment Report is published to support the release for public consultation of the draft Community herbal monograph on *Plantago lanceolata* L., folium. It should be noted that this document

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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.

Table of contents

1. Introduction

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

- Herbal substance(s)

Plantaginis lanceolatae folium (European Pharmacopoeia)

Definitions of the herbal substance

- European Pharmacopoeia 6th ed. 2010 (6.7): 'Ribwort plantain'
  'Whole or fragmented, dried leaf and scape of *Plantago lanceolata* L.s.l.'
- Deutsches Arzneibuch 2005 (DAB 2005 - German Pharmacopoeia): 'Spitzwegerichkraut'
  'The whole or cut, dried herb of *Plantago lanceolata* L.'

The monograph for ribwort plantain herb, which had appeared in the German Pharmacopoeia has been replaced by the monograph for ribwort plantain leaf, published in the European Pharmacopoeia. Ribwort plantain herb mainly consists of leaves, therefore the title '*Plantaginis lanceolata,* folium' has been chosen.

- ESCOP Monographs 2nd ed. 2003: 'Plantaginis lanceolatae folium/herba - Ribwort plantain leaf/herb'
  'Ribwort plantain leaf consists of the dried leaves of *Plantago lanceolata* L.'
  'Ribwort plantain herb consists of the dried flowering aerial parts of *Plantago lanceolata* L.'
- Österreichisches Arzneibuch (ÖAB 90 - Austrian Pharmacopoeia): 'Folium Plantaginis, Spitzwegerichblatt'
  'The dried leaf of *Plantago lanceolata* L.'
- Pharmacopoea Helvetica VII (Swiss Pharmacopoeia): 'Plantaginis folium'
  'Ribwort plantain leaf consists of the dried leaf of *Plantago lanceolata* L. sensu latiore'

Name

Plantago lanceolata L. is a species of genus Plantago and Plantaginaceae family known by the following common names:

German: Spitzwegerich, Heilwegerich, Wundwegerich (Wichtl 2004);

English: Ribwort plantain, Ribwort, English plantain, Narrow-leaf plantain, Lance-leaf plantain, Ribgrass (Wichtl 2004), Tinker-tailor grass, Buckhorn plantain, Lancell, Windles (Bond *et al.* 2007);

French: Feuilles (herbe) de plantain (Blaschek *et al.* 2008);

Italian: Piantaggine (Blaschek *et al.* 2008).

Occurrence

Plantago lanceolata L. is a common perennial weed of arable fields and grassland (Bond *et al*. 2007), abundant throughout Europe, North- and Central Asia (Wichtl 2002). It is native in grassy places on neutral or basic soils (Bond *et al*. 2007).The herb is a common roadside plant (Bond *et al*. 2007) and is found in lawns (Sagar and Harper 1964). It is relatively drought resistant and is able to grow on dry sites such as embankments and chalk grassland (Bond *et al*. 2007).

Biology

Plantago lanceolata L. has a slight, unspecific odour similar to hay and a slightly salty and faintly bitter taste (Blaschek *et al.* 2008). The plant is a rosette-forming perennial herb, achieving a tallness of 5-50 cm, with a thick short rhizome and with a leafless, hairy flower stem. The basal rosette consists of 20 cm long and linear-lanceolate leaves with parallel venation. The brownish, inconspicuous flowers appear in cylindrical spikes on long stalks, protruding from the leaves. Conspicuous are the spreading, yellowish white stamens (Wichtl 2004).

Plantago lanceolata L. generally flowers from May to August (Bond *et al.* 2007) but flowering may begin in April and continue till the first frost (Sagar and Harper 1964). Flowers are wind pollinated although insects visit to collect pollen (Warwick and Briggs 1979).

Adulteration and Confusion

Confusion with leaves of *Plantago major*, *Plantago media* or *Digitalis lanata* is possible (Blaschek *et al.* 2008).

Principal components of the herbal substance

Iridoidglycosides:

The herbal substance contains about 2-3 % iridoidglycosides with aucubin and catalpol as the main compounds, as well as asperuloside, globularin and desacetylasperuloside-acid methylester. The iridoid content depends on the maturity of the leaves. Young leaves contain up to 9%, while in the older ones iridoids are present only in traces. In young leaves, catalpol is the dominant constituent, and in older leaves, aucubin is the major compound (Wichtl 2004). Depending on the time of harvesting the content of aucubin and catalpol varies. Before the flowering period the content of aucubin is very low in every organ and reaches its maximum in autumn (Blaschek *et al.* 2008) with aucubin at levels of 1-3% and catalpol up to 1% (Long 1995, Wichtl 2004). After harvesting the herb has to be dried directly to avoid fermentative processes. After hydrolysis aucubin is converted to dark brown polymers, which are responsible for the dark coloration of improperly dried drug material (Wichtl 2004).

The herbal substance is commonly dried at temperatures of 40-50°C. During this process the content of aucubin decreases. Drying at room temperature results in aucubin contents twice as high (Blaschek *et al.* 2008).

Mucilage:

Other drug constituents include 2-6.5% mucilage. An arabinogalactan, a glucomannan and a rhamnogalacturonan with an arabinogalactan side-chain as well as a rhamnoarabinogalactan and a linear (1-6)-α-D-glucan have been isolated (Wichtl 2004).

Flavonoids:

Flavonoids include apigenin and luteolin as well as their derivatives with the main compounds apigenin-6,8-di-C-glucoside and luteolin-7-O-glucuronide, luteolin-7-O-glucoside and 7-O-glucuronide-3'-glucoside, in addition to the 7-O-glucuronyl-glycosides of apigenin and luteolin as well as apigenin-7-O-glucoside and 7-O-glucuronide (Wichtl 2004).

Other constituents:

The herbal substance also contains 6.5% tannins, phenolic carboxylic acids including p-hydroxybenzoic-, protocatechuic, gentisinic-, chlorogenic- and neochlorogenic acid, among others. The coumarin aesculetin, the xanthophyll decomposition product loliolide and small amounts of a hemolytic

and antimicrobial saponin are also present, as well as volatile oil. Inorganic constituents include 1% silicilic acid and mineral salts with a high proportion of zinc and potassium (Wichtl 2004).

Herbal preparation(s):

A rather broad spectrum of different herbal preparations has been marketed so far. According to the overviews of the market in the Member States of the European Union there were herbal preparations with a well-established use status and there were also herbal preparations under traditional use (details from the overviews see below). With respect to the overall evaluation of the existing data on efficacy the monograph addresses only the traditional use. The following list summarises the herbal preparations from both reported categories which fulfil the criteria for traditional use and which are included in the monograph (The reference to the herbal preparation in the monograph is given in parenthesis.). Due to the broad spectrum of existing herbal preparations they were pooled to build a single entry if justified because of their similarity.

Herbal preparations which have been reported to be marketed so far under well-established use:

i.	Herbal substance, cut	(a)
ii.	Dry extract (3-6:1); extraction solvent: water	(c)
iii.	Liquid extract (1:0.9-1.1); extraction solvent: ethanol 35% (V/V)	(d)
iv.	Liquid extract (1:1); extraction solvent: ethanol 25% (V/V)	(d)
v.	Liquid extract (1:1); extraction solvent: ethanol 20% (V/V)	(d)
vi.	Liquid extract (1:1); extraction solvent: ethanol 24.6% (V/V)	(d)
vii.	Liquid extract (1:1); extraction solvent ethanol 40% (V/V)	(d)
viii.	Liquid extract (1:0.9-1.1); extraction solvent: ethanol 40% (V/V)	(d)
ix.	Soft extract (1.5-1.7:1); extraction solvent: ethanol 20% (m/m)	(e)
x.	Expressed juice from the fresh herb (1:0.5-0.7)	(f)
xi.	Expressed juice from the fresh herb (1:0.6-0.9)	(f)

Herbal preparations which have been reported to be traditionally used:

i.	Herbal substance, cut	(a)
ii.	Powdered herbal substance	(b)
iii.	Liquid extract (1:0.8-1.2); extraction solvent: ethanol 40% (V/V)	(d)
iv.	Liquid extract (1:1); extraction solvent: ethanol 35% (V/V)	(d)
v.	Liquid extract (1:11); extraction solvent water	(g)

- 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.

In many countries *Plantaginis lanceolatae* folium is used in combinations with other herbal substances/herbal preparations usually administered for the treatment of complaints associated with colds or for the treatment of inflammations of the mouth and throat. The main combination substances are Thymi herba, Foeniculi fructus, Salviae folium, Primulae radix, Sambuci nigrae flos, Tiliae flos, Liquiritiae radix, Matricariae flos, Menthae piperitae herba, Althaeae radix, Rubi fruticosi folium, Lupuli

flos, Serpylli herba, Salviae officinalis herba, Polygonii avicularis herba, Urticae herba, Farfarae folium, Verbasci flos, Cynosbati fructus sine semine, Gentianae radix, Primulae radix, Pini montanae turioni, Menthae piperitae aetheroleum, Foeniculi aetheroleum and Anisi aetheroleum. This monograph refers exclusively to *Plantaginis lanceolatae* folium.

Vitamin(s)

Not applicable.

Mineral(s)

Not applicable.

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

According to the information provided by the National Competent Authorities[1]

The following herbal substances and herbal preparations have been on the European market. The data are derived from the overview of marketed products in Europe:

Austria:

In Austria, a syrup prepared from *Plantago lanceolata* leaf according to the instructions of ÖAB 2009 is commonly used. It is administered for the treatment of catarrhs of the upper airways at a dosage of 1 tablespoon 3-4 times per day. In children a dosage of 1 teaspoon is given (BGB 1, II 2004).

Germany:

In Germany, for herbal preparations of *Plantago lanceolata* both a traditional and a well-established use has been documented. Considering the requirements established by the HMPC the data are not sufficient to support well-established use in the monograph.

Herbal Preparations:

Well-established use	**Traditional use**
1, 2) dry extract (3-5:1); extraction solvent: ethanol 20% m/m	• extract (1:5.8-5.9); extraction solvent: water
3) liquid extract (1:0.9-1.1); extraction solvent: ethanol 35% V/V	• *Plantaginis lanceolatae* herba, powder
4) liquid extract (1:1); extraction solvent: ethanol 25% V/V	• liquid extract (1:0.8-1.2); extraction solvent: ethanol 40% V/V
5) expressed juice from fresh *Plantaginis lanceolatae* herba (1:0.5-0.7)	• liquid extract (1:1); extraction solvent: ethanol 35% V/V
6, 7, 14, 17, 18) liquid extract (1:1); extraction solvent: ethanol 20% m/m	
8) liquid extract (1:1); extraction solvent: ethanol 24.6% V/V	
9, 10, 11) expressed juice from fresh Plantaginis lanceolatae herba (1:0.6-0.9)	

12, 16) dry extract (3-6:1); extraction solvent: water	
13) soft extract (1.5-1.7:1); extraction solvent: ethanol 20% m/m	
15) liquid extract (1:1); extraction solvent: ethanol 40% V/V	
19) Plantaginis lanceolatae herba, cut	
20) liquid extract (1:0.9-1.1); extraction solvent: ethanol 40% V/V	

Since when are the preparations on the market:

Well-established use	**Traditional use**
1, 2) 2004	1-4) at least since 1976
3, 4, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20) at least since 1976	
5) at least since 1980	
6, 7) 2005	

Pharmaceutical form

Well-established use	**Traditional use**
1, 2) effervescent tablet	1, 3, 4) oral liquid
3, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 17, 18, 20) syrup	2) lozenge
4, 12) oral liquid	
16) coated tablet	
19) herbal tea	

Posology

Well-established use	**Traditional use:**
all for oral use except 16)	all for oral use except 2)
1, 2) ≥ 12 years: 3-4 times daily 1 tablet containing 300 mg dry extract (corresponding to 3.6-4.8 g Plantaginis lanceolatae herba)	1) 100 ml liquid contain 41 g extract 1-4 years: 3-4 times daily 4 ml (corresponding to 5 g) 4-12 years: 3 times daily 8 ml (corresponding to10 g) ≥ 12 years: 3-5 times daily 4 ml (corresponding to 5 g)
3) ≥ 12 years: 3-4 times daily 10 ml containing 10% m/m liquid extract	2) oromucosal use ≥ 12 years: 9 times daily 1 containing 190 mg

Well-established use	Traditional use:
(corresponding to 3.9-5.2 g liquid extract)	powder (daily dose 1.71 g *Plantaginis lanceolata*e herba)
4) 100 ml liquid contain 100 ml liquid extract 1-5 years: 3 times daily 10 drops 6-12 years: 3 times daily 20 drops ≥ 12 years: 3 times daily 30 drops	3) 10 ml (corresponding to 12 g) contain 0.8 g liquid extract ≥ 12 years: 3 times daily 5 ml
5) 100 ml liquid contain 100 ml expressed juice ≥ 12 years: 3 times daily 10 ml (daily dose 27.6 g expressed juice resp. 6 g Plantaginis lanceolatae herba)	4) 100 g contain 10 g liquid extract ≥ 12 years: 4 times daily 4 ml (corresponding to 5 g)
6) 10 ml liquid contain 2.5 g liquid extract 1-4 years: 2-3 times daily 2.5 ml (corresponding to 1.25-1.875 g Plantaginis lanceolatae herba) 5-11 years: 2-3 times daily 5 ml (corresponding to 2.5-3.75 g Plantaginis lanceolatae herba) ≥ 12 years: 3-4 times daily 5 ml (corresponding to 3.75-5 g Plantaginis lanceolatae herba)	
7) 10 ml liquid contain 1.25 g liquid extract 1-4 years: 2-3 times daily 5 ml (corresponding to 1.25-1.875 g Plantaginis lanceolatae herba) 5-11 years: 2-3 times daily 10 ml (corresponding to 2.5-3.75 g Plantaginis lanceolatae herba) ≥ 12 years: 3-4 times daily 10 ml (corresponding to 3.75-5 g Plantaginis lanceolatae herba)	
8) 100 g (= 79.37 ml) syrup contain 10 g liquid extract ≥ 12 years: 3-4 times daily 10 ml	
9, 10, 11) 100 ml liquid contain 100 ml expressed juice 4-12 years: 2 times daily 5 ml ≥ 12 years: 3 times daily 10 ml	
12) 100 ml liquid contain 2.330 g dry extract 1-4 years: 3 times daily 5 ml 5-12 years: 2-3 times daily 10 ml ≥ 12 years: 3 times daily 10 ml	
13) 100 ml syrup contain 8.04 g soft extract 1-4 years: 3 times daily 5 ml	

Well-established use		Traditional use:
	5-12 years: 3 times daily 10 ml ≥ 12 years: 4 times daily 10 ml (corresponding to 3.84 g Plantaginis lanceolatae herba)	
14)	7.5 ml (corresponding to 9.357 g) syrup contain 1.875 g liquid extract 2-6 years: 3 times daily 2.5 ml (daily dose 1.9 g liquid extract) 7-12 years: 3 times daily 5 ml (daily dose 3.8 g liquid extract) ≥ 12 years: 4 times daily 7.5 ml (daily dose 5.6 g liquid extract)	
15)	100 g (corresponding to 83.33 ml) syrup contain 10 g liquid extract ≥ 12 years: 3-4 times daily 10 ml containing 10% m/m liquid extract (corresponding to 3.36-4.48 g Plantaginis lanceolatae herba)	
16)	oromucosal use ≥ 12 years: every 2 hours 2 containing 80 mg dry extract each at least 8 and at most 16 per day	
17)	100 g (corresponding to 80 ml) syrup contain 5 g liquid extract babies and infants: 4-6 times daily 2.5 ml (TE 01/08) school children: 4-6 times daily 5 ml (TE 01/08) ≥ 12 years: 4-6 times daily 15 ml (B 1999 und TE 01/08)	
18)	200 ml (corresponding to 240 g) syrup contain 24 g liquid extract 2-4 years: 3 times daily 5 ml (single dose 0.6 g, daily dose 1.8 g liquid extract) 4-12 years: 3 times daily 10 ml (single dose 1.2 g, daily dose 3.6 g liquid extract) ≥ 12 years: 3 times daily 15 ml (single dose 1.8 g, daily dose 5.4 g liquid extract)	
19)	1 tea bag contains 2 g herbal substance ≥ 12 years: 2-3 times daily 1 cup of fresh prepared tea (1 tea bag, 150 ml boiling water, 5 min extraction time)	
20)	100 g (corresponding to 79.62 ml) syrup contain 10 g (= 10.12 ml) liquid extract ≥ 12 years: 3 times daily 10 ml	

Indications

Well-established use	Traditional use
1, 2) For the relief of symptoms in colds of the respiratory tract and for inflammations of oral and pharyngeal mucosa.	1, 2,4) Traditionally used for the strengthening of the respiratory tract.
3, 17) Colds of the respiratory tract.	3) Traditionally used as an expectorant in the respiratory tract.
4, 8, 14) Colds of the respiratory tract, inflammation of the oral and pharyngeal mucosa.	
5, 9, 10) Catarrhs of the respiratory tract and inflammation in the mouth or the throat.	
6, 7, 13, 15, 20) For the relief of symptoms in colds of the respiratory tract.	
11, 16) Colds (catarrhs of the respiratory tract); inflammations of the oral and pharyngeal mucosa.	
18) For the relief of dry cough associated with colds of the respiratory tract.	
19) For the relief of symptoms in colds of the respiratory tract. For relief of symptoms in inflammation in the mouth and throat.	

Poland:

Traditional use: In Poland various herbal preparations containing *Plantago lanceolata*e with a traditional indication are on the market. None of them, however, fulfils the requirement of a medical use for at least 30 years.

Herbal Preparations	Since when are the preparations on the market:	Pharmaceutical form
1. liquid extract (1:2-2.5) extraction solvent ethanol 60% (V/V)	Since 12 years	syrup
2. liquid extract (1:1-2) extraction solvent ethanol 30% (V/V)	Since 9 years	syrup
3. extract (1:7) extraction solvent ethanol /water (95:5)	Since 15 years	syrup
4. liquid extract (0.7-1.3:1) extraction solvent ethanol 20% (m/m)	Since 14 years	syrup
5. liquid extract (1:3) extraction solvent ethanol 60%	Since 16 years	syrup
6. dried leaf	Since 17 years	herbal tea

Posology	Indications
1. Oral use:	1. Catarrhs of the upper respiratory tract; oral

Posology	Indications
7.5 -15 ml (1.125-2.25 g of extract) 4-5 times daily	and pharyngeal mucosa inflammatory changes
2. Oral use: 5 ml 3-4 times daily or 10 ml 2 times daily (100 g syrup contains 10 g of extract)	2. Upper airways inflammations with remained secretion and difficult expectoration
3. Oral use: 5-10 ml (2.17-4,34 g of extract) 3-4 times daily	3. Adjuvant in upper airways inflammations with difficult expectoration
4. Oral use: 6.4-19.2 g (0.32-0.96 g of extract) 2-5 times daily	4. Adjuvant in common cold symptoms such as cough and hoarseness
5. Oral use: 5-15 ml (0.647-1.941 g of extract) 3-4 times daily	5. Upper airways catarrhs and common cold, adjuvant in pharyngitis
6. Oral and oromucosal use, cutaneous use: 1.5-3 g 2-3 times daily Children: 50-100 ml of infusion (using 3 g in 250 ml of water) up to 2 times daily	Oral use: Upper airways inflammations and catarrhs Oromucosal use: Oral and pharyngeal mucosa inflammations Cutaneous use: Skin inflammations

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations and syrup
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Since 1997 and combinations
Denmark	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Since 1993 combinations and food supplements
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	At least since 1976 and combinations
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Before(?) 2002 food supplements
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:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Poland	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	As mono preparations and in combinations
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

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

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

1.3. Search and assessment methodology

<Rapporteur to include text>

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

See 1.2.

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

The following traditional uses and posologies have been recorded for *Plantago lanceolata*:

- *Monograph* Plantaginis lanceolatae herba *of the German Commission E* (1985)

Indications for the internal administration are catarrhs of the respiratory tract and inflammation of oral and pharyngeal mucosa. Externally applied it is used for inflammation of the skin.

The mean daily dosage is 3-6 g of the herbal substance or equivalent preparations.

- *ESCOP Monograph* Plantaginis lanceolatae *folium/herba* (2003)

Indications for the oral administration are catarrhs of the respiratory tract and temporary, mild inflammations of the oral and pharyngeal mucosa.

The average daily dose in adults and elderly is 3-6 g of the herbal substance or equivalent preparations. The average daily dose for children is 1-2 g for the age 1-4 years, 2-4 g for the age 4-10 years, and 3-6 g for the age 10-16 years.

- *German standard registration "Spitzwegerichkraut"* (1996)

For a tea from the herb of *Plantago lanceolata* indications are the same as listed in the monograph Plantaginis lanceolatae herba of the German Commission E.

The dosage for the tea is 3-4 cups per day. An infusion for a cup of tea is prepared with 150 ml hot water and 1.4 g of the herb which stirs for 10-15 minutes.

For rinsing and gargling as well as for compresses a cold macerate is prepared 3-4 times a day with 150 ml cold water and 1.4 g of the herb which stirs for 1-2 hours.

Based on literature and on the results of a survey in physicians according to Madaus (1976) *Plantago lanceolata* is administered in medical practise for the strengthening of mucosa and skin. It is given with very good success in diseases of the respiratory tract with severe mucous production and is also administered in diseases of the urinary bladder and gastrointestinal tract. Furthermore, its use as haemostypic and local application in wounds and ulcers has been described. The usual dosage is 3 g of the herb for a cold macerate or hot infusion, 2-3 spoons of the juice or ½ teaspoon of the fresh plant comminution 3 times per day.

- The use of *Plantago lanceolata* for the treatment of wounds in folk medicine extensively described by Brøndegaard (1963).

Loew *et al*. (1997) mention *Plantago lanceolata* as mucilage drug which can be used against dry cough caused by pharyngitis. According to Hoppe (1975) *Plantago lanceolata* is used as a mucilage drug and mild expectorans. In folk medicine it is administered in catarrhs of the upper respiratory tract. Due to its positive benefit-risk-ratio *Plantago lanceolata* is recommended by Wegener and Kraft (1999) even for children for the treatment of moderate chronic irritative cough, Büechi and Wegener (2005) recommend the administration in moderate irritative cough as well as its topical application in cases of inflammation of the skin and mucosa.

There are further reports of the use of *Plantago lanceolata* in folk medicine:

- In Turkey fresh *Plantago lanceolata* leaves are applied to abscess to promote suppuration (Sezik *et al.* 2001).
- In Guatemala the drug is administered in conjunctivitis/eye irritation and for the treatment of wounds, ulcers, bruises and sores (Cáceres *et al.* 1987).
- In North-West Greece infusions of *Plantago lanceolata* leaves are used for curing stomach spasms (sedative action) (Tammaro and Xepapadakis 1986).

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

See 1.2. and 2.2.

3. Non-Clinical Data

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

Plantago lanceolata has traditionally been regarded as a mucilage drug. The mucilage polysaccharides, mainly arabinose and galactose (Bräutigam and Franz 1985), are not resorbed and cover the mucosa with a protective layer against local irritations (Franz 1989, Müller-Limmroth 1980). Schmidgall *et al.* (2000 were the first to show moderate adhesive effects of polysaccarides from *Plantago lanceolata* extracts on mucus membranes by means of an *ex vivo* system based on porcine buccal membranes.

Beyond this, pharmacological effects are attributed to the following constituents of *Plantago lanceolat*a (Blaschek *et al.* 2008, Marchesan *et al.* 1998a):

- Iridoid glycosides: mainly aucubin and catalpol
- Mucilage polysaccharides
- Flavonoids: mainly apigenin and luteolin
- Phenylethanoids: acetoside, plantamajoside
- Phenol carboxylic acids
- Tannins

In vitro and *in vivo* pharmacological investigations have been performed with the total extract and with isolated agents from the total extract.

Anti-inflammatory, antioxidant, antibacterial, immunstimulant, epithelizing, antitoxic and procoagulant effects have been observed for extracts from *Plantago lanceolata* (Paper and Marchesan 1999, Büechi

and Wegener 2005). In addition, spasmolytic and antiviral effects have been described by the authors for single compounds of *Plantago lanceolata*.

Other effects reported for isolated agents of *Plantago lanceolata* include anthelmintic and cytotoxic properties.

Anti-inflammatory and antioxidant effects

The anti-inflammatory efficacy of extracts from *Plantago lanceolata* has been investigated by means of the modified hen's egg chorioallantoic membrane test (HET-CAM) (Marchesan *et al.* 1998b). Four different freeze-dried liquid extracts (28% ethanol) were used. At a 10-fold higher concentration (500 µg/pellet vs. 50 µg) the anti-inflammatory activity of the extracts was comparable to that of hydrocortisone, phenylbutazone and sodium diclofenac.

The effects of extracts from *Plantago lanceolata* (leaves, flowers, roots) on mediators of inflammation have been investigated *in vitro* in murine macrophages (Vigo *et al.* 2005). They inhibited the production of nitric oxide in this cell line and significant scavenging of nitric oxide radicals. Pre-treatment with these extracts did not affect COX-1 mRNA production, COX-2 mRNA and PGE_2 levels induced by lipopolysaccharide/interferon-γ challenge. The authors assume that the anti-inflammatory effects of *Plantago lanceolata* extracts are based on the inhibition of nitric oxide and not a reduced prostaglandin production.

Herold *et al*. (2003a) investigated *in vitro* if a standardized hydroalcoholic extract from *Plantago lanceolata* leaves can suppress in cell-free systems the activities of 5-lipoxygenase and COX-2 which are key enzymes in the formation of pro-inflammatory eicosanoids from arachidonic acid. The *Plantago lanceolata* extract displayed significant efficacy concerning a dose-dependent inhibition of COX-2 activity.

In vivo studies with dried frozen extracts from *Plantago lanceolata* leaves showed that in Wistar–Albino mice the inflammatory effects caused by carrageenan and prostaglandin E1 were reduced (Shipochliev *et al.* 1981). In Wistar rats an 80% ethanol extract from dried *Plantago lanceolata* leaf reduced carrageenan produced foot edema by 11 % (Mascolo *et al.* 1987).

Anti-inflammatory properties have also been established for single compounds of *Plantago lanceolata* by means of *in vivo* and *in vitro* experiments. The phenylethanoids acteoside and plantamajoside (Murai *et al.* 1995, Ravn *et al.* 1990, Hausmann *et al*. 2007, Hayashi *et al.* 1994, Molnár *et al.* 1989) and the iridoidglycosides catalpol and aucubin (del Recio *et al.* 1994) showed anti-inflammatory activity (*in vitro* and *in vivo* investigations). For flavonoids anti-inflammatory effects have been described, too (Spilková and Hubík 1988; Mascolo *et al.* 1988, Tordera *et al*. 1994).

In connection with the anti-inflammatory activity of *Plantago lanceolata* its antioxidant properties have also been studied, since free radicals may play a role in inflammatory diseases.

Herold *et al.* (2003b) investigated the possible mode of action of the antioxidant potential of a hydroalcoholic extract from *Plantago lanceolata* leaves standardized to mucilaginous substances. The antioxidant property was measured using a colorimetric assay and the free radical scavenging potential by means of activated human PMN–neutrophils. For the extract a minor antioxidant status and the capacity of scavenging free radicals released by activated PMNs were observed.

The antioxidant activity of a methanol extract from the aerial parts of *Plantago lanceolata* was studied by Gálvez *et al.* (2005) using the DPPH scavenging test and lipid peroxidation inhibition assay, in which this extract was found to be the most active as compared to methanol extracts from other *Plantago* species.

Antioxidant effects have also been observed for single compounds such as acteoside (Ji *et al*. 1993, Pan and Hori 1996; Wang *et al.* 1996; Li *et al.* 1996; Hausmann *et al.* 2007), various polysaccharides (Kardosová and Machová, 2006) and flavonoids (Catapano 1997, van Acker *et al.* 1996, Fraga *et al*. 1987).

Antibacterial effects

In vitro investigations with pressed juice and aqueous extracts of *Plantago lanceolata* showed antibacterial effects against *Staphylococcus aureus*, *Streptococcus β-hemolyticus*, *Proteus vulgaris*, *Salmonella*, *Shigella*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Bacillus subtilis* (Haznagy 1970; Felklova 1958; Elich 1962). An ethanolic maceration showed an *in vitro* inhibition of *Staphylococcus aureus* (Cáceres *et al.* 1987).

It is assumed that aucubigenine is responsible for the *in vitro* antibacterial effects of *Plantago lanceolata* (Elich 1962; Hänsel 1966, Elich 1966; Elich 1961), as aqueous extracts with inactivated β-glucosidase showed to be ineffective (Elich 1966; Elich 1961). β-glucosidase is the relevant enzyme which splits aucubin into glucose and aucubigenin.

The antibacterial and antifungal activity of an ethanolic extract from *Plantago lanceolata* were also investigated by Orhan *et al.* (2002) by agar diffusion and microdilution methods using *E. coli*, *Proteus mirabilis*, *Enterococcus faecalis*, *Acinetobacter baumanni*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumonia*, *Candida albicans*, *Candida kruzei* and *Candida parapsilosis*. Antibacterial or antifungal effects were not observed for *Plantago lanceolata*.

Regarding single compounds of *Plantago lanceolata* acteoside exerted only weak antibacterial effects on *E. coli* (Molnár *et al.* 1989). The isolated compounds aucubin and saponin and extract of the herbal substance *Plantago lanceolata* leaves showed antibiotic effect. Extract of *Plantago lanceolata* leaves and aucubin had antibiotic effects on *Streptococcus aureus* 209 P and *Micrococcus flavus*, whereas the antibiotic activity of the saponin compound was limited to *Micrococcus flavus* (Tarle *et al*. 1981).

Spasmolytic effects

An ethanolic extract from *Plantago lanceolata* herba (DEV 1:1) (Fleer *et al.* 1997) and an ethanolic (20 %) spissum extract of *Plantago lanceolata* (Fleer and Verspohl 2007) inhibited the ileum contractions caused by acetylcholine, histamine, potassium and barium ions and barium induced tracheal contractions in guinea-pigs. These effects were comparable to those of atropine and papaverine.

Spasmolytic activity has been attributed to the iridoids aucubin and catalpol (Urbina *et al.* 1994) and acteoside (Schapoval *et al.* 1998). Fleer and Verspohl (2007) observed antispasmodic effects for luteolin, acteoside, plantamajoside, and catalpol peracetate.

Antiviral effects

Abdin (2006) observed positive effects of tea from *Plantago lanceolata* leaves in one patient with AIDS-related Complex and suggests that further research might explore a possible role for *Plantago lanceolata* in the treatment of HIV-infection.

Antiviral effects on Aujezky virus (Molnár *et al*. 1989) and RS-virus (Kernan *et al.* 1998) were observed for acteoside. Aucubin, as a prodrug for aucubigenin, inhibited *in vitro* DNS-replication of hepatitis B virus (Chang 1997). Catalpol showed to be active against hepatitis B virus antigens (HBsAg) in HBsAg positive serum (Mehrotra *et al*. 1990). For caffeic acid and chlorogenic acid (Chattopadhyay *et al.*

2008, Zanon *et al*. 1999, Chiang *et al.* 2002) as well as saponines and tanning agents (Büechi 1998, Büechi 1996) antiviral acitivity was shown, too.

Antitoxic effects

Protective effects have been attributed to *Plantago lanceolata*. It has been reported that pressed juice from *Plantago lanceolata* had antitoxic effects on the damaging effects of 5-fluoruracil on the mucosa in mice with Ehrlich-tumors (Zueva and Yaremenko, 1989; Borovskaya *et al.* 1987). Celik and Aslantürk (2006) also observed *in vitro* anti-mitotic and anti-genotoxic effects with aqueous extracts from *Plantago lanceolata* leaves.

Antitumor activity was observed *in vitro* for acteoside and seems to be due at least in part to inhibition of protein kinase C (Herbert and Maffrand 1991). Flavonoids were shown to inhibit tumor promoter-induced histamine release in a concentration-dependent manner (Middleton *et al.* 1987) and to inhibit hyaluronidase (Kuppusamy *et al.* 1990) and cyclic AMP phosphodiesterase (Kuppusamy and Das 1992).

The hepatoprotective activity of an ethanolic extract from *Plantago lanceolata* leaves was investigated using pentobarbital-induced hypnosis model in mice treated with carbon tetrachloride as hepatotoxin. Significant hepatoprotective effects (25.5% inhibition) were observed (Deliorman *et al.* 1999). In a study performed in rats, however, the extract from *Plantago lanceolata* leaves showed no protective efficacy in hepatotoxicity caused by carbon tetrachloride (Aktay *et al.* 2000). In another *in vitro* investigation by Aktay *et al*. (2001) an ethanolic extract from *Plantago lanceolata* leaves showed no inhibition of lipid peroxidation which is implicated as a molecular mechanism in the pathogenesis of several chronic diseases.

Hepatoprotective effects were observed for aucubin (Chang *et al*. 1984, Chang and Yamaura 1993), acteoside (Xiong *et al.* 1998, Yamahara *et al.* 1990, Pan and Hori 1996) and catalpol (Garg *et al.* 1994*)*.

Immunostimulant effects

In vitro and *in vivo* a aqueous extract from *Plantago lanceolata* leaves caused a significant increase of antibody formation and release of angiogenesis factor in lymphocytes of man and mouse (Strzelecka *et al.* 1995). An aqueous decoction of *Plantago lanceolata* leaves stimulated the production of interferon in mice (Plachcinska *et al.* 1984).

Immunomodulatory effects were shown for several compounds of *Plantago lanceolata*: Polysaccharides derived from *Plantago lanceolata* leaves (Bräutigam 1985, Ebringerová *et al.* 2003), aucubin and chlorogenic acid (Chiang *et al*. 2003), catalpol (Wegener and Kraft 1999, Garg *et al.* 1994) and acteoside (Marchesan *et al.* 1998). For acteoside immunosuppressive effects were reported by Sasaki *et al*. (1989).

Epithelizing effects

Aqueous extracts from *Plantago lanceolata* are said to promote epithelizing and scaring of wounds and to reduce hyperemia (HagerROM 2006, Heil and Kammerer 1993). According to Pahlow (1984) fresh ground *Plantago lanceolata* leaves are effective in inflammation or irritation of the skin caused by insect stings (Brøndegaard 1963).

Müller-Limmroth and Fröhlich (1980) report that aucubin supports the epithelization of defects in bronchial mucosa, whereas the mucopolysaccharides contained in *Plantago lanceolata* cover epithelial defects in the hypopharynx which are responsible for triggering the cough reflex.

Procoagulant effects

Aqueous extracts increased coagulation *in vitro* and *in vivo* (Blaschek *et al.* 2008, Keeser 1939). An extract (1:1) stimulated the coagulation of blood in rabbits, a 1:10-infus reduced coagulation time in dilutions of 1:5 to 1:40. Following injection into the V. femoralis of the cat an acceleration of coagulation was observed.

Antihelmintic effects

Ethanolic and aqueous extracts from *Plantago lanceolata* leaves displayed significant anthelmintic activity against pinworms in mice (Kozan *et al.* 2006).

Cytotoxic effects

Cytotoxic effects for single compounds of *Plantago lanceolata* have been observed by Gàlvez *et al.* (2003). Methanolic extracts from *Plantago lanceolata* leaves showed growth inhibitory and cytotoxic effects on breast adenocarcinoma and melanoma tumoral cell lines which might be due to the cytotoxic activity of the flavone luteolin-7-O-β-glucoside, the major flavonoid in *Plantago* species. According to the authors topoisomerase-mediated DNA damage is the possible mechanism of cytotoxicity.

In an *in vitro* investigation in rat hepatoma cells an increased breaking of DNA chains as well as increased proapoptoctic effects occurred following luteolin concentrations > 100 µM (Steffan 2005). In contrast to this observation for flavonoids anticancerogenic effects have been described after *in vitro* concentrations of 0.1-1 mM (Watzl and Rechkemmer 2001).

A saponin substance isolated from the leaves of *Plantago lanceolata* showed haemolytic activity (Tarle *et al.* 1981).

Effects on mucociliary transport

Mucociliary transport was investigated by viscosimetry using a ciliated epithelium preparation of a frog. A 4.6% extract from *Plantago lanceolata* did not increase mucociliary activity (Müller-Limmroth and Fröhlich 1980).

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

There is a report on the pharmacokinetics of aucubin in rats (Suh *et al.* 1991). Linear kinetics were observed following the intravenous administration of 40-400 mg/kg bodyweight. Post-distributional half-life $t_{1/2,\beta}$ was 43 minutes. Binding capacity to plasma proteins was 9%. For a dose of 100 mg/kg bodyweight bioavailability was 83.5% (hepatoportal application) resp. 76.8% (intraperitoneal application) and 19.3% (oral application). Investigations regarding the stability of pH at a temperature of 37°C showed a fast degradation of aucubin at pH values of 1.2, 1.6 and 2.0 with half-lives of 5.1, 5.8 and 14.8 h. The authors thus assume that the low bioavailability of aucubin may be explained by its instability at a low pH, the low gastrointestinal absorption and an intensive first-pass metabolism.

In rabbits aucubigenin accumulates in urine when fed with the drug (Freerksen 1950).

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

No acute or chronic toxicity tests were performed on any herbal preparation of Plantago lanceolata.

Acute toxicity

Aucubin can cause gastroenteritis and central palsy following oral administration (Blaschek *et al.* 2008).

Following maximum aucubin doses of 900 mg/kg bodyweight no deaths occurred in mice (Chang 1985).

Chronic toxicity

Maximum aucubin doses of 800 mg/kg bodyweight 4 times a week did not cause significant changes of liver transaminases, alkaline phosphatase, triglycerides, glucose, blood urea nitrogen and total protein. Liver biopsies did not reveal relevant changes (Chang 1985).

Mutagenicity and cancerogenicity

An Ames-test was performed with a tincture (1:5) from *Plantago lanceolata* (70% ethanol). Both with and without metabolic activation by the S-9 fraction mutagenic effects were not observed with the *Salmonella typhimurium* TA 98 and TA 100 (Schimmer *et al.* 1994).

Ruiz *et al.* (1996) screened several plants for genotoxic activity by means of induction of somatic segregation in *Aspergillus nidulans*. A fluid extract from *Plantago lanceolata* (40% ethanol) showed no statistically significant increase in the frequency of segregant sectors per colony and thus no genotoxic effects.

Cytotoxicity

Cytotoxic effects of a methanol extract from *Plantago lanceolata* were observed by Gàlvez *et al.* (2003), haemolytic activity was described by Tarle *et al.* (1981) for a saponin substance isolated from the leaves of *Plantago lanceolata*. In an *in vitro* investigation in rat hepatoma cells an increased breaking of DNA chains as well as increased proapoptoctic effects occurred following luteolin concentrations > 100 µM (Steffan 2005) (see section 3.1).

Local tolerance

In an investigation with 1000 dogs *Plantago lanceolata* caused atopic dermatitis in > 15% of the animals (Mueller *et al.* 2000).

3.4. Overall conclusions on non-clinical data

Pharmacology

A variety of pharmacological effects have been reported for *Plantago lanceolata* extracts and its compounds. Most of the investigations have been performed in earlier times, more recent investigations have mainly been performed with isolated agents of the plant. As so far, however, only the concentration of the iridoidglycosides aucubin and catapol has been determined (Long *et al*. 1995, Jurisic *et al.* 2004), the assessment to which extent the different effects of *Plantago lanceolata* extracts reported can be attributed to single compounds is not possible.

The pharmacological effects described in literature, however, support both the oral and oromucosal traditional use of herbal preparations of *Plantago lanceolata* as a demulcent for the symptomatic treatment of irritations of oral and pharyngeal mucosa with associated dry

Pharmacokinetics

So far, pharmacokinetic investigations have only been performed with aucubin and not with the total extract. Data on pharmacokinetics in man are not available. Due to the low bioavailability of aucubin it is unclear to which extent the pharmacological effects observed *in vitro* and *in vivo* experiments contribute to the efficacy of the total extract and are of clinical relevance.

Toxicology

There are no data available on the toxicity tests with preparations from Plantago lanceolata. No reproduction or developmental toxicity tests have been performed. An administration of *Plantago lanceolata* thus cannot be recommended during pregnancy and lactation. The investigation of genotoxiciy by Schimmer *et al.* (1994) is assessed as insufficient, as the Ames test performed included only 2 stems of *Salmonella typhimurium* instead of 5 as required.

Regarding the cytotoxic effects observed for luteolin it is supposed that there is no risk in man, as the bioavailability of flavonoids following oral administration is only poor and only low concentrations of the mutagenic active flavonoids can be found (Teuscher *et al.* 2004). The luteolin concentration used in the *in vitro* experiments thus is not reached under physiological conditions.

With regard to the potential toxicity of aucubin, its minimum lethal dose in mouse of > 0.9 g have to be taken into account so that aucubin is regarded as a low toxic substance (Chang *et al.* 1983). Due to the low content of aucubin in *Plantago lanceolate* the safety of the drug does not seem to be affected when used in clinical practice and intoxications with *Plantago lanceolata* have not been observed, so far.

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 human data available.

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

No human data available.

4.2. Clinical Efficacy

4.2.1. Dose response studies

Dose response studies have not been performed.

4.2.2. Clinical studies (case studies and clinical trials)

There is only one post-marketing study conducted by Kraft (1997). The aim of this prospective, multicenter study was to obtain data on the administration of a cough syrup (100 ml syrup contains 20 g fluid extract from *Plantago lanceolata* herb, DER 1:1, extraction agent ethanol) and to assess its efficacy and safety in patients with unspecific acute respiratory diseases. For the assessment of therapeutic course subjective symptoms, efficacy and tolerability were rated by the patient and the doctor by means of scores from 0-5.

A total of 593 patients (mean age 42 years, range 1-88 years) were included, in 15% of the patients age was < 18 years. The main diagnoses were acute respiratory infections (32% of the patients), acute bronchitis (28%) and irritative cough following acute respiratory infections (18%). The mean duration of administration of the cough syrup was 10 days with a mean daily dose of about 30 ml of the syrup corresponding to about 6.0 g of the drug.

After 3-14 days of treatment intensity and frequency of coughing was reduced by 67% and 66%, respectively. Thoracal pain decreased by 80%, irritative cough and dyspnea by 69%. Subjective finding and general condition as assessed by the doctor improved by 43% and 37%, respectively. Global efficacy was assessed as good by the doctor in 62% of the patients, and as excellent by 26% of the patients. Moderate to insufficient efficacy was reported by about 13% of the patients, whereby the assessments by patients and doctors showed great similarity.

As controlled clinical trials with extracts from *Plantago lanceolata* have not been performed a well-established use cannot be accepted. The results of the post-marketing study and references in literature, however, support the traditional use of *Plantago lanceolata*.

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

The results of the post-marketing study by Kraft (1997) were analyzed separately for the subgroup of 91 patients with an age < 18 years (Kraft 1998). 20 children were ≤7 years, 38 children had an age between 8 and 12 years, and 33 children were adolescents between 13 and 17 years old. The mean daily drug dosage in this group was 22.4 ml of the syrup (corresponding to about 4.5 g of the drug), the mean duration of administration 9 days. As compared to baseline symptoms decreased by 58% on average. The patients' and doctors' final assessments of efficacy were comparable to those of the adults.

A dosage recommendation for children is given by the Kooperation Phytopharmaka (1998) and was calculated on basis of the dosage for adults which correspond to the dosage as defined in the monograph of the Commission E. The mean daily dose of the herbal substance for children is as follows (internal administration):

Age (years)	0-1:	-
	>1-4:	1-2 g
	<4-10:	2-4 g
	>10-16:	3-6 g

The mean daily dose for children based on the results obtained by a survey in 31 doctors are as follows (internal administration):

	Fluid, without alcohol	Fluid, with alcohol
Age (years)	<1 (n=3): 1.26 g	-
	1- <4 (n=20): 2.56 g	(n=6) 2.25 g
	4-12 (n=21): 6.76 g	(n=10) 4.31 g

In children only data for the oral administration are available.

4.3. Overall conclusions on clinical pharmacology and efficacy

Controlled clinical studies, which might support a well-established use, have not been performed with *Plantago lanceolata*.

The traditional use, however, is well documented. Apart from the results of one post-marketing study in 593 patients mainly with acute respiratory infections, among them 91 children and adolescents below 18 years of age (58 and 33 respectively), there is sufficient evidence in literature for the traditional internal use of *Plantago lanceolata* as a mucilage in the treatment of irritations of oral and pharyngeal mucosa with associated dry cough both. Since the mucilage polysaccharides are not resorbed and most probably do not reach the trachea or bronchi the medicinal use only in the upper departments of the respiratory tract seems plausible. The data available support a safe oral administration in adults and children older than 3 years. Due to the lack of sufficient data and safety considerations (see chapter II.3.3.6) the oral use in children younger than 3 years cannot be recommended. There is also sufficient evidence in literature on the traditional oromucosal use of *Plantago lanceolata* in adults; for children and adolescents no data are available. Thus, the oromucosal administration should be limited to adults.

In literature there is also evidence of a traditional use of Plantago lanceolatae for the external treatment of irritations of the skin, but so far only one medicinal product has been registered in Poland. This preparation, however, does not fulfil the requirement of a traditional use for at least 30 years.

5. Clinical Safety/Pharmacovigilance

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

In the post-marketing study by Kraft (1997) tolerability of the syrup from *Plantago lanceolata* (see chapter II.3.2.2) was assessed as excellent by 49% of the patients and 51% of the doctors. The assessment "moderate" was given by about 2% of the patients and doctors. Adverse events were rare and of low severity. In 7 patients (1%) adverse events were recorded, 5 of them were diarrhea – among them one child (age 10 years) - occurring in one center only. In 6 cases a causal relationship of the adverse event with the medication was assumed. Allergic reactions were not reported. Since all cases of diarrhea occurred in one center only the investigator suspected that this adverse event had an infectious cause.

So far, side-effects with *Plantago lanceolata* have not been reported in literature. Neither the monograph of the Commission E (1985) nor the ESCOP monograph (2003) mentions adverse reactions.

Nevertheless, for *Plantago lanceolata* a high risk of sensitization is reported by Blaschek *et al.* (2008). About 30% of patients with pollinosis are allergic to pollen from *Plantago lanceolata* (Wüthrich *et al.* 1977, Horak and Jäger 1980). 28% out of 82 patients with a clinical history of seasonal, respiratory

allergy were skin test positive to plantain pollen extract, 34% of serum samples of 354 similar patients showed positive RAST(radio-allergo-sorbens-test)-results (Mehta and Wheeler 1991).

One report of an allergic adverse event was received by the German Health Authority. Following the drug intake of a medicinal product containing *Plantago lanceolata,* a 35-year old patient developed angio-edema, swelling of eyes and lips and urticaria. As several medications were administered to the patient the causal relation, however, cannot be assessed definitely.

5.2. Patient exposure

Apart from its medicinal use, *Plantago lanceolata* is also available on the food-market in form of e.g. candies and teas. It is also used in cosmetics. There is no information available on the extent of its use in the general population.

5.3. Adverse events and serious adverse events and deaths

See chapter 5.1.

5.4. Laboratory findings

None reported for *Plantago lanceolata*.

5.5. Safety in special populations and situations

See chapter 5.1.

5.6. Overall conclusions on clinical safety

The oral and oromucosal administration of Plantago lanceolata is generally recognised as safe. Due to the lack of adequate data, however, its use cannot be recommended during pregnancy and lactation. In children younger than 3 years the drug should not be used, as there are only limited data on the oral use in children. In addition, children at this age should consult a doctor for making a diagnosis before the start of treatment because otherwise there is a risk that severe infectious diseases of the upper respiratory tract such as laryngitis are misinterpreted as a common cold. Data on a safe oromucosal application in children and adolescents are missing, too.

The local use of *Plantago lanceolata* is not recommended at all, since data on the topical application are completely missing.

6. Overall conclusions

The traditional medicinal use of *Plantago lanceolata* as demulcent in the treatment of irritations of oral and pharyngeal mucosa with associated dry cough fulfils the requirement of at least 30 years (including at least 15 years with the Community) according to Directive 2001/83/EC as amended.

There is sufficient evidence in literature for the traditional oral and oromucosal use in the above mentioned indication. Although various pharmacological effects have been described for the total extract of *Plantago lanceolata* and constituents thereof, these effects have never been verified in controlled clinical studies. A well-established use of the herbal substance thus cannot be postulated.

The internal administration has been investigated in a post-marketing study in 598 patients which confirms the safe use in adults and children. As there are only limited data on the use of *Plantago lanceolata* in children < 3 years and due to their special medical conditions internal use is not

recommended for this age-group. Due to the lack of data of its safe administration during pregnancy and lactation this patient group should also be excluded from administration. The oromucosal administration is recommended only for adults, as data in children and adolescents are completely missing.

An incomplete Ames-test is only available for a tincture of *Plantago lanceolata*. The general inclusion of the drug in the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products thus cannot be recommended.

Annex

List of references