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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Plantago lanceolata* L., folium

Final - Revision 1

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Plantago lanceolata* L., folium (Ribwort plantain)
Herbal preparation(s)	Comminuted herbal substance Powdered herbal substance Dry extract (DER 3-6:1), extraction solvent: water Liquid extract (DER 1:0.9-1.1), extraction solvent: ethanol 24-35% V/V Soft extract (DER 1.5-1.7:1), extraction solvent: ethanol 20% m/m Expressed juice (DER 1:0.5-0.9) from the fresh herb Liquid extract (DER 1:11), extraction solvent: water Dry extract (DER 3-5:1), extraction solvent: ethanol 20% m/m Liquid extract (DER 1:5.8-5.9), extraction solvent: water Liquid extract (DER 1:0.8-1.2), extraction solvent: ethanol 40% (V/V) Liquid extract (DER 1:3) extraction solvent: ethanol 60% (V/V)
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral and oromucosal use.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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		Comminuted herbal substance as macerate for oromucosal and cutaneous use. Herbal preparations in liquid, semi-liquid or solid dosage forms for oral and/or oromucosal use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.
Initial assessment	Rapporteur	J. Wiesner, W. Knoess
	Peer-reviewer	I. Chinou
First revision	Rapporteur	J. Wiesner
	Peer-reviewer	I. Chinou

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1. Introduction

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

- Herbal substance(s)

Plantaginis lanceolatae folium (Ribwort plantain) consists of the whole or fragmented, dried leaf and scape of *Plantago lanceolata* L. s.l. with a minimum of 1.5% of total ortho-diphenolic compounds expressed as acteoside ($C_{29}H_{36}O_{15}$; Mr 625) in the dried drug (Ph. Eur. 07/2025:1884).

In DAB 2005 (German Pharmacopoeia) the monograph 'Spitzwegerichkraut' ('The whole or cut, dried herb of *Plantago lanceolata* L.') was replaced by the monograph for ribwort plantain leaf, published in the European Pharmacopoeia, since the used plant material consisted mainly of leaves and scapes. Therefore, also all references to the former DAB material (herb) were kept for the purpose of this AR.

- Relevant constituents for this assessment report

Iridoid glycosides:
The herbal substance contains about 2-3% iridoid glycosides with aucubin and catalpol as the main compounds. 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), with aucubin at levels of 1-3% and catalpol up to 1% (Long *et al.*, 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*., 2021).

Mucilage:
The content varies between 2-6.5% mucilage (Wichtl and Blaschek, 2016).

Other constituents are flavonoids (including apigenin and luteolin), tannins, phenolic carboxylic acids and the coumarin aesculetin, the xanthophyll decomposition product loliolide and small amounts of a haemolytic and antimicrobial saponin are also present, as well as volatile oil (Wichtl, 2004).

- Herbal preparation(s)

No pharmacopoeia monographs are available for preparations.

Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable.

1.2. Search and assessment methodology

Revision 1
For the review 1 of the monograph, literature research was performed for the period January 2010-October 2020 in scientific/medical/toxicological databases EBSCO Discovery Service (Medline Complete, Pub Med, Embase, DynaMed). Key words were "*Plantago lanceaolata*" (SU) (in English, French or German). During the review, 306 new references not yet available during the first/previous assessment were identified.

Additional hand searches were performed in books, book chapters, articles and letters in Journals, Medical press reviews, Acts of law and regulations in the BfArM owned library. The bibliographies of included trials and other relevant reviews were searched to identify further potential trials.

Pharmacovigilance resources were the EudraVigilance database (EVDAS) and information provided by the Member States. For pharmacovigilance data a search in the EudraVigilance database (EVDAS) for "*Plantaginis lanceolatae* folium extractum fluidum", "*Plantago lanceolata*", "Pressed juice from fresh *Plantaginis lanceolatae* folium (1:0.60-0.90)", "Ribwort extract (1:1)" was performed.

1.3. Main changes introduced in the first revision

During the first revision, new information on medicinal use from products on the market, indications and posologies fulfilling traditional use have been introduced in chapter 2. 'Data on medicinal use'.

In chapters 3. 'Non-Clinical Data' and 5. 'Clinical Safety/Pharmacovigilance' additional studies / data have been introduced. New Publications containing safety findings regarding allergy to *P. lanceolata* pollen were identified. The strong allergy of *P. lanceolata* pollen should be mentioned and added in the monograph.

2. Data on medicinal use

2.1. Information about products on the market

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

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:

Table 1: Overview of data obtained from marketed medicinal products

Active substance	**Indication**	**Pharmaceutical form** **Strength (where relevant)** **Posology** **Duration of use**	**Regulatory Status**
Comminuted herbal substance	Traditional herbal medicinal product as a demulcent for the symptomatic treatment of oral or pharyngeal irritations and associated dry cough.	Herbal tea, to be prepared as infusion. 1 bag contains 1.2 g herbal preparation Adolescents and adults: 3-4 times daily 1 bag Children 4-12 years of age: 3 x daily 1 bag Children 2-4 years of age: 2 x daily 1 bag Duration of use: 2 weeks	AT, THMP, 2011
Plantaginis lanceolatae folium	a) Oral use: for adjuvant treatment of inflammations of the upper respiratory tract	Herbal tea in bags *Oral use:* children from 10 years of age, adolescents and adults: 1-2 tea bags (corresponding to 1.5–3 g of herbal substance)/250 ml of boiling water three times daily Children 3-9 years of age: 1-2 tea bags (corresponding to 1.5–3 g of herbal substance)/250 ml of boiling	CZ, THMP, on the market since 1999, switched to TUR 03/2011

	b) oromucosal use: for adjuvant treatment of mild inflammations in oral cavity c) cutaneous use: for adjuvant treatment of mild skin inflammations, poor healing wounds and ulcers, weeping eczema	water twice daily *oromucosal and cutaneous use:* 1-2 tea bags (corresponding to 1.5–3 g of herbal substance)/250 ml of boiling water for gurgle, poultice, washing, bath or irrigation several times daily	
Plantaginis lanceolatae herba	Internal administration: • Catarrhs of the respiratory tract • inflammation of oral and pharyngeal mucosa	Herbal tea SD: 1.4 g DD: 4.2-5.6 g Oral use: in 150 ml of boiling water 15 min as herbal infusion	DE, WEU, 1986-1996 (Standard-zulassung)
Plantaginis lanceolatae herba	Internal administration: • Catarrhs of the respiratory tract • inflammation of oral and pharyngeal mucosa External administration: • inflammation of the skin	Herbal tea SD: 1.4 g DD: 4.2 – 5.6 g Oral use: in 150 ml of boiling water 15 min as herbal infusion oromucosal and cutaneous use: in 150 ml cold water 1-2 h as cold extract (maceration) 3-4 x daily	DE, WEU, 1996 (Standard-zulassung)
Plantaginis lanceolatae herba, cut	For the relief of symptoms in colds of the respiratory tract. For relief of symptoms in inflammation in the mouth and throat.	Herbal tea 1 tea bag contains 2 g herbal substance Adults and adolescents ≥ 12 years of age: 2-3 times daily 1 cup of fresh prepared tea (1 tea bag, 150 ml boiling water, 5 min extraction time)	DE, WEU, at least 1976
Plantago lanceolata, comminuted herbal substance	Traditional herbal medicinal product used as an emollient in symptomatic treatment of mouth and throat mucosa irritations and dry cough connected	Herbal tea, infusion 2 g of the herbal substance pour with 150 ml of boiling water, infuse 15 min, under cover, strain, drink 2–3 times daily (DD 4–6 g)	PL, THMP, 1994
Plantago lanceolata, comminuted herbal substance	Supplementary in upper respiratory ways catarrhs, mouth and throat inflammatory states. Also externally in skin inflammatory states.	Herbal tea, infusion, made of 1.5 g of the herbal substance poured with 150 ml of boiling water	PL, THMP, 1994
Plantaginis lanceolatae herba, powder	Traditionally used for the strengthening of the respiratory tract.	1 lozenge contains 190 mg powder Oromucosal use: Adults and adolescents ≥ 12 years of age: 9 times daily 1 lozenge (DD=1.71 g powder)	DE, THMP, at least 1976
expressed juice from fresh Plantaginis lanceolatae herba (1:0.6-0.9)	Catarrhs of the respiratory tract (colds) and inflammation in the mouth or the throat.	100 ml liquid contain 100 ml expressed juice Children 3-12 years of age: 2 times daily 5 ml Adults and adolescents ≥ 12 years of age: 3 times daily 10 ml	DE, WEU, at least 1976

expressed juice from fresh Plantaginis lanceolatae herba (1:0.5-0.7)	Catarrhs of the respiratory tract and inflammation in the mouth or the throat.	100 ml liquid contain 100 ml expressed juice Adults and adolescents ≥ 12 years of age: 3 times daily 10 ml	DE, WEU, 1980
expressed juice from fresh *Plantaginis lanceolatae* herba (1:0.6-0.9)	Traditional herbal medicinal product for the symptomatic treatment of dry cough associated with oral or pharyngeal irritations.	Expressed juice adolescents and adults: SD=10 ml DD=30 ml children 3-12 years of age: SD=5 ml DD=10 ml	DE, WEU, 1976 (in 2012 registration as THMP)
Macerate (1:11) extraction solvent: water (Syrup according ÖAB 2009)	Treatment of catarrhs of the upper airways	Syrup: Dosage: 1 tablespoon 3-4 times per day Children: 1 teaspoon 3-4 times a day	AT, THMP, at least since 1980
Liquid extract (1:11), extraction solvent: water	Traditional herbal medicinal product as a demulcent for the symptomatic treatment of oral or pharyngeal irritations and associated dry cough.	Syrup: 100 ml = 130.75 g contain 50.236 g liquid extract. Adolescents and adults: 3-4 times daily 7.5 g liquid extract Children 3-11 years of age: 3-4 times daily 2.5 g liquid extract	AT, THMP, 2016
liquid extract (1:5.8-5.9); extraction solvent: water	Traditionally used for the strengthening of the respiratory tract.	Oral liquid 100 ml liquid contain 53.3 g extract Children 1-4 years of age: 3-4 times daily 2 ml oral liquid Children 5-12 years of age: 2-4 times daily 3 ml oral liquid Adults and adolescents ≥ 12 years of age: 3-5 times daily 4 ml oral liquid	DE, THMP, at least 1976
liquid extract from *Plantaginis lanceolatae* folium (1:5.8-5.9); extraction solvent: water	Traditional herbal medicinal product as a demulcent for the symptomatic treatment of oral or pharyngeal irritations and associated dry cough.	Syrup: 100 ml contain 53.3 g extract Adolescents and adults: SD=4 ml (=2.1 g extract) DD=12-20 ml (=6.4-10.6 g extract) children 5-11 years of age: SD=3 ml (=1.6 g extract) DD=6-12 ml (=3.2-6.4 g extract) children 1-4 years of age: SD=2 ml (=1.1 g extract) DD=4-6 ml (=2.1-3.2 g extract)	DE, WEU. 1976 (in 2011 registration as THMP)
dry extract (3-6:1); extraction solvent: water	Colds (catarrhs of the respiratory tract) inflammations of the oral and pharyngeal mucosa	Oral liquid: 100 ml liquid contain 2.330 g dry extract Children 1-4 years of age: 3 times daily 5 ml Children 5-12 years of age: 2-3 times daily 10 ml	DE, WEU, at least 1976

		Adults and adolescents ≥ 12 years of age: 3 times daily 10 ml Tablet, 1 tablet contains 80 mg dry extract: oromucosal use adults and adolescents ≥ 12 years of age: every 2 hours 2 tablets at least 8 and at most 16 tablets per day	
Liquid extract (1:1), extraction solvent: ethanol 20% (m/m)	Traditional herbal medicinal product as a demulcent for the symptomatic treatment of oral or pharyngeal irritations and associated dry cough.	Syrup: 200 ml = 240 g contain 24 g liquid extract Adolescents and adults: 3 times daily 1.8 g liquid extract Children 4-12 years of age: 3 x daily 1.2 g liquid extract Children 2-4 years of age: 3 x daily 0.6 g liquid extract	AT, THMP, 2010
Liquid extract (1:1), extraction solvent: ethanol 25% (V/V)	Traditional herbal medicinal product as a demulcent for the symptomatic treatment of oral or pharyngeal irritations and associated dry cough.	Syrup: 1 ml = 1.26 g contain 101.2 mg liquid extract Adolescents and adults: 3-4 times daily 1 g liquid extract Children 5-11 years of age: 3 x daily 1 g liquid extract Children 3-4 years of age: 3 x daily 0.5 g liquid extract Duration of use: 7 days	AT, THMP, 2018
Plantaginis extractum fluidum (DER 1:1), extraction solvent: ethanol 20% (m/m)	a) an adjuvant for treatment of inflammations of upper respiratory tract and b) cold associated with cough	Syrup: 100 g contain: 5 g Plantaginis extractum fluidum Adolescents from 15 years and adults: 4 – 6 x daily 15 ml Syrup Children and adolescents from 6 – 14 years: 4 – 6 x daily 5 ml Children from 3 years age till 5 years age: 4 – 6 x daily 2.5 ml	CZ, THMP, on the market since 1999, switched to TUR 04/2011
liquid extract (1:1); extraction solvent: ethanol 20% (m/m)	For the relief of symptoms in colds of the respiratory tract. Colds of the respiratory tract, inflammation of the oral and pharyngeal mucosa.	Liquid • 10 ml liquid contain 2.5 g liquid extract Children 1-4 years of age: 2-3 times daily 2.5 ml (DD=1.25-1.875 g liquid extract) Children 5-11 years of age: 2-3 times daily 5 ml (DD=2.5-3.75 g liquid extract) Adults and adolescents ≥ 12 years of age: 3-4 times daily 5 ml (DD=3.75-5 g liquid extract) • 10 ml (corresponding to 12.48 g) syrup contain 2.5 g liquid extract Children 2-6 years of age:	DE, WEU, at least 1976

		3 times daily 2.5 ml (DD=1.875 g liquid extract) Children 7-12 years of age: 3 times daily 5 ml (DD=3.75 g liquid extract) Adults and adolescents ≥ 12 years of age: 4 times daily 7.5 ml (DD=7.5 g liquid extract)	
	Colds of the respiratory tract.	• 10 ml (corresponding to 12 g) syrup contain 0.625 g liquid extract babies and infants: 4-6 times daily 2.5 ml (DD=0.625-0.9375 g liquid extract) school children: 4-6 times daily 5 ml (DD=1.25-1.875 g liquid extract) Adults and adolescents ≥ 12 years of age: 4-6 times daily 15 ml (DD=3.75-5.625 g liquid extract)	
	For the relief of dry cough associated with colds of the respiratory tract.	• 10 ml (corresponding to 12 g) syrup contain 1.2 g liquid extract Children 2-4 years of age: 3 times daily 5 ml (DD=1.8 g liquid extract) Children 4-12 years of age: 3 times daily 10 ml (DD=3.6 g liquid extract) Adults and adolescents ≥ 12 years of age: 3 times daily 15 ml (DD=5.4 g liquid extract)	
liquid extract from *Plantaginis lanceolatae* herba (1:1); extraction solvent: ethanol 20% (m/m)	Internal use: treatment of symptoms of cough and cold.	Syrup adolescents and adults: SD=1.25 g extract DD=3.75-5 g extract children 5-11 years of age: SD=1.25 g extract DD=2.5-3.75 g extract children 1-4 years of age: SD=0.625 g extract DD=1.25-1.875 g extract	DE, WEU, 2005
liquid extract (1:1); extraction solvent: ethanol 25% (V/V)	Colds of the respiratory tract, inflammation of the oral and pharyngeal mucosa.	Oral liquid 100 ml liquid contain 100 ml liquid extract Dosage: children 1-5 years of age: 3 times daily 10 drops children 6-12 years of age: 3 times daily 20 drops Adults and adolescents ≥ 12 years of age: 3 times daily 30 drops	DE, WEU, at least 1976
liquid extract (1:1);	Colds of the respiratory tract, inflammation of the	Syrup 100 g (= 79.37 ml) syrup	DE, WEU, at least 1976

extraction solvent: ethanol 24.6% (V/V)	oral and pharyngeal mucosa.	contain 10 g liquid extract Adults and adolescents ≥ 12 years of age: 3-4 times daily 10 ml	
Liquid extract from *Plantago lanceolata*, folium (0.9-1.1:1); extraction solvent: ethanol 20% (m/m)	Traditional herbal medicinal product for use in specified indications based on long-term use only indicated for relieve of oral or pharyngeal irritation and dry cough.	1 g (0.8 ml) of syrup contains 50 mg of liquid extract Adolescents, adults, and elderly patients: 15 ml of syrup 4-6 times a day at regular intervals. children 6-12 years of age: 5 ml of syrup 4-6 times a day at regular intervals children 3-6 years of age: 2.5 ml of syrup 4-6 times a day at regular intervals Use in children under 3 years of age is not recommended	LT, THMP, 1995
liquid extract (0.7-1.3:1); extraction solvent: ethanol 20% (m/m)	Adjuvant in common cold symptoms such as cough and hoarseness	Syrup Oral use: 6.4-19.2 g (0.32-0.96 g of extract) 2-5 times daily	PL, THMP, 1996
soft extract (1.5-1.7:1); extraction solvent: ethanol 20% (m/m)	For the relief of symptoms in colds of the respiratory tract.	Syrup 100 ml syrup contain 8.04 g soft extract Children 1-4 years of age: 3 times daily 5 ml Children 5-12 years of age: 3 times daily 10 ml Adults and adolescents ≥ 12 years of age: 4 times daily 10 ml	DE, WEU, at least 1976
Dry extract (3-5:1), extraction solvent: ethanol 20% (m/m)	Traditional herbal medicinal product as a demulcent for the symptomatic treatment of oral or pharyngeal irritations and associated dry cough.	Syrup, 100 ml = 120.8 g contain 3 g dry extract Adolescents and adults: 3-4 times daily 0.3 g dry extract Children 5-11 years of age: 3 x daily 0.3 g dry extract Children 3-4 years of age: 3 x daily 0.15 g dry extract Duration of use: 7 days	AT, THMP, 2018
dry extract (3-5:1); extraction solvent: ethanol 20% (m/m)	Oral and oromucosal use: For the relief of symptoms in colds of the respiratory tract and for inflammations of oral and pharyngeal mucosa.	Effervescent tablet, 1 tablet contains 300 mg dry extract Adults and adolescents ≥ 12 years of age: 3-4 times daily 1 tablet	DE, WEU, 2004
liquid extract (1:1-2); extraction solvent: ethanol 30% (V/V)	Upper airways inflammations with remained secretion and difficult expectoration	Syrup; 100 g syrup contain 10 g extract Oral use: 5 ml 3-4 times daily or 10 ml 2 times daily	PL, THMP, 2001
liquid extract (1:1); extraction solvent: ethanol 35% (V/V)	Traditionally used for the strengthening of the respiratory tract.	Oral liquid 100 g contain 10 g liquid extract Adults and adolescents ≥ 12 years of age: 4 times daily 4 ml (corresponding to 5 g)	DE, THMP, at least 1976

liquid extract from *Plantaginis lanceolatae* herba (1:1); extraction solvent: ethanol 35% (V/V)	Treatment of a) symptoms of cough and cold b) inflammation of oral and pharyngeal mucosa.	Syrup; 100 g Syrup (=77.4 ml) contains 20 g extract adolescents and adults: SD=2.6 g extract DD=5.2 g extract children 6-11 years of age: SD=1.3 g extract DD=3.9 g extract children 1-5 years of age: SD=1.3 g extract DD=2.6 g extract	DE, WEU, 1990
liquid extract (1:0.9-1.1); extraction solvent: ethanol 35% (V/V)	Colds of the respiratory tract.	Syrup Dosage: adults and adolescents ≥ 12 years: 3-4 times daily 10 ml containing 10% m/m liquid extract (corresponding to 3.9-5.2 g liquid extract)	DE, WEU, at least 1976
liquid extract (1:1); extraction solvent: ethanol 40% (V/V)	For the relief of symptoms in colds of the respiratory tract.	Syrup 100 g (corresponding to 83.33 ml) syrup contain 10 g liquid extract Adults and adolescents ≥ 12 years of age: 3-4 times daily 10 ml (corresponding to 3.6-4.8 g liquid extract)	DE, WEU, at least 1976
liquid extract (1:0.9-1.1); extraction solvent: ethanol 40% (V/V)	For the relief of symptoms in colds of the respiratory tract.	Syrup 100 g (corresponding to 79.62 ml) syrup contain 10 g (= 10.12 ml) liquid extract Adults and adolescents ≥ 12 years of age: 3 times daily 10 ml (corresponding to 3.77 g liquid extract)	DE, WEU, at least 1976
liquid extract (1:0.8-1.2); extraction solvent: ethanol 40% (V/V)	Traditionally used as an expectorant in the respiratory tract.	Oral liquid 10 ml (corresponding to 12 g) contain 0.8 g liquid extract Adults and adolescents ≥ 12 years of age: 3 times daily 5 ml	DE, THMP, at least 1976
liquid extract (1:3); extraction solvent: ethanol 60% (V/V)	Traditionally used in upper respiratory airways catarrhs (chronic inflammatory states) and in common cold. Supplementary in throat inflammations.	Syrup; 100 g syrup contain 10 g extract Oral use Children 6-12 years of age: 5 ml of the syrup, 3–4 times daily. Adolescents and adults: 15 ml of syrup 3–4 times daily	PL, THMP, 1994
liquid extract (1:2-2.5); extraction solvent: ethanol 60% (V/V)	Catarrhs of the upper respiratory tract; oral and pharyngeal mucosa inflammatory changes	Syrup Oral use: 7.5-15 ml (1.125-2.25 g of extract) 4-5 times daily	PL, THMP, 1998
fluid extract (1:2); extraction solvent:	Traditionally in upper respiratory catarrhs (inflammatory states) and inflammatory changes of mouth and throat mucosa.	Syrup; 100 g contain 12 g of fluid extract Children 6-10 years of age: 7.5 ml 5 times daily children 10-12 years of age:	PL, THMP, 1998

ethanol 60% (V/V)		10 ml 4 times daily Adolescents: 10-15 ml 5 times daily It the symptoms persist or not resolve after 7 days it is advised to introduce another therapy	
liquid extract (1:7); extraction solvent: ethanol /water (95:5)	Adjuvant in upper airways inflammations with difficult expectoration	Syrup Oral use 5-10 ml (2.17-4.34 g of extract) 3-4 times daily	PL, THMP, 1995

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

No information available.

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

Not applicable.

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

Not applicable.

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

Traditional use of *Plantago lanceolate* has been reported since ancient times. Madaus (1976) summarized historical references (including e.g., Dioscurides, Albertus Magnus, Paracelsus, Matthiolus), and traditional uses from different countries as Denmark, Lithuania, Norway, Poland, Hungaria. In North-West Greece infusions of *Plantago lanceolata* leaves are used for curing stomach spasms (Tammaro and Xepapadakis, 1986).

The usage of fresh or dried herbal substance and/or preparations thereof were reported in several handbooks. Indications mentioned were use as mucilage drug, as mild expectorants, in cases of inflammations of the upper respiratory tract and topically as haemostypic, in the treatment of wounds and ulcers (e.g. mastitis); inflammations of the skin and mucosa; stings of insects (Brøndegaard, 1963; Hoppe, 1975; Pahlow, 1984; Commission E, 1985; Heil and Kammerer, 1993; Loew *et al*., 1997; ESCOP, 2003; Büechi and Wegener, 2005; Schilcher *et al.*, 2007; Wichtl, 2016; Blaschek *et al.,* 2021).

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).

2.3. Overall conclusions on medicinal use

The data describe three different indications, which are acceptable for a traditional use monograph. The wording in the respective monograph is adjusted to the wording used for similar indications.

1.) Oral or oromucosal (gargling and rinsing) use:
Traditional herbal medicinal product used as a demulcent for the symptomatic treatment of oral or pharyngeal irritations and associated dry cough.

2.) Oral use:
Traditional herbal medicinal product used for the relief of cough associated with cold.

3.) Cutaneous use:
Traditional herbal medicinal product used for the treatment of minor inflammation of the skin.

Table 2: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	**Indication**	**Posology, Strength**	**Period of medicinal use**
a) Comminuted herbal substance	Indication 1), 2)	Oral use, herbal tea *Adolescents, adults and elderly:* comminuted herbal substance in 150-250 ml of boiling water as an herbal infusion SD=1.4-2 g; 2-3 times daily DD=4-6 g	1986 (DE), 1996 (DE); 1994 (PL)
	Indication 1)	Oromucosal use, macerate *children from 3 years of age; adolescents, adults and elderly:* comminuted herbal substance in 150 ml of cold water; left to stand for 1 to 2 hours, stirring frequently SD=1.4 g; 3-4 times daily DD=4.2-5.6 g	1996 (DE)
	Indication 3)	Cutaneous use, herbal tea for compresses: *children from 3 years of age; adolescents, adults and elderly:* comminuted herbal substance in 150 ml of cold water; left to stand for 1 to 2 hours, stirring frequently SD=1.4 g; 3-4 times daily DD=4.2-5.6 g	1996 (DE)
b) Powdered herbal substance	Indication 1)	Oromucosal use Adults and adolescents ≥ 12 years of age: SD=190 mg; 9 times daily DD=1.71 g	1976 (DE)
c) Dry extract (DER 3-6:1); extraction solvent: water	Indication 1), 2)	Oral use *Adolescents, adults and elderly:* SD=233 mg dry extract; 3 times daily DD=699 mg *Children:* *5-11 years of age* SD=233 mg dry extract; 2-3 times daily DD=466-699 mg *3-4 years of age:* SD=117 mg dry extract, 3 times daily DD=351 mg Oromucosal use SD=160 mg	1976 (DE)

Herbal preparation Pharmaceutical form	**Indication**	**Posology, Strength**	**Period of medicinal use**
		DD=640-1280 mg administered as lozenge	
d) Liquid extract (DER 1:0.9-1.1); extraction solvent: ethanol 24-35% (V/V)	Indication 1), 2)	Oral use *Adolescents, adults and elderly* SD=0.94-2.6 g liquid extract; 3-6 times daily DD=3.75-7.5 g *Children* *5-11 years of age:* SD=0.31-1.3 g liquid extract; 2-3 times daily DD=1.25-3.9 g *3-4 years of age:* SD=0.16-1.3 g liquid extracts; 2-6 times daily DD=0.62-2.6 g	1976 (DE)
e) Soft extract (DER 1.5-1.7:1); extraction solvent: ethanol 20% (m/m)	Indication 1), 2)	Oral use *Adolescents, adults and elderly:* SD=804 mg soft extract; 4 times daily DD=3216 mg *Children* *5-11 years of age:* SD=804 mg soft extract; 3 times daily DD=2412 mg *3-4 years of age:* SD=402 mg soft extract; 3 times daily DD=1206 mg	1976 (DE)
f) Expressed juice (DER 1:0.5-0.9) from the fresh herb	Indication 1), 2)	Oral use *Adolescents, adults and elderly:* SD=10 ml expressed juice, 3 times daily DD=30 ml *Children* *3-11 years of age:* SD=5 ml expressed juice, 2 times daily DD=10 ml	MA, at least since 1976 (DE)
g) Liquid extract (DER 1:11); extraction solvent: water	Indication 1), 2)	Oral use *Adolescents, adults and elderly:* SD=7.5 g liquid extract; 3-4 times daily DD=22.5-30 g liquid extract *Children* *3-11 years of age:* SD=2.5 g liquid extract; 3-4 times daily DD=7.5-10 g liquid extract	MA, at least since 1980 (AT)
h) Dry extract (DER 3-5:1); extraction solvent: ethanol 20% (m/m)	Indication 1), 2)	Oral use *Adolescents, adults and elderly:* SD=300 mg dry extract; 3-4 times daily	2004 (DE)

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
		DD=900-1200 mg *Children* *5-11 years of age:* SD=300 mg dry extract; 3 times daily DD=900 mg *3-4 years of age:* SD=150 mg dry extract; 3 times daily DD=450 mg	
i) Liquid extract (DER 1:5.8-5.9); extraction solvent: water	Indication 1), 2)	Oral use *Adolescents, adults and elderly:* SD=2.1 g liquid extract, 3-5 times per day. DD=6.3-10.6 g *Children* *5-11 years of age:* SD=1.6 g liquid extract; 2-4 times daily DD=3.2-6.4 g *3-4 years of age:* SD=1.1 g liquid extract; 2-3 times daily DD=2.2-3.3 g	1976 (DE)
j) Liquid extract (DER 1:0.8-1.2); extraction solvent: ethanol 40% (V/V)	Indication 1), 2)	Oral use *Adolescents, adults and elderly:* SD=0.4-1.26 g liquid extract, 3-4 times per day DD= 1.2-4.8 g	1976 (DE)
k) Liquid extract (1:3); extraction solvent: ethanol 60% (V/V)	Indication 1), 2)	Oral use *Adolescents, adults and elderly:* SD=1.9 g liquid extract, 3-4 times daily DD=5.8-7.8 g *Children* *6-12 years of age:* SD=0.65 g liquid extract, 3-4 times daily DD=1.9-2.6 g	1994 (PL)

The dry extract (DER 3-5:1) with the extraction solvent ethanol 20% (m/m) has only been on the market since 2004. Since the soft extract (DER 1.5-1.7:1) with the extraction solvent ethanol 20% (m/m), however, can be regarded as the direct precursor of this extract, it has been included in the monograph.

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

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 and Fröhlich, 1980). Schmidgall *et al*. (2000) were the first to show moderate adhesive effects of polysaccharides 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 also to iridoid glycosides (mainly aucubin and catalpol), flavonoids (mainly apigenin and luteolin), phenylethanoids (acteoside, plantamajoside), phenol carboxylic acids and tannins (Blaschek *et al.*, 2008; Marchesan *et al.*, 1998a).

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

Anti-inflammatory effects

***In vitro* experiments**

Comparable/similar preparations to preparations of the monograph
Ethanolic extracts

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). Four different freeze-dried liquid extracts (28% ethanol, no further information) were used; 50 mg of the freeze-dried extracts in 1 ml of a hot (about 60°C) 2.5% agarose' solution; 10 µl solution was used for the pellet preparation). The irritation was stimulated with 50 µg sodium dodecyl sulphate per pellet. At a 10-fold higher concentration (500 µg/pellet; 67-100% inhibition), the anti-inflammatory activity (membrane irritation) of the extracts was comparable to that of hydrocortisone (100% inhibition), phenylbutazone (100% inhibition) and sodium diclofenac (64% inhibition) (each substance was used at 50 µg/pellet) (Marchesan *et al.*, 1998b).

Herold *et al.* (2003) investigated *in vitro* if a standardized ethanol extract (200 g of *Plantago lanceolata* leaves were extracted for 2-3 hours by maceration and refluxing with ethanol 16%, freeze–dried, DER unknown) 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 extract displayed only inhibition activity against COX-2 (200 µg extract = 37% inhibition; 600 µg extract = 58% inhibition). With the COX-2 inhibitor nimesulide 42% inhibition was obtained with 10 µg.

Assessor's comment:

The in vitro data were performed with comparable/similar preparations to some of the preparations of the monograph, showing decrease of inflammatory reactions documented by controls. The concentrations/dosages used are relatively high, so a potential clear clinical relevance cannot be estimated.

In vivo

Comparable/similar preparations to preparations of the monograph
Ethanolic extracts

In a broad screening 75 plant species have been studied for their anti-inflammatory activity using carrageenan foot oedema in rats. The extracts were administered orally one hour before eliciting foot oedema. An extract from *Plantago lanceolata* leaf (DER 1:3; extraction solvent: ethanol 80%; freeze-dried; 100 mg of plant extract per kg bw) reduced carrageenan produced foot oedema by 11%. Indomethacin 5 mg/kg inhibited the oedema by 45%. *Plantago lanceolata* was categorized as plant with relevant inhibition (>10% inhibition) but not with special interest (comparable with indomethacin) (Mascolo *et al*., 1987).

Isolated compounds

Anti-inflammatory properties have also been established for single compounds of *Plantago lanceolata* by means of *in vivo* experiments. The phenylethanoids acteoside and plantamajoside showed anti-inflammatory activity in the acid-induced mouse ear oedema with 1 and/or 3 mg/ear (Murai *et al.*, 1995), in the dextran sulphate sodium induced colitis in mice with 30 mg/kg bw (Hausmann *et al.*, 2007) and the iridoid glycosides aucubin (100 mg/kg) showed anti-inflammatory activity in the carrageenan-induced mouse paw oedema (100 mg/kg bw, p.o.) and catapol and aucubin showed anti-inflammatory activity in the TPA-induced mouse ear oedema (1 mg/ear, topical) (del Recio *et al*., 1994).

Epithelizing effects

***In vivo* experiments**

Comparable/similar preparations to preparations of the monograph

Aqueous extracts

Kakooei *et al.* evaluated *Plantago lanceolata* ointment as a topical treatment of collagenase-induced tendonitis in rats, histopathologically. The used extract was a dry extract of the aerial parts (extraction solvent: water; 90°C, no further information). The ointment (10%) was produced by dissolving of 10 g of the dry extract in 10 ml water and adding eucerin until 100 g of ointment. The duration of treatment was 4 weeks. The study was placebo controlled. During the 4 weeks, in the treatment group, significant proliferation of endotendon, earlier disappearance of adipose, inflammatory cells and tendon lobulation, and faster collagen fibre rearrangement were observed. The authors concluded, the ointment could accelerate the process of tendon healing (Kakooei *et al.*, 2013).

Wound healing

***In vivo* experiments**

Comparable/similar preparations to preparations of the monograph

Aqueous extracts

In an experimental study the effect of *Plantago lanceolata* leaves water extract (10 g with 100 ml water, no further information) with two different concentrations (DER 1:10) as infusion (PL-10%) and a 10 times diluted concentration (PL-1%) on skin, wound healing was studied in Sprague-Dawley rats. In the control groups, the animals remain not treated or wounds were daily topically washed by sterile water. The infusion was topically applied three timed a day during the first 3 days after the surgery. Wound treated with both concentrations of the infusion at day 14 and 21 after surgery significantly improved wound closure. At day 14, the presence of fibronectin and collagen-III was enhanced in wounds treated with the PL extracts. It was shown that open wounds treated with PL extract contained myofibroblasts and demonstrated significantly higher contraction rates. Furthermore, significantly increased wound incisions – wound tensile strengths were recorded in treated rats because of increased organization of extracellular matrix proteins, such as the collagen type 1. The most prominent organisation of collagen into fibres was seen in the 10% group (Kováč *et al*., 2015).

The efficacy of an ointment with 10% or 20% of *Plantago lanceolata* distillate of the aerial parts of the plant (DER 1:10; distillation solvent: water) for wound healing was investigated in a mouse model. 72 mice were allocated in four groups of 18. An excisional 1 cm wound was created in the skin on the back of the mice in all groups. Vaseline was used as control, and no treatment was evaluated. On day 14 epithelialization was more prominent in the 20% group. Vascularization and collagen deposition was more advanced in both verum groups with 10% and 20% ointment, than in the control groups. Positive effects on wound healing were found in a mouse model (Kurt *et al.*, 2018).

In a study the wound healing and anti-inflammatory effects of the aqueous and methanol extract (60 g plant material: 1500 ml; and vapour dried, no further information) of *P. lanceolata* were investigated in mice and rats. The ointment was prepared by mixing the extracts with ointment base of glycol stearate, propylene glycol and liquid paraffin (concentration unknown). A final product containing *Centella asiatica* was used topically as the reference drug. The aqueous extract of *P. lanceolata* was found to have wound healing activity in both incision and excision wound models. Significant anti-inflammatory activity was also detected for both extracts. Additionally, *P. lanceolata* was found to have capacity to increase the levels of tissue $Zn^{+2}$and Cu^{+2}, both of which are important indicators in the process of wound healing and collagen synthesis (Kuranel *et al.*, 2016).

Assessor's comment:

The studies were performed with higher concentrated aqueous preparations of leaves or aerial parts. Therefore, a potential clear clinical relevance cannot be estimated.

Spasmolytic effects

***Ex vivo* experiments**

Comparable/similar preparations to preparations of the monograph

Ethanolic extracts

Fluid extract from *Plantago lanceolata* herb (DER 1:1; extraction solvent: ethanol 20%), at 10 and 20 µg/ml inhibited the Guinea-pig ileum contractions caused by acetylcholine, histamine, potassium and barium ions and barium induced tracheal contractions in guineapigs by 50% and 100% at higher concentrations. Spasmolytic activity has been attributed to isoacteoside (EC_{50}=56 nM), acteoside (EC_{50}=114 nM), catalpolperacetate (EC_{50}=63 nM), catalpol (EC_{50}=70 nM), plantamajoside (EC_{50}=64 nM), lavandulifolioside (EC_{50}=66 nM) and luteolin (EC_{50}=551 nM) (Fleer and Verspohl, 2007).

Table 3: Overview of the main non-clinical data/conclusions (of comparable/similar preparations to preparations of the monograph)

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
Comparable/similar preparations to preparations of the monograph				
Dry extract; extraction solvent: water	Ointment 10%: 10 g of the dry extract in 100 g 0.1 g ointment as a topical treatment placebo group: vehicle of the ointment duration: 4 weeks	*In vivo* collagenase-induced tendonitis in mice and rats	Kakooei *et al*. (2013)	epithelizing effects
Extract (DER 1:10);	Infusion 1. group: 10%	*In vivo*	Kováč *et al.* (2015)	wound healing

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
Extraction solvent: water	2. group: 1% 3. group: sterile water 4. group: untreated 3 times a day topically 3 days long	Wound healing in rats (after surgery)		
Other preparations				
Dry extract (DER 1:3); extraction solvent: ethanol 80%	5 mg/kg bw or 100 mg/kg bw; orally	*In vivo* carrageenan induced foot oedema in Wistar rats	Mascolo *et al*. (1987)	anti-inflammatory effects
Dry extract (drug:extrac-tion solvent 6:150); extraction solvent: water Dry extract (drug extraction solvent: 6:150); extraction solvent: methanol	Topical use (9 days) once a day 0.5 g ointment 1. Aqueous extract in ointment 2.MeOH extract in ointment 3. reference: *Centella asiatica* ointment 4. vehicle 5. negative control	*In vivo* Wound healing in rats, incision and excision model	Kuranel *et al.* (2016)	wound healing

3.1.2. Secondary pharmacodynamics

Antibacterial effects

Comparable/similar preparations to preparations of the monograph

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).

Ethanolic extracts showed *in vitro* inhibition of *E. coli*, *Proteus mirabilis*, *Enterococcus faecalis*, *Acinetobacter baumanni*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumonia*, *Candida albicans*, *Candida kruzei* and *Candida parapsilosis* (Cáceres *et al*., 1987; Orhan *et al*., 2002).

Effects in models of hepatoxicity

Comparable/similar preparations to preparations of the monograph

A dry extract from *Plantago lanceolata* leaves (extraction solvent: ethanol 80%; DER 10.4:1) was investigated using pentobarbital-induced hypnosis model in mice treated with carbon tetrachloride as hepatotoxin. In a dose of 50 mg/kg a 25.5% inhibition was observed (Deliorman *et al*., 1999).
In a study performed in rats, however, the same extract from *Plantago lanceolata* leaves showed no protective efficacy in hepatotoxicity caused by carbon tetrachloride (Aktay *et al.*, 2000).

Immunostimulant effects

Comparable/similar preparations to preparations of the monograph

An aqueous extract from *Plantago lanceolata* leaves (no further information) caused a significant increase of antibody formation and release of angiogenesis factor in lymphocytes of man and mouse *in*

vitro and *in vivo* (Strzelecka *et al*., 1995) and stimulated the production of interferon in mice (Plachcinska *et al.*, 1984).

Anthelmintic effects

Comparable/similar preparations to preparations of the monograph

Ethanol (90% ethanol; yield: 10.95%) and aqueous (yield: 7.22%) extracts from *Plantago lanceolata* leaves at 100 mg/kg displayed significant anthelmintic activity against pinworms in mice with 60 and 45%, respectively. The positive control was doramectin at 0.2 mg/kg (100% efficacy) (Kozan *et al.*, 2006).

3.1.3. Safety pharmacology

No publications containing significant pharmacological safety findings were identified in the scientific non-clinical literature.

3.1.4. Pharmacodynamic interactions

No information available.

3.1.5. Conclusions

The main pharmacological effects (anti-inflammatory, spasmolytic, wound healing) in *in vitro* or *in vivo* experiments were shown for ethanolic and/or aqueous extracts, comparable to preparations of the monograph. Results from relevant experimental studies on *Plantago lanceolata* to support the proposed indications are limited. The reported pharmacological effects are not considered contradictory to the traditional uses.

No publications containing significant pharmacological safety findings were identified in the scientific non-clinical literature.

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

Isolated substances

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 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

3.3.1. Single dose toxicity

No single dose toxicity studies were performed on any herbal preparation of *Plantago lanceolata*.

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

2021). Following maximum aucubin doses of 900 mg/kg bodyweight no deaths occurred in mice (Chang, 1983).

3.3.2. Repeat dose toxicity

The study by Mansoor *et al*. (2017) was designed to evaluate the oral toxicity of *P. lanceolata* leaf extract-containing syrup (2.5 g dry extract (3-5:1; extraction solvent: ethanol 20%; 70% native) of *P. lanceolata* herba/100 ml). No hint of toxicity emerged from 14-day repeat dose toxicity testing in rats. The animals were given doses of 3, 6, or 12 ml of syrup per kg body weight (appr. 75, 150 and 300 mg dry extract/kg bw.) by gavage twice daily. All animals showed normal appearance and behaviour. Body and organ weights at the end of the study were similar to those in the control group.

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 and Yun, 1985).

3.3.3. Genotoxicity

An Ames-test was performed with a tincture (1:5) from *Plantago lanceolata* herb (70% ethanol) with and without metabolic activation by the S-9 fraction. Mutagenic effects were not observed with *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* leaves (40% ethanol) showed no statistically significant increase in the frequency of segregant sectors per colony and thus no genotoxic effects.

Assessor's comment:

The published tests on genotoxicity cannot be used to assess the genotoxic potential of the preparations covered by the monograph. The tests are not according to OECD Guideline and only a preparation not covered by the monograph, was tested.

3.3.4. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

In an investigation with 1000 dogs *Plantago lanceolata* allergen extract (no further information) caused atopic dermatitis in >15% of the animals (Mueller *et al*., 2000).

3.3.7. Other special studies

No data available.

3.3.8. Conclusions

3.4. Overall conclusions on non-clinical data

The potential mechanism of action for *Plantaginis lanceolate folium* is not known.
Results from relevant experimental studies on *Plantago lanceolata* to support the proposed indications are 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 *Plantago lanceolata* is scarce. As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

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

4. Clinical Data

4.1. Clinical pharmacology

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

No data available.

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

No human data are 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)

Oral use
One post-marketing study was conducted by Kraft (1997). The aim of this prospective, multicentre 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 solvent: 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 herbal substance.
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 dyspnoea 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.

Assessor's comment:

As controlled clinical trials with extracts from Plantago lanceolata leaf have not been performed, a well-established use cannot be accepted.

Table 4: Clinical studies on humans, in cough associated with cold

Type	Study	Test Product(s)	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Kraft (1997)	Post-marketing, prospective, multicentre, uncontrolled study	Cough syrup (100 ml syrup contains 20 g fluid extract from *Plantago lanceolata* herb (DER 1:1); extraction solvent: ethanol 20% (m/m) Medium Daily dose 30 ml	593 patients (mean age 42 years, range 1-88 years)	Patients with acute respiratory diseases. a) acute respiratory infections (32% of the patients), b) acute bronchitis (28%) c) irritative cough following acute respiratory infections (18%)	after 3-14 days of treatment: • intensity and frequency of coughing reduced by 67% and 66%, respectively • thoracal pain decreased by 80% • irritative cough and dyspnoea decreased by 69%	N.A.	Because of the design of the study no clinical relevance. However, it supports the use in context of cough associated with cold.

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

Oral use

The results of the post-marketing study by Kraft (1997) were analysed separately for the subgroup of 91 patients with an age <18 years (Kraft, 1998). Twenty children were ≤7years, 38 children had an age between 8 and 12 years, and 33 adolescents were between 13 and 17 years old. The mean daily dosage in this group was 22.4 ml of the syrup (corresponding to about 4.5 g of the herb), 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 Dorsch *et al*. (2002) 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 (herb) 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:

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

In children, only data for the oral administration are available. The HMPC decided in 2012 to accept the oral use in children from 3 years of age and older.

4.4. Overall conclusions on clinical pharmacology and efficacy

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

5. Clinical Safety/Pharmacovigilance

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

Oral use

In the post-marketing study by Kraft (1997) tolerability of the syrup from *Plantago lanceolata* (fluid extract (DER 1:1); extraction solvent: ethanol 20% (m/m); medium daily dose 30 ml; 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 diarrhoea – among them one child (age 10 years) - occurring in one centre 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 diarrhoea occurred in one centre, only the investigator suspected that this adverse event had an infectious cause.

The results contribute to safety information in adults and children. They show a safe administration in adults and children from 3 years and older under the conditions described.

Inhalation of pollen

For *Plantago lanceolata* a high risk of sensitization is reported by Blaschek *et al*. (2021). 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).

Skin prick tests

Forkel *et al*. (2020) investigated the currently most frequent weed allergy between mugwort (*Artemisia vulgaris*), ragweed (*Ambrosia artemisiifolia*), plantain (*Plantago lanceolata*), chamomile (*Matricaria chamomilla*), nettle (*Urtica dioica*), and oilseed rape (*Brassica napus*) and time trends in prevalence of sensitization to weed pollen in the middle of Germany over the last 20 years. The study monocentrically evaluated the prick test results of a total of 6,220 patients with suspected RCA over a period of 20 years (1998-2017). In the study cohort, sensitization rates to plantain almost doubled from 26.6% in the decade 1998-2007 to 50.5% in 2008-2017. The most prominent increase in positive skin prick tests to plantain was mainly observed in younger patients. Further, a trend toward polysensitization, currently dominated by plantain and ragweed, was identified.

To elucidate genuine versus cross-reactive sensitization, Stemeseder *et al*. (2018) investigated IgE reactivity patterns and inhibition capacities of plantain-sensitized patients. Sera of 35 rhinoconjunctivitis patients from the north-east of France with positive skin prick tests (SPT) to *Plantago lanceolata* pollen were tested with clinically relevant allergen sources. The patients were multisensitized with additional reactivity to grass (ryegrass, timothy, and Bermuda grass) (94.3%), European ash (*Fraxinus excelsior*) (74.3%), silver birch (*Betula pendula*) (71.4%), and mugwort (*Artemisia vulgaris*) (55.2%) pollen. In immunoblot, IgE reactivity to plantain pollen was inhibited with relevant pollen extracts. Two sera did not reveal any IgE cross-reactivity, while reactivity to plantain was efficiently inhibited by grass pollen in the sera of 10 patients. The sera from 17 different patients could be inhibited by grass, birch, or ash pollen to varying degrees. Thus, only 37.1% of the patients demonstrated true plantain pollen sensitization, while 62.9% were solely positive due to IgE cross-reactive molecules from other clinically relevant pollen. Plantain pollen-sensitized patients are multi-reactors demonstrating varying and complex IgE-reactivity profiles.

Because of the findings concerning the strong allergy of *P. lanceolata* pollen it is mentioned in the monograph.

Table 5: Clinical safety data from clinical trials

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments on clinical relevance of results
Kraft (1997)	Post-marketing, prospective multicentre uncontrolled study	Cough syrup (100 ml syrup contains 20 g fluid extract from *Plantago lanceolata* herb (DER 1:1);	593 patients (mean age 42 years, range 1-88 years)	Patients with acute respiratory diseases a) acute respiratory infections (32% of the patients), b) acute	In 7 patients (1%) adverse events were recorded; 5 of them were diarrhoea	As no control group is available, and diarrhoea is known to occur in patients with cough and cold, the

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments on clinical relevance of results
		extraction solvent: ethanol) Oral use: daily dose 30 ml		bronchitis (28%) c) irritative cough following acute respiratory infections (18%)		causality is unclear. Therefore, not to be mentioned in the monograph.

5.2. Patient exposure

There is no information available on the extent of its use in the general population. Aside from market presence and data from studies, there are no concrete data concerning patient exposure.

5.3. Adverse events, serious adverse events and deaths

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.

In the Eudravigilance database for the period up to October 2020, there were 20 spontaneous reports of suspected adverse drug reactions associated with *Plantago lanceolata*. Eight reports were related to the oral use of combination products and/or co-medication or to parenteral use. For 4 reports (gastrointestinal discomfort; dizziness, nausea, feeling bad, tiredness; diarrhoea; localized itching, pustular skin eruption) no case narrative was provided. For the remaining 8 reports no causality could be rated.

Assessor's comment:

No new information from MS to pharmacovigilance data from products of Plantago lanceolata preparations already on the market, including SmPC and PSUR, was provided.

No recommendations from PSUSA are available. The pharmacovigilance data identified no well-documented cases with a proved causality to new risks. No new adverse effects are included in the monograph.

Since extracts from Plantago lanceolata leaf, do not contain pollen and the preparations are not inhaled, allergic reactions due to these preparations are unlikely. Patients with known intolerance to Plantago lanceolata, folium, or plants of the family are excluded from the use per contraindication. As a publication (Forkel et al., 2020) containing safety findings, regarding allergy to Plantago lanceolata pollen were identified in the scientific literature, a contraindication is added in the monograph (according in the HMPC-monograph on Betulae folium), hypersensitivity to the active substance or to "…" pollen.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

No data available.

5.5.1. Use in children and adolescents

The oral, oromucosal and cutaneous use has been shown for all preparations reflected to in the monograph for adolescents.

The oral use in children was shown for the following preparations:

- a) Comminuted herbal substance as herbal infusion (from 12 years)
- c) Dry extract (DER 3-6:1); extraction solvent: water (from 3 years)
- d) Liquid extract (DER 1:0.9-1.1); extraction solvent: ethanol 24-35% V/V (from 3 years)
- e) Soft extract (DER 1.5-1.7:1); extraction solvent: ethanol 20% m/m (from 3 years)
- f) Expressed juice (DER 1:0.5-0.9) from the fresh herb (from 3 years)
- g) Liquid extract (DER 1:11); extraction solvent: water (from 3 years)
- h) Dry extract (DER 3-5:1); extraction solvent: ethanol 20% m/m (from 3 years)
- i) Liquid extract (DER 1:5.8-5.9); extraction solvent: water (from 3 years)
- k) Liquid extract (DER 1:3) extraction solvent: ethanol 60% (V/V) (from 6 years).

The oromucosal use in children was shown for the following preparation:

- a) Comminuted herbal substance as macerate (from 3 years).

The cutaneous use in children was shown for the following preparation:

- a) Comminuted herbal substance as macerate (from 3 years).

The marketing data show that the traditional oral, oromucosal and cutaneous use is established for many preparations from 3 years of age. The oral (preparation k) use in children under 6 years of age is not recommended due to the lack of adequate data. The oral (preparations a, b and j) and oromucosal (preparations b and c) use in children under 12 years of age is not recommended due to the lack of adequate data.

5.5.2. Contraindications

Hypersensitivity to the active substance or to *Plantago lanceolata* pollen.

5.5.3. Special warnings and precautions for use

The oral and oromucosal use in children under 3 years of age is not recommended because of concerns requiring medical advice. The cutaneous use in children under 3 years of age is not recommended due to the lack of adequate data.

The oral (preparation k) use in children under 6 years of age is not recommended due to the lack of adequate data. The oral (preparations a, b and j) and oromucosal (preparations b and c) use in children under 12 years of age is not recommended due to the lack of adequate data.

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

For extracts containing ethanol, the appropriate labelling for ethanol, taken from the 'Guideline on excipients in the label and package leaflet of medicinal products for human use', must be included.

5.5.4. Drug interactions and other forms of interaction

None reported.

5.5.5. Fertility, pregnancy and lactation

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 are available.

5.5.6. Overdose

No case of overdose has been reported.

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

No studies on the effect on the ability to drive and use machines have been performed.

5.5.8. Safety in other special situations

No data.

5.6. Overall conclusions on clinical safety

The oral, oromucosal and cutaneous use of *Plantago lanceolata* leaf is generally recognised as safe for the short-term use of one week. If the symptoms persist longer than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Due to the lack of adequate data, the use cannot be recommended during pregnancy and lactation.

In children younger than 3 years of age the drug should not be used for oral and oromucosal use, as there are only limited data on the oral use in children and in addition, children at this age should consult a doctor for making a diagnosis before the start of treatment due to the potential risk of severe infectious diseases of the upper respiratory tract such as laryngitis misinterpreted to common cold.

The oral (preparation k) use in children under 6 years of age is not recommended due to the lack of adequate data. The oral (preparations a, b and j) and oromucosal (preparations b and c) use in children under 12 years of age is not recommended.

The cutaneous use in children under 3 years of age is not recommended due to the lack of adequate data.

The pharmacovigilance data identified no well-documented cases with a proved causality to new risks.

Publications containing safety findings, regarding allergy to *P. lanceolata* pollen were identified in the scientific and medical literature. The contraindication in the monograph is revised according the HMPC-monograph on Betulae folium.

6. Overall conclusions

The data do not support efficacy as well-established use for *Plantago lanceolatae* leaf preparations. 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.

There is sufficient information on the plausibility for the traditional medicinal use in Europe for *Plantago lanceolatae* leaf preparations. The following preparations fulfil the requirement of at least 30 years (including at least 15 years with the Community) according to Directive 2001/83/EC as amended:

i) Herbal substance

Not applicable.

ii) Herbal preparations

a) Comminuted herbal substance

b) Powdered herbal substance

c) Dry extract (DER 3-6:1); extraction solvent: water

d) Liquid extract (DER 1:0.9-1.1); extraction solvent: ethanol 24-35% (V/V)

e) Soft extract (DER 1.5-1.7:1); extraction solvent: ethanol 20% (m/m)

f) Expressed juice (DER 1:0.5-0.9) from the fresh herb

g) Liquid extract (DER 1:11); extraction solvent: water

h) Dry extract (DER 3-5:1); extraction solvent: ethanol 20% (m/m)

i) Liquid extract (DER 1:5.8-5.9); extraction solvent: water

j) Liquid extract (DER 1:0.8-1.2); extraction solvent: ethanol 40% (V/V)

k) Liquid extract (DER 1:3) extraction solvent: ethanol 60% (V/V)

Based on the long-standing use as seen in the market overview, clinical monographs and literature the efficacy is plausible for the following indications:

1) Oral or oromucosal (gargling and rinsing) use: traditional herbal medicinal product used as a demulcent for the symptomatic treatment of oral or pharyngeal irritations and associated dry cough.

2) Oral use: traditional herbal medicinal product used for the relief of cough associated with cold.

3) Cutaneous use: traditional herbal medicinal product used for the treatment of minor inflammation of the skin.

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. The oral and oromucosal use in children under 3 years of age is generally not recommended for self-medication, because of concerns requiring medical advice.

The cutaneous use (preparation a) in children below the age of 3 is not recommended due to the lack of adequate data.

Exceptions for the usage in all age groups above the age of 3 years of age are:

- Preparation k (oral use)
  The oral use in children under 6 years of age is not recommended due to the lack of adequate data.
- Preparations a, b and j (oral use)
  The oral use in children under 12 years of age is not recommended due to the lack of adequate data.
- Preparations b and c (oromucosal use)
  The oromucosal use in children under 12 years of age is not recommended due to the lack of adequate data.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed. No fertility data are available. Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

The use is contraindicated in patients with hypersensitivity to the active substance or to ribwort plantain pollen.

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

No adverse effects are mentioned in the monograph. Interactions with other medicinal products and other forms of interaction are not reported.

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

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

Annex

List of references