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EMA/HMPC/572844/2009
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Symphytum officinale* L., radix

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Symphytum officinale* L., radix
Herbal preparation(s)	Liquid extract prepared by extraction with ethanol 65% (V/V) followed by partial evaporation and adjustment to a DER 2:1.
Pharmaceutical forms	Herbal preparations in semi-solid dosage forms for cutaneous use
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1. Introduction

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

Symphytum officinale L. (Boraginaceae) or common comfrey is a perennial native of Europe and Asia and has been naturalised throughout North America (Longe, 2005). It is very common in all of Europe, especially in damp soils (Bruneton, 1999). There are about 25 species of the genus, including further medicinal plants apart from common comfrey (e.g. *S. asperum* Lepechin, *S. tuberosum* L., and *S.* × *uplandicum* Nyman (syn. *S. peregrinum*, *S. asperum* × *officinale*, according to Tutin, 1992) (Longe, 2005; De Smet *et al*., 1992).

Comfrey grows well in rich, moist, low meadows, or along ponds and river banks, where it may reach a height of 1.2 m (usually 0.3-1.2 m). Comfrey root is large, branching, and black on the outside with a creamy white interior containing slimy mucilage. The root is slimy and horn-like when dried. Hollow, erect stems, also containing mucilage, are covered with bristly hairs that cause itching when in contact with the skin. The thick, somewhat succulent, veined leaves are covered with rough hairs. They are alternate and lance shaped, with lower leaves as large as 25 cm in length, and dark green on top and light green underneath. The lower ones and the basal ones are ovate-lanceolate and pulled together in the petiole; the upper ones are lanceolate and broad. Small, bell shaped flowers grow from the axils of the smaller, upper leaves on red stalks. Flowers are mauve to violet and form in dense, hanging clusters, blooming in summer. They are arranged in crowded, apical, 2-fayed hanging cymes. The calyx is fused and has 5 tips. The corolla is also fused and is cylindrical-campanulate with a pentangular tube and 5-tipped border. The tips are revolute and there are 5 awl-shaped scales in the mouth of the tube. The scales are close together in a clavate form and have a glandular tipped margin. There are 5 stamens and 1 style. The ovary is 4-valved. The fruit consists of 4 smooth, glossy nutlets (Longe, 2005; Gruenwald *et al*., 2000).

Both roots and leaves are reported to be used for medicinal purposes. Comfrey is occasionally used as an ingredient of soups and salads. It is listed by the Council of Europe as natural source of food flavouring (category N4). This category indicates that although comfrey is permitted for use as food flavouring, insufficient data are available to assess toxicity (Barnes *et al*., 2007). The herb has long been used as a cooked green vegetable in early spring, and the fresh, young leaves have been added to salads. The widespread suffering caused by the Irish potato famine of the 1840s motivated Henry Doubleday, an Englishman, to fund research into comfrey's potential as a nutritional food crop. Farmers have valued comfrey as a nutritious fodder for cattle (Longe, 2005).

Constituents

Carbohydrates: gum (arabinose, glucuronic acid, mannose, rhamnose, xylose); mucilage (glucose, fructose) (Barnes *et al.*, 2007)

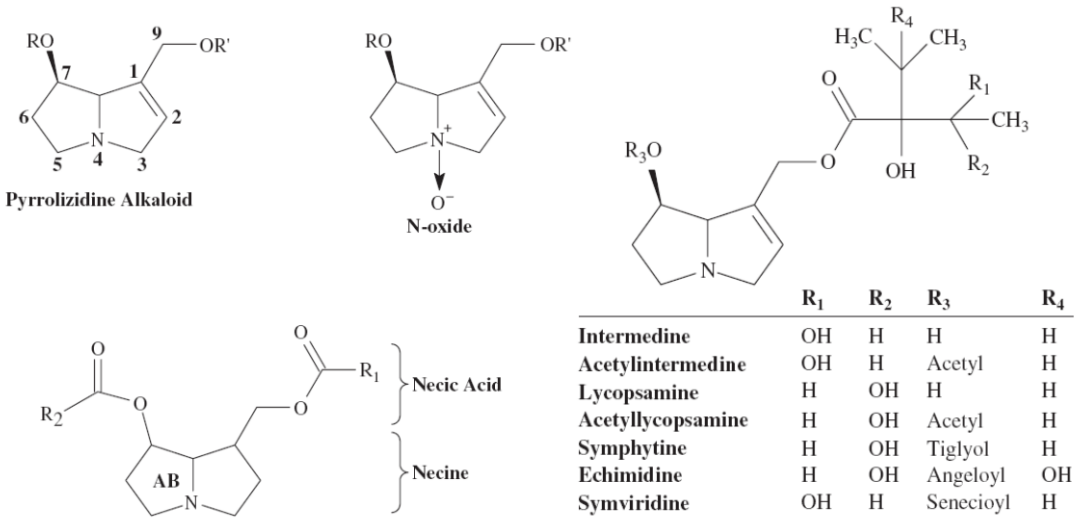
Tannins: pyrocatechol-type, 2.4% (Barnes *et al.*, 2007)

Triterpenes: sitosterol and stigmasterol (phytosterols), steroidal saponins, isobauerenol, triterpene saponins symphytoxide A, cauloside D, leontoside A, leontoside B, leontoside D (Barnes *et al.*, 2007; Ahmad *et al.*, 1993; Mohammad *et al.*, 1995)

Other constituents: allantoin 0.75-2.55%, caffeic acid, carotene 0.63%, chlorogenic acid 0.037%, caffeic acid 0.035%, choline, lithospermic acid, rosmarinic acid and silicic acid (Barnes *et al.*, 2007; Aftab *et al.*, 1996); vitamins A and B12, calcium, potassium and phosphorus (Longe, 2005)

Alkaloids: Comfrey roots contain 0.2-0.4% pyrrolizidine alkaloids: symphytine, lycopsamine/intermedine (diastereoisomers), acetyl-lycopsamine/acetyl-intermedine (diastereoisomers), myoscorpine, lasiocarpine, heliosupine, viridiflorine, echiumine, symlandine and echimidine (Figure 1) (Barnes *et al.*, 2007; Coulombe, 2003). A considerable proportion of the pyrrolizidine alkaloids may be present as their *N*-oxides (De Smet *et al.*, 1992). Notable quantities of echimidine are often reported, apparently because other species that are morphologically very close, such as *S. asperum* Lepechin and *S.* × *uplandicum* Nyman, are mistaken for *Symphytum officinale*, which in theory contains no echimidine at all (Blumenthal *et al.*, 1998). The presence of echimidine and symlandine may refer to the falsification of the herbal substance with *Symphytum peregrinum* roots, since these two alkaloids are not present in the roots of *Symphytum officinale* (Hänsel and Sticher, 2004).

The pyrrolizidine content of *Symphytum* varies with plant part, season, natural biological variation, and species. Small young leaves early in the season possess higher total alkaloid content than older leaves, and the roots contain greater concentrations of total pyrrolizidine alkaloids than above-ground plant parts (Barceloux, 2008). In a study of commercial samples of common comfrey (*Symphytum officinale*), analysis of the total pyrrolizidine alkaloid content demonstrated values ranging from 1380-8320 µg/g root compared with 15-55 µg/g leaf (Couet *et al.*, 1996). The major pyrrolizidine alkaloids were symphytine and symlandine along with lesser concentrations of echimidine, lycopsamine, and acetyl-lycopsamine. Analysis of comfrey tablets indicated that total alkaloid concentrations are similar to the alkaloid content of comfrey roots (Barceloux, 2008).



	R_1	R_2	R_3	R_4
Intermedine	OH	H	H	H
Acetylintermedine	OH	H	Acetyl	H
Lycopsamine	H	OH	H	H
Acetyllycopsamine	H	OH	Acetyl	H
Symphytine	H	OH	Tiglyol	H
Echimidine	H	OH	Angeloyl	OH
Symviridine	OH	H	Senecioyl	H

Figure 1. General structures of pyrrolizidine alkaloids and chemical structures of pyrrolizidine alkaloids in *Symphytum officinale* (Barceloux, 2008).

- Herbal substance(s)

Dried rhizome and roots of *Symphytum officinale* L. (Kern W 1976, British Herbal Pharmacopoeia 1974, 1983, 1996).

- Herbal preparation(s)

Liquid extract prepared by extraction with ethanol 65% (V/V) followed by partial evaporation and adjustment to a DER 2:1; liquid extract in an ointment base (100 g ointment contains 10 g extract), for cutaneous use.

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

Regulatory status overview

Table 1: Overview of data obtained from marketed medicinal products EU

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
liquid extract of fresh root; DER 1:2; extraction solvent: ethanol 60% (V/V) (extract is free of pyrrolizidine alkaloids)	Used in case of bruises, contusions, sprains (injuries due to sport or accidents), joint- and muscle pain.	cream 100 g containing 35 g liquid extract adolescents and adults: apply 2-6 cm of cream several times daily not to be used longer than 8 weeks; only on intact skin	WEU; 2012; AT
tincture (1:5)			Granted in the old legislative frame; 1994 – 2006; CZ registration was refused on 22.02.2006 as the marketing authorisation holder was not able to guarantee limited content of pyrrolizidine alkaloids
liquid extract; DER 1:2; extraction solvent: ethanol 60% (V/V)	Traditionally used topically as a soothing and anti-pruriginous application for dermatological ailments and as a protective treatment for cracks, grazes, chapped skin and insect bites.	cream 100 g cream containing 35 g of fluid extract 2 to 4 times daily	TRAD; 2007; FR
liquid extract; DER 1:2; extraction solvent: ethanol 60% (V/V), containing 0.13-0.25% sodium hydroxide and 1% PPG-1-PEG-9 lauryl glycol ether	contusion, strain, sprain	cream 100 g containing 35 g liquid extract children over 3 years, adolescents and adults: depending on the size of the treated part of the body and the strength of the complaints 2-4 daily approximately 1.2-6 g corresponding to a string of ointment of 4-18 cm length should be applied on the affected parts of the body and massaged thoroughly;	WEU; at least since 1976; DE

		in case of heavier complaints an ointment bandage could be applied: once daily 10-20 cm ointment should be applied and covered with adequate bandage material children from 3 to 11 years: Do not use longer than 1 week	
liquid extract; DER 1:2; extraction solvent: ethanol 60% (V/V), containing 0.13-0.25% sodium hydroxide and 1% PPG-1-PEG-9 lauryl glycol ether	contusion, strain, sprain	cream 100 g containing 35 g liquid extract adolescents and adults: depending on the size of the treated part of the body and the strength of the complaints 2-4 times daily a string of ointment of 2-6 cm length should be applied on the affected parts of the body and massaged thoroughly	WEU, at least since 1976; DE
liquid extract; DER 1:2; extraction solvent: ethanol 60% (V/V), containing 0.13-0.25% sodium hydroxide and 1% PPG-1-PEG-9 lauryl glycol ether	contusion, strain, sprain	poultice 100 g containing 35 g liquid extract adolescents and adults: could be applied 1-2 x daily up to 5 h (warm poultices not longer than 2 h), normally applied cold for warm poultices tube should be tempered in a water bath accordingly a moist piece of bandage material is coated approximately. 1 mm thick with the paste, put on the affected part of the body and covered with a cloth; fixation can be carried out by a bandage to avoid strong maceration of sensitive skin, a pause of approximately 2-4 h should be observed before the poultice can be renewed after few days of application a treatment break of 1-2 days is recommended	WEU, at least since 1976; DE

liquid extract, DER 1:5; extraction solvent: ethanol	For the treatment of swellings and bruising resulting from closed injuries, contusions, sprains, as an adjuvant treatment after fractures, as an antiphlogistic to treat phlebitis and local dermatitis, to relieve rheumatic pains.	liquid after cleaning the intact skin, depending on the size of the skin surface to be treated, 5-15 doses of the dozier pump should be applied 2-3 times daily on the skin, and massaged gently; not to be applied longer than 4-6 weeks per year	TRAD ("Healing product"); 2006; HU
liquid extract; DER not known; extraction solvent: ethanol	To relieve the symptoms associated with bruises, sprains and dislocations, and rheumatic pain.	liquid (30 ml liquid containing the ethanol extract of 3 g herbal substance) to be rubbed on the aching part of the body or applied as a compress; max. dose 5 times 5-10 drops daily; not to be applied longer than 4-6 weeks per year and on children under 2 years of age	TRAD ("Healing product"); 1999; HU
tincture; DER 1:4; extraction solvent: not known	For the treatment of different closed injuries and sport injuries, bruises, strains, inflammations related to dislocations and sprains, swellings and haematoma, to improve motor functions after injuries. For the treatment of local skin inflammations and phlebitis.	cream 100 g containing 10 g tincture + 6 g paraffin oil extract of Calendulae flos and Matricariae flos max. daily dose = 15 cm of cream; not to be applied more than 1-2 times daily not to be applied longer than 4-6 weeks per year	TRAD ("Healing product"); 1998; HU
liquid extract; DER 1:2; extraction solvent: ethanol 60% (V/V)	Treatment of bruises, pulled muscles and ligaments, sprains and painful joints.	cream 100 g containing 35 g liquid extract depending on the size of the part of the body to be treated and the severity of the symptoms, a thread of cream of 2-6 cm in length should be applied 2-4 times daily	WEU; 2009; HU
liquid extract; DER 1:2; extraction solvent: ethanol 60% (V/V)	For the symptomatic treatment of joint pain, sprains, inflammation and strains associated with restricted joint mobility.	cream 100 g containing 35 g of liquid extract Adults and the elderly: depending on the size of the joint to be treated and the severity of the symptoms, a thread of	TRAD ("authorised herbal medicinal product as a traditional remedy based on traditional use"); 2006; UK

		cream of 2-6 cm in length should be applied 4 times daily for 8 days treatment duration should not exceed 21 days . Application may only be made to intact skin Not recommended in children under 18 years of age.	
liquid extract (prepared by exhaustive extraction with ethanol 65% (V/V) followed by partial evaporation of the extracting solvent and dilution with ethanol to gain an extract with a DER 2:1 with respect to mass of the starting plant material) from dried comfrey root	A traditional herbal remedy used for the symptomatic relief of bruises and sprains.	ointment 100 g containing 10 g liquid extract adults: after bathing the affected areas in warm water apply the ointment should be applied in the morning and over night Not to be applied over breaks in the skin. Not to be used longer than ten days at a time. Not recommended in children under 18 years of age.	TRAD ("registered herbal medicinal product"); at least since 1968; UK

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

The WEU products authorised in many European countries (AT, DE, HU) are not taken into account for the purpose of making a monograph since the extract used for those products is produced using a production process including several intermediate steps to lower the content of pyrrolizidine alkaloids. Therefore the final composition of the product is not known. Furthermore this extract is produced from fresh comfrey root. For some of the other extracts the 30 years of use could not been proven and/or their exact description is not known. Therefore the extract taken into the monograph is: liquid extract prepared by exhaustive extraction with ethanol 65% (V/V) followed by partial evaporation of the extracting solvent and dilution with ethanol to gain an extract with a DER 2:1 (with respect to mass of the starting plant material) from dried comfrey root.

1.3. Search and assessment methodology

Databases assessed and other sources used:
Databases Science Direct, SciFinder, PubMed and Web of Science were searched using the terms [Symphytum], [comfrey] and [pyrrolizidine alkaloid]. Handbooks and textbooks on the topic were also used. A detailed literature search was made by 31 October 2012; data on cutaneous absorption of pyrrolozidin alkaloid were searched for up to 28 February 2015.

Inclusion and exclusion criteria for literature:
Data concerning *Symphytum* species other than *Symphytum officinale* L. were excluded.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Symphytum officinale L. root and other parts of the herb have been valued medicinally for more than 2,000 years. The specific name "*officinale"* designates its inclusion in early lists of official medicinal herbs. Comfrey has been prepared as a poultice or compress with healing properties for blunt injuries, fractures, swollen bruises, boils, carbuncles, varicose ulcers, and burns. Poultices were also applied to ease breast pain in breastfeeding women. Comfrey, taken internally as a tea or expressed juice, has been used to soothe ulcers, hernias, colitis, and to stop internal bleeding. As a gargle it has been used to treat mouth sores and bleeding gums. The herbal tea has also been used to treat nasal congestion and inflammation, diarrhoea, and to quiet coughing. The hot, pulped root, applied externally, was used to treat bronchitis, pleurisy, and to reduce pain and inflammation of sprains (Longe, 2005).

Comfrey use was first documented by the ancient Romans and Greeks. Around 200 AD, the Greek physician Dioscorides praised the therapeutic uses of comfrey in his book *Materia Medico,* and coined the genus name *Symphytum* from the Greek word *symphuo,* which means "to make to grow together." During the Middle Ages, comfrey in the form of an external poultice became popular for healing broken bones. As the popularity of comfrey grew over the centuries so did its indications for use. Comfrey has been used to treat respiratory problems (bronchitis, catarrh, haemoptysis, pleurisy, whooping cough), gastrointestinal diseases (cholecystitis, colitis, dysentery, diarrhoea, ulcers, hematemesis), metrorrhagia, phlebitis, and tonsillitis. Comfrey has also been touted for its nutritional value; it has been considered a good source of protein and vitamin B12, which is unusual for a plant (Cupp, 2000).

Symphytum officinale has been known by many names, including boneset, knitbone, bruisewort, black wort, salsify, ass ear, wall wort, slippery root, gum plant, healing herb, consound, or knit back. The common name comfrey is from the Latin "*confirmare"* meaning to join together. The herb is named after its traditional folk use in compress and poultice preparations to speed the healing of fractures, broken bones, bruises, and burns (Longe, 2005).

Symphytum officinale has a long tradition and is still applied nowadays as an external treatment for inflammatory disorders of joints, wounds, gout, bone fractures, distortions, haematomas and thrombophlebitis. It is also applied as a decoction for oral and pharyngeal gargle. For internal application, comfrey is claimed to benefit gastritis and gastroduodenal ulcers, though its effects have never been demonstrated in controlled investigations. In addition, herbal practitioners recommend comfrey capsules for the treatment of rheumatoid arthritis, bronchitis, various allergies and for diarrhoea, regardless of the pathogenic cause (Stickel and Seitz, 2000).

In the UK, the Medicine Control Agency (now the Medicines and Healthcare products Regulatory Agency (MHRA)) recently included comfrey in a list of herbs under consideration for restriction to physician prescription only (Rode, 2002).

The use of comfrey root in Germany is limited to external products. The Commission E suggest the external use of comfrey root (crushed root, extracts, the pressed juice of the fresh plant for semi-solid preparations and poultices) in case of bruising, pulled muscles and ligaments, and sprains (Blumenthal *et al.*, 1998).

According to the Commission E, the daily dose should not exceed more than 100 µg pyrrolizidine alkaloids with 1,2 unsaturated necine structure, including its *N*-oxides. The duration of treatment should not be longer than 4-6 week per year (Blumenthal *et al.*, 1998).

In France, the only indication that may be claimed for the comfrey root is as follows: as an adjunct in the emollient and anti-pruriginous treatment of skin disorders, and as a trophic protective agent for cracks, bruises, frostbite and insect bites (Bruneton, 1999).

Outside Europe: the distribution of comfrey in Canada has been restricted; in the USA, the Food and Drug Administration has requested voluntary compliance for removal of products containing comfrey (Rode, 2002).

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

The preparation which has been on the market for more than 30 years is the following:

Liquid extract prepared by extraction with ethanol 65% (V/V) followed by partial evaporation and adjustment to a DER 2:1; liquid extract in an ointment base (100 g ointment contains 10 g extract)

Therapeutic indication: A traditional herbal remedy used for the symptomatic relief of bruises and sprains.

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

Ointments or other preparations for external use are made up of 5-20% of the drug and prepared accordingly. According to Blumenthal *et al.*, the daily dose should not exceed more than 100 µg pyrrolizidine alkaloids with 1, 2 unsaturated necine structure, including its *N*-oxides. The duration of treatment should not be longer than 4-6 week per year (Blumenthal *et al.*, 1998). However, according to the regulations in Germany, products for cutaneous use with less than 10 µg pyrrolizidine alkaloids in the daily dosage can be used without any limitation on the duration of use (BGA, 1992).

In the British Herbal Pharmacopoeia (1974 and 1983), fresh *Symphytum* root is indicated externally for the treatment of ulcers, wounds, fractures and hernia with the following posology (for this preparation, no data are available concerning the preparation of the extract):

- Ointment: *Symphytum* root 10–15% root extractive in usual type ointment basis applied topically three times daily.

In the United Kingdom, a *Symphytum* product is on the market at least since 1968:

Liquid extract prepared by extraction with ethanol 65% (V/V) followed by partial evaporation and adjustment to a DER 2:1; liquid extract in an ointment base (100 g ointment contains 10 g extract) Posology: For external use only. Adults: Bathe the affected areas in warm water and apply the ointment morning and night. Not to be applied over breaks in the skin. Use no longer than ten days at a time.

Although internal use of comfrey was not advised, dosages for oral administration for traditional uses were recommended in older standard herbal reference texts. The recommended oral (unless otherwise stated) doses of The British Herbal Pharmacopoeia (1974 and 1983) for the treatment of gastric and duodenal ulcer, colitis and hematemesis were as follows:

- Dried root/rhizome: 2-4 g (in the 1983 edition) or 2-8 g (in the 1974 edition) as a decoction three times daily.
- Root, liquid extract: 2-4 ml (in the 1983 edition) or 2-8 ml (in the 1974 edition) (1:1 in 25% alcohol) three times daily.

The HMPC "Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs)" (EMA/HMPC/572844/2009) considers the possible oral use for products containing less than 0.007 µg/kg/day. However, such products can not been found on the market with 30 years of safe documented medicinal use. Therefore the monograph does not contain any preparation for oral use.

3. Non-Clinical Data

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

Pharmacodynamics

Anti-inflammatory effect

In a screening study evaluating 29 traditionally used European herbal drugs used for anti-inflammatory purposes, COX-1 and 2 inhibitory activities of extracts were tested. The n-hexane extract of *Symphytum officinale* roots (no further information) (50 µg/ml) inhibited markedly COX-1 and COX-2 (56.6% and 79.6%) (Lohmann *et al.*, 2000).

A bioassay-guided fractionation of the aqueous extract from *Symphytum officinale* roots (5 g air dried roots were extracted with 150 ml water at room temperature) led to the isolation of an antiphlogistic glycopeptide. The compound with an isoelectric point at pH 4.8 was found to contain 16 amino acids as well as galactose, fructose, arabinose and glucose. The calculated molecular mass was approximately 9,000 Da. On carrageenan-induced rat paw oedema the isolated glycopeptide exerted a remarkable, dose dependent antiphlogistic effect. The ED_{50} was 61 µg/kg p.o. (control: indomethacin 10 mg/kg). Investigations on the release of arachidonic acid, cyclooxygenase and lipoxygenase metabolites as well as on arachidonic acid induced platelet aggregation indicated that the isolated glycopeptide (0.1-1000 ng/ml) inhibited dose-dependently the release of prostaglandins and leukotriens *via* decreasing the expression of phospholipase A_2. The cyclooxygenase metabolite thromboxane A_2 was released when arachidonic acid was given as a substrate and therefore the glycopeptide does not represent a COX inhibitor (Hiermann and Writzel, 1998).

In an experiment, the concentration of pyrrolizidine alkaloids in crude *Symphytum officinale* extract (no further information) was changed by a factor of about 0.1 using protonated cation exchangers. Using an *in vivo* model it could be shown that the reduction of pyrrolizidine alkaloids result in a small but measurable decrease in antiphlogistic efficacy. The model was based on measuring the decrease of redness and pain sensitivity of UV-B irradiated human skin after treatment with the extracts suspended in ointment base. Concomitant with the removal of pyrrolizidine alkaloids, the concentrations of Cu^{2+} and Mn^{2+} were also reduced. It should be taken into consideration, that these ions are important catalysts for the oxidation of *o*-substituted polyphenols (e.g. caffeic acid derivatives) to pharmacologically more active products (Andres *et al.*, 1990).

It was also reported, that the anti-inflammatory properties are probably mediated through rosmarinic acid, which is also likely to account for the analgesic and astringent effects. These antiphlogistic properties are conveyed not only through inhibition of the arachidonic acid metabolism, but seem also to be the result of inhibitory actions of plant extracts upon the classical and alternative pathway of complement activation. High molecular glycoproteins (>300 kDa) so far uncharacterised have been isolated which seem to interact with the complement factors C_3 and C_4 in a dose-dependent fashion but do not affect factors C_1 and C_2 (Stickel and Seitz, 2000; Van den Dungen *et al.*, 1991).

Rosmarinic acid isolated from *Symphytym officinale* possessed an inhibitory activity on the formation of malondialdehyde in human platelets by the TBA method. The IC_{50} for rosmarinic acid was 3.37 mM.

Structurally related minor constituents, chlorogenic acid and caffeic acid did not show significant activity in this model (Gracza *et al.*, 1985).

Andres *et al.* (1989) evaluated the antiphlogistic efficacy of 10 ointments containing comfrey root extract (no further information) with an *in vivo* model. Circular erythema was generated using UV-B radiation, which was then treated with the dermatics to be studied. The healing process was monitored by measuring redness and pain sensitivity. The products studied were then characterized by chemical profiles using HPLC and GC/MS including allantoin, caffeic acid derivatives, pyrrolizidine alkaloids, carbohydrates. Though Andres *et al.* state that chemometric methods were used to find correlations between clinical and analytical data, no details are given on these correlations. Similarly, the exact composition of the applied ointments were not published.

Assessor's comment:
Since there are no data on the human bioavailability of the compounds/extracts studied for anti-inflammatory activity in the presented articles, no conclusion can be drawn for the efficacy of cutaneously applied comfrey products.
Due to the absence of relevant data (concentration of the extracts/compounds, bioavailability data) the presented articles on the anti-inflammatory effect of comfrey cannot be taken into consideration in the assessment of in vivo and clinical efficacy of cutaneously applied comfrey products.

Wound healing effect

The pharmacological mechanisms are thought to be based partly upon allantoin, which is responsible for the stimulation of connective tissue proliferation and regeneration (Stickel and Seitz, 2000).

In an animal experiment, the crude juice of the leaves of *Symphytum officinale* afforded the cicatrization process by increasing at first (at the 7^{th}, 11^{th} and 14^{th} days) the number of fibroblasts and, in a later phase (after 14 days), the number of collagen fibers in experimental lesions produced in rats. The number of blood vessels was also increased at the 7^{th} day of treatment. On the experimental oedema induced by carrageenin in rat's paws, the crude extract at doses of 150 and 300 mg/kg *per os* showed no effect compared to 75 mg/kg phenylbutazone. Analgesic effect was seen with doses 300 mg/kg *per os* (Goldman *et al.*, 1985). Since these results were obtained with comfrey leaf preparations, they are not relevant for root extracts.

Other effects

In an *in vitro* study, it was found that the total aqueous extract obtained from *Symphytum officinale* roots precipitated human glycoproteins, agglutinated sheep red blood cells (SRBC) and stimulated lymphocyte adherence to nylon fibers. The extract precipitated human gammaglobulins. If the cells were pretreated with rabbit antibodies against SRBC, the extract agglutinated the cells. The adherence of mouse but not human lymphocytes to nylon fibers were stimulated by extract of *Symphytum officinale*. This process was neither stimulated nor inhibited by mannose (Man), galactose (Gal), glucose (Glc), N-acethyl-galactose (GalNAc) and *N*-acethyl-glucose (Glc-NAc). These biological effects of the extract could be the expression of a lectin-like ability to bind various sugars other than those mentioned (Lenghel *et al.*, 1995).

In an *in vitro* study, 70% ethanol extract of *Symphytum officinale* was concentrated by tangential flow ultrafiltration. In the extract some polyphenolic compounds were identified by HPLC: chlorogenic acid, cafeic acid, ferulic acid, coumaric acid, rutin, rosmaric acid, luteolin and quercetin. The cytostatic activity of the total plant extract was studied on HeLa cells culture. By comparison to the bystander value of 100%, it was noticed that *in vitro* treatment of HeLa neoplasic cells with the concentrated extracts determined a mitoinhibitory effect with statistical and cytostatical significant amplitude. These values were almost 57.6% for *Symphytum officinale* (Roman *et al.*, 2008).

In anaesthetised rats the ethanol extract of *Symphytum officinale* root and the bidesmosidic triterpene glycoside symphytoxide A caused a fall in systolic as well as diastolic blood pressure in a dose-

dependent manner. The hypotensive responses of both crude extract and the pure compound were quite similar, very briefly returning to normal within 1 minute while no significant decrease was observed on heart rate (Ahmad *et al*., 1993).

Pharmacodynamic interactions

No relevant pharmacodynamic interactions have been documented. According to Barnes *et al.* (2007), the potential for preparations of comfrey to interact with other medicines administered concurrently, particularly those with similar or opposing effects, should be considered.

However, regarding the toxicity of comfrey, a study involving rats showed that phenobarbital induces the metabolism of pyrrolizidine alkaloids to their lethal metabolites. In a study using perfused organs, it was shown that some of the pulmonary damage caused by monocrotaline, a pyrrolizidine alkaloid is mediated by hepatic biotransformation of the compound. This metabolism was inducible with phenobarbital (a P-450 type II monooxygenaseinducer) pretreatment (Lafranconi and Huxtable, 1984).

Based on the assessed preclinical data the clinical plausibility cannot be proven since it is not demonstrated that the preclinically active extracts/compounds are present at the site of action in sufficient concentration to exert their effect.

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

Absorption

In *ex vivo* experiments, permeation of rosmarinic acid across excised rat skin was about 8 times higher from alcoholic solution than from water, indicating that ethanol may act as a sorption promoter. The flux from water or alcoholic solution was 4.4 or 10 µg/cm^2/h, and the lag time (tlag) was 7.8 or 3.7 h, respectively. Upon topical administration of rosmarinic acid in form of a W/O (water in oil) ointment (25 mg/kg, 50 cm^2), the absolute bioavailability was 60% (Ritschel *et al*., 1989).

For available pharmacokinetic data concerning pyrrolizidine alkaloids it is referred to the "Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs)" (EMA/HMPC/893108/2011).

Rats suckled by mothers fed lasiocarpine, a pyrrolizidine alkaloid found in comfrey, developed liver damage (Cupp, 2000). After oral administration of tritiated senecionine and seneciphylline to lactating rats, radioactivity was excreted into the milk with concentrations 50% less compared to the blood concentrations. After 6 h 83% of the radioactive necine bases remaining in the blood were not dialyzables, indicating a tight (possibly covalent) binding to macromolecules, such as albumin. Six hours after administration of the pyrrolizidine alkaloids the highest concentrations were detected in the liver and lungs of the rats (De Smet *et al*., 1992). A study performed with lactating mice, using the same pyrrolizidine alkaloids but ^{14}C-labeled and injected via the intraperitoneal route, showed that 66-75% of the radioactivity was excreted in the urine, 14-18% in the faeces, 1.14% in the milk of the animals, and 0.2-0.5% was expired as CO_2. The highest concentrations of radioactivity were found in the liver (De Smet *et al*., 1992).

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

The therapeutic application of comfrey is overshadowed by the well-recognised toxicity of pyrrolizidine alkaloids (Barnes *et al.*, 2007). There are no studies on single or repeated dose toxicity with Symphytum preparations available, neither for PA-containing preparations nor for PA-reduced preparations. It is often reported that acute/chronic ingestion of the (PA-containing) plant material is toxic due to its pyrrolizidine alkaloids content.

The hepatotoxicity, carcinogenicity and mutagenicity of pyrrolizidine alkaloids are discussed in detail in the Public statement on pyrrolizidine alkaloids (HMPC, 2014).

Hepatotoxicity

In one study, the activity of various hepatic drug-metabolising enzymes in liver homogenates was examined. Three groups of six male Long-Evans rats were fed a 5%, 10%, or 30% comfrey diet ad libitum for 3 weeks (Garrett *et al.*, 1982). The activity of aminopyrine *N*-demethylase was found to be increased, but the activity of glutathione S-transferase and epoxide hydrolase was not affected by comfrey. Epoxide hydrolase activity has previously been reported to be increased by carcinogens, and is thought to play a role in the neoplastic process (Cupp, 2000).

Mutagenicity

Mei *et al.* (2006) identified comfrey-induced gene expression profile in the livers of rats. Groups of 6 male transgenic Big Blue rats were fed a basal diet and a diet containing 8% comfrey roots, a dose that resulted in liver tumours in a previous carcinogenicity bioassay (Mei *et al.*, 2005). The animals were treated for 12 weeks and sacrificed one day after the final treatment. A rat microarray containing 26,857 genes was used to perform genome-wide gene expression studies. Dietary comfrey resulted in marked changes in liver gene expression, as well as in significant decreases in the body weight and increases in liver mutant frequency. When a two-fold cut off value and a P-value less than 0.01 were selected, 2,726 genes were identified as differentially expressed in comfrey-fed rats compared to control animals. Among these genes, there were 1,617 genes associated by Ingenuity Pathway Analysis with particular functions, and the differentially expressed genes in comfrey-fed rat livers were involved in metabolism, injury of endothelial cells, and liver injury and abnormalities, including liver fibrosis and cancer development.

The methanol extract of *Symphytum officinale* roots was investigated by Behninger *et al.* (1989) for its chromosome-damaging effect in human lymphocytes *in vitro*. In concentrations of 1.4 µg/ml and 14 µg/ml the extract had no effect; in concentrations of 140 µg/ml and 1400 µg/ml sister chromatid exchanges (SCE) as well as chromosome aberrations occurred. Additionally, the influence of rat liver enzymes (S9) was tested. The SCE-inducing capacity and the clastogenic effect of the *Symphytum* extract were increased by simultaneous application of S9-mix.

Furmanowa *et al*. (1983) investigated the mutagenic effect of 3 alkaloidal fractions of *Symphytum officinale* roots, aqueous extract of roots and the alkaloid lasiocarpine. Mitotic index and chromosomal aberrations were measured on the lateral roots of *Vicia faba* L. var. *minor*. Alkaloid fraction I had antimitotic and mutagenic effects, fraction II showed no such effects, fraction III had only antimitotic action. The alkaloid fraction I containing lasiocarpine had a stronger mutagenic effect than lasiocarpine alone (metaphases with chromosomal aberrations: 18.9% and 4.9-7.5%, respectively; the concentration of lasiocarpine was of the same magnitude: 10^{-3} M). Aqueous extracts had similar mutagenic effects (metaphases with chromosomal aberrations: 4.2-6.1%).

Acetone extract of common comfrey herb was evaluated for mutagenic activity with Ames test utilising tester strains TA98 and TA100 and in the presence and absence of induced liver miocrosomes. The extract produced toxic responses that were abolished in the presence of the microsomal bioactivation system S-9 mix (White *et al.*, 1983).

Chou and Fu (2006) determined that the metabolism of tumorigenic pyrrolizidine alkaloids (riddeliine, intermedine, symphytine, lycopsamine, senecionine, lasiocarpine, heliotrine, senkirkine, clivorine) resulted in the formation of a set of 6, 7-dihydro-7-hydroxy-1-hydroxymethyl-5H-pyrrolizidine (DHP)-derived DNA adducts. From the compounds listed above, symphytine, intermedine, lycopsamine, lasiocarpine can be found in common comfrey. It was also shown that DHP-derived DNA adducts were also formed in the liver of rats treated orally with comfrey root extract, comfrey compound oil and comfrey leaves (all in forms of dietary supplements). Rats were treated by oral gavage with dietary

supplements for three consecutive days. The doses were ten-fold greater than the recommended human daily oral dose of the commercial products based upon an estimated 60-kg human body weight. As positive control, riddeliine at 1.0 mg/kg/day was applied for 3 consecutive days. DHP is a reactive metabolite of pyrrolizidine alkaloids. The quantity of pyrrolizidine alkaloids and the quantity of formed DHP is proportional. Compared with the positive control group (1350±127 adducts/10^8 nucleotides), the livers of rats gavaged with the commercial comfrey root extract and comfrey compound oil contained 22.0±3.8 and 31.9±5.1 adducts/10^8 nucleotides, respectively. In case of pyrrolizidine alkaloid-free comfrey leaf products, DHP-derived DNA adducts were not detected. It was also found that the levels of DHP-derived DNA adducts in liver cells, hepatocytes, and endothelial cells of rats treated with riddeliine correlated with the incidence of hepatocellular sarcoma and haemangiosarcoma (Chou and Fu, 2006).

Comfrey root liquid extract (liquid extract from fresh *Symphytum officinale* root; extraction solvent: ethanol 60% (V/V), DER 1:2, pyrrolizidine alkaloid content <1 ppm) was investigated for its ability to induce gene mutations in the bacterial reverse mutation assay (Ames test) in *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 with and without metabolic activation using the mammalian microsomal fraction S9 mix (liver microsomal fraction derived from male Wistar rats) and plated on selective medium according to the direct plate incorporation and the pre-incubation method. Reference mutagens (4-NOPD, 2-AA, NaN_3, MMS) were used to check the validity of the experiments. Comfrey root fluid extract showed no biologically relevant increases in revertant colony numbers of any of the five tester strains in 6 different concentrations (0.0306-5 µl/plate), neither in the presence nor in the absence of metabolic activation. The reference mutagens induced a distinct increase of revertant colonies indicating the validity of the experiments. In conclusion, the comfrey root fluid extract was not mutagenic in the bacterial reverse mutation assay (Benedek *et al.*, 2010).

Mei *et al.* (2005) evaluated the mutagenicity of comfrey in the liver *cII* gene of Big Blue rats. To determine an appropriate dose for treatment, a preliminary experiment was conducted by feeding diets containing 2, 4 and 8% comfrey. Based on a minimum effect on weight gain, lack of overt toxicity to the liver, and a maximum effect on mutagenicity, a diet containing 2% comfrey root was chosen for the mutagenesis experiment. Groups of six 6-week-old male Big Blue rats were fed either a basal diet or the comfrey diet. The animals were killed after 12 weeks of treatment. Mutant frequencies (MFs) were determined for the liver *cII* gene of the rats treated with comfrey. The MF for rats fed comfrey was 146±15x10^{-6}, which was significantly greater than the MF for control rats, 30±16x10^{-6}. This result suggests that comfrey induces liver tumours by a genotoxic mechanism. The mutational spectrum from comfrey-treated rats suggests that pyrrolizidine alkaloids in the plant are responsible for mutation induction and tumour initiation in rat liver.

Carcinogenity

All the carcinogenity studies on animals were carried out with the oral administration of the herbal substance or extract. For external use, no data are available.

Long-term studies in animals (usually rats) have shown that comfrey is carcinogenic (Cupp, 2000). Guo *et al.* (2007) suggested that the carcinogenicity of comfrey results from pyrrolizidine alkaloid. To confirm this hypothesis, the expression of genes and processes of biological functions that were altered by comfrey (mixture of the plant with pyrrolizidine alkaloids) and riddelliine (a prototype of carcinogenic pyrrolizidine alkaloid) in rat liver for carcinogenesis was compared in their study. Groups of 6 Big Blue Fisher 344 rats were treated with riddelliine at 1 mg/kg body weight by gavage five times a week for 12 weeks or fed a diet containing 8% comfrey root for 12 weeks. Animals were sacrificed one day after the last treatment and the livers were isolated for gene expression analysis. The gene expressions were investigated using Applied Biosystems Rat Whole Genome Survey Microarrays and the biological functions were analysed with Ingenuity Analysis Pathway software. Although there were large differences between the significant genes and between the biological processes that were altered

by comfrey and riddelliine, there were a number of common genes and function processes that were related to carcinogenesis. There was a strong correlation between the two treatments for fold-change alterations in expression of drug metabolising and cancer-related genes. These results suggested that the carcinogenesis-related gene expression patterns resulting from the treatments of comfrey and riddelliine were very similar, and pyrrolizidine alkaloids contained in comfrey are the main active components responsible for carcinogenicity of the plant.

In a study published in 1978 (Hirono *et al.*, 1978a), seven groups of inbred strain ACI rats were fed dried comfrey leaves (*Symphytum officinale*) or dried comfrey roots (*Symphytum officinale*) over a 480 to 600 day period. Three groups of rats consisting of 19-28 rats were fed comfrey leaves as 8–33% of their diet, and four groups consisting of 15-24 rats were fed comfrey roots as 0.5-8% of their diets. A control group was fed a normal diet. All groups of rats fed comfrey roots or leaves developed hepatocellular adenomas (metastatic foci were not observed), while the rats in the control groups did not develop liver tumours. The results also showed that the highest incidence of liver tumours occurred in those rats being fed comfrey roots (Hirono *et al.*, 1978a).

Gomes *et al*. (2010) investigated the effects of chronic oral treatment of rats with 10% comfrey ethanolic extract in a 'resistant hepatocyte model' (RHM). In this model, it is possible to observe easily the phenomena related to the early phases of tumour development, since pre-neoplastic lesions (PNLs) rise in about 1-2 months of chemical induction. Wistar rats were sequentially treated with *N*-nitrosodiethylamine (intraperitoneal) and 2-acetilaminofluorene (*per os*), and submitted to hepatectomy to induce carcinogenesis promotion. Macroscopic/microscopic quantitative analysis of PNL was performed. Comfrey treatment reduced the number of pre-neoplastic macroscopic lesions up to 1 mm, the percentage of oval cells and mitotic figures, as well as the number of Proliferating Cell Nuclear Antigen (PCNA) positive cells and acidophilic pre-neoplastic nodules. On the other hand, the percentage of cells presenting megalocytosis and vacuolar degeneration was increased. Scores of fibrosis, glycogen stores and the number of nucleolus organising regions were not altered. The study indicated that oral treatment of rats with 10% comfrey alcoholic extract reduced cell proliferation in this model.

Hirono *et al.* (1978b) concluded that the highest incidence of tumours might be attributed to the regimen of normal and 0.5% comfrey root diets alternately administered at 3-week intervals after a 1% comfrey diet was given for a long period. Their finding was in accordance with the observation of McLean (1970) that pyrrolizidine alkaloids produce tumours most frequently when doses were interrupted or ceased altogether several months before the death of the animal.

Reproductive toxicology

No studies are available for comfrey preparations.

A study with heliotrine injected at doses 15-300 mg/kg to pregnant rats in the second week of gestation produced abnormalities in the litters only at doses, which affected the dams as well. Similar results were obtained in another study with heliotrine and its toxic metabolite dehydroheliotrine, moreover the pyrrole metabolite was five times as effective as the corresponding alkaloid. Teratogenic effects of heliotrine have also been demonstrated in *Drosophila* larvae fed with low doses of the pyrrolizidine alkaloid (De Smet *et al.*, 1992).

Conflicting data are available regarding the toxicity of pyrrolizidine alkaloids on embryonic livers. On the one hand, foetal liver seems to be more resistant to toxic pyrrolizidine alkaloids than maternal ones; on the other hand, lasiocarpine given at doses of 35 mg/kg to pregnant rats on days 13 and 17 of pregnancy was harmful for the foetal livers without affecting the mother (De Smet *et al.*, 1992).

3.4. Overall conclusions on non-clinical data

The non-clinical data concerning the pharmacology of *Symphytum officinale*, including the studies on the anti-inflammatory effects of the extracts, probably account at least in the supposed therapeutic value of the preparations in indications specified in section 2. However, little is known about the pharmacologically active constituents of comfrey and the mechanism(s) of action(s).
Data on pharmacokinetic and toxicity concerning the herbal substance or herbal preparations are incomplete. Symphyti radix contains pyrrolizidine alkaloids that (either in pure form or in an alkaloid rich comfrey extract) exhibited hepatotoxic, carcinogenic and mutagenic activities in preclinical studies, after oral administration. For assessment of these data it is referred to the "Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs)" (EMA/HMPC/893108/2011). Studies using different preparations of comfrey suggest that genotoxic/carcinogenic activities can also be found with comfrey preparations.

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 relevant data available.

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

No relevant data are available. Concerning pyrrolizidine alkaloids it is referred to the "Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs)" (EMA/HMPC/893108/2011).

4.2. Clinical Efficacy

4.2.1. Dose response studies

According to the available literature, no dose-finding studies have been conducted with Symphyti radix.

4.2.2. Clinical studies (case studies and clinical trials)

Four randomised, controlled studies and one open-observational study were performed with a special comfrey extract (SCE) and one study with a combination product. SCE is different from the herbal preparation included in the monograph, owing the fact that the exact production process (due to several steps to lower the content of pyrrolizidine alkaloids) and therefore the final composition of the product is not known. SCE is produced from fresh comfrey root, 100 g ointment contains 35 g pyrrolizidine alkaloid reduced ethanol (ethanol 60% (V/V)) liquid extract (1:2), with an allantoin content of 0.2–0.5% (m/m); 99% of the pyrrolizidine alkaloids are removed; end products contain pyrrolizidine alkaloids less than 35 ppm.

Koll *et al.* (2004) investigated the percutaneous efficacy of SCE in a double-blind, multicentre, randomised, placebo-controlled, group comparison study on patients suffering from unilateral acute ankle sprains (n=142, 18-60 years of age, mean age 31.8 years, 78.9% male). Out of 143, 80

(55.9%) received verum and 63 received placebo (44.1%). The duration of treatment (6 cm strand of 2 g verum/placebo ointment) was 8 days.

According to the publication the following results were observed:
In the verum group, there was a significantly stronger (p<0.0001) alleviation of pain (tonometrically recorded pressure pain) during the course of the study compared to the placebo group.
The reduction of swelling (figure-of-eight method) was significantly more rapid and substantial (p=0.0001, p=0.0012), the joint mobility (neutral zero method) was significantly increased in the verum group when compared to placebo. There was no statistically significant difference between the two groups with respect to the resting and movement pain (visual analogue scale). The final evaluations of global efficacy (physician's and patient's judgment, 4-step scale) were significantly better in the verum group compared to placebo for both the physicians and the patients (p<0.0001 and p=0.0009, respectively). Under active treatment, no adverse drug reactions were reported.

Predel *et al.* (2005) carried out a single-blind (differences between the two products - cream versus gel colour, odour – thus just the investigator could been blinded), controlled, randomised, parallel group multicentre study to compare the efficacy and tolerability of SCE with that of diclofenac gel (DG-100 g contained 1.16 g diclofenac, diethyldiamine sodium salt) in the treatment of acute unilateral ankle sprain (distortion).Treatment (6 cm of the preparations four times daily) period was 7±1 days. A total of 164 patients (mean age 29 years, 47.6% female) were included (SCE n=82, DG n=82).

According to the publication the following results were observed:
The 95% CI the area under curve (AUC) of the pain reaction to pressure (tonometer) on the injured area (*Symphytum officinale* extract minus diclofenac gel) was 19-104 h*N/cm^2 (significant difference between groups, p=0.0012), above the margin of non-inferiority. After 7 days of treatment, pain at rest and at movement improved by 92/83% (comfrey) and 85/72% (diclofenac), ankle circumference by 3.7% (comfrey) and 3.2% (diclofenac) and the reduction of swelling by 80% (comfrey) and 69% (diclofenac), but without significant difference between the two groups. Tenderness values improved by 86% in the comfrey and 80% in the diclofenac group, the difference between groups was statistically different (p=0.0070). The investigators rated the comfrey extract superior to the diclofenac preparation (p=0.0130), 78% of the comfrey group and 61% of the diclofenac patients rated the treatment as good or excellent (D'Anchise *et al*., 2007).

Grube *et al.* (2007) investigated the effect of a daily application of 6 g SCE (3×2 g 6 cm long thread) over a 3 week period with patients suffering from osteoarthritis of the knee in a randomised, double-blind, bicenter, placebo-controlled clinical trial. The included 220 patients examined consisted of 153 women and 67 men of an average age of 57.9 years. In the course of the trial, the visual analog scale (VAS) total score (primary target value) in the verum group dropped significantly (verum vs placebo=54.7% vs 10.7%, p<0.001). The intensity of pain was reduced considerably in the verum group from "moderate pain" (47.1%) to "mild pain" (21.3%). The difference between the treatment groups increased systematically, in parallel with the term of the treatment.

According to the publication the following results were observed:
The pain at rest declined significantly in the verum group when compared to placebo (56.6% vs 12.2%, p<0.001). With regard to pain on movement, the verum group had undergone a reduction of pain on movement of 30.7 mm (53.5%) while the placebo group had only undergone a reduction of 5.6 mm (9.9%). In respect of the explorative secondary target values SF-36 (quality of life), angle measurement (mobility of the knee), CGI (clinical global impression) and global assessment of efficacy by the physician and the patient, a significant superiority (p<0.001 each) of the verum group over the placebo group was also proven. At the end of the trial (visit 4), a global assessment of tolerance was performed by the physician and the patient using a scale. Only "good" and "very good" ratings were issued. In the verum group the "very good" ratings predominated (73.6%, physician and patient) and in the placebo group, the "good" ratings (50.9% physician and 53.6% patient).The results suggested

that the comfrey root extract ointment is useful in the short-term treatment of osteoarthritis of the knee. Pain is reduced, mobility of the knee improved and quality of life increased (Chrubasik, 2007, Grube *et al.*, 2007).

The objective of the study carried out by Giannetti *et al.* (2010) was to show the superiority of SCE to placebo ointment in patients with acute upper or low back pain. The study was conducted as a double-blind, multi-centre, randomised clinical trial with parallel group design over a period of 5±1 days. The patients (n=120, mean age 36.9 years) were treated with verum or placebo ointment three times a day, 4 g ointment per application. The trial included four visits. The primary efficacy variable was the area under the curve (AUC) of the visual analogue scale (VAS) on active standardised movement values at visits 1 to 4. The secondary efficacy variables were back pain at rest using assessment by patient on VAS, pressure algometry (pain-time curve; AUC over 5 days), global assessment of efficacy by the patient and the investigator, consumption of analgesic medication, and functional impairment measured with the Oswestry Disability Index.

According to the publication the following results were observed:
There was a significant treatment difference between comfrey extract and placebo regarding the primary variable. In the course of the trial the pain intensity on active standardised movement decreased on average (medians) about 95.2% in the verum group and 37.8% in the placebo group. The results of this clinical trial were clear-cut and consistent across all primary and secondary efficacy variables (Giannetti *et al.*, 2010).

Koll and Klingenburg (2002) conducted a prospective open multicentre observational study involving 162 general practitioners to analyse the anti-inflammatory and analgesic properties of the topical comfrey preparations: SCE, SCE-Plasma (100 g contains 30 g Symphyti radix fluid extract (1:2)) and SCE-Balsam (100 g contains 35 g Symphyti radix fluid extract (1:2) and 1.2 g methylnicotinate) applied to bruises, sprains and distortions and painful conditions of the muscles and joints. During the 2 weeks of observation the patients received an average of 1-3 applications of the comfrey preparation per day. Altogether 492 questionnaires were evaluated. Efficacy and tolerability were assessed by both physician and patient.

According to the publication the following results were observed:
Pain at rest and movement, as well as tenderness have improved in the overall observation group by an average of 45-47%. The duration of morning joint stiffness decreased from 20 minutes initially to 3 minutes. There were only slight differences between the global efficacy scores of the three SCE preparations: 1.76 for SCE-Plasma, 1.73 for SCE-Balsam, 1.69 for SCE. During the course of the treatment with comfreys, more than 2/3 of the patients were able to reduce or even discontinue their intake of non-steroidal anti-inflammatory drugs and other specific concomitant medication. In most of the cases, both effectiveness and tolerability were assessed to be excellent or good.

Table 2. Randomised, controlled clinical studies with a special *Symphytum officinale* preparation (SCE)

Study	**Design**	**Study population**	**Treatment**	**Endpoints**	**Results (comfrey vs. placebo/comparator)**
Koll *et al*., 2004	double-blind multicenter randomised placebo-controlled	unilateral ankle sprain n=143, 78,9% male mean age: 31.8 years (18-60)	80 patients SCE ointment 60 patients placebo ointment ~2 g (~6 cm) ointment duration: 8 days	1 pressure pain AUC for pressure differences 2 swelling AUC of the difference 2 resting pain VAS 2 movement pain VAS 2 limitation of movement 2 use of emergency medication 2 final global evaluation of efficacy (physician) 2 final global evaluation of efficacy (patient) 2 evaluation of cosmetic properties (patient)	-2.44 kp/cm^2 vs. -0.95 kp/cm^2 (p=0.0001) 5.03 visit*kp/cm^2 vs. 6.68 visit*kp/cm^2 (p < 0.0001) -1.70 cm vs. -1.08 cm (p=0.0001) 6.38±4.23 cm vs. 3.8±5.05 cm (p = 0.0012) -3.42 cm vs. -3.25 cm -4.46 cm vs. -3.72 cm dorsiflexion and plantar flexion: p = 0.002 and 0.0116 0 vs. 2 excellent or good: 86.3% vs. 22.6% (p<0.0001) excellent or good: 81.3% vs. 50% (p=0.0009)
Predel *et al*., 2005	single blind multicentric randomised controlled	acute unilateral ankle sprain n=164, 47.6% female mean age: 29 years	82 patients SCE ointment 82 patients diclofenac containing gel ~6 cm of the preparations 4 times daily duration: 7±days	1 pressure pain AUC 2 swelling 2 resting pain VAS 2 movement pain VAS 2 limitation of movement 2 use of emergency medication 2 final global evaluation of efficacy (physician) 2 final global evaluation of efficacy (patient)	95% CI AUC (comfrey minus diclofenac): 19-104 h*N/cm^2 -3.67% vs. -3.19% 92.01% vs. 84.96% 83.2% vs. 72.37% data not shown 0 vs. 0 excellent or good: 78% vs. 61% excellent or good: 84.2% vs. 70.8%
Reassessment of the data of the Predel *et al.*, 2005 study by D'Anchise *et al*., 2007				1 pressure pain AUC 2 swelling 2 resting pain VAS 2 movement pain VAS	+61.1 h*N/cm^2 greater in comfrey group (p=0.0012) difference not significant difference not significant (p=0.2949)

				2 final global evaluation of efficacy (physician)	difference not significant comfrey superior to diclofenac
Grube *et al*., 2007	double-blind bicenter randomised placebo-controlled	painful osteoarthritis in knee n=220, 69.5% female mean age: 57.9 years	110 patients SCE ointment 110 patients placebo ~6 cm of the preparations 3 times daily duration: 21 days	1 VAS total score pain at rest VAS pain at movement VAS 2 WOMAC total score pain score stiffness score function score 2 quality of life (SF-36) physical function score mental function score 2 angle measurement knee flexion extension of knee 2 Clinical Global Impression	51.6 mm (54.7%) vs. 10.1 mm (10.7%) (p< 0.001) 20.9 mm (56.6%) vs. 4.6 mm (12.2%) (p<0.001) 30.7 mm (53.5%) vs. 5.6 mm (9.9%) 60.4 mm (58.0%) vs. 14.7 mm (14.1%) (p< 0.001) 12.1 mm (58.2%) vs. 2.7 mm (12.9%) (p<0.001) 4.8 mm (55.8%) vs. 1.2 mm (13.2%) (p<0.001) 43.4 mm (58.2%) vs. 10.7 mm (14.4%) (p< 0.001) 11.9 pts (38.1%) vs. 1.3 pts (4.2%) (p<0.001) 4.2 pts (9.5%) vs. 1.1 pts (2.5%) (p = 0.006) 7.5 (7.0%) vs. 0 (p<0.001) -2.0 (-65.8%) vs. 6.4 (19.6) (p<0.001) improvement: 92.7% of the patients vs. 17.4% (p<0.001)
Giannetti *et al*., 2010	double-blind multicenter randomised placebo-controlled	acute upper or low back pain n=120 mean age: 36.9 years	3 times 4 g ointment duration: 5±days	1 AUC of the VAS on active standardized movement values 2 back pain at rest VAS 2 pressure algometry AUC 2 global assessment of efficacy (investigator) 2 global assessment of efficacy (patient) 2 consumption of analgesic medication 2 Oswestry Disability Index	significant treatment difference

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

Staiger and Wegener (2008) carried out a multicentric, prospective post-marketing surveillance study on the tolerability and efficacy of an ointment containing comfrey root fluid extract (SCE). Three hundred and six children (148 girls, 158 boys) aged between 3 and 12 years (average age 7.7 years) were included in the study. Altogether 31 paediatricians applied SCE to treat bruises (61.4%), luxations (30.4%) and sprains (14.1%) or similar injuries (6.9%) of children until recovery or significant improvement of the symptoms or for a maximal interval of 1 week. For treatment, 4-6 cm ointment was applied 2-4 times daily. At the end of the treatment the tolerability was assessed and the adverse events were recorded. To assess the efficacy, pain, restriction of movement, haematoma and the decrease of the general health state were recorded (each on a 5-grade scale). Children assessed the pain on a 5-grade Smiley-scale. Pain sensitivity, restriction of movement, general health state, pain at rest, pain at movement, pain at night improved until the end of the treatment with an average of 61.4%, 62%, 55.8%, 62.6%, 60.3%, and 59.3%, respectively, as assessed by the patients and their parents. Paediatricians assessed the improvement of tenderness, restriction of movement, haematoma, general health state, swelling to 59.7%, 59.8%, 53.2%, 54.9%, and 8.4%, respectively. 88.4% of the paediatricians assessed the tolerability of the treatment as very good or good. In case of the patients/their parents the same values was 98.7%. The authors concluded that the topical application of the studied comfrey preparation is effective and safe also for children. However, due to the study design (open study, heterogenous study population) the efficacy of comfrey in children in special indications cannot be confirmed from this study.

4.3. Overall conclusions on clinical pharmacology and efficacy

No relevant information is available with regard to the pharmacodynamic properties of common comfrey and no dose-response studies are available. However, some studies with positive outcomes were reported regarding a special preparation of *Symphytum officinale* (SCE) in the treatment of sprains, these clinical studies cannot be taken into consideration for the preparation of a well-established use monograph, because of the exact production process (due to several steps to remove the pyrrolizidine alkaloids) and therefore the final composition of the product is not known. The preparations applied in the studies presented in this assessment report are different from the herbal preparation included in the monograph.

No appropriate clinical studies have been carried out in special populations, e.g. elderly and children.

5. Clinical Safety/Pharmacovigilance

Common comfrey has been a traditional medicinal herb, which earlier was used both externally and internally. While comfrey is the most widely-recognised source of dietary pyrrolizidine alkaloids in developed countries, other herbal preparations that contain pyrrolizidine alkaloids also have been implicated in liver disease in humans. The oral application of comfrey is not part of the rational phytotherapy and occurs only sparsely in Europe. The intake from root-tea has been estimated at between 8 and 26 mg per cup (Abbott, 1988). The estimated daily intakes of certain pyrrolizidine alkaloids leading to fatal intoxications range from 0.5 to 3.3 mg/kg (De Smet *et al.*, 1992). However, little is known about the chronic ingestion of smaller doses of pyrrolizidine alkaloids.

In case of *Symphytum officinale*, there are no data on acute adverse events in case of the cutaneous therapeutic application of medicinal products. According to Barnes *et al.* (2007), percutaneous absorption of pyrrolizidine alkaloids present in comfrey is reported to be low, although application of comfrey preparations to the broken skin should be avoided.

For further information referring to pyrrolizidine alkaloids see (EMA/HMPC/893108/2011).

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

No data exist for preparations covered by the monograph.

From the clinical trials with the SCE basically good or excellent tolerability/local tolerance was reported with overall more than 500 patients (verum). It is important to emphasise that in cases of medicinal products for cutaneous use the vehicle of the preparation and the excipients in it might have great influence of the absorption of the active/toxic components. Therefore the data from the studies Koll *et al.* (2004), Predel *et al.* (2005), Grube *et al.* (2007), Staiger and Wegener (2008), Schmidtke-Schrezenmeier *et al.* (1992) and Koll and Klingenburg (2002) do not add relevant safety information for the preparation in the monograph.

5.2. Patient exposure

No data exist for the preparation covered by the monograph.

The four controlled clinical trials with SCE evaluated in the assessment report comprised altogether 647 patients (Knoll *et al.*, 2004; Predel *et al.*, 2005; Grube *et al.*, 2007; Giannetti *et al.*, 2010). In one multicentric, prospective post-marketing surveillance study 306 children were exposed to comfrey treatment (Staiger and Wegener, 2008).

Products containing comfrey extracts are on the European market since at least 1968.

5.3. Adverse events and serious adverse events and deaths

Although there are human data on the central nervous system and pulmonary system affecting effects of certain pyrrolizidine alkaloid-containing plants, common comfrey is toxic primarily on the liver. In almost all cases of severe or fatal *Symphytum* intoxications, the patients developed liver damage with cirrhosis and ascites.

Liver toxicity

For the hepatotoxicity of pyrrolizidine alkaloids, see the “Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs)” (HMPC, 2014).

Case studies

The daily consumption of comfrey root-based food supplement containing an estimated ~15 µg total pyrrolizidine alkaloids/kg body weight (total estimated minimal dose = 85 mg) over 6 months along with camomile tea and vitamin supplements was associated with the development of veno-occlusive disease in a 49-years old woman. Budd-Chiari syndrome was diagnosed on the basis of a liver biopsy specimen that showed centrilobular necrosis. The patient had portal hypertension associated with obliteration of the smaller hepatic venules. A liver biopsy specimen showed centrilobular necrosis and congestion. The clinical and analytic findings were consistent with chronic pyrrolizidine intoxication, indicating that low-level, chronic exposure to such alkaloids can cause venocclusive disease (Ridker *et al.*, 1985).

A 13 year old boy was admitted in July 1986 for investigation of hepatomegaly and ascites. Three years earlier Crohn's disease had been diagnosed. He was treated with prednisolone and sulphasalazine with benefit. At his parents' request these drugs were discontinued and he was treated with acupuncture and comfrey root, prescribed by a naturopath. Up to 1986 he had been regularly given a herbal tea containing comfrey leaf. The exact quantities of leaves given and frequency of administration are unknown. An exacerbation of his inflammatory bowel disease in 1984 required a further course of prednisolone. In June 1986 he presented with fatigue, diarrhoea, and weight loss and a few weeks later developed fever, abdominal pain, and swelling. He was taking prednisolone and sulphasalazine. On examination, he had ascites and tender hepatomegaly but no dehydration, jaundice, or heart failure and no stigmata of chronic liver disease. He had raised serum bilirubin

concentration and aspartate aminotransferase activity. Percutaneous liver biopsy showed the thrombotic variant of hepatic veno-occlusive disease. He was treated with spironolactone, salt restriction, and bed rest with a good response. The authors supposed that the only possible causal factor for hepatic veno-occlusive disease in the patient was comfrey (Weston *et al.*, 1987).

Hepatic venom-occlusive disease was also observed in 47-year old women who had used large amounts of comfrey tea (10 cups of tea per day) and comfrey pills for eight years (Bach *et al*., 1989).

Carcinogenity

For Symphyti radix, no data are available.

Concerning the carcinogenity of pyrrolizidine alkaloids, see the Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs) (HMPC, 2014).

5.4. Laboratory findings

In the clinical setting, hepatic function is commonly assessed by monitoring the serum concentrations of proteins of hepatic origin. For example, elevations in aspartate aminotransferase (AST) might reflect liver pathology, γ-glutamyltransferase (GGT) and bilirubin are elevated with choleostasis, and α-fetoprotein (AFP) is a specific marker for liver cancer. Although these markers are not necessarily elevated in every case of veno-occlusive disease, Anderson and McLean determined the serum concentration of AST, GGT and bilirubin in 29 long-term comfrey users, and AFP in a subgroup of seven comfrey leaf users. Although this cohort is too small to ascertain risk, it is interesting that AST, GGT, bilirubin and AFP were considered normal, and there was no evidence of liver injury even after prolonged consumption of comfrey leaf (0.5–25 g day-1 for 1–30 years) (Anderson and McLean, 1989; Rode, 2002).

5.5. Safety in special populations and situations

According to Barnes *et al.* (2007), in view of the toxicity associated with the alkaloid constituents, comfrey should not be taken during pregnancy or lactation. However, Commission E suggests that during pregnancy comfrey should be used only after consultation with a physician (Blumenthal *et al.*, 1998).

Though no information is available concerning the application of comfrey on neonates, two neonatal deaths were reported in Canada after mothers used comfrey as a cream on the nipples; consequently it was banned in Canada (Schaefer *et al.*, 2007).

No information is available on drug interactions, overdose, abuse and effects on ability to drive or operate machinery or impairment of mental ability.

5.6. Overall conclusions on clinical safety

Due to the List of herbs and herbal derivatives with serious risks dated 1992 prepared by Committee for Proprietary Medicinal Products and other measures made by national medicine authorities there is no product containing *Symphyti radix* for oral use as herbal medicine in Europe (CPMP, 1992).
Only some preparations for cutaneous use are available as well with limited content of unsaturated pyrrolizidine alkalkaloids (PA).

Based on “Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs)” prepared and issued by HMPC (EMA/HMPC/893108/2011) the following recommendations were taken into account for the purpose of the monograph on Symphyti radix:

Because of their known involvement in human poisoning and their putative carcinogenicity, exposure to toxic, unsaturated PAs should be kept as low as practically achievable.

In the evaluation of HMPs/THMPs containing toxic, unsaturated PAs Member States should take steps to ensure that the public are protected from exposure and the following thresholds should be applied.

Cutaneous use

Until now only rudimentary data concerning absorption of PAs through the skin exist. The study by Brauchli *et al*. (1982) suggests that at least in rats, the dermal absorption could be 20-50 times less than absorption via the intestinal route. The used test model (rat) is not sufficient for the risk assessment in humans.

It is to ensure that the amount of toxic, unsaturated PA within the daily dose is <0.35 µg for adults (short-time usage). The use is restricted to intact skin.

Higher contents of toxic, unsaturated PA within the products would be possible if for the relevant product (means the relevant matrix, because absorption might be greatly influenced by the excipients, for instance essential oils as enhancers) low absorption rates (generated with modern analytical techniques; in animal species which are more comparable to human beings in relation to the skin or *in vitro* human skin preparations) can be shown, not exceeding the daily intake of 0.35 µg toxic, unsaturated PA for adults.

Sensitive groups

Children:
If children are included in the usage of certain products the daily amount of toxic, unsaturated PA has to be adjusted to the body weight of the age group: e.g. body weight of 20 kg would lead to an acceptable short-time (maximum 14 days) daily intake (herbal medicinal products) of 0.14 µg toxic, unsaturated PA/day.

Pregnant and breast feeding woman:
Sensitive groups such as pregnant and breast feeding woman are also covered by the limit calculated above. If these limits are complied with, the chapter 4.6 of the SmPC of the products concerned should be phrased according to the Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005) (CHMP 2008).

6. Overall conclusions

Based on the provided data on comfrey products by National Competent Authorities, the traditional medicinal cutaneous use of *Symphytum officinale* has been confirmed in the treatment of bruises and sprains throughout a period of at least 30 years, including at least 15 years within the EU.

Although the efficacy in bruises, sprains, osteoarthritis and back pain is clinically investigated for a specific product a well-established monograph cannot be granted since the exact composition of preparations applied in clinical trials is not known.

There are no rational objections (self medication character, plausibility and safety) to the traditional use of comfrey products with limited pyrrolizidine alkaloid content, and the data provided support the long standing use of *Symphytum officinale* preparations. However, even with products for cutaneous use, the main concern for the clinical safety of comfrey preparations is the content of pyrrolizidine alkaloids, the potential of absorption through intact skin and metabolic activation in the liver; all factors which influence the hepatotoxicity/carcinogenicity of these preparations. Information on the pyrrolizidine alkaloid content of the traditional preparations needs to be determined for individual products.

Based on the HMPC “Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs)” (EMA/HMPC/572844/2009) the acceptable daily intake is maximum 0.007 µg/kg/day for cutaneous preparations.

Generally for adults the calculation is done with a body weight of 50 kg. Therefore the daily dosage would be: 0.007 µg/kg/day x 50 kg body weight = **0.35 µg/person/day for short-time use only (maximum 2 weeks).** The use is restricted to intact skin.

The public statement does not exclude the use of the preparations with a lower limit on the PAs content (0.014 µg PA/day) in children and during pregnancy, however, taking into consideration the general rule that there are not adequate data on the use of the preparation mentioned in the monograph in these populations for more than 30 years, the use is not recommended.

Annex

List of references