EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Arnica montana* L., flos

Draft – 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)	*Arnica montana* L., flos (arnica flower)
Herbal preparation(s)	a) Comminuted herbal substance b) Tincture (ratio herbal substance to extraction solvent 1:10); extraction solvent: ethanol 70% (V/V) c) Tincture (ratio herbal substance to extraction solvent 1:10); extraction solvent: ethanol 60% (V/V) d) Fluid extract (DER 1:1); extraction solvent: ethanol 60% (V/V) e) Liquid extract of fresh flowers (DER 1:20); extraction solvent: ethanol 50% (m/m) f) Liquid extract (DER 1:3.5-4.5); extraction solvent: refined sunflower oil
Pharmaceutical form(s)	Herbal preparations in semi-solid and liquid dosage forms for cutaneous use.
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Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Arnica montana* L., flos. It is a working document, not yet edited, and

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shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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1. Introduction

1.1. Description of the herbal substance, herbal preparations or combinations thereof

- **Herbal substance(s)**

Definition of the herbal substance
The definition of the herbal substance is available in the European Pharmacopoeia 11.2. Arnica Flower (07/2022:1391): The whole or partially broken, dried flower-heads of *Arnica montana* L. The minimum content of sesquiterpene lactones is 0.4%.

Principal components of the herbal substance
The most relevant constituents are considered helenalin and 11,13-dihydrohelenanin and their derivatives (Willuhn, 1983). The content is varying with respect to the geographical origin.
Arnica flos contain e.g. the following constituents: terpenoids, coumarins (scopoletin, umbelliferone), flavonoids, volatile oils (thymol, thymol derivatives) and bitter principle (MedicinesComplete, 2024; Blaschek et al., 2021).

Adulteration
Adulteration can occur with *Chrysanthemum segetum*, *Crepis biennis*, *Hieracium lachmalii*, *Hypochoeris-Arten*, *Picris hieracioides*, *Taraxacum officinalis* und *Tussilago farfara*. The most common adulteration is with the Mexican Arnica, *Heterotheca inuloides* CASS. (Asteraceae) (Blascheck et al., 2021).

- **Herbal preparation(s)**

Arnica tincture is defined in the European Pharmacopoeia 11.2 (07/2022:1809) as a tincture produced from Arnica flower with a minimum content of 0.04% sesquiterpene lactones expressed as dihydrohelenalin tiglate. The tincture is produced from 1 part of the drug and 10 parts of ethanol (60-70% (V/V)).

- **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.**

There are combinations on the European Market, which are combining preparations of different plants. This monograph refers exclusively to mono-preparations.

1.2. Search and assessment methodology

Review 1
A search was performed for the period of January 2013-May 2023 in the EBSCO Discovery database (Medline Complete, Pub Med, Embase, DynaMed). Key words were "*Arnica montana*" (SU), language English. Further searches were performed with additonal key words as "clinical study", "toxicology" and "adverse events".
Additional hand search was performed in books, book chapters, articles and letters in journals, medical press reviews, acts of law and regulations in the BfArM owned library.

Pharmacovigilance resources were the EudraVigilance database (EVDAS) and information provided by the Member States. A search was performed for the period of 01.01.2013-30.05.2023 in EVDAS

(EudraVigilance) database. Key words were "Spontaneous, Other, Not available to sender (unknown), Report from studies, suspect interacting, from the European economic area (EEA)". The EURD-list was checked if a PSUSA-procedure has been finalised during the review period.

All EU member states were asked to give information on products on the market. A new market overview from 2022, including information on the indication and pharmacovigilance actions taken in member states, was included in the assessment. A check of consistency (e.g. scientific decisions taken by HMPC) with other monographs was performed.

In the period of review, the Ph.Eur. monograph was updated in Ph.Eur. 11.2. No changes result for the HMPC monograph.

1.3. Main changes introduced in the first revision

From the updated market overview, the following changes for the monograph are implemented:

The dose for administration in semi-solid dosage form is changed from 20-25% to 5-25% tincture in base.
The administration as diluted tincture (dilution ratio 1:3-10) with water was added.

New preparations added: herbal infusion (liquid dosage form) only for the external use for impregnated compresses; fluid extract (1:3.5-4.5); extraction solvent: refined sunflower oil in semi-solid dosage form (10 g extract in 100 g cream).

Former preparation tincture (DER 1:5), extraction solvent: ethanol 60% (V/V) was corrected to liquid extract (DER 1:1), extraction solvent: ethanol 60% (V/V), with 4% liquid extract in base. This was due to an error in the first version of the monograph.

Indication: from the market overview, it was seen that the traditional medicinal use is also fulfilled for the topical use of inflammations as a result of insect bites and for treatment of small boils (furuncles) for some preparations. The indications were adopted accordingly.

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

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	**Indication**	**Pharmaceutical form** **Strength (where relevant)** **Posology** **Duration of use**	**Regulatory status**
tincture (DER 1:10); extraction solvent: ethanol 70% (V/V)	Traditional herbal medicinal product for the relief of bruises, sprains and localised muscular pain.	100 g ointment contain 21.5 g tincture (21.5%) *Adolescents and adults:* 2-3 x daily If the symptoms persist after 3 to 4 days during the use of the	2008; AT; TU

Active substance	**Indication**	**Pharmaceutical form** **Strength (where relevant)** **Posology** **Duration of use**	**Regulatory status**
		medicinal product, a doctor or a qualified health care practitioner should be consulted.	
tincture (DER 1:10); extraction solvent: ethanol 70% (V/V)	Traditional herbal medicinal product for the relief of bruises, sprains and localised muscular pain.	100 g ointment contain 21.5 g tincture (21.5%) *Adolescents and adults:* 2-3 x daily If the symptoms persist after 3 to 4 days during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.	2008; AT; TU
tincture (DER 1:10); extraction solvent: ethanol 70% (V/V)	Traditional herbal medicinal product for the relief of bruises, sprains and localised muscular pain.	100 g gel contain 24 g tincture (24%) *Adolescents and adults:* 2-3 x daily If the symptoms persist after 3 to 4 days during the use of the medicinal product a doctor or a qualified health care practitioner should be consulted.	2016; AT; TU
liquid extract from fresh flowers (DER 1:20); extraction solvent: ethanol 50% (V/V)	Traditional herbal medicinal product for the relief of bruises, sprains and localised muscular pain.	100 g gel contain 50 g liquid extract (50%) *Adults:* 2 x daily If the symptoms persist after 10 days during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.	2011; AT; TU
tincture from the flowers of *A. montana* L. (DER: 1:10); extraction solvent: ethanol 60-70% (V/V)	Topically used as an antiphlogistic and pain relieving medicinal product in the treatment of sprains and it is indicated for the treatment of haematomas or oedemas at acute injuries. Any serious illness must be excluded.	1 g cream contains 250 mg tincture (25%) Apply 2 to 3 times a day on the skin to be treated. Rub in gently until the cream has completely penetrated. 3 cm of ointment is sufficient to treat an area the size of the hand. It can be used in children	2002; BE; WEU commercialisation 2007-2017; radiation: 2021
liquid extract of fresh flowers of *A. montana* L. (DER 1:20); extraction solvent: ethanol 58% (V/V)	For the relief of pain symptoms, inflammation from rheumatism, joint pain, back pain, muscle pain, (muscle) strains, bruises, swelling from bruising, sprains, inflammation of tendons, bruising from a blow, muscle and joint stiffness.	1 g gel contains 500 mg extract (50%) Gently apply a thin layer (2 to 10 cm) to the affected area 2 to 4 times a day. Not recommended for children under 12 years old. If the symptoms do not improve after 3 or 4 days of using the medicine, contact a doctor.	2016; BE; TU

Active substance	**Indication**	**Pharmaceutical form** **Strength (where relevant)** **Posology** **Duration of use**	**Regulatory status**
	Can also be applied in case of injuries related to sports practice.		
Arnicae flos	For supportive therapy of strains, bruises, sprains, muscle and joint pain, swelling due to contusions and blunt injuries, promotion of the resorption of haematomas and wound healing.	for impregnated dressings Preparation of an infusion for impregnated dressings from 2-3 g /150 ml boiling water 10-15 min Apply several times daily on the affected area	1986-1996; DE; Standard Marketing Authorisation according to section 36 of the German Medicinal Products Act
Arnicae flos	For the treatment of the symptoms of injuries and accidents, e.g. bruises, sprains, contusions, bruises, oedema as a result of broken bones, rheumatic muscle and joint complaints. Furunculosis and inflammations as a result of insect bites. Superficial phlebitis.	for for impregnated dressings Preparation of an infusion for impregnated dressings from 2 g /100 ml boiling water 10-15 min Apply several times daily on the affected area	since 1996; DE; Standard Marketing Authorisation according to section 36 of the German Medicinal Products Act
tincture (ratio drug:extraction solvent 1:10); extraction solvent: ethanol 70% (V/V)	For the treatment of the symptoms of injuries and accidents, e.g. bruises, sprains, contusions, bruises, oedema as a result of broken bones, rheumatic muscle and joint complaints. Furunculosis and inflammations as a result of insect bites. Superficial phlebitis.	for impregnated dressings For preparation of an impregnated dressing, dilute 3-10 times with water. Apply several times daily on the affected areas. If the disorders last longer than 1-2 weeks or unclear or new disorders occur, a doctor should be consulted.	2005; DE; Standard Marketing Authorisation
tincture (1:10); extraction solvent: ethanol 70% (V/V)	For the treatment of the symptoms of injuries and accidents, e.g. bruises, sprains, contusions, bruises.	1 g ointment for cutaneous use contains 80 mg tincture (8%) *Adults and adolescents over 12 years of age:* apply 2-3 times daily on the affected parts of the body	1990; DE; WEU
tincture (DER 1:7-9); extraction solvent: ethanol 70% (V/V)	THMP for the relief of localised muscle pain, bruises and sprains in adults and adolescents.	100 ml liquid contain 22.455 g tincture (22.455%) *Adults and adolescents over 12 years of age:* Apply 1-2 times daily on the affected parts of the body	2016; DE; TU

Active substance	**Indication**	**Pharmaceutical form** **Strength (where relevant)** **Posology** **Duration of use**	**Regulatory status**
		No longer than 3-4 days without advice from an heath care expert	
liquid extract (DER 1:3.5-4.5); extraction solvent: refined sunflower oil	For the treatment of the symptoms of injuries and accidents, e.g. bruises, sprains, contusions, bruises, oedema as a result of broken bones, rheumatic muscle and joint complaints. Furunculosis and inflammations as a result of insect bites.	100 g cream contain 10 g extract (10%) *Adults and adolescents over 12 years of age:* Apply several times daily and massage gently, for instance a string of ointment of 8 cm length for the area of the lower leg, for bigger or smaller areas correspondingly more or less. If after 1-2 weeks you do not feel better or even worse or unclear or new symptoms occur, you should consult a doctor.	1993; DE; WEU
liquid extract from fresh flowers (DER 1:20); extraction solvent: ethanol 50% (m/m)	Traditional herbal medical product for symptomatic relief of muscular aches, pains and stiffness, sprains, after contusions	1 g contains 500 mg of liquid extract (50%) Apply 2-10 cm to the affected area 2-4 times daily	2008; ES; TU
liquid extract from fresh flowers of *A. montana* L., equivalent to 120-200 mg of fresh flowers and 25 mg of dry flowers, extraction solvent: ethanol 58% (V/V)	THMP for the symptomatic of bruises, sprains and localized muscular pain.	1 g of gel for cutaneous use contains 500 mg of liquid extract (50%) Adolescents, adults and elderly: Apply a thin layer on the affected area, two to four times daily.	2009; ES; TU
liquid extract (DER 1:1); extraction solvent: ethanol 60% (V/V)	Traditional herbal medicine used in the symptomatic treatment of bruises, sprains and localized muscle pain.	100 g cream contain 4 g extract (4%) *Adults, adolescents and children above the age of 30 months:* Apply 2-3 times daily in a thin layer to the affected areas.	1959, FR, TU
tincture (ratio drug:extraction solvent 1:10); extraction solvent: ethanol 60% (V/V)	Traditionally used in the symptomatic treatment of bruising.	Dressing impregnated with tincture 1 impregnated dressing (135 mm x 165 mm cellulose pad) contains 2.5 ml solution	1982; FR; TU
tincture (ratio drug:extraction solvent 1:5); extraction	Traditional herbal medicine used in the symptomatic treatment of minor trauma: bruises,	100 g gel contain 20 g tincture (20%) *Adults, adolescents and children above the age of 30 months:*	2004;FR; TU

Active substance	**Indication**	**Pharmaceutical form** **Strength (where relevant)** **Posology** **Duration of use**	**Regulatory status**
solvent: ethanol 60% (V/V)	contusions, strains and localised muscle pain.	Apply 2 to 3 times daily in a thin layer to the affected areas.	
tincture (DER 1:9-10); extraction solvent ethanol 70% (V/V)	Traditional herbal medicine used in the symptomatic treatment of contusions, sprains and localised muscular pain.	100 g gel contain 20 g tincture (20%) *Adults, adolescents and children above the age of 30 months:* Apply 2 to 3 times daily in a thin layer to the affected areas.	2006-??; FR; TU
tincture (DER 1:10); extraction solvent: ethanol 70% (V/V)	Traditional herbal medicinal product for the relief of bruises, sprains and localised muscular pain.	100 g gel contain 24 g tincture (24%) *Adolescents, adults and elderly:* Apply a thin layer on the affected area two to three times daily. Duration of use: Up to 3 to 4 days if the symptoms persist; max use up to two weeks.	2021; HR; TU
tincture (DER 1:10); extraction solvent: ethanol 70% (V/V)	Treatment of closed lesions – strain, bruise, distortion, luxation. To decrease inflammation due to lesions, to promote resorption of local swelling of suffusion. To alleviate articular or muscular pain. Warming up before sport activities. Relief of insect bites.	100 g ointment contain 5 g tincture (5%) Rub the ointment into the skin of the affected region several times a day but no more than five times. Apply the preparation carefully to wounds, and then cover the wound with light dressing	1992; HU; TU
tincture from fresh *A. montana* L., flos equivalent to 120-200 mg of fresh Arnica flos, extraction solvent: ethanol 50% (m/m)	A traditional herbal medicinal product for the symptomatic relief of muscular aches, pains and stiffness, sprains, bruises and swelling after contusions, exclusively based on long-standing use.	1 g of gel contain 500 mg tincture (50%)	2011; IE; TU
tincture (DER 1:10); extraction solvent: ethanol 70% (V/V)	Traditional herbal medicinal product for the relief of bruises, sprains and localised muscular pain.	100 g gel contain 24 g tincture (24%) Apply a thin layer on the affected area, two to three times daily. Do not use for more than two weeks. If the symptoms persist after 3 to 4 days during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.	2017; IT; TU
tincture (DER 1:10); extraction solvent: ethanol 70% (V/V)	Traditional herbal medicinal product for indications based on long-term use only for the symptomatic treatment of	1 ml solution contains 1 ml tincture (100%) Apply a few milliliters of skin solution to the affected area 2 to 4 times a day.	1994; LT; TU

Active substance	**Indication**	**Pharmaceutical form** **Strength (where relevant)** **Posology** **Duration of use**	**Regulatory status**
	muscle pain and stiffness, bruising following minor blunt injuries, superficial haematomas and bruising (bruising).	*Pediatric population* Due to lack of data, the use of the medicinal product on the skin in children under 6 years of age is not recommended.	
tincture (DER 1:10); extraction solvent: ethanol 70% (V/V)	A traditional herbal medicine for reducing local muscle pain, sprain and bruising.	100 g gel contain 24 g tincture (24%) Unless your doctor tells you otherwise, apply a thin layer to the affected area two to three times a day. *Pediatric population* Not recommended for use in children under 12 years of age. Duration of use Do not use for more than two weeks.	2019; LT; TU
tincture (DER 1:10); extraction solvent: ethanol 70% (V/V)	Traditional herbal medicines used to reduce bruising, sprains and localized muscle pain.	100 g of gel contain 24 g tincture (24%) *Adults and adolescents from 12 years of age:* Unless your doctor tells you otherwise, apply 2 to 3 times a day in a thin layer on the affected areas.	2019; LV; TU
liquid extract of the fresh flowers (DER 1:20); extraction solvent: ethanol 50% (m/m)	Traditional herbal medicinal product for cutaneous use for stiffness, muscular aches, pains and sprains, bruises and swelling after contusions. The use is exclusively based on long-standing use.	Gel (no further information) for cutaneous use 2-4 times daily	2009; NL; TU
tincture (DER 1:10); extraction solvent: ethanol 70% (V/V)	Haematomas, sprains, bruises, oedemas, furunculosis, vains inflammations caused by insect bites, gingivitis, aphthae.	Diluted tincture (1:3-1:10)	1992; PL; TU
tincture (DER 1:10); extraction solvent: ethanol 70% (V/V)	Traditional herbal medicinal product for the relief of bruises, sprains and localised muscular pain.	100 g gel contain 24 g tincture (24%) Unless otherwise prescribed by a physician, apply a thin layer on the affected area, two to three times daily. *Paediatric population* The use in children under 12 years of age is not recommended. Duration of use	2016; SK; TU

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory status
		The duration of use is limited to two weeks. If the symptoms persist after 3 to 4 days during the use, a doctor or a qualified health care practitioner should be consulted.	
liquid extract from *A. montana* L., flos (DER 1:20); extraction solvent: ethanol 57.9% (V/V)	Traditional herbal medicinal product for symptomatic relief of minor muscular and articular pain, sprains bruises.	1 g gel contains 0.5 g extract (50%) Apply a thin layer 2-4 times daily If the symptoms worsen or persist for more than 2 weeks a doctor should be consulted.	2008; SI; TU

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

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

No information on combination products were submitted by the Member States.

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

The homeopathic preparations are not prepared of *Arnicae flos*, but of different parts of the plant, as the whole plant. Some homoeopathic, diluted preparations are available for oral use. They are completely different to the preparations of the HMPC-monograph.

Arnica extracts are also included in cosmetics (Blaschek et al., 2021; MedicinesComplete, 2024).

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

Not applicable.

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

Madaus (1938) summarized pharmaceutical and medicinal knowledge, historical references and traditional uses from different countries in a monograph: Traditional use of *Arnicae flos* has been reported since ancient times. A wound healing effect was already attributed to Arnica in a manual of Tabernaemontanus in 1613. During the medieval age, Arnica was used as a medical plant in numerous indications, such as topical for hematoma, injuries, varicose, phlebitis, gout, rheumatism, indigestion and internally for cardiovascular disease.

No references to the use of Arnica as a medicinal plant can be found in ancient Greek or Roman writings (Jennet-Siems, 2019). Schmidt (2023) summarizes that from the Middle Ages onwards, Arnica was shown and mentioned in various old herbal books and gained importance as a remedy up to the 18th and early 19th century. It was used in a variety of ways, including for phlebitis, injuries,

haematomas and rheumatic complaints, but also internally as an analeptic and abusively as an abortifacient (Jennet-Siems, 2019).

Arnicae flos is included in a lot of monographs related to efficacy and safety as: different editions of the „Hager" (Frerichs et al., 1949; List & Hörhammer, 1972; Hänsel et al., 1992; Blaschek et al., 2021), monograph of the Commission E (Blumenthal et al., 2000), ESCOP (ESCOP, 2003) and WHO (WHO, 2007).

Table 2: Overview of historical data

Herbal preparation	**Documented use / Traditional use**	**Strength, Posology, Duration of use**	**Reference**
flos tincture Arnica oil: (DER 1:5) extraction solvent: fatty oil	for external use only for injury and for consequences of accidents, e.g. bruises, sprains, contusions, fracture-oedema, rheumatic muscle and joint pain inflammation of the mouth and throat furuncolosis and inflammation as a result of insect bites, phlebitis	infusions: 2 g flos per 100 ml of water cataplasms tincture in 3-10 times dilution mouth rinses: tincture in 10 times dilution ointments: not more than 20-25% tincture; not more than 15% Arnica oil	Blumenthal et al. (2000) [quoting Commission E monograph (1984)]
tinctures fluid extracts flowers	only external use Treatment of bruises sprains and inflammation caused by insect bites; gingivitis and aphthous ulcers; symptomatic treatment of rheumatic complains.	ointments, creams, gels or compresses: 5-25% (V/V) tinctures or 5-25% fluid extracts diluted tincture (1:3 to 1:10) diluted fluid extracts or a decoction of 2.0 g of dried Arnica flower in 100 ml of water	ESCOP (2003) [quoting Wichtl (ed.) (1989), Hänsel et al. (1992)]
tincture (1:10); ethanol 60 to 70% (V/V) Ph.Eur. 10.0 tinctures (1:10) with ethanol 45% (V/V) according BPC 49, BHP 83 flowers "Arnika-Öl" (DER 1:5) with fatty oil fluid extract one part herbal drug and maximum 2 parts ethanol	for external use only for injury and for consequences of accidents, e.g. bruises, sprains, contusions, fracture-oedema, rheumatic muscle and joint pain inflammation of the mouth and throat furuncolosis and inflammation as a result of insect bites, phlebitis	ointments, creams, gels or compresses: not more than 20-25% (V/V) tinctures diluted tincture (1:3 to 1:10) decoction or infusions: 2.0 of dried Arnica flower in 100 ml of water ointments: not more than 15% Arnica oil mouth rinses: tincture in 10 times dilution	Hänsel et al. (1992) [quoting Kommission E (1984); ÖAB (1990); Standard marketing authorisation (1986)] Blaschek et al. (2021) [quoting Commission E (1984); ESCOP (2009); Standard marketing authorisation (1986); HMPC (2014)]

Herbal preparation	Documented use / Traditional use	Strength, Posology, Duration of use	Reference
flos tincture Arnica oil: (DER 1:5) extraction solvent: fatty oil	As a topical counterirritant for treatment of pain and inflammation resulting from minor injuries and accidents, including bruises, ecchymoses, haematomas and petechiae. Treatment of inflammation of the oral mucous membranes. Insect bites and superficial phlebitis	infusions: 2 g flos per 100 ml of water compresses: tincture (1:10, ethanol 70% (V/V)) in 3-10 times dilution mouth rinses: tincture in 10 times dilution ointments: not more than 20-25% tincture; not more than 15% Arnica oil	WHO (2007) [quoting Commission E monograph (1984); British Herbal Pharmacopoeia (1996)]
herbal substance tincture Arnica oil: (ratio drug:extraction solvent 1:4 or 1:5) extraction solvent: fatty oil	only external use according to Commission E	ointments: not more than 20-25% tincture or max. 15% Arnica oil compresses: diluted tincture (1:3 to 1:10) decoction of 2.0 of dried Arnica flower in 100 ml of water mouth rinses: tincture in 10 times dilution	Schilcher (2007)

A lot of literature includes reports of medicinal uses from experts. Rountree (2014) reported *A. montana* gel has been a popular herbal treatment for a wide range of arthritides over years. Arnica is toxic to use orally (other than homeopathic remedy) and the herb should not be used on broken skin. However, as a topical anti-inflammatory, it can be quite helpful for addressing acute joint and muscle pain, based on his clinical experience.

2.2. Overall conclusions on medicinal use

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Arnicae flos	Traditional herbal medicinal product for the relief of bruises sprains and localised muscular pain, for	Herbal infusion for external use (impregnated dressings) only: *Adults, adolescents and children above the age of 3 years:*	1996

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
	inflammations as a result of insect bites. Traditional herbal medicinal product for the treatment of small boils (furuncles).	Preparation of an infusion for impregnated dressings from 2 g /100 ml boiling water 10-15 min Apply several times daily on the affected area. <u>Herbal infusion for external use (impregnated dressings) only:</u> *Adults, adolescents:* Preparation of an infusion for impregnated dressings from 2 g /100 ml boiling water 10-15 min Apply several times daily on the affected area.	
tincture (ratio of herbal substance to extraction solvent 1:10); extraction solvent: ethanol 70% (V/V)	Traditional herbal medicinal product for the relief of bruises sprains and localised muscular pain. Traditional herbal medicinal product for inflammations as a result of insect bites. Traditional herbal medicinal product for treatment of small boils (furuncles).	<u>Semi-solid dosage form (5-25% tincture in base):</u> *Adults, adolescents and children above the age of 3 years:* Apply a thin layer on the affected area, 2 to 4 times daily <u>Liquid dosage form (only diluted tincture: 1:3-10 with water)</u> *Adults, adolescents and children above the age of 3 years:* Apply a few millilitres of dilution to the affected area directly or as impregnated dressing 2 to 4 times daily <u>Semi-solid dosage form (5% tincture in base):</u> *Adults, adolescents and children above the age of 3 years:* Apply a thin layer on the affected area, 2 to 4 times daily <u>Liquid dosage form (only diluted tincture: 1:3-10 with water)</u> *Adults, adolescents and children above the age of 3 years:* Apply a few millilitres of dilution to the affected area directly or as impregnated dressing 2 to 4 times daily <u>Liquid dosage form (only diluted tincture: 1:3-10 with water)</u> *Adults, adolescents:* Apply a few millilitres of dilution to the affected area directly or as impregnated dressing 2 to 4 times daily	1990

Herbal preparation Pharmaceutical form	**Indication**	**Posology, Strength**	**Period of medicinal use**
tincture (ratio of herbal substance to extraction solvent 1:10); extraction solvent: ethanol 60% (V/V)	Traditional herbal medicinal product for the relief of bruises sprains and localised muscular pain.	Dressing impregnated with tincture *adults, adolescents:* 1 impregnated dressing contains 2.5 ml solution	1982 (FR)
fluid extract (DER 1:1); extraction solvent: ethanol 60% (V/V)	Traditional herbal medicinal product for the relief of bruises sprains and localised muscular pain.	Semi-solid dosage form (4% fluid extract in base): *Adults, adolescents and children above the age of 3 years:* Apply a thin layer on the affected area, two to three times daily.	1959 (FR)
liquid extract of fresh flowers (DER 1:20); extraction solvent: ethanol 50% (m/m)	Traditional herbal medicinal product for the relief of bruises sprains and localised muscular pain.	Semi-solid dosage form (50% liquid extract in base): *Adults and adolescents:* Apply a thin layer on the affected area, two to four times daily.	2008 (ES)
liquid extract (DER 1:3.5-4.5); extraction solvent: refined sunflower oil	Traditional herbal medicinal product for the relief of bruises sprains and localised muscular pain, for inflammations as a result of insect bites and for treatment of small boils (furuncles).	Semi-solid dosage form (10% extract in base): *Adults and adolescents over 12 years of age:* Apply a thin layer on the affected area, 3 to 4 times daily.	1993 (DE)

The range of 20-25% tincture (extraction solvent: ethanol 70% (V/V)) in base was included in the first version of the monograph. This range was not derived from products on the market but was based on literature data, even though this literature does not show consistent use over more than 30 years. For reasons of regulatory consistency, this high range was retained into the monograph, in order to also reflect the regulatory decisions of recent years based on the monograph. Only the lower percentage of products (5-8% in the base) that have been on the market for more than 30 years was added.

Also, the liquid extract of fresh flowers (DER 1:20); extraction solvent: ethanol 50% (m/m) was included in the first version of the monograph, although no use for more than 30 years could be demonstrated for the EU. This preparation was also retained for the reasons of regulatory consistency described above.

Some preparations have also been on the market for over 30 years for children aged 30 months or older, or even without any age restrictions. Taking into account the indications, it was decided to allow the use of these preparations for children aged 3 years or older.

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

Anti-inflammatory/antiphlogistic effects

Preparations covered by the monograph

In-vitro

Klaas et al. (2002) compared two Arnica tinctures for their ability to inhibit the binding of the transcription factors NF-κB and NF-AT (responsible for the transcription of genes encoding various inflammatory mediators) and their influence on the release of the cytokines IL-1 and TNF-α. Arnica tinctures according German Pharmacopoeia (DAB) prepared from the flowers of the Spanish chemotype and from type "Arbo" cultivated in Germany were used. Results show, that 5 µg/ml of the Arbo tincture and 10 µg/ml of the Spanish tincture completely inhibited NF-kB-DNA binding. The IC_{50} for Arbo tincture was 0.12 µl/ml and 0.38 µl/ml for the Spanish chemotype tincture for inhibition of IL-1ß.

Lass et al. (2008) examined anti-inflammatory effects of Arnica tinctures and possible immune-regulatory mechanisms. Tinctures from two chemotypes of *A. montana* were applied: the Spanish SP chemotype and the central European CL chemotype (tinctures prepared by percolation according to the European Pharmacopoeia, 1997). The tinctures suppressed NF-κB activation and IL-12 production in dendritic cells at high concentrations, but had immunostimulatory effects at low concentrations.

In-vivo

Lass et al. (2008) investigated anti-inflammatory effects of Arnica tinctures and possible immune-regulatory mechanisms with respect to contact hypersensitivity to *A. montana* in the mouse contact hypersensitivity model. Tinctures from two chemotypes of *A. montana* were applied: the Spanish SP chemotype and the central European CL chemotype (tinctures prepared by percolation according to the European Pharmacopoeia, 1997). Arnica tinctures failed to induce contact hypersensitivity in mice. Contact hypersensitivity could not be induced in the mouse model, even when Arnica tinctures were applied undiluted to inflammated skin. However, contact hypersensitivity to Arnica tincture could be induced in acutely CD4-depleted MHC II knockout mice. The authors concluded that induction of contact hypersensitivity by Arnica is prevented by its anti-inflammatory effect and immunosuppression as a result of immune regulation in immunocompetent mice.

Lass et al. (2010) investigated the inflammatory potential of different weak contact allergens and of the strong sensitizer 2,4,6-trinitrochlorobenzene (TNCB) using the contact hypersensitivity model, the mouse model for allergic contact dermatitis. Tinctures from two chemotypes of *A. montana* were applied: the Spanish SP chemotype and the central European CL chemotype (tinctures prepared by percolation according to the European Pharmacopoeia, 1997). Weak contact sensitizers as Arnica tinctures (20 µl on both ears) caused a weak enhancement of pro-inflammatory cytokines like IL-1b, IL-6 or IFN-c, whereas the contact sensitizer TNCB strongly enhances the expression of these cytokines. Enhanced expression of the anti-inflammatory cytokine IL-10 was caused by Arnica tinctures. The authors discussed that these findings support the results of the publication from 2008.

Preparations not covered by the monograph

In-vitro

Roehrl et al. (2023) analysed the content in sesquiterpene lactones (the sum of the detected helenalin and dihydrohelenalin derivatives) in an extract of Arnicae flos (DER 1:1.1; extraction solvent: ethanol 30% (m/m)). The extract showed inhibition of NF-κB and arachidonate 5-lipoxygenase (ALOX5). As positive control, cyclosporine A inhibited NF-κB activation with an IC_{50} of 6.79 nM. The inhibitory effect of *A. montana* extracts was not due to cytotoxicity. Also 5-lipoxygenase (5-LO) and cyclooxygenase-2 (COX-2) enzymatic activity was inhibited in a concentration-dependent manner (IC_{50}=47.8 µg/ml for 5-LO and 33.1 µg/mL for COX-2). Treatment of human primary polymorphonuclear leukocytes (PMNL) resulted in an inhibition of 5-LO product release (IC_{50}=>300 µg/ml).

In-vivo

Sharma et al. (2016) examined the effects of oral administration of a methanolic extract (ratio drug:extraction solvent 1:10) from *A. montana* in type II collagen-induced arthritis (CIA) in rats. Dexamethasone (1 mg/kg bw) was used as positive control. No toxicity was seen in treated rats. Treatment with the extract and dexamethasone reduced clinical signs and improved the histological and radiological status of the hind limb joints in rats. Arnica treated rats (75 mg/kg bw) had lower expression levels of nitric oxide, tumour necrosis factor-α, interleukins (IL-1β, IL-6 and IL-12) and titre of anti-type II collagen antibody compared with untreated CIA rats.

Da Silva Prade et al. (2020) investigated the therapeutic effect of topical application of *A. montana* after UVB-induced cutaneous injuries in mice. The animals were treated with 30 µg topical application of *A. montana* ointment (250 mg tincture (no further information) /g ointment) in the ear. At the time of 16 hours after treatment, reduction of ear oedema, inhibition of myeloperoxidase activation, decrease of nuclear factor kappa B levels and reduction of pro inflammatory cytokines levels, such as interleukin-1beta, interleukin-6, tumour necrosis factor-alpha and interferon gamma were shown.

Roehrl et al. (2023) investigated the anti-inflammatory properties of an Arnicae flos extract (DER 1:1.1; extraction solvent: ethanol 30% (m/m)) upon three consecutive topical applications (1 mg, 3 mg, or 10 mg per mouse, each) to the right hind paw of ICR mice, prior to the intraplantar injection of carrageenan. Aspirin administered orally (150 mg/kg) served as a positive control (reference inhibitor). Foot swelling was measured 4 h after the carrageenan injection. Maximum inhibition of paw oedema was observed with three applications of 10 mg *A. montana* extract, 62% and 47% reduction in foot swelling relative to the vehicle for Arnicae flos and Aspirin. The reduction of the paw oedema was statistically significant (vs. vehicle) for higher doses of *A. montana* extract.

Isolated compounds

Lass et al. (2008) investigated anti-inflammatory effects sesquiterpene lactones from *A. montana.* They did not induce contact hypersensitivity (abdomen and ear). Contact hypersensitivity could not be induced in the mouse model, even when sesquiterpene lactones were applied undiluted to inflammated skin.

Lass et al. (2010) investigated anti-inflammatory effects of sesquiterpene lactones (SL) from *A. montana* and possible immune-regulatory mechanisms with respect to contact hypersensitivity in the mouse contact hypersensitivity model. SL did not induce contact hypersensitivity (abdomen and ear);

Klaas et al. (2002) performed with the isolated compounds (1.0 µmol/cm^2) dihydrohelenalinacetate and dihydrohelenalinmethacrylat the croton oil-induced mouse ear oedema test. The substances showed a reduction of 54 /77% of the oedema, indomethacin 44% reduction.

Berges et al. (2009) reported, helenalin (in concentrations from 0.5 -2 µM) suppresses essential immune functions of activated $CD4^+$ T-cells (2.25x10^6 cells/ml) by multiple mechanisms. It was shown

that helenalin induced apoptosis in activated CD4+ T-cells by triggering the mitochondrial pathway of apoptosis. The authors concluded helenalin might be a new immunosuppressive compound suited for the treatment of deregulated and unwanted T-cell-mediated immune responses.

Lyss et al. (1997) examined the treatment of three different cell types, T-cells, B-cells and epithelial cells, with micromolar concentrations of helenalin (1-20 µM). The treatment resulted in inhibition of the activation of NF-κB, which controls the transcription of various cytokines and adhesion molecules. The authors concluded that by inhibiting NF-κB-activation, helenalin, and to a much lesser degree, 11,13-dihydrohelenalin (at a concentration of 200 µM) might decrease the production of many inflammatory cytokines and will prevent the recruitment of immune cells, T-cells, B-cells and macrophages and neutrophils, thereby reducing inflammation.

Hall et al. (1979) reported that helenalin and 1,3-dihydrohelenalin significantly suppresses various parameters of inflammation in enzyme assays performed on mouse and rat liver homogenates and human poymorphonuclear neutrophils. At $5x10^{-5}$ M they inhibited the chemotactic migration of human neutrophils by 100% and 20%, respectively. Helenalin (5 mg or 2.5 mg/kg bw i.p.) reduced in the carageenan-rat paw oedema and in the adjuvants-arthritis-test reduction of oedema by 72 and 77%, respectively. In mice, 20 mg helenalin/kg bw (i.p.) provoke a 93% reduction of flections.

Table 4: Overview of the main non-clinical data/conclusions

Herbal preparation tested	**Posology**	**Experimental model**	**Reference**	**Main non-clinical conclusions**
Arnica flos tincture (Ph.Eur., 1997) from Spanish and central European chemotype	20 µl of undiluted tincture on 3 consecutive days	in-vivo; topical application mouse contact hyper-sensitivity model	Lass et al. (2008)	contact hypersensitivity to Arnica tincture could be induced in acutely CD4-depleted MHC II knockout mice, but not in healthy mice
Arnica flos tincture (Ph.Eur., 1997) from Spanish and central European chemotype	20 µl on both ears	in-vivo, topical application mouse contact hyper-sensitivity model	Lass et al. (2010)	- weak ↑ of pro-inflammatory cytokines (IL-1β, IL-6, IFN-γ) - enhanced ↑ expression of anti-inflammatory cytokine IL-10
methanolic extract (ratio drug: extraction solvent 1:10)	75 mg/kg bw positive control: dexamethasone (1 mg/kg bw)	in-vivo, oral application type II collagen-induced arthritis in rats	Sharma et al. (2016)	- no oral toxicity seen - ↓ of clinical signs + improvement of histological and radiological status of the hind limb joints in rats - ↓ expression levels of NO, TNF-α, IL-1β, IL-6; IL-12) and titre of anti-type II collagen antibody
tincture (no further information)	30 µg ointment (250 mg tincture/1 g)	in-vivo, topical application UVB-induced cutaneous	da Silva Prade et al. (2020)	16 hours after treatment: - ↓ of ear oedema - ↓ of myeloperoxidase activation

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
		injuries in mice (mice ear oedema)		- ↓ of NF-κB levels - ↓ of pro-inflammatory cytokines levels (IL-1β, IL-6, TNF-α, INF-γ)
extract (DER 1:1.1; extraction solvent: ethanol 30% (m/m)	1 mg, 3 mg, or 10 mg per mouse as 3 consecutive applications positive control: 150 mg/kg bw aspirin (p.o.)	in-vivo; topical application hind paw oedema of ICR mice, prior to intraplantar injection of carrageenan.	Roehrl et al. (2023)	Foot swelling measured 4 h after the carrageenan injection: - 62% inhibition with 3 applications of extract - 47% with aspirin

3.1.2. Secondary pharmacodynamics

Anti-leishmaniasis effect

Robledo et al. (2018) investigated the effect of Arnica tincture Ph.Eur. (ethanol 70%) on the lesions caused by infection with *Leishmania braziliensis* in a model with golden hamsters. Male and female golden hamsters, six or seven week-old, were infected with 5×10^7 stationary growth phase promastigotes of *L. braziliensis* in the dorsum. When exhibiting a skin ulcer greater than 25 mm^2, they were randomly distributed into three experimental groups (n=5 animals per group). Hamsters were treated topically with 100 µl per lesion per day of Arnica tincture during 28 days. Meglumine antimonate was administered by intralesional injection at 200 µg (100 µl) twice per week for four weeks. One group of hamsters remained untreated. After the end of treatment, animals were kept under observation for a period of 90 days. The area of the ulcer was measured every two weeks using an electronic caliper. The evaluation time points were: pretreatment day (TD0), end of treatment (TD28) and post treatment days (PTD) 30, 60 and 90, respectively. As a result, Arnica tincture fully cured three out of five hamsters while one animal showed an improvement and another one suffered from a relapse. The result was slightly better than that obtained with the positive control, meglumine antimonate. Similar results could be shown in Robledo et al. (2022) in hamsters infected with cutaneous leishmaniasis caused by *L. braziliensis* or *L. tropica*.

Uterine stimulant effects

According to Blaschek et al. (2021) effects on the uterus were shown in older preclinical studies Uterine stimulant effects were shown in cats from i.v. administration of 0.3 ml extrakt of fresh Arnica flowers (extract no specified; quoting Kreitmeier, 1936).

3.1.3. Safety pharmacology

No information available.

3.1.4. Pharmacodynamic interactions

No information available.

3.1.5. Conclusions

Antiphogistic effects were shown for local application of Arnica flowers ethanolic tincture and for substances thereoff.
While some literature reported anti-inflammatory effects, also contradictory effects were described. Older preclinical safety studies reported uterine stimulant effects.

No data on further safety pharmacology and pharmacodynamic interactions are available.

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

Specific data on resorption and distribution, metabolism and elimination are not available.

Wagner et al. (2004b) investigated skin penetration of topically used Arnica preparations and of isolated sesquiterpene lactones using a stripping method with adhesive tape and pig ear skins to measure penetration into stratum corneum. Different Arnica preparations, two tinctures (tincture 1 Spanish chemotype, tincture 2 ARBO type) and one gel were tested. For all preparations tested penetration of helenalin isobutyrate and dihydrohelenalin acetate into the stratum corneum was demonstrated. Interestingly, penetration of sesquiterpene lactones from extracts was about 10-fold higher than that of isolated compounds. Dihydrohelenalin acetate showed better penetration characteristics than the helenalin derivatives. The penetration rate of sesquiterpene lactones from Arnica gel preparations decreased after 4 hours, while from ointment preparations penetration was taking place continuously. The authors concluded that the mode of Arnica formulations has an influence on the penetration behaviour.

Wagner and Merfort (2007) investigated the penetration behaviour of one gel preparation and two ointment preparations. The sesquiterpene lactones (SLs) of all preparations show a comparable penetration in and a permeation through the stratum corneum, the uppermost part of the skin. Interestingly, the gel preparation showed a decrease of the penetration rate over 4h, whereas the penetration rate of ointments kept constant over time. Moreover, it was demonstrated that the totally penetrated amount of SLs only depends on the kind of the formulation and of the SLs-content in the formulation but not on the SLs composition or on the used extraction agent.

Bergonzi et al. (2005) evaluated of skin permeability of sesquiterpenes from a supercritical carbon dioxide Arnica extract by HPLC/DAD/MS. The skin permeation study was performed using modified Franz diffusion cells and the human stratum corneum and epidermis as membrane, sampled from human abdomen skin, obtained by surgical operation. The results of the study demonstrated penetration of sesquiterpene lactones, by using dimethylsulfoxide and oleic acid, lauroglycol, isopropyl myristate and Tween 80. The better results could be shown for oleic acid in all investigated times (after 4, 7 and 24 hours).

Wagner et al. (2004a) investigated the effect of sesquiterpene lactones and sesquiterpene lactone-containing plant preparations on human blood, plasma and human serum albumin solutions. 11,13-dihydrohelenalin acetate and 13-dihydrohelenalin methacrylate were isolated from *A. montana* (Spanish chemotype), helenalin isobutyrate was provided from a pharmaceutical manufacturer. Arnica tincture 1 contained predominantly 11,13-dihydrohelenalin esters (0.40 mg/ml), tincture 2 and 3 consisting of helenalin and 11,13-dihydrohelenalin esters with a total amount of 0.82 mg/ml (tincture 2) and 0.72 mg/ml (tincture 3). 0.7 ml of blood or human serum albumin-solution was incubated with 50 µl of the sesquiterpene solution or tincture (adjusted to 7.5 mM, 3 mM or 1.5 mM total amount of sesquiterpene lactones). The concentrations of the sesquiterpene lactones were 500, 200 and 100 µM,

respectively. The extent of protein binding in human plasma was varying, 30-50% of the sesquiterpene lactones were bound to plasma. Sesquiterpene lactones in the ethanolic preparations showed a lower degree of protein binding.

Juergens et al. (2022) performed in-vitro metabolism experiments with liver microsomes of different species (rat, pig and human) with the helenalin acetate and 11α,13 dihydrohelenalin acetate. Phase I and phase II metabolism experiments were performed, as well as a combination of both. Glutathione conjugation plays a major role in the metabolism, as could be expected based on previous reports on their reactivity. Besides glutathione conjugates, several other metabolites were formed, e.g., water conjugates and hydroxides. Hydroxylation is likely catalysed by CYP450 which are involved in phase I metabolism of approximately 75% of pharmaceuticals. The authors concluded the fast and extensive formation of glutathione conjugates makes it unlikely that low absorbed levels of these compounds, as expected after dermal absorption from Arnica tincture, could be of toxicological concern.

Chapman et al. (1991) reported helenalin decreased male BDF1 mouse hepatic microsomal cytochrome P450 contents in vivo and in vitro. A single i.p. dose of 25 mg helenalin/kg body weight significantly ($P<0.05$) decreased microsomal cytochrome P450 contents and inhibited cytochrome P450-dependent mixed-function oxidase activities within 1-2 hr post-exposure. Helenalin (1.0 mM) decreased microsomal cytochrome P450 contents in vitro by 11% in the absence of NADPH and by 32% in the presence of NADPH. These in vitro and in vivo decreases in cytochrome P450 were accompanied by comparable decreases in total microsomal heme contents. The increased loss of microsomal cytochrome P450 produced by helenalin in the presence of NADPH suggests that a helenalin metabolite may be responsible for heme loss and the in vitro destruction of cytochrome P450.

Jodynis-Liebert et al. (2000) reported that helenalin inhibited rat and mouse cytochrome P450 monooxygenases (CYP450) activity. The majority of the compounds increased the hepatic activity of glutathione peroxidase, glutathione reductase, and catalase, but superoxide dismutase activity was distinctly lowered by five lactones. A few of the compounds tested caused a decrease in the hepatic cytochrome P450 content and reduced the activity of NADPH-cytochrome P450 reductase, aminopyrine demethylase, aniline hydroxylase and glutathione-S-transferase. Results for the kidney showed fewer changes in activities of both classes of enzymes when compared to the liver. Not all lactones affected the enzymes under test, the most active were: linifolin, helenalin, mexicanin 1 and telekin.

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

3.3.1. Single dose toxicity

Extracts

The oral LD_{50} of an extract (not further specified) was >5 g/kg in rats and 123 mg/kg in mice. The LD_{50} using intraperitoneal administration was 31 mg/kg for mice (CIR Expert Panel, 2001).

Helenalin

Chapman et al. (1988) examined the acute toxicity of the sesquiterpene lactone helenalin in male BDF1 mice. The 14-day LD_{50} for a single i.p. dose of helenalin in male mice was 43 mg/kg. A single i.p. injection of 25 mg helenalin/kg increased serum alanine aminotransferase (ALT), lactate dehydrogenase (LDH), urea nitrogen (BUN) and sorbitol dehydrogenase within 6 hours of treatment. Injection of 25 mg helenalin/kg/day i.p. for 3 days increased differential polymorphonuclear leukocyte counts and decreased lymphocyte counts, serum ALT, BUN and cholesterol levels were significantly

increased. Moreover, helenalin significantly reduced liver, thymus and spleen relative weights, and histological evaluation revealed substantial effects of multiple helenalin exposures on lymphocytes of the thymus, spleen and mesenteric lymph nodes. Helenalin-induced histological changes were not observed in the liver or kidney. Multiple helenalin exposures (25 mg/kg/day) also significantly inhibited hepatic microsomal enzyme activities (aminopyrine demethylase and aniline hydroxylase) and decreased microsomal cytochrome P450 and b5 contents.

Witzel et al. (1976) determined LD_{50} values of helenalin as 150 mg/kg body weight in mice, 125 mg/kg in rats, 90 mg/kg in rabbits and 85 mg/kg in hamsters, and estimated as 100-125 mg/kg in sheep.

3.3.2. Repeat dose toxicity

No data available.

3.3.3. Genotoxicity

Arnica extract

The mutagenic potential of an extract of Arnica (100 µl of extract correspond to 100 mg dried Arnica plant material, extract not further specified) was determined in the Ames test using *S. typhimurium* TA98 and TA100 (with and without metabolic activation). The Arnica extract (10-400 ml) produced a two to 4-fold increase in the number of revertants (except TA100 without metabolic activation). The authors ascertained that the mutagenic effects could be ascribed to flavonols present in Arnica (Göggelmann and Schimmer, 1986).

Helenalin

MacGregor (1977) examined the effects of three sesquiterpene lactones including helenalin in the Ames test using the *S. typhimurium* strains TA10, TA98, TA1535 and TA1537 without and with metabolic S9 activation. Helenalin showed no mutagenic effect up to concentrations of 1000 µg/plate. In the Salmonella/microsome assay, helenalin was not mutagenic in *S. typhimurium* strains TA102, TA98 or TA100 at concentrations of up to 30 µg/ml.

3.3.4. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

Lass et al. (2008) reported, Sesquiterpene lactones (0.7 mg/ml calculated as 11,13 dihydrohelenalinmethacrylate) and (0.83 mg/ml calculated as helenalinisobutyrate) from *A. montana* did not induce contact hypersensitivity (abdomen and ear); Arnica tinctures fail to induce contact hypersensitivity in mice. Contact hypersensitivity could not be induced in the mouse model, even when Arnica tinctures or sesquiterpene lactones were applied undiluted to inflammated skin.The tincture decreased TNCB-induced contact eczema and showed no induction of contact hypersensitivity in local application in mice.

Several tests examined the sensitisation potential of different Arnica extracts/preparations (not further specified) in guinea pigs. In some tests no sensitisation potential was observed while in two

publications (raw extract, tincture, ether extract – all not further specified) sensitise potential was reported (CIR Expert Panel, 2001).

3.3.7. Other studies

Ocular irritation:
Several dermal irritation tests were performed using different Arnica extracts/preparations (not further specified) in rabbits. Different results ranging from non to minimally irritating were found (CIR Expert Panel, 2001).

Phototoxicity:
Several phototoxicity tests were performed using different Arnica extracts/preparations (not further specified), different animal species and different test models. No phototoxic effects were observed (CIR Expert Panel, 2001).

3.3.8. Conclusions

Specific data on toxicity including genotoxicity, carcinogenicity and reproductive toxicity are not available.

Toxicological data regarding the herbal substances/herbal preparations of the monograph are not available. Tested, unspecified Arnica preparations were not phototoxic to mouse or guinea pig skin, while tests examined the sensitisation potential of these preparations in guinea pigs showed contradictory results.

Arnica preparations can induce toxicity when used internally. They should not be use internally (no tea for internal comsumption), as pharmacokinetic studies are missing and no information is available to dose/efficacy relations.

3.4. Overall conclusions on non-clinical data

Results from relevant non-clinical experimental studies to support the proposed indications are very limited. The reported pharmacological anti-inflammatory and antiphlogistic effects are not considered contradictory to the traditional uses.

Specific data on pharmacokinetics and interactions are not available. It seems that the mode of Arnica formulations has an influence on the skin penetration behaviour of the sesquiterpenes.

Non-clinical information on the safety of Arnicae flos is scarce. Adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed. As there is no adequate information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

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

Not available.

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

Not available.

4.2. Clinical efficacy

4.2.1. Dose response studies

Not available.

4.2.2. Clinical studies (case studies and clinical trials)

There are numerous clinical studies performed with preparations from Arnicae flowers. In accordance with the Guideline 'Assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products' (EMA/HMPC/104613/2005 – Rev. 1), the assessment of well-establish use should also include if the products reported in the market overview can be considered as similar to the product studied in relevant clinical studies found in the literature (see chapter 2.1.1. 'Information about products on the market in the EU/EEA Member States'). Therefore, the scope of the assessment in this section are the indications connected to the relief of bruises, sprains and localised muscular pain and to inflammations as a result of insect bites. Only studies related to these indications are included below. Beside these investigations, preparations from Arnicae flowers have been tested for clinical efficacy for instance in chronic venous insufficiency and primary varicosis, arthrosis/periarthropathy of the knee, osteoarthritis, facial telangiectasia or umbilical cord medication. There is no information available that preparations from Arnicae flowers have been in medicinal use for more than 10 years in EU in these indications (see chapter 2.1.1. 'Information about products on the market in the EU/EEA Member States'). Thus, these studies will not be considered for a well-establish use monograph.
Also studies concerning oral use of homeopathic preparations and/or studies not performed in Europe were not included.

Acute ankle joint distortion

Preparations of the monograph
In the double-blind study of Kučera et al. (2011), 570 patients with acute ankle joint distortion were randomized to four treatment groups: a combination spray of Arnica tincture and hydroxyethyl salicylate (group A, n=228); Arnica tincture (1:10, no further information) (group B, n=57); HES (group C, n=228) and placebo (group D, n=57).
The medication was applied 4-5 times daily for 10 days. Efficacy was assessed on day 3-4 by evaluating pain on motion on a visual analogue scale (VAS). Pain improvement in group A was significantly superior over groups B–D (t-test with unadjusted baseline values, $P<4\times10^{-7}$ and ANCOVA after adjustment, $P<5\times10^{-11}$) and approximately corresponded to the cumulative effect of the single constituents (12.1, 7.5, and 18.7 mm VAS for A versus B, A versus C, and A versus D; 95% CI 8.0–16.2, 4.7–10.4, and 14.8–22.5 mm). The subgroup analyses for the primary efficacy parameter generally confirmed the sequence of effects A>C>B>D. For the secondary parameter ankle swelling, the superiority of the combination versus group B was nominally significant (P=.047; 2-tailed t-test), but not versus the other groups (A versus C: P=.074; A versus D: P=.5). At the end of the study, global assessment of efficacy by the physician was judged with 85% good to very good assessments in group A, 46% in group B, 58% in group C, and 23% in group D.

Local intolerability reactions (burning, reddening, itching, urticaria) were observed in 4/228 patients of group A (1.75%), in 2/228 patients of group C (0.88%), and in 3/57 patients of the control group D (5.26%). No such reactions were observed in group B (n=57).

Assessor´s comment:
The results show that the group B was more effective as the placebo group D (with unknown difference to placebo). Global assessment of efficacy by the physician was judged with good to very good assessments of 46% in group B and 23% in the placebo group.

Postoperative oedema and ecchymosis

Simsek et al. (2016) investigated the effects of local Arnica gel (no further information) and mucopolysaccharide polysulfate treatment on the regression of postoperative edema and ecchymosis in patients who have undergone open technique rhinoplasty.
One hundred eight patients were included in the study. Participants were randomized into three groups, all of whom had undergone rhinoplasty. Group 1 (n=36) received postoperative Arnica cream treatment, and group 2 (n=36) received postoperative mucopolysaccharide polysulfate cream treatment. Group 3 (n=36, control group) consisted of patients who received no postoperative local treatments. Patients were evaluated for 24 hours on days 2, 5, 7, and 10 after the operation. For the evaluation of postoperative oedema and ecchymosis, a scale ranging from 0 to 4 was used, and the groups were compared.
In groups 1 and 2, postoperative ecchymosis was significantly less than in the control group during postoperative days 1, 5, and 7 ($p<0.005$). The regression of the oedema was also more rapid in groups 1 and 2 than in the control group during evaluations on postoperative days 1, 5, and 7 ($p<0.005$). Neither oedema nor ecchymosis was significantly different between groups 1 and 2 ($p>0.005$).
The authors suggest that a rapid regression of oedema and ecchymosis may be achieved by local treatments of Arnica and mucopolysaccharide polysulfate cream.

Assessor´s comment.
The preparation used was not described.

Table 5: Clinical studies with Arnica preparations in indications similar to the indications of products on the European market

Study	Type	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Kučera et al., 2011	Double-blind study, placebo controlled	group A (n=228): combination spray of Arnica tincture and hydroxyethyl salicylate group B (n=57): Arnica tincture (DER 1:10) group C (n=228): HES group D (n=57): placebo	570 patients	acute ankle joint distortion	pain improvement assessed on day 3-4 by evaluating pain on motion on a visual analogue scale (VAS) group A significantly superior over other groups B–D	t-test with unadjusted baseline values, ANCOVA after adjustment	group B (Arnica tincture) to small to assess efficacy
Simsek et al., 2016	randomized, controlled, prospective clinical trial	group 1 (n=36): Arnica cream (no further information) group 2 (n=36): mucopolysaccharide polysulfate cream group 3 (n=36): no postoperative local treatment evaluation for 24 hours on days 2, 5, 7, and 10 after the operation	108 patients	postoperative edema and ecchymosis in patients who have undergone open technique rhinoplasty	scale ranging from 0 to 4 groups 1 and 2: postoperative ecchymosis significantly less than in the control group regression of the oedema more rapid in groups 1 and 2 than in control group neither oedema nor ecchymosis significantly different between groups 1 and 2	Kolmogorov-Smirnov test for normality of distribution Kruskal-Wallis analysis of variance to compare the non-normally distributed variables in groups 1 through 3 Mann-Whitney U test with Bonferroni adjustment to compare the non-normally distributed variables	no clinical relevance since no further information about preparation and method-logical shortcomings such as non validated scale

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

No data are available for use in children. No special studies have been performed for elderly.

4.4. Overall conclusions on clinical pharmacology and efficacy

Clinical pharmacological studies are not available.

Adequate controlled clinical studies, which might support a well-established use, have not been performed with Arnicae flos preparations.

5. Clinical Safety/Pharmacovigilance

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

Allergenic potential

A lot of clinical experimental studies investigated the allergenic potential in Arnica. In the 70ies and 80ies of the 20th century, the prevailing opinion was that Arnica with its sesquiterpene lactones is a plant with a high risk to contact sensitisation.

Hausen (1979) reported about 25 patients with known or suspected to be allergic to Compositae plants tested epicutaneously, only 2 patients were allergic to Arnica, after they sensitised themselves by treatment with Arnica tincture. In 1980, Hausen reported, that from the literature more than 100 cases of contact dermatitis could be cited, the first case was reported in 1844 (Hausen, 1980).

Eberhartinger (1984) reported on the results of skin testing in a hospital in Linz, only stationary patients with hand and lower leg eczema were taken into account. From 1969 to 1975 in 206 patients with hand eczema, 82 positive results of contact dermatitis occurred. Nine cases were Arnica-induced contact dermatitis. In the period from 1976 to 1983 in 136 patients with hand eczema, 61 positive cases, 11 of them were triggered by Arnica. In the lower leg eczema significantly more positive results of Arnica have been found, from 1969 to 1975, from a total of 205 patients, 81 positive and 16 Arnica cases. In the period from 1976 to 1983 from a total of 170 patients, 98 patients had positive results and 38 cases referred to Arnica.

Paulsen (2002) and Paulsen et al. (2008) assessed the significance of direct plant allergen contact via Compositae-derived cosmetics and herbal remedies in Asteraceae – allergic patients with special reference to Arnica. Five to 6 persons sensitive to Arnica were tested positive on Arnica based products. It was concluded that patients allergic to Asteraceae should be warned against topical use of Asteraceae containing products.

Jocher et al. (2009) included eight patients with a previous history of Arnica allergy in a study, tested positive with a commercial Arnica flower extract containing 0.5% within the previous 2 years. The standard Arnica patch test was compared to six different Arnica preparations and the vehicle as negative controls. Positive test results were detected in five of eight patients. Two patients showed no reaction, and three patients showed positive patch tests to 1, 2, or 3 of the 6 preparations. One patient reacted positive to every Arnica preparations.

Willuhn (1983) stated, that helenalin and his esters are the substances responsible for the immunological reactions as allergic contact dermatitis as this is known for sesquiterpene lactones having a exocyclic methylene group in the lactone ring and Reider et al. (2001) reported that

sesquiterpene lactones of *A. montana* possess a strong sensitising potency, with divergent results in recent studies. He tested a total of 443 patients. Only 5 of them showed positive reaction to Arnica.

Clinical safety data from clinical trials

In the placebo-controlled, randomised double-blind study Brock (1991) with 159 patients (divided in tree groups) and 60 patients (divided in two groups) with treatment over 3 weeks with either an ointment containing oil from *A. montana* flowers or a combination preparation, only 2 patients in the combination group reported allergic reactions. No adverse events were reported in patients treated with the Arnica mono-preparation.

In the clinical study Brock (2001) two of 50 patients dropped out because of allergic symptoms.

In the non-controlled study Knuesel et al. (2002) in 79 patients with mild to moderate osteoarthritis of the knee, treated with an Arnica gel for six weeks, six patients experienced dermatological adverse events which were possibly related to the study medication. All were mild or moderate local reactions: allergy with red spots and itching (1x), localized rash (1x), pruritus (1x), petechiae (1x), dry skin (2x). The relation of systemic adverse events occurring in 14 patients to the study preparation was unlikely.

In the reference-controlled, randomised, double blind study Widrig et al. (2007) in 204 patients with osteoarthritis of interphalangeal joints, topical treatment with an Arnica gel or ibuprofen gel (5%) for 3 weeks was well tolerated. Adverse events were reported by six patients (6.1%) of the ibuprofen group and by five patients (4.8%) of the Arnica group.

In the clinical study Kučera et al. (2011) in 570 patients, with four treatment groups, no adverse events occurred in the Arnica group.

Table 6: Clinical safety data from clinical trials

Study	Type	Test Product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
Brock (1991)	double blind, randomised study a) placebo-controlled	1. combination ointment: 100 g contain: 10 g extract from Arnica flowers with sunflower oil (1+5); 4000 IU heparin; 5 mg Ol. Chamomillae; 5 mg guajazulen) 2. monopreparation-ointment: 100 g contain: 10 g extract from Arnica flowers with sunflower oil (1+5) 3. placebo: ointment base duration: 3 weeks	study a) 159 patients (divided into 3 groups) study b) 60 Patients (divided into 2 groups)	study a) chronic venous insufficincy study b) primary varicosis without signs of chronic venous insufficiency	no adverse reactions in the Arnica group	-
Brock (2001)	double blinded; placebo controlled	group 1: gel containing 25% Arnica tincture group 2: placebo duration: 3 weeks	100 patients, 50 per group woman: 77 men: 23 average age: 59.2 years	chronic venous insufficiency	allergic symptoms as adverse reactions in 2 patients	allergic skin reactions such as itching, redness of the skin and eczema are known for Arnica preparations
Knuesel et al. (2002)	open, multicenter trial	50 g of an Arnica fresh plant tincture (DER 1:20), extracting solvent ethanol 50% (m/m) thin layer in the morning and evening duration: 6 weeks	women: 53 men: 26	osteoarthritis of the knee	adverse drug reaction in 6 out of 79 patients such as red spots, itching allergy, local rush, pruritus, petechien and dry skin	allergic skin reactions such as itching, redness of the skin and eczema are known for Arnica preparations

Study	Type	Test Product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
Widrig et al. (2007)	double blinded	group 1: ibuprofen 5% gel group 2: gel containing 50% tincture of fresh Arnica flos, (DER 1:20) duration: 3 weeks	group 1: 99 patients group 2: 105 patients	osteoarthritis pain or stiffness in the hand or finger; hard tissue enlarge-ment; DIP and PIP joints	adverse events group 1: 6 patients (6.1%) group 2: 5 patients (4.8%); most allergic skin reactions	allergic skin reactions such as itching, redness of the skin and eczema are known for Arnica preparations
Kučera et al. (2011)	double-blind study, placebo controlled	group A (n=228): combination spray of Arnica tincture and hydroxyethyl salicylate group B (n=57): Arnica tincture (DER1:10) group C (n=228): HES group D (n=57): placebo	570 patients	acute ankle joint distortion	local intolerability reactions (burning, reddening, itching, urticaria) observed in group A: 4/228 patients (1.75%) group C: 2/228 patients (0.88%) group D: 3/57 patients (5.26%), no reactions in group B	-

5.2. Patient exposure

There are data from 1280 patients, tested for safety, due to marketing authorisation, with a good result on safety, only skin sensations was shown. The reported skin sensations were allergic such as itching, redness and eczema, in very rare cases contact dermatitis may occur. The adverse effects may occur with a frequency of 1:100. The most often adverse events were allergic reactions. Serious adverse reactions did not occur.

Apart from its medicinal use, patients are exposed to *A. montana* preparations in cosmetics and in homeopathy.

5.3. Adverse events, serious adverse events and deaths

Information from the labelling of traditional used preparations:
From the licenced preparations side effects as hypersensitive reactions as redness of the skin are known.

Information from monographs and literature
Oral use is considered potentially unsafe from toxicological viewpoint. Oral administration of Arnica is often accompanied by severe side effects, such as gastrointestinal and nervous system disturbances up to fatal gastroenteritis, both tachycardia and bradycardia, and collapse, muscle paralysis (voluntary and cardiac) and may even lead to death (Commission E monograph, 1984; Barnes et al., 2007; MedicinesComplete, 2023). Serious, but not fatal symptoms have been reported following ingestion of 30 ml of a 20% Arnica tincture (no information on DER) (MedicinesComplete, 2023).
Helenalin is stated to be the toxic principle responsible for these effects (MedicinesComplete, 2023).

The topical application of Arnica has been documented to cause dermatitis. Arnica is a strong sensitiser, with the sesquiterpene lactone constituents implicated as the contact allergens (Willuhn, 1983; MedicinesComplete, 2023). It should only be applied to unbroken skin and withdrawn at the first sign of reaction (Blumenthal et al., 2000).
Prolonged treatment can give rise to eczema or dermatitis with formations of blisters (Blumenthal et al., 2000; Blaschek et al., 2021).
Tinctures should be diluted before use. Undiluted tinctures or preparations containing higher concentrations of the drug can cause primary toxic skin reactions with formation of vesicles or even necroses may occur (Willuhn, 1983; Schilcher, 2007; MedicinesComplete, 2023).

Case reports
Hausen (1985): Allergic contact dermatitis of the face and hands occur after handling with Gaillardia and additional treatment with a body lotion containing extracts of Arnica worsened the skin lesions.

Pirker et al. (1992): A man, hobby gardener for about 30 years, appeared with a facial eczema 24 hours after touching an Arnica plant. He had never developed eczema after contact with Compositae before.

Spettoli et al. (1998): A hobby gardener presented a chronic eczema involving the face and the hands, being present for 6 month and worsened after handling with plants. He showed positive response to Arnica tincture.

Delmonte et al. (1998): After a woman had applied a cream containing 1.5% Arnica on the face and three days later on the leg, she appeared with enlarging necrotic lesions of the face and left leg, together with malaise and high fever. The clinical presentation prompted the diagnosis Sweet's

Syndrome, which is often correlated with leukaemia. In the authors opinion the lesions were clearly related to pathergy to Arnica.

Machet et al. (1993) reported a case on a 60-year-old farmer who was referred for suspected sun-exposed dermatitis which consisted of itchy erythematous papules involving the face, neck, backs of hands and forearms. The lesions were present from June to September and had recurred each year for five years. The patient was patch-tested with the European standard series and with an additional plant series including Arnica tincture (20%). Positive results were shown with a fragrance mix and Arnica tincture. Positive allergy testing and cross-reaction to sun flowers was shown.

Eudravigilance database

A search was performed in the Eudravigilance database for the period of 01.01.2013-30.05.2023. The selected active substance was "extract from fresh arnica flower, extraction solvent: ethanol 58% V/V, liquid extract from Arnica chamissonis flower (DER 1:1), extraction solvent: ethanol 60% (V/V), liquid extract of Arnica flower/Birch leaf (1:1) (DER 1:10.94), extraction solvent: ethanol/sunflower oil (2.3/97.7), öliger Auszug aus Arnikablüten (1:3,5 - 4,5) (Auszugsmittel: Raffiniertes Sonnenblumenöl, enthält Antioxidantien (Tocopherole))". The report type was "objects from the list, spontaneous, other, not available to sender, report from studies". The medical product characterisation was "suspect, interacting".

Ninety-six cases were reported. The most frequent reported suspected adverse events were skin and subcutaneous tissue disorders as pruritus, rash, erythema, pruritic, vesicular or papular rash, blister, allergic dermatitis, eczema, skin burning sensation, skin swelling and urticaria.
The search in the pharmacovigilance database provided several cases of adverse events related to redness of the eyelid, application site itching and eye redness after not intended contact of Arnica ointment with the eye.

Conclusion:
Hypersensitive reactions are known from clinical experimental studies, from literature are labelled in licenced preparations and are reported in the pharmacovigilance database. The reactions occur not only in cases of misuse (long use, and high concentration), but also under normal conditions of use. The chapter 4.8 "Undesirable effects" of the monograph contains the information that allergic and hypersensibility reactions such as itching, redness of the skin and eczema may occur.
In chapter "Special warnings and precautions for use" a warning is included that the preparations should not be applied near the eyes or mucous membranes.

5.4. Laboratory findings

Information on laboratory findings (results of laboratory testing in blood, urine, etc., changes of blood pressure or heart rate or ECG parameters) is not available.

5.5. Safety in special populations and situations

Not available.

5.5.1. Use in children and adolescents

No safety information on the use in children is available.

preparations a, b, d:

The use in children under 3 years of age is not recommended because of concerns requiring medical advice.

preparations c, e, f:
The use in children under 12 years of age has not been established due to lack of adequate data.

5.5.2. Contraindications

A contraindication for patients with "hypersensitivity to the active substance and to other plants of the Asteraceae (Compositae) family" is included.

5.5.3. Special warnings and precautions for use

Undiluted tinctures can cause contact dermatitis. In treatment involving higher concentrations of the drug, primary toxic skin reactions with formation of vesicles or even necroses may occur. Toxic allergic skin reactions have occurred following application of the tincture.

Hypersensitivity reactions have been reported after the accidental exposure to the eyes or mucous membranes. Also pharmacovigilance data identified well-documented cases with a proved causality to risks regarding the accidental use/misuse to the eyes or mucous membranes. The information is in compliance with information from literature.

Taken from literature, case reports and marketed products, the following warnings are included in the monograph:

- Not to be used on broken skin.
- Tinctures should be diluted before use.
- The preparations should not be applied near the eyes or mucous membranes.
- Indications 2 and 3: If fever or signs of exacerbating skin infection are observed, a doctor or a qualified health care practitioner should be consulted.
- Indication 3: Small boils (furuncles) in the face should be treated by a medical doctor.

5.5.4. Drug interactions and other forms of interaction

One case of an interaction between warfarin and Arnica was reported. An 81-year-old woman with nosebleeds in the setting of a high INR (Chetak, 2011). The only change in her medication was topical Arnica. She applied a large amount to her back, which may have increased absorption. It was concluded that there was an interaction between Arnica and warfarin.

5.5.5. Fertility, pregnancy and lactation

Safety during pregnancy and lactation has not been investigated.

According LactaMed (2021) no information is available on the excretion of Arnica components in breastmilk. Oral ingestion of botanical Arnica products should be avoided because of its toxic components, but homeopathic products and topical application are usually safe during breastfeeding. Further, a case of an infant´s haemolysis probably caused by internal use of Arnica tea is reported. A 9-day-old breastfed infant developed haemolytic anaemia 48 hours after his mother had begun drinking tea made from Arnica flowers. After exchange transfusion and phototherapy, the anaemia corrected and bilirubin lowered.

Drug abuse was reported in older literature; regarding the use of Arnica preparations internally for provoke abortion (Madaus, 1938).

Assessor´s comment:
The internal use is obsolete. Arnica preparations covered by the HMPC monograph are intended for topical use only. Topical application are usually safe during breastfeeding. However, *since safety during pregnancy and lactation has not been established and in the absence of sufficient data, the use during pregnancy and lactation is not recommended.*

5.5.6. Overdose

Intoxication following overdose of preparations containing *Arnicae flos* is not 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. No effects are reported. From the known constituents no effects are anticipated.

5.5.8. Safety in other special situations

No data exist for patients with impaired renal or liver function. No information is available on intrinsic factors (e.g. patients' characteristics such as gender, race, polymorphic metabolism).

5.6. Overall conclusions on clinical safety

Based on its traditional use, Arnicae flos preparations proves not to be harmful in the specified conditions of use (in recommended indications/recommended preparations).

Clinical experimental studies investigated the allergenic potential in Arnica preparations or sesquiterpene lactones and hint to a risk of contact sensitisation. Arnica may cause allergic skin reactions, as well as cross reactions, in those allergic to other plants of the Asteraceae (Compositae) family. From the available clinical studies, adverse case reports from pharmacovigilance database and literature, allergic skin reactions such as itching, redness of the skin and eczema and hypersensitivity reactions are reported. The frequency is not known. The use is contraindicated for persons with hypersensitivity to the active substance and/or to other plants of the Asteraceae (Compositae) family.

Arnica flower is irritant to mucous membranes and when ingested has produced severe symptoms including gastrointestinal and nervous system disturbances, both tachycardia and bradycardia, and collapse. Arnicae flos preparations should be used only externally. Internal use is obsolete.

Undiluted tinctures can cause contact dermatitis. In treatment involving higher concentrations of the drug, primary toxic skin reactions with formation of vesicles or even necroses may occur. Tinctures should be diluted before use.

Arnica is indicated only for the short term use. Prolonged treatment often causes oedematous dermatitis with the formation of pustules. Long use can also give rise to eczema. If the symptoms persist after 3 to 4 days during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Hypersensitivity reactions have been reported after the accidental exposure to the eyes or mucous membranes from the Eudravigilance database. A warning is included, that Arnica preparations should

not be applied near the eyes or mucous membranes. The preparation should not be used on broken skin.

Safety data in special populations and situations are not available. No data exist for patients with impaired renal or liver function. Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy is not recommended. The use in children under 3 years of age is not recommended for preparations a, b and d, because of concerns requiring medical advice; the use in children and adolescents under 18 years of age (preparation c) or children under 12 years of age (preparation e, f) has not been established due to lack of adequate data.

6. Overall conclusions

There is sufficient evidence for the traditional medicinal use in Europe for Arnicae flos 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:

a) Comminuted herbal substance
b) Tincture (ratio herbal substance to extraction solvent 1:10); extraction solvent: ethanol 70% (V/V)
c) Tincture (ratio herbal substance to extraction solvent 1:5); extraction solvent: ethanol 60% (V/V)
d) Fluid extract (DER 1:1); extraction solvent: ethanol 60% (V/V)
e) Liquid extract of fresh flowers (DER 1:20); extraction solvent: ethanol 50% (m/m)
f) Liquid extract (DER 1:3.5-4.5); extraction solvent: refined sunflower oil.

The traditional use (in dependence from the preparation) is plausible for the following indications:

a) for the relief of bruises, sprains and localised muscular pain (all preparations)
b) for inflammations as a result of insect bites (preparations a, b, f).
c) for treatment of small boils (furuncles) (preparations a, b, f).

Results from relevant preclinical, experimental studies to support the proposed indications are very limited. The reported pharmacological effects are not considered contradictory to the traditional uses. Tested Arnica preparations were not phototoxic to mouse or guinea pig skin. Several in-vivo tests examined the sensitisation potential of different Arnica preparations and reported contradictory results. Adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

Adequate controlled clinical studies, which might support a well-established use, have not been performed with Arnicae flos preparations. Clinical pharmacological studies are not available. Based on the long traditional medicinal use and in accordance with literature the use the efficacy is plausible for the relief of bruises, sprains and localised muscular pain, for inflammations as a result of insect bites and for treatment of small boils (furuncles).

Arnica preparations should not be administered orally. The HMPC monograph includes only the topical use. Cutaneous administration of Arnicae flos can be regarded as safe at traditionally used doses and specified conditions.

The use is contraindicated for persons with hypersensitivity to the active substance and/or to other plants of the Asteraceae (Compositae) family.

The use in children under 3 years of age is not recommended for preparations a, b and d, because of concerns requiring medical advice; the use in children under 12 years of age (preparation c, e, f) has not been established due to lack of adequate data. The preparations should not be applied near the eyes or mucous membranes. The preparation should not be used on broken skin. Treatment involving

higher concentrations of the drug, especially undiluted tincture, can result in allergic contact dermatitis, or even necroses may occur. The tincture should be use only diluted.

The preparations are not intended for long-standing use. If the symptoms persist after 3 to 4 days during the use of the medicinal product a doctor or a qualified health care practitioner should be consulted.

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

Undesirable effects as allergic and hypersensibility reactions such as itching, redness of the skin and eczema may occur. No cases of overdose are available.

The intended indications are adequate for the use in self-medication. The efficacy for the cutaneous use is plausible. The safety information in the monograph is adequate to exclude possible risks for special user groups.

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

Annex

List of references