6 May 2014
EMA/HMPC/198794/2012
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Arnica montana* L., flos

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)	*Arnica montana* L., flos
Herbal preparation(s)	a) Tincture (DER 1:10), extraction solvent: ethanol 70% (V/V) b) Tincture (DER 1:10), extraction solvent: ethanol 60% (V/V) c) Tincture (DER 1:5), extraction solvent: ethanol 60% (V/V) d) Liquid extract of fresh flowers (DER 1:20), extraction solvent: ethanol 50% (m/m)
Pharmaceutical forms	Herbal preparations in semi-solid and liquid 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

Arnica is a plant genus including about 30 species. It belongs to the Asteraceae family. Arnica species are native to the mountains of Alps, Pyrenees, Balkan mountains, Scandinavia and the Baltic states.

The species accepted for medicinal use is *Arnica montana* L. A monograph Arnica flower (1391) on quality of the herbal substance has been published in the European Pharmacopoeia. The herbal substance consists of the dried flower heads of *Arnica montana*. The minimum content of sesquiterpene lactones according to Ph. Eur. is 0.4%. Arnica tincture according to the Ph. Eur. (1809) is defined 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% (V/V) to 70% (V/V)) by an appropriate procedure.

The flowers of Arnica species contain especially sesquiterpene lactones which have a pseudo-guajonolide structure, which often may occur as ester derivatives. Beside essential oil compounds other constituents are flavonoids, hydroxycoumarins and phenyl acrylic acids.

The medicinal usage of Arnica has stimulated extensive research on constituents. Different sesquiterpenes were isolated already in the 50ies and 60ies of the 20th century (Faber, 1953; Labadie, 1968; Jestrowa, 1969; Powlawski, 1970). The most relevant constituents so far are helenalin and 11,13-dihydrohelenanin and their derivatives (Willuhn *et al*., 1981; Willuhn *et al*., 1983). The content is varying with respect to the geographical origin. More recent investigations led to the detection of methylated flavonoids (Merfort, 1987) and further sesquiterpene lactones (Kos *et al*., 2005). The natural variability of sesquiterpene lactones in the herbal substance is 0.3 to 1.0%. Other natural constituents of *Arnica montana* are flavonoids (0.4 to 0.6%), essential oil (0.2 to 0.35%), mono- and sesquiterpenes.

Among those herbal preparation(s) containing *Arnica montana* which have been used in the European Union and which were identified to fulfil the criteria of traditional use there are three preparations which are manufactured using herbal substance complying with the monograph in Ph. Eur. (a, b and c). The liquid extract d) is produced using fresh flowers.

a) Tincture (1:10), extraction solvent: ethanol 70% (V/V)
b) Tincture (1:10), extraction solvent: ethanol 60% (V/V)
c) Tincture (1:5), extraction solvent: ethanol 60% (V/V)
d) Liquid extract (1:20), extraction solvent: ethanol 50% (m/m)

Only the herbal preparations mentioned above were included into the monograph, because for other herbal preparations either the Arnica species used was not complying with the species according to the monograph of the Ph. Eur., the tradition of 30 years of medicinal use were not proven or a specified posology was not reported.

Information about products on the market in the Member States

Medicinal products containing herbal preparations derived from Arnica flowers have been marketed in at least 10 Member States of the European Union.

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	2 preparations
Belgium	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no product as single ingredient preparation
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	last 40-50 years not licensed
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no preparations
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no preparations
France	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	3 preparations
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	10 preparations
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	2 preparations
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Latvia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Poland	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	2 preparations
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no preparation
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no preparations
Slovenia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.2. Search and assessment methodology

All relevant databases in life sciences were accessed via DIMDI, the German authority for data evaluation, in October 2010, and updated for public consultation. Key words used for literature search were “Arnika”, ”Arnica”, “Arnica montana”, “Helenalin”, “Dihydrohelenalin”.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

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 hematoma, injuries, varicose, phlebitis, gout, rheumatism, indigestion and cardiovascular disease. In Germany, Arnica is used since 1957 as a remedy in different indications as: in cases of injury and as consequences of accidents, e. g. hematoma, distortions (dislocation, sprains), contusions (bruises), against oedema due to fracture, for systematic treatment of rheumatic muscle and joint complaints, against furunculosis, inflammations caused by insect bites and superficial phlebitis, and to treat inflammations of the oral and throat region like gingivitis and aphthuous ulcers.

In 1984 a monograph on Arnica was established by the Commission E. The indication was covering a broad range of therapeutic conditions: for external use for injury and accidents, such as bruises, sprains, contusions, fracture-oedema, rheumatic muscle and joint pain, inflammation of the mouth and throat, furuncolosis and imflammation as a result of insect bites, phlebitis. Because of possible risks the application was limited to external use, the internal use was not accepted.

There is a WHO monograph on Arnicae flos, which was developed with reference to the British Herbal Pharmacopoeia and the German Commission E monograph, and which is listing the following indications: as a topical counterirritant for treatment of pain and inflammation resulting from minor injuries and accidents, including bruises, ecchymoses, haematomas and petechiae, and treatment of inflammation of the oral mucous membranes, insect bites and superficial phlebitis.

The ESCOP monograph on Arnicae flos attributed the following indications: Treatment of bruises, sprains and inflammation caused by insect bites; gingivitis and aphthous ulcers; symptomatic treatment of rheumatic complains.

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

The following data are derived from the request (dated 25 June 2010) for information concerning the marketed products of Arnica preparations. After public consultation products were added from comments by interested parties, if they were relevant for the monograph:

Austria: Traditional use

1. Ointment (registration in 2008):
100 g containing 21.5 g tincture (1:10), extraction solvent: ethanol 70% (V/V)
Indication: Traditional herbal medical product for external use at blunt traumas, sprain, bruise, contusion and dislocation, and at painful muscle and joint disorders.
Posology: Apply 3-5 times daily to the affected area in slight massage, not for persons under 18 years recommended.

2. Gel (registration in 2011):
100 g containing 50 g liquid extract from fresh Arnica flowers (1:20), extraction solvent: ethanol 50% (m/m)
Indication: Traditional herbal medical product for external use at blunt traumas, sprain, bruise, contusion and dislocation, and at painful muscle and joint disorders.
Posology: Apply 2 times daily 4 cm to the affected area in slight massage, not for persons under 18 years recommended.
If symptoms persist, lasting longer than 10 days, a doctor should be consulted.

France: Traditional use
1. Cream for cutaneous use (since 1959):
100 g containing liquid extract (1:1), extraction solvent: ethanol 60% (V/V)
Indication: Traditional used in the symptomatic treatment of ecchymosis.
Posology: Apply 2-3 times daily.

2. Gel for cutaneous use (since 2006):
100 g containing 20 g tincture (1:9), extraction solvent: ethanol 70% (V/V)
Indication: Traditional used in the symptomatic treatment of ecchymosis.
Posology: Apply 2-3 times daily.

3. Gel for cutaneous use (since 2004):
100 g containing 20 g tincture (1:5), extraction solvent: ethanol 60% (V/V)
Indication: Traditional used in the symptomatic treatment of ecchymosis.
Posology: Apply 3-4 times daily.

4. Dressing impregnated with solution for cutaneous use (since 1982):
One impregnated dressing contains 2.5 ml solution.
100 ml solution contains 100 ml tincture (1:10), extraction solvent: ethanol 60% (V/V)
Indication: Traditionally used in the symptomatic treatment of bruises.
Posology: Apply the dressing locally.

Germany: Well established use
1. Gel for external use (as a compress and liniment) (since 1976):
100 g contain 25 g tincture from Arnica flowers (1:10), extraction solvent: ethanol 70% (V/V)
Indication: for external use after injuries and accidents, i.e. hematomas, sprains, bruises, contusion.
Posology: Apply 3 times daily a string of gel of 3-5 cm length per area of the size of palm of the hand and massage gently, in adults and adolescents over 12 years.

2. Gel for external use (since 1976):
100 g contain 25 g tincture from Arnica flowers (1:10), extraction solvent: ethanol 70% (V/V)
Indication: For external use after injuries and accidents, i.e. hematomas, sprains, bruises, contusion.
Posology: Apply 2 times daily a string of gel of 3 cm length per area of the size of palm of the hand and massage gently, in adults and adolescents over 12 years.

3. Gel for external use (since 1976):
10 g contain 2.4 g tincture from Arnica flowers (1:10), extraction solvent: ethanol 70% (V/V)
Indication: for external use after injuries and accidents, i.e. hematomas, sprains, bruises, contusion.
Posology: Apply up to 2 times daily a string of gel of size of a pea per area of the size of palm of the hand and massage gently into the affected parts of the skin, in adults and adolescents over 12 years.

4. Gel for external use (since 1976):
100 g contain 25 g tincture from Arnica flowers (1:10), extraction solvent: ethanol 70% (V/V),
Indication: For external use after injuries and accidents, i.e. hematomas, sprains, bruises, contusion.
Posology: Apply 2 times daily a string of gel of 3 cm length per area of the size of palm of the hand and massage gently, in adults and adolescents over 12 years.

5. Cream for external use (since 1976):
10 g contain 2 g tincture from Arnica flowers (1:10), extraction solvent: ethanol 70% (V/V)
Indication: for external use at blunt traumas, i.e. hematomas, sprains, bruises, contusion.
Posology: apply up to 3 times daily a string of cream of 3 cm length per area of the size of palm of the hand and massage gently, in adults and adolescents over 12 years.

6. Cream for external use (since 1976):
10 g Cream contain 2.15 g tincture from Arnicae flos (1:10), extraction solvent: ethanol 70% (V/V)
Indication: For external use after injuries and accidents, i.e. hematomas, sprains, bruises, contusion.
Posology: Apply 2-3 times daily a string of cream of 3 cm length per area of 10 x 10 cm, in adults and adolescents over 12 years.

7. Cream for external use (since 1976):
100 g contain 20 g tincture from Arnica flowers (1:10), extraction solvent: ethanol 70% (V/V)
Indication: For external use after injuries and accidents, i.e. hematomas, sprains, bruises, contusion.
Posology: apply several times a day a string of cream of 2-3 cm length on the affected parts of the body and massage, in adults and adolescents over 12 years.

8. Cream for external use (since 1976):
100 g contain 25 g tincture from Arnicae flos (1:10), extraction solvent: ethanol 70% (V/V)
Indication: for external use after injuries and accidents, i.e. hematomas, sprains, bruises, contusion.
Posology: Apply up to 2-3 times daily a string of cream of 3 cm length per area of the size of palm of the hand and massage gently, in adults and adolescents over 12 years.

9. Cream for external use (since 1990):
1 g contains 80 mg tincture from Arnica flowers (1:10), extraction solvent: ethanol 70% (V/V)
Indication: For external use after injuries and accidents, i.e. hematomas, sprains, bruises, contusion.
Posology: Apply 2-3 times daily to the affected parts of the skin and massage gently, in adults and adolescents over 12 years.

10. Ointment for external use (since 1993):
100 g contain 10 g extract from Arnica flowers (1:3.5-4.5), extraction solvent: sunflower oil
Indications: For external use after injuries and accidents, i.e. hematomas, sprains, bruises, contusion; oedema in the tissue as a result of fractures; rheumatic muscle and join pain; inflammation from insect bites.
Posology: Apply several times daily and massage gently, for instance a string of ointment of 8 cm length for the area of the lower leg, in adults and adolescents over 12 years.

Hungary: Traditional use
1. Ointment (since 1992):
100 g containing 5 g Arnica tincture (1:10), extraction solvent: ethanol 70% (V/V)

Indications: Treatment of closed lesions, sprain, 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.
Posology: Rub the ointment into the skin of the affected region several times a day, but not more than 5 times. Apply the preparation carefully to wounds and then cover the wound with light dressing.
Risk: Rarely allergic skin reactions can occur. Long term use or application of big quantity can caus inflammation of the skin, vesication, eczema, or skin necrosis. The application of the substance on injured skin surface, or on ulcus cruris can cause oedematous dermatitis.

2. Cream (since 1996):
60 g containing 6 g Arnica tincture (1:10), extraction solvent: ethanol 70% (V/V)
Indications: Treatment of closed lesions, sprain, 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.
Posology: After cleaning the affected area apply the cream in thin layer and rub it 2-3 times daily.
Risk: Allergic skin reactions can occur. Long term use can cause eczema.

Latvia: Well-established use
1. Ointment for external use (marketed since 2002):
Ointment 10%, containing tincture (1:10), extraction solvent: ethanol 70% (V/V)
Indications: Antiseptic, anti-inflammatory and local irritant for the reduction of pain and inflammation of joints and muscles; for the treatment of bruises, dislocation, sprains, strains, mild frostbites and burns, inflammation after insect bites; for the relief of subcutaneous haemorrhage and hematomas.
Posology: Apply 3-4 times daily to the affected area of skin by gently massaging.

Netherlands: Traditional use
1. Gel for cutaneous use (registration since 2009):
Liquid extract (1:20), extraction solvent: ethanol 50% (m/m)
Indications: 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.
Posology: Apply 2-4 times daily.

Poland: Traditional use
1. Tincture for cutaneous use only (since 1992):
Arnica tincture (1:10), extraction solvent: ethanol 70% (V/V), diluted tincture (1:3 to 1:10)
Indications: Hematomas, sprains, bruises, oedemas, furuncolosis, veins inflammation, inflammation caused by insect bites, rheumatic complains.
Risk: Hypersensitivity, skin irritations, contact dermatitis.

2. Extract for cutaneous use only (since 1994):
Arnica anthodii extractum: 2-4 times daily.
Indications: Adjuvant in bruises, sprains (oedema), insect bites, rheumatic complains.
Risk: Possibility of skin allergic reactions (contact allergy), hypersensitivity, skin irritations, contact dermatitis.

Slovenia: Well-established use
1. Gel for cutaneous use only (registration in 2007):
1 g contains 0.5 g of tincture of fresh Arnica flowers (*Arnica montana* L.) (1:20), extraction solvent: ethanol 57.9% (V/V)

Indications: Herbal medical product for cutaneous use: for supportive treatment of rheumatic complains (osteoarthritis) and other conditions with muscular aches, pains and stiffness symptomatic relief of aches, pains and stiffness, sprains, after contusions, exclusively based on long-standing use.
Posology: Apply the gel gently to the affected area 2-3 times daily.

Spain: Traditional use
1. Gel (registration in 2008):
1 g contains 500 mg of liquid extract (1:20), extraction solvent: ethanol 50% (m/m).
Indications: Traditional herbal medical product for the symptomatic relief of muscular aches, pains and stiffness, sprains, after contusions, exclusively based on long-standing use.
Posology: Apply 2-10 cm to the affected area 2-4 times daily.

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

For data on posology refer to information presented in section 2.2 for specific extracts. Herbal preparations containing Arnica flowers are for cutaneous use in semi-solid dosage forms (ointment, cream, gel) and liquid dosage forms (dressing impregnated with solution). The frequency of application is varying between 2 to 3, 3 to 4 and 2 to 4 times daily. Only for a few products a restriction of the duration of use is reported (10 days).

3. Non-Clinical Data

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

Many pharmacological studies have investigated effects of Arnica extracts and its constituents *in-vivo* and *in-vitro*. The studies with relevance for the assessment report have been selected.

There are only few pharmacological studies with extracts, which are listed in the monograph. The majority of studies have focused on well-known isolated components of Arnica.

Primary pharmacology

Anti-inflammatory effects

In-vitro studies
Tinctures/ethanolic or lipophilic extracts:
Arnica was studied for the capability to impair activation of the transcription factors (nuclear factors) NF-κB and NF-AT. Both proteins are responsible for the transcription of genes encoding various inflammatory mediators. Additionally the influence on the release of the cytokines IL-1 and TNF-α was examined. Arnica tincture, Arbo (German Pharmacopoeia, DAB), and ArnikaGel (Kneipp Company) were tested. No further details on composition of the tested materials were described. Jurkat T cells (5-6 x 10^5 cells/ml) were incubated with various amounts of Arnica tincture or Arnica gel. 5 µg/ml of the Arbo tincture completely inhibited NF-kB-DNA binding. Arnica Gel was less active since a concentration of 50 µg/ml was necessary for a complete inhibition. No cytotoxic effects could be observed. The inhibitory activities correlate with the quantitative and qualitative content of sesquiterpene lactones (Klaas, 2002).

Other extracts:
A methanolic Arnica extract (no further details were described) in a quantity of 100 µg/ml significantly reduced the protein level of inducible NO synthase (iNOS) and cyclooxigenase-2 (COX-2) in J774 murine macrophages. Furthermore it was shown that the extract prevented the lipopolysaccaride-

mediated nuclear translocation of NF-κB. The authors concluded that these results are demonstrating the anti-inflammatory potential of Arnica (Mol, 2010).

Isolated compounds:
Helenalin (in concentrations from 0.5 -2 µM) was reported to suppress 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 may be a new immunosuppressive compound suited for the treatment of deregulated and unwanted T-cell-mediated immune responses (Berges *et al*., 2009).

The treatment of three different cell types, T-cells, B-cells and epithelial cells, with micromolar concentrations of helenalin (1-20 µM) resulted in inhibition of the activation of NF-κB which controls the transcription of various cytokines and adhesion molecules. Thus, 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 (Lyss, 1997).

The dual role of sesquiterpene lactones as anti-inflammatory compounds and contact allergens *in vitro* was examined. In dentritic cells the activation of NF-κB and the secretion of interleukin (IL-12) in the presence of different doses of sesquiterpene lactones was tested. Arnica tinctures suppressed NF-κB activation and IL-12 production at high concentrations, but had immunostimulatory effects at low concentrations (Lass 2008, 2010).

<u>In-vivo studies</u>
Tinctures/ethanolic or lipophilic extracts:
Lass *et al*. (2008) investigated anti-inflammatory effects of sesquiterpene lactones and possible immune-regulatory mechanisms with respect to contact hypersensitivity to *Arnica montana* L. In this study the role of sesquiterpene lactones as anti-inflammatory compounds and contact allergens was examined. The mouse contact hypersensitivity model was used. Two chemotypes of *Arnica montana* were applied: the Spanish SP chemotype, with isolated 11alpha,13-dihydrohelenalinisobutyrate and methacrylates (0.7 mg/ml calculated as 11alpha,13-dihydrohelenalinmethacrylate) and the central European CL chemotype with helenalinisobutyrate (0.83 mg/ml calculated as helenalinisobutyrate). The concentrations used for helenalinisobutyrate (1.2 mM=39.89 mg/100 ml tincture or ethanol 12 mM), 11alpha,13-dihydrohelenalin methacrylate (2.12 mM=69.93 mg/100 ml tincture or EtOH and 21.2 mM and for 11alpha,13-dihydrohelenalin isobutyrate 2.12 and 21.2 mM.
Sesquiterpene lactones and tinctures (0.7 mg/ml calculated as 11,13 dihydrohelenalinmethacrylate) and (0.83 mg/ml calculated as helenalinisobutyrate) from *Arnica montana* did not induce contact hypersensitivity (abdomen and ear); dose dependent effects of sesquiterpene lactones on NF-κB activation (inhibition of NF-κB-DNA binding at high concentrations and activation of NF-κB-DNA at low concentrations, immunostimulatory effects, Arnica suppressed contact hypersensitivity to the strong contact sensitiser trinitrochlorobenzene-TNCB). The authors concluded that sesquiterpene lactones and tinctures from Arnica are weak inducers of skin inflammation and that Arnica tinctures (prepared from *Arnica montana* flowers, CE chemotyp, by percolation according to the European Pharmacopoeia 1997 containing mainly helenalinesters 0.83 mg/ml calculated as helenalinsobutyrate) decrease TNCB-induced contact eczema.

The dual role of sesquiterpene lactones as anti-inflammatory compounds and contact allergens was examined *in-vivo* in the mouse contact hypersensitivity model. Contact hypersensitivity could not be induced in the mouse model, even when Arnica tinctures or sesquiterpene lactones were applied undiluted to inflammated skin. Contact dermatitis could be induced in acutely CD-4 depleted MHC II knockout mice. The authors suggested 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 2008, 2010).

Secondary pharmacology

Tinctures/ethanolic or lipophilic extracts:
In a concentration of 50-150 µg/ml Arnica could markedly reduce the level in nitrotyrosine in blood platelet proteins treated with peroxynitrite. The effect observed was attributed to polyphenolic-polysaccharide conjugates. The authors concluded that the compounds from Arnica possess antioxidative properties and protect blood platelet proteins against peroxinitrite toxicity *in-vitro* (Saluk-Juszczak *et al*., 2010).

Other extracts:
Iauk (2003) reported a study designed to evaluate the antibacterial activity of amongst others Arnica against anaerobic and facultative aerobic periodontal bacteria (18 overall). As a positive control a macrolide antibiotic, spiramycin was used. A methanol extract and a decoction were assayed, each 10% from 10 g powder for decoction and 15 g of the drug for extraction. The methanol extract showed an inhibiting activity against many of the species tested (MIC=2048 mg/l).

Isolated compounds:
Cytotoxicity of 21 flavonoids and 4 sesquiterpene lactones against GLC4 (a human small cell lung carcinoma cell line) and COLO 320 (a human colorectal cancer cell line) cell lines was assayed. Most flavonoids showed moderate to low cytotoxicity, as compared to the reference compound cisplatin (IC_{50}=1.1 µM against GLC4 and 2.9 µM against COLO 320). Their IC_{50} values varied from 17 to 200 µM. The most toxic compound was the flavone jaceopsidin. For helenalin the IC_{50} was 0.44 µM against GLC4 cells and 1.0 µM against COLO 320 cells. COLO 320 cells were more sensitive than GLC4 cells (Woerdenbag *et al*., 1994).

Anti-trypanosomal activity of helenalin and structurally related sesquiterpene lactones was investigated in assay systems with African *Trypanosoma brucei rhodesiense* and American *Trypanosoma cruzi*. Helenalin was the most active compound with IC_{50} values of 0.051 and 0.695 µM (Schmidt, 2002).

Helenalin, dihydrohelenalin and their acetates showed activities against asexual blood forms of *Plasmodium falciparum in-vitro*, helenalin was found to be the most active compound. The IC_{50} values measured were in the range of 0.23 to 7.41 µM (Francois, 2004).

Safety Pharmacology

No data available.

Pharmacodynamic Interactions

No data available.

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

Skin penetration of topically used Arnica preparations and of isolated sesquiterpene lactones was investigated 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 authors concluded that the mode of Arnica formulations has an influence on the penetration behaviour.

Also it was observed that the penetration rate of sesquiterpene lactones from Arnica gel preparations decreased after 4 hours, while from ointment preparations penetration was taking place continuously (Wagner *et al*., 2004).

Evaluation of skin permeability of sesquiterpenes from a supercritical carbon dioxide Arnica extract by HPLC/DAD/MS was reported by Bergonzi *et al*. (2005). The aim of this study was to evaluate by HPLC analysis the effects of different skin permeation enhancers on the percutaneous absorption of sesquiterpene lactones of Arnica. The skin permeation study was performed using a modified Franz diffusion cell and the human stratum corneum and epidermis as membrane, sampled from human abdomen skin, obtained by surgical operation. Overall 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).

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

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

Single dose toxicity:
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).

Repeated dose toxicity:
No information found in literature.

Genotoxicity:
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 2 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).

Carcinogenicity:
No information found in literature.

Reproductive toxicity:
No information found in literature.

Local tolerance:
Several dermal irritation tests were performed using different Arnica extracts/preparations (not further specified), different animal species and different test models. In most tests no irritation was observed while a few preparations/tests revealed slight patchy erythema (CIR Expert Panel, 2001).

Sensitisation:
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) sensitiser potential was reported (CIR Expert Panel, 2001).

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).

3.4. Overall conclusions on non-clinical data

Results from relevant experimental studies on *Arnica montana* to support the proposed indications are very limited. The reported pharmacological effects are not considered contradictory to the traditional uses.

Non-clinical information on the safety of *Arnica montana* flowers is scarce. Nonetheless, neither the chemical composition nor the long-term widespread use in the European Community suggests that there is a high risk associated with the use of Arnica preparations.

Specific (or adequate) tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed. A community list entry cannot be supported.

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

Ex-vivo studies
The study analysed the parameters of venous blood from healthy volunteers without any other anti-inflammatory medication during the last 2 weeks. Helenalin and 11,13-dihydrohelenalin were reported to inhibit collagen-induced platelet aggregation, thromboxane formation and 5-hydroxytryptamine secretion in a concentration dependent manner at 3-300 µM. Helenalin was found to be more potent (Schröder *et al*., 1990).

The effect of sesquiterpene lactones and sesquiterpene lactone-containing plant preparations on human blood, plasma and human serum albumin solutions was investigated. 11,13-dihydrohelenalin acetate and 13-dihydrohelenalin methacrylate were isolated from *Arnica 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 (Wagner *et al*., 2004).

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

No data available.

4.2. Clinical Efficacy

There is only a limited number of clinical investigations. Most of them are not in accordance with current standards and cannot be regarded to substantiate well-established use. Nevertheless, the clinical trials support the traditional use of Arnica preparations.

Dose response studies are not available.

4.2.1. Clinical studies (case studies and clinical trials)

Placebo controlled studies

Alonso *et al*. (2002): Effects of topical Arnica gel on post-laser treatment bruises, a randomised, double-blinded, placebo-controlled study, n=19 with facial telangiectasia, age unknown. The patients were divided in 2 groups, a pre-treatment and a post-treatment group. The pre-treatment group applied either Arnica (*A. montana* tincture with 45% alcohol, purified water with hazel, trolamine, carboner, EDTA, and methyl/propyl paraben) or vehicle alone on both sides of the face twice a day for 2 weeks prior to laser treatment. The post-treatment group followed the same procedure for 2 weeks after laser treatment (5 mm spot size with 6.3 J/cm^3 fluency). For assessment of bruising a visual analogue scale (VAS) 10 cm line with 0=no bruising and 10=worst bruising on days 0, 3, 7, 10, 14, and 17 was used. In addition photographs were taken and later evaluated by a second doctor. No significant difference was found between topical Arnica and vehicle either in the prevention of bruising, or in resolution of bruising. In both groups no side effects were seen.

Assessor's comment:
Although this is a placebo-controlled study, the results are not suited to demonstrate the effectiveness, there was no difference between Arnica gel and placebo in the treatment of post-laser treatment bruises. Adverse drug reactions were not seen, however, only 19 patients were included in the study, so the significance is low.

Rosenzweig *et al*. (2002): A pilot study with an Arnica compress to relieve acute soft-tissue pain (placebo-controlled study, n=39, age and gender unknown) was performed. Most frequent sites of pain were: foot/ankle, knee and neck/shoulder. The treatment was either active compress, 0.7% Arnica, prepared from whole plant extract (Arnica essence; Weleda) or placebo containing water and food colouring for 30-45 min over the affected body. Serial visual analog pain scores (VAS) were obtained at times 0, 30 and 60 min. The duration of therapy was 4 weeks. 30 patients completed the study, 16 received Arnica and 14 received placebo. An Arnica compress prepared from a 0.7% solution applied for 30-45 min provided no statistically significant analgesic effect compared to placebo one hour after initiation of therapy. One patient in the placebo group reported itching, no other adverse reactions occurred.

Assessor's comment:
Although a placebo-controlled study, the results are not suited to demonstrate efficacy in the treatment of acute soft-tissue pain, because there was no difference between Arnica and placebo. Moreover, it is not a standard phytotherapeutic formulation, but a specific anthroposophic formulation using the whole plant. Only one adverse drug reaction was seen, one patient out of 39 enrolled patients perceived itching.

Brock (1991): Two studies were reported, one of them placebo controlled. The first study was a three-arm study, n=159, double blind and randomised. Three treatments were 1: a combination ointment (100 g stand. Ol. arnicae (extract from Arnica flowers with sunflower oil 1+5) 10 g; Heparine 4000 IU; Ol. chamomillae 5 mg; guaiazulene 5 mg) 2: a single ointment (100 g stand. Ol. arnicae (extract from Arnica flowers with sunflower oil 1+5) 10 g and 3: placebo (ointment base), in patients with chronic

venous insufficiency. The therapy constituted a 4 cm ointment strand per leg, four times daily rubbing the legs from the foot up to the lower leg to below the knee for three weeks. The improvement in symptoms was measured the venous capacity. The changes were strongest in the group, receiving the combination treatment. However changes were neither within nor between the groups significant (statistically and clinically). Only 2 patients got allergic symptoms as adverse reactions.
In the second study, a two-arm study in 60 patients with primary varicosis, without signs of chronic venous insufficiency, the combination ointment, same as above was tested against the mono product. The treatment consisted of four applications per day, 4 cm ointment strand per leg, for 3 weeks. The venous capacity and venous outflow velocity improved in both groups. The improvement was significant in both groups. No adverse reactions were seen.

Assessor's comment:

The first study was a placebo-controlled, three arm study performed in 159 patients with venous insufficiency. The changes were neither within nor between the groups significant. A trend, although not significant, was recognized in the group treated with the combination preparation. Proof of the efficacy has not been demonstrated. Only 2 patients got allergic symptoms as adverse reactions.
The second study was not placebo-controlled. A mono-Arnica preparation against a combination preparation of Arnica, heparin, chamomile and guaiazulene was tested in 100 patients with varicosis. The improvement was significant in both groups. Because of the lack of the placebo group, the study cannot be considered as proof for efficacy.

Brock (2001): In a randomised, placebo controlled study 100 patients with chronic venous insufficiency were treated for 3 weeks three times daily with a 6 cm long gel strand of 100 g gel contain 25 g Arnica tincture or placebo, on the skin on both lower legs and feet, in addition patients received a standardised hydrotherapy. The improvement in venous capacity was significant in both groups, with a significantly better effect in the verum group. Two patients dropped out due to allergic reactions.

Assessor's comment:

In this study 100 patient with chronic venous insufficiency were treated with Arnica gel or placebo, the results were positive, the improvement in the verum group in all tested symptoms is significantly better than in the placebo group, where there is an improvement too. This new study from 2001 provided some evidence that Arnica may act in chronic venous insufficiency. The safety was judged as well, only 2 patients got allergic reactions.

Studies with other controls (Standard therapy)

Totonchi *et al.* (2007): A randomised, controlled comparison between Arnica and steroids in the management of postrhinoplasty ecchymosis and oedema, n=48, 11 male and 37 female patients, ranging from 15 to 65 years, who had undergone a primary rhinoplasty with osteotomy. Patients were randomised into three groups. The first group received 10 mg of intravenous dexamethasone, followed by a 6-day oral tapering dose of methyl-prednisone. The second group received Arnica (SinEcch, Alpine Pharmaceuticals, San Raphael, Calif.) three times a day for 4 days. The last group received neither agent and served as the control group. This study suggests that both remedies may be effective in reducing oedema during the early postoperative period. In ecchymosis Arnica has no benefit. It is not really clear, what dosage form was used.

Assessor's comment:

In this study Arnica is as effective as intravenous dexamethasone, resp. oral methyl-prednisone in the treatment of oedema in the early postoperative period, treated were 48 patients. However, the formulation of Arnica is not a phytotherapeutic preparation, but a homeopathic one, therefore this study is not useful for the assessment.

Widrig *et al*. (2007): Choosing between NSAID and Arnica for topical treatment of hand osteoarthritis in a randomised, double-blind study, n=204 patients, age and gender unknown, from 20 clinics (12 general practices, 6 rheumatologie clinics, 2 general medicine) in three Swiss cantons, for 21 days. Patient selection was conducted according to the Osteoarthritis Research Society International (OARSI) guidelines and their recommendations for studying polyarhtritis of finger joints. Ibuprofen Gel 5% (Optifen) was tested against Arnica Gel (A. Vogel Arnica Gel, *Arnica montana* fresh herbal tincture 50 g/100 g gel; DER of the tincture 1:20). There were no differences between the two groups in pain and hand function improvements, and all other parameters (number of painful joints in both hands, intensity of stiffness in the worst affected hand and more). Adverse events were reported for both treatments, 9 in the ibuprofen group and 14 in the Arnica group, treatment related were 6 in the ibuprofen group and 5 in the Arnica group, mostly allergic skin reactions.

Assessor's comment:
In this study improvement of symptoms of osteoarthritis such as pain intensity and in general an improvement of hand function was seen in both groups. The study seems to be effective in this indication for Arnica gel.
The rate of adverse drug reactions is tolerable with 5 cases out of a total of 89 patients treated with Arnica.

Ross (2008): the same study as above is reported.

Leu *et al*. (2010): A rater-blinded randomised controlled trial, n=16, aged 21-65, from a university based dermatology department was performed. Bruises were induced using a 595 nm variable long-pulsed pulsed-dye laser, to the volunteers' inner arms, for each subject four standard bruises of 7 mm diameter. Randomisation was used to assign one topical agent (5% vitamin K, 1% vitamin K and 0.3% retinol, 20% Arnica or white petrolatum) to exactly one bruise per subject, which was then treated under occlusion twice a day for 2 weeks. There was significant difference in the change in the rater score. Pairwise comparisons indicated that the mean improvement associated with 20% Arnica was greater than with white petrolatum and the improvement with Arnica was greater than with the mixture of 1% vitamin K and 0.3% retinol. Improvement with Arnica was not greater than with 5% vitamin K. Topical 20% Arnica ointment may be able to reduce bruising more than low-concentration vitamin K formulations. 4 patients reported redness and swelling, one patient blistering and one reported a contact dermatitis, the reports could not be related to a specific treatment.

Assessor's comment:
In this study it could be shown that topical Arnica can reduce bruises more than placebo. Arnica seems to be effective in this indication, although the number of patients is too small to make a statistical prediction. The rate of adverse drug reactions is: 4 patients (out of 16) reported redness and swelling, one patient blistering and one reported a contact dermatitis.

Open studies

Knuesel *et al*. (2002): Arnica gel was used for the treatment of osteoarthritis of the knee, an open, multicentre clinical trial, n=26 men and 53 women, age between 19 and 79 with a mild to moderate arthrosis/periarthtopathy of at least one knee. Patients applied a thin layer of *A. montana* gel to the affected knee in the morning and in the evening for 6 weeks. The gel contained 50 g of an Arnica fresh plant tincture (DER 1:20, extracting medium: ethanol 50% (m/m)). After 3 and 6 weeks significant decreases in median total scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were evident. Scores on pain, stiffness and function subscales also showed significant reductions on this time points. The tolerability was good, with only one allergic reaction. Due to lack of placebo-group this study could not be considered for proof of efficacy. Six patients experienced adverse drug reaction, such as red spots, itching allergy, local rush, pruritus, petechien and dry skin.

Assessor's comment:
In this open study it could be shown that Arnica reduces significant scores on pain and stiffness. The study seemed to demonstrate some effectiveness in this indication. Due to lack of a placebo-group this study could not be considered for proof of efficacy.
The rate of adverse effects at 6 patients out of 79 showed the familiar picture of the side effects.

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

No data are available for use in children. In some of the studies, the patients included had an age up to 65 years, but no special studies have been performed for elderly.

4.3. Overall conclusions on clinical pharmacology and efficacy

The clinical trials have limitations and are not suitable to support a well-established use of Arnica.

authors years	study design control type	duration of treatment	study and control drugs	number of subjects by arms dose; age	diagnosis inclusion criteria	exclusion criteria	primary endpoints	secondary endpoints	efficacy results	safety results
Alonso *et al*., 2002	double blinded placebo controlled	2 weeks, either in pre-or post-treatment	1. Arnica-Gel (*A. montana* with 45% alcohol, purified water, with hazel, trolamine, carboner, EDTA, methyl/ propyl paraben) 2. vehicle	9 pre-treatment, 10 post-treatment; dose not specified; age unknown	facial tele-angiecta-siaes	patients on anti-coagulant therapy	prevention or resolution of bruises	none	no statistically significant difference in both groups	no side effects in both groups
Rosen-zweig *et al*., 2002	double blinded placebo controlled	4 weeks	1. Arnica-compress (prepared from the whole plant extract, 0.7%) 2. placebo compress (contained-water and food coloring)	16 Arnica 14 placebo; one compress; age unknown	acute soft tissue pain (foot/ ankle, knee, neck/ shoulder)	not reported	change in pain intensity	none	no statistically significant analgesic benefit compared to placebo one hour after therapy	1 patient in the placebo group reported iching

authors years	study design control type	duration of treatment	study and control drugs	number of subjects by arms dose; age	diagnosis inclusion criteria	exclusion criteria	primary endpoints	secondary endpoints	efficacy results	safety results
Brock, 1991	double blinded; placebo controlled	3 weeks	1. combi-nation 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. mono-ointment: (100 g contain: 10 g extract from Arnica flowers with sunflower oil (1+5)) 3. placebo ointment base	159 overall; not reported, how many per group; age not reported	chronic venous in-sufficiency	no diuretica	Improve-ment of venous capacity; decrease in calf circum-ference	none	changes were in the combina-tion treatment but differences were not statistically significant	2 patients got allergic symptoms

authors years	study design control type	duration of treatment	study and control drugs	number of subjects by arms dose; age	diagnosis inclusion criteria	exclusion criteria	primary endpoints	secondary endpoints	efficacy results	safety results
Brock, 1991	double blinded	3 weeks	1. combi-nation 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. mono-ointment (100 g contain: 10 g extract from Arnica flowers with sunflower oil (1+5)) combinated with hydro-therapy in both groups	30 per group; age not reported	primary varicosis without signs of chronic venous in-sufficiency	not reported	improve-ment of venous capacity	none	statistically significant improve-ment in both groups	no adverse events reported

authors years	study design control type	duration of treatment	study and control drugs	number of subjects by arms dose; age	diagnosis inclusion criteria	exclusion criteria	primary endpoints	secondary endpoints	efficacy results	safety results
Brock, 2001	double blinded; placebo controlled	3 weeks	1. 100 g Arnica gel (contained 25 g arnica tincture) 2. placebo	50 per group; 77 woman; 23 men; age in average 59.2	chronic venous in-sufficiency	not reported	vein closure plethis-mography heaviness in the legs	pain in the legs; tightness and heaviness in the legs	statistically significant imrove-ment in both groups; a significant better effect in the verum group	2 patients with allergic reactions
Totonchi *et al*., 2007	double blinded; corticosteroid controlled	6 day, resp. 4 days	1. intravenous dexa-methasone intraopera-tively, followed by a six day dose of prednisone 2. Arnica SinEcch 3. none (as control)	48 overall; 11 male; 37 female; age from 15-65	primary rhinoplasty with osteotomy	not reported	extent, intensity of ecchymosis and severity of oedema	none	statistically no significance between the groups in ecchymosis ; statistically significance in reducing oedema in both groups	no data

authors years	study design control type	duration of treatment	study and control drugs	number of subjects by arms dose; age	diagnosis inclusion criteria	exclusion criteria	primary endpoints	secondary endpoints	efficacy results	safety results
Widrig *et al*., 2007	double blinded; ibuprofen control	3 weeks	1. ibuprofen 5% 2. 50 g Arnica tincture/100 g; DER 1:20	99 ibuprofen; 105 Arnica; age unknown	osteo-arthritis pain or stiffness in the hand or finger; hard tissue enlarge-ment; DIP and PIP joints	secondary osteo-arthritis, trauma to the hand or arm in the previous months	number of painful joints; intensity of morning stiffness; duration of morning stiffness	paracetamol consumption	no differences in pain and hand function improve-ment	5 patients with allergic reactions
Leu *et al*., 2010	rater blinded controlled	2 weeks	1. 5% vitamin K 2. 1% vitamin K and 0.3% retinol 3. 20% Arnica 4. white petrolatum	16 overall; each 4; bruises; age 21-65	healthy volunteers	no anti-coagulation therapy; no history of bleeding	rate on VAS standard-isised photo-graphs	at the end of study reporting adverse events	not significant reducing bruising	4 patients reported redness and swelling; 1 blistering; 1 contact dermatitis
Knuesel *et al*., 2002	open	6 weeks	50 g of an Arnica fresh plant tincture (DER 1:20), extracting solvent EtOH 50% (m/m)	26 men; 53 women; thin layer in the morning and evening	osteo-arthritis of the knee	allergy to asteracea; skin lesions of the knee; no other medication	osteo-arthritis index self-question-naire for patients	global efficacy	significant reduction of scores on pain, stiffness	6 patients reported red spots; itching, allergy; local rush pruritus; petechiae; dry skin

5. Clinical Safety/Pharmacovigilance

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

The incidence of allergic contact dermatitis after topical applications of preparations containing Arnica is well known, but not everyone who comes into contact with Arnica flowers is sensitised, and acquires a contact allergy. The incidence of getting a contact allergy depends on the immune system of the person, the balance of T-helper and T-suppressor lymphocytes and on the duration and intensity of exposure. It seems important especially at the first contact to the decision whether to activate the effector and the suppressor mechanism. Given the wide distribution of Arnica, the occurrence of contact allergy is relatively low.

There are many studies, which 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 potential risk to contact sensitisation, with corresponding studies:

Hausen (1979):
The article 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.

Eberhartinger (1984):
The article 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, 9 of Arnica-induced contact dermatitis occurred. 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 last time period from 1976 to 1983 from a total of 170 patients, 98 with positive result and 38 Arnica cases.

Hausen (1980):
In this article it was reported, that from the literature more than 100 cases of contact dermatitis could be cited, the first case was reported in 1844. Hausen described 4 additional cases. More recent studies were not in line with this data. Probably, the high number of reported cases was mostly due to skin sensations.

Reider (2001):
Reider (2001) reported that sesquiterpene lactones of *Arnica montana* L. possess a strong sensitising potency, with divergent results in recent studies. In this study a total of 443 patients were tested, only 5 of them showed positive reaction to Arnica.

Paulsen (2002, 2008):
The main aim in this study was to assess the significance of direct plant allergen contact via compositae-derived cosmetics and herbal remedies in Asteraceae – allergic patients with special reference to Arnica. 5 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.

Corazza *et al*. (2009):
The objectives of the study were to evaluate the prevalence of herbal compound usage (one of them was Arnica) and to estimate the incidence of cutaneous side-effects. 400 patients were included. 241 of them used natural topical products, 66 of them reported adverse reactions after using herbal products. The reported skin reactions were retrospectively self-reported and not corroborated by clinical assessment by a dermatologist, possible risk factors for contact dermatitis were not investigated. No more information what kind of adverse reactions occurred.

Jocher *et al*. (2009):
The study included 8 patients with a previous history of Arnica allergy, they were 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.

5.2. Patients exposure

There are data from 1280 patients, tested for safety, due to marketing authorisation, with a good result on safety, only the known 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 compatibility can, unlike previously thought, be regarded as relatively good. The adverse effects may occur with a frequency of 1:100. While there are allergic reactions, serious adverse reactions did not occur. If patients with known intolerance to Arnica, or plants of the Asteraceae family are excluded, a traditional use is possible if application is following appropriate instructions.

5.3. Adverse events and serious adverse events and deaths

No cases of death were reported.
The most reported adverse events were allergic skin reactions such as itching, redness of the skin and eczema. In some cases contact dermatitis may occur.

Hausen (1978): three patients, all involved in either cultivation of the plant Arnica or engaged in the chemical investigation or have had contact to Arnica tincture as employee in a pharmacy

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.

Leeuw (1987): A female got dermatitis after using jogging cream, a multi-combination with 32 constituens, one of them Arnica.

Pirker (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.

Spetolli (1998): a man, a hobby gardener, presents a chronic eczema involving the face and the hands, being present for 6 month and worsened after handling with plants.

Delmonte (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, a strong sensitizer and irritant.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

One case report was about drug interaction between warfarin and Arnica: 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. Therefore it was

concluded that there was an interaction between Arnica and warfarin. Because it is the first report about interaction with Arnica, it doesn't have to be labelled.

The safe use in pregnancy and lactation has not been investigated, therefore a use is not recommended.

Also, there have been no conclusive reports about use in children. Therefore, the use in children up to 12 years is not recommended.

5.6. Overall conclusions on clinical safety

Due to the long standing use and numerous safety studies, which have demonstrated the safe use, the use could be regarded as safe when patients with history of allergic reactions to Arnica, but also. the other Asteraceae are excluded. Likewise for pregnant women and children up to 12 years it is recommended not to use Arnica preparations due to lack of data.

6. Overall conclusions

Application of herbal preparations derived from Arnicae flos is widespread in Europe. Four specific herbal preparations could be identified which fulfil the requirements of traditional use. The safety of cutaneous use is well-documented for adults and adolescents. There are no adequate data for use in children below 12 years of age and also usage during pregnancy and lactation has not been established; the use in these special populations and situations is not recommended. Pharmacological data weakly support the traditional use though the knowledge on the bioavailability of Arnica constituents is limited. Clinical data demonstrate the safety with only a reasonable frequency of adverse events. Because of the allergic potential patients with a hypersensitivity to plants of the Asteraceae family are to be excluded. Clinical data are also supporting the traditional use of Arnica, however, the clinical trials are of limited quality and a well-established use cannot be justified. Because of inadequate data on genotoxicity a list entry is not supported.

On the basis of the available information the HMPC has concluded that no constituent with known therapeutic activity could be defined for the Arnica preparations listed in the monograph.

Annex

List of references