



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Juniperus communis* L., pseudo-fructus

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)	<i>Juniperus communis</i> L., pseudo-fructus (juniper berry)
Herbal preparation(s)	Comminuted cone berries Liquid extract (DER 1:1) extraction solvent ethanol 25% v/v Tincture (ratio of herbal substance to extraction solvent 1:5) extraction solvent ethanol 45% v/v Soft extract (DER 1.7-1.8:1) extraction solvent water
Pharmaceutical forms	Solid or liquid dosage forms
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1. Introduction

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

- Herbal substance(s)

The herbal substance is mentioned in the DAB 10, ÖAB 90, Ph. Fr. X, Ph. Helv. VII, British Herbal Pharmacopoeia 1983 and the European Pharmacopoeia 6.0. It is described as 'dried ripe cone berry of *Juniperus communis* L.'. The plant part is described as Juniperi pseudo-fructus. The English name is Common Juniper. Juniper belongs to the family of the Cupressaceae and the class of the Gymnosperma (Ph. Eur. 2008).

The plant has its origin in Northern Europe and mountain areas. The herbal substance is imported among others from Italy, from the countries on the Adriatic coast and from Albania. Leaves and needles occur with three on the branches. The berry-like fruits are open on the apex with a triradiate mark and depression which indicate the sutures of the three scales. They are violet to black-brown, often bluish pruinose and up to 10 mm in diameter. There are usually three, very hard, oblong, triangular seeds (Bruneton, 1999; Wichtl, 1994).

There are 4 subspecies of *Juniperus communis* occurring in Europe: ssp. *alpine* (NEILR.) CELAK; ssp. *communis*; ssp. *hemisphaerica* (J. et C. PRESL), ssp. *nana* (Willd.) Syme (Hänsel *et al.* 1993). Adulteration is occasionally observed with fruits of other *Juniperus* species. Fruits from *Juniperus oxycedrus* L. (cade- or prickly-jumper) are brown-red and larger than genuine juniper berries. *Juniperus sabina* L. (savine) has almost black fruits with a diameter of only 5-8 mm (Wichtl, 2002).

Other species of Juniper mentioned in literature are *Juniperus oxycedrus*, *Juniperus phoenicea* and *Juniperus virginiana*. Their oils are used only as fragrance ingredients in cosmetics (Anonymous, 2001).

Composition of the cone berries has been described by Hänsel *et al.* (1993), Schilcher & Heil (1994), Bruneton (1999), Barnes *et al.* (2007), Duke (1988), in the ESCOP monograph (ESCOP, 2003), Martin *et al.* (2006) The cone berries contain between 0.5 and 3.42 % of essential oil. The content of essential oil may vary depending on the origin of the herbal substance (Banthorpe *et al.* 1973).

The ESCOP monograph refers to cone berries from Greek plant material as containing high levels of essential oil. The cone berries may not contain less than 10 ml/kg of essential oil. The amount of essential oil can be up to 3%. The essential oil of Juniper cone berries contains about 105 constituents (ESCOP, 2003).

The following constituents were identified in Juniperi pseudo-fructus:

- Monoterpenes (about 58% of the essential oil); the essential oil contains mainly α -pinene (20%), limonene (8.7%), myrcene (8.5%) and β -pinene, myrcene, sabinene, 1,4-cineol, camphene, Δ^3 -carene, terpinen-4-ol, terpinolene, 4-terpineol, β -elemene-7-ol
- Sesquiterpenes: δ -cadinene, α -cadinene, β -cadinene
- Diterpenic acids: isocommunic acid; labdane diterpenes
- C₁₂ terpenoid: geijerone
- Tannins: proanthocyanidines (condensed), gallocatechin and epigallocatechin
- Flavonoids: amentoflavone, quercetin, isoquercitrin, apigenin and various glucosides

- Invert sugar (30%); glucose + fructose (about 30%) and pectin
- Organic acids: malic acid, ascorbic acid, glucuronic acid
- Lignan: desoxypodophyllotoxin
- Cerin
- Resins
- Juniper in: an amorphous substance isolated from decoctions (most probably a complex of sugars and tannins)

There is no consensus about the possible role of sugars, salts and saponins in the cone berries. The content of the cone berries varies with the origin and the ripening.

- Herbal preparation(s)

See above.

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

Not applicable.

1.2.

Information about products on the market in the Member States

Country	Specifications	Classification
Austria	Juniper cone berries It is recommended to start on day 1 with 5 cone berries , increasing the number every day by 1 cone berry (well chewed) up to 15 cone berries, then decrease the number (1 per day less) until 5 cone berries. So the duration of the therapy is 21 days, the maximum daily dose 15 cone berries.	Traditional use
Denmark	1. Salus herbal tea nr. 23 – a combination of Fructus carvi, aetheroleum eucalypti oil and fennel oil) Juniperi pseudo-fructus (11%) and Folium uvae ursi, folium betulae, <i>solidago</i> , equiseti herba and java tea leaf. 2. Salus tea – a combination of fructus Juniperi (12%) and birch leaf and horsetail (equisetum).	Authorised preparations
Estonia		All products containing Juniper cone berries are classified as non medical products.
Finland	No authorised preparations on the market	
Germany	Juniperi communis pseudo-fructus (1.7-1.8:1) extraction solvent: water. Pharmaceutical form: syrup for oral use in adults, Posology: once daily 2 g syrup (100 g syrup contains 28.5 g extract) [that means 0.57 g extract daily = ~ 1 g Juniperi pseudo-fructus]; traditionally used to support the elimination function of the kidney	WEU > 1976
Italy	Last mixed preparation withdrawn from the market in 2008 (lozenges and syrup in case of respiratory tract affections) (mixed combinations)	No authorised preparation
Romania	Liquid extract from Juniperi pseudo-fructus (2:10) Solvent: ethanol 70 % V/V: oral drops Dose: 3 times 10-15 drops daily, for maximum 4 weeks Warning: renal impairment Comminuted herbal substance for herbal tea Daily dose: 2.5 g Warning: renal impairment	Traditional use: on the market since 08/2006 as a diuretic Traditional use: on the market since 2004 as a diuretic These products are not traditional herbal medicinal products since they are not on the market for 30 years (or 15/15).
Spain	No products on the market registered as medicinal products Other preparations can be included with information the period of use (Not known, if on the market for 30 years and if they all have 1 and more indications)	

Regulatory status overview

Member State	Regulatory Status				Comments (not mandatory field)
Austria	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
Belgium	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input checked="" type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
Bulgaria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information
Czech Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
Denmark	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input checked="" type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Mixed preparations with pseudo-fructus authorised
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Only food supplements
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
France	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information
Germany	<input checked="" type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Pseudo-fructus and Preparations thereof authorised
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
Hungary	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information
Liechtenstein	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information
Lithuania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information
Luxemburg	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information
Malta	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
The Netherlands	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information
Norway	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information
Poland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information
Portugal	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
Romania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Juniperi pseudo-fructus as long standing traditional use
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input checked="" type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or

Member State	Regulatory Status				Comments (not mandatory field)
					registered preparations
Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
Spain	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
Sweden	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No authorised or registered preparations
United Kingdom	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No information

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

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

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

1.3. Search and assessment methodology

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Historically, the cone berries were used in a diuretic wine recommended by Cato the Ancient in his book '*De re rustica*'. Leclerc (1966) mentions also case studies in the treatment of rheumatoid arthritis with a preparation of 8 g essential oil mixed with 4 g diethylether, to be taken in a dose of 10 drops a day. The famous Oil of Haarlem or 'Haarlemmer olie' contains Juniper pseudo-fructus extracts.

Cone berries were traditionally used for dyspepsia (tincture and fluid extract), acute and chronic cystitis, arteriosclerosis, gout and inflammations. Furthermore, menstruation pain and bleeding, irritative cough, flu related bronchitis and diabetes are mentioned. Topical use is related to muscle pain and acute arthritic conditions (Hänsel *et al.* 1993; Barnes *et al.* 2007).

Babulka (2000) describes the use of medicinal herbs in Hungary. *Juniperus communis* is reported to be used for gastro-intestinal complaints, against rheumatic conditions and urinary tract diseases. It is considered as one of the 50 plant species with a long-standing tradition (at least 100 years).

Schulz (1929 cited by Schilcher & Heil, 1994) mentions the successful use of Juniper berry juice for treatment of nephritic hydrops. Whereas Klare (1927 cited by Schilcher & Heil, 1994) reports its use in case of paediatric tuberculosis. The first reports about the diuretic action in humans date from more than one century ago (Raphael, 1894 and Breitenstein, 1902, both cited by Schilcher & Heil, 1994). Most probably Raphael used 300 mg essential oil, two times daily during several months. Raphael considered the essential oil as a whole and not just one group of compounds, more particularly terpenes.

The German Commission E considered Juniper only for 'Dyspeptische Beschwerden' or dyspepsia as a general complaint (Commission E, 1984).

In France, *Juniperi pseudo-fructus* can only claim the following traditional therapeutic indications: (1) appetite stimulant; (2) renal evacuation of water; (3) diuretic adjuvant in case of minor urinary complications (Bruneton, 1999). In France, a toxicological dossier must be prepared for tinctures or extracts with an alcohol strength above 30% (V/V). No toxicological data have to be explicated for tinctures and extracts with an alcohol strength of 30% or lower (De Smet *et al.* 1993).

According to the ESCOP monograph, Juniper has a widely documented use as a remedy to enhance the renal elimination of water and for dyspeptic complaints. For these indications, the monograph refers to handbooks and not to original research (ESCOP, 2003).

Besides for its diuretic action, sometimes Juniper is also used as a urinary antiseptic, an indication which is disputed. The activity should be mainly limited to water diuresis, mainly due to an irritative action of terpinen-4-ol on the kidney tissue. More particularly, hyperaemia of the glomeruli should stimulate the activity of the secretory epithelium (Wichtl, 1994; Barnes *et al.* 2007).

The cone berries are widely used as a flavouring component in spirits (e.g. gin, genever). They play a traditional culinary role as an ingredient of 'choucroute' (France). Juniper is listed by the Council of Europe as a natural source of food flavouring (fruit N2). Category N2 indicates that the cone berries can be added to foodstuffs in small quantities, with a possible limitation of an active principle (as yet unspecified) in the final product (Barnes *et al.* 2007).

The highest average maximum use level reported for the oils is 0.006% in alcoholic beverages and 0.01% for the extract of pseudo-fructus in alcoholic and non alcoholic beverages (Duke, 1988).

In Belgium only *Juniperus sabina* L. cannot be used in food or food supplements. The cone berries of *Juniperus communis* L., *Juniperus procera* Hochst. and *Juniperus virginiana* L. are allowed as notified ingredients of food supplements. Also the use of *Juniperus oxycedrus* L. is allowed (Anonymous, 1997).

Assessor's comments

Preparations made of *Juniperi pseudo-fructus* mentioned in this assessment report can be considered as traditional herbal medicinal products as direct and indirect evidence exist that the sources date back for at least 30 years of medicinal use.

The most frequently cited traditional use of *Juniperi pseudo-fructus* concerns the renal elimination of water and dyspepsia. Apart from these indications some other uses are mentioned. They are related to infections (acute and chronic cystitis), arteriosclerosis, inflammatory conditions (muscles, joints, gout) and pain (menstruations). Also irritative cough, flu related bronchitis and diabetes are mentioned, these last indications mostly claimed for mixtures to be inhaled.

There is a lot of discussion about the safe use of *Juniperi pseudo-fructus* as a diuretic. Some sources refer to terpenes in the essential oil fraction as being the active substances. Their action should be based on hyperaemia of the glomeruli which is considered as an irritative action. Experimental pharmacological and toxicological data will be important in a constructive therapeutic approach.

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

Use of herbal preparations

- * Decoctions and infusions are traditionally used (Hänsel *et al.* 1993)
- * Liquid extract with 25% ethanol (DER 1:1 W/V) (Hänsel *et al.* 1993; Barnes *et al.* 2007)
- * Tincture with 45% ethanol (DER 1:5 W/V) (ESCOP, 2003; Barnes *et al.* 2007)
- * Soft extract with water (DER 1.7-1.8:1 W/V) (since 1976 on the German market).

Although decoctions as well as infusions are traditionally used, most standard sources with information for therapeutic practice prefer infusions. All secondary sources referring to the liquid extract and the tincture cite the British Herbal Pharmacopoeia (1983) as a source. Most probably the preparations are used already more than 30 years in Europe. The British Herbal Pharmacopoeia 1996 contains a shortened version of Juniper berry and contains information taken from the British Herbal Pharmacopoeia 1971. As the 1996 edition is a shortened version, no details are given about preparations. In this edition, the British Herbal Pharmacopoeia 1983 is mentioned as the second consolidated edition comprising parts 1 (1976), 2 (1979) and 3 (1981). As a consequence, the information in the 1983 edition is from a date former than 1983.

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

Route of administration

All preparations are used orally.

Posology

The dried herbal substance is used in a dose of 2 g with a maximum dose equivalent to 10 g per day. According to some authors, this posology corresponds with respectively 20 and 100 mg essential oil (Hänsel *et al.* 1993; Barnes *et al.* 2007; Ph. Eur. 2008).

In some traditions (Sebastian Kneipp) it is recommended to start on day 1 with 5 cone berries , increasing the number every day by 1 cone berry (well chewed) up to 15 cone berries, then decrease the number (1 per day less) to 5 cone berries. So the duration of the therapy is 21 days, the maximum daily dose 15 cone berries. In case of therapeutic result the duration should be limited to 3 weeks. It is not recommended to continue the treatment for more than 2 weeks if the symptoms persist (Anonymous, 2009).

Preparation of infusion (the concentration may vary according to the method of preparation):

- 2 to 3 g with 150 ml hot water, infusion time 10 minutes: to be drunk 3 to 4 times a day (Hänsel *et al.* 1993; ESCOP, 2003).
- 1:20 (W/V) with boiling water: 100 ml 3 times daily (Barnes *et al.* 2007).

The latter is more concentrated and most sources limit the single dose equivalent to 2 g. Therefore an amount of 2 g 2 to 3 times a day is preferred as recommended dose.

Powder: 2 to 8 g per day (Delfosse, 1998). It is not clear whether the use of powdered pseudo-fructus can be considered as tradition. Therefore the powdered form has not been taken to the monograph.

Tincture (1:5 W/V in 45% ethanol): 1-2 ml, 3 times daily (ESCOP, 2003; Barnes *et al.* 2007). As mentioned earlier there is indirect evidence for more than 30 years of medicinal use of the tincture. This preparation is taken to the monograph.

Tinctura Juniperi (Codex Français): 5 to 15 g to be enhanced and tapered progressively (Van Hellemont, 1985). Data about the duration of use are missing. Also the original source is not specified. This preparation is not included into the monograph.

Liquid extract (1:1 W/V in 25% ethanol): 2-4 ml 3 times daily (Barnes *et al.* 2007). As mentioned earlier, there is indirect evidence for more than 30 years of medicinal use of the liquid extract. This preparation is taken to the monograph.

Duration of use

As the duration of use for self medication is concerned, Juniper preparations should not be used for more than 2 weeks if the symptoms persist or worsen. Traditional use of the pseudo-fructus can be extended to 3 weeks if the symptoms alleviate (cf. Kneipp). For longer duration of use, medical advice should be sought.

Assessor's comments

According to several sources infusions may contain a maximal dose of 10 g cone berries per day. This dose is subject to some considerations.

As several authors mention the same dose, they may have copied each other.

The approximate weight of 100 cone berries is 16 g (Schilcher & Heil, 1994). A dose of 10 g would correspond to approximately 60 cone berries. This amount seems quite high.

The content of essential oil in cone berries may vary from 0.5 to 3.42%. When the content of essential oil is high, a daily dose of 10 g corresponds to about 342 mg of essential oil, whereas a maximal daily dose of 100 mg is recommended according to several sources.

It can be hypothesised that, when making an infusion, the volatile components of Juniper pseudo-fructus will not be extracted at 100%.

Taking the cone berries as such, a maximum dose of 15 cone berries per day is recommended. By this way of administration, the cone berries are not taken with water.

As a result of these considerations, for use as an infusion, a maximal dose of 2 g taken 3 times daily can be considered as a safe margin as, even with a 100% extraction in case of a high content on essential oil, the amount will be lower than 100 mg per day.

3. Non-Clinical Data

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

Diuretic activity

Although this assessment report is focused on Juniperi pseudo-fructus studies with essential oil are also included. In several studies, extracts as well as the essential oil were included in the same experimental setting. As a consequence, it is difficult to separate them.

SPECIES (references)	PREPARATION & INTERVENTION	RESULTS	COMMENTS
Rats receiving ADH by i.p. doses of 0.004 IU/100g 0.04 IU/100g 0.4 IU/100g (Stanic <i>et al.</i> 1998)	p.o.: 5 ml/100g body weight of (1) 10% aqueous infusion of <i>Juniperus</i> ; or (2) 0.1% aqueous solution of <i>Juniper</i> oil (with 0.2% of tween 20® solubilizer); or (3) 0.01 solution of terpinen-4-ol; or control solution of (4) water or water + 0.2% tween (rats not receiving ADH)	Day 1: reduction of diuresis: - 6% /24h with (1) and (2) - 30%/24h with (3) Day 2 and 3: stimulation of diuresis: + 43-44% with (1) (P<0.05) No stimulation with the other solutions.	These results are not convincing for the essential oil. The activity may be due to hydrophilic substances in the infusion.
Rats (Schilcher & Leuschner 1997)	p.o.: (1) <i>Juniper</i> oil 100 mg/kg/day (2) <i>Juniper</i> oil 333 mg/kg/day Duration: 28 days	No significant diuresis	Essential oil did not give a positive result.
Adult rats (Hänsel <i>et al.</i> 1993)	Infusions of cone berries: dissolved in 5 ml water and administered p.o. Doses of 8; 16; 32.5; 65; 125 and 250 mg plant equivalent or control	Total urine over a 4 h period; content of Cl ⁻ and urinary nitrogen enhanced with variable doses as compared to controls. With some doses a lower volume was excreted (with 8 and 250 mg).	No further specifications about the preparation used. Doses not adapted to animal weight No indications for dose dependency
Male rats (Lasheras <i>et al.</i> 1986)	All animals received 25 ml/kg (1) lyophilized water extract of <i>Juniperus pseudo-fructus</i> : 1000 mg/kg p.o.; or (2) the same volume of water	Volume urine excreted after 6 h and excretion of Na ⁺ , K ⁺ and Cl ⁻ was not increased versus controls	Only one dose tested.
Rats (Janku <i>et al.</i> 1957 ; Janku <i>et al.</i> 1960)	s.c. injection (1) <i>Juniper</i> oil: 1 ml/kg (2) NaCl solution (3) Terpinen-4-ol 0.1 ml/kg	Stimulation of diuresis after 4 / 24 h with (3) 78.4 ± 7.1 / 157.6 ± 7.1% (1) 44.0 ± 6.9 / 85.3 ± 7.6% (2) 14.3 ± 4.1 / 43.8 ± 4.6%	Essential oil less active than pure compound terpinen-4-ol

SPECIES (references)	PREPARATION & INTERVENTION	RESULTS	COMMENTS
Rats (Vollmer & Hübner 1937)	p.o. administration of: (1) aqueous infusion equivalent to 125 mg of <i>Juniper</i> ; or (2) same volume of water	+ 36% diuresis with (1) + 119% chloride excretion with (1)	A dose dependency is not clearly shown as twice or half of the dose had less effect.
Rabbits and mice (Vollmer & Weidlich 1937)	p.o. administration of: (1) aqueous infusion equivalent to 750 mg of <i>Juniper</i> (rabbits); or aqueous infusion equivalent to 50 mg of <i>Juniper</i> (mice); or (2) same volume of water	+ 20% diuresis with (1) in rabbits + 38% diuresis with (1) in mice	A dose dependency is not clearly shown as twice or half of the dose had less effect.

ADH = antidiuretic hormone (vasopressin)

p.o. = peroral

i.p. = intraperitoneal

s.c. = subcutaneous

Hypoglycemic activity

SPECIES (references)	PREPARATIONS & INTERVENTIONS	RESULTS	COMMENTS
Adult male mice treated or not with streptozotocin 200 mg/kg (Swanston-Flatt <i>et al.</i> 1990)	Dried cone berries of <i>Juniperus</i> were homogenized in the solid food as 6.25% by weight of the diet. + at the same time <i>Juniperus</i> supplied as infusion: of 1 g per 400 ml boiling water and during 15 min. This preparation replaced the drinking water Duration: 30 days	Basal plasma glucose significantly lower as compared to controls (P < 0.05) Body weight and fluid intake significantly less lowered as compared to controls (P < 0.05) No influence on food intake. No influence on residual plasma insulin by <i>Juniperus</i>	The study dealt with screening of several plants and plant extracts of which <i>Juniperus</i> .
Adult mice i.p. treated with streptozotocin 200 mg/kg (Hänsel <i>et al.</i> 1993)	Food with powder of cone berries 6.25% and drinking water with 1 g powder/400 ml = intervention group Food / drinking water without any addition = control	Weight loss, drinking volume and glycaemia: intervention < control (P < 0.05)	Streptozotocin used to provoke hyperglycaemia; No explainable mechanism for hypoglycaemia
Normal rats and Streptozotocin diabetic rats	p.o. administered during 24 days: Normal rats: Decoction of Juniper:	Significantly lowered glycaemia in normal and streptozotocin treated rats	Streptozotocin to provoke hyperglycaemia

SPECIES (references)	PREPARATIONS & INTERVENTIONS	RESULTS	COMMENTS
(Sánchez de Medina <i>et al.</i> 1994)	250 -500 mg/kg Streptozotocin rats: Decoction of Juniper: 125 mg/kg		Effect attributed to an increase in peripheral absorption of glucose, independent from plasma insulin levels
Streptozotocin diabetic mice (Gray & Flatt, 1997)	Juniper preparation	No hypoglycaemic effect	Lack of information about the methodology and results
Sealed dialysis tube (Gallagher <i>et al.</i> 2003)	<i>In vitro</i> diffusion of solution of glucose and NaCl (0.15 M) Measurement of glucose in external solution 1 g of powdered Juniper cone berries in 40 ml distilled water, heated until boiling and infused during 15 min.	Dialysis of glucose decreased by 6% after application of 50 g/l plant material	No physiological action. Effect mainly due to physicochemical properties Least active of all plants applied

i.p. = intraperitoneal

p.o. = peroral

Other activities

SPECIES (references)	PREPARATIONS & INTERVENTIONS	RESULTS	COMMENTS
Rats: carrageenan used as a pro-inflammatory agent (Mascolo <i>et al.</i> 1987)	p.o. administered: (1) Ethanol extract (80%) of <i>Juniperus pseudo-fructus</i> (1:3) 100 mg/kg (2) Indomethacin 5 mg/kg	Reduction of paw oedema: (1) -60 % (2) -45 % (1) > (2) : P < 0.01	Only one dose tested: no dose response relationship investigated
Male anesthetized (pentobarbital) normotensive rats (Lasheras <i>et al.</i> 1986)	i.v. administration of a lyophilized juniper pseudo-fructus extract: 25 mg/kg	Blood pressure enhanced and later lowered (-27%) as compared to the initial values	Results extracted from a screening program
Cell cultures (Hänsel <i>et al.</i> 1993;	Extract of juniper pseudo-fructus prepared with hot isopropanol	DNA-replication of HSV-1 lowered in isolated amnion cells	No cytotoxicity seen in a range of 1.5 to 7000 ng/ml

SPECIES (references)	PREPARATIONS & INTERVENTIONS	RESULTS	COMMENTS
Barnes <i>et al.</i> 2007)			Activity may be due to desoxy podophyllotoxin
Male mice (Lasheras <i>et al.</i> 1986)	i.v. administration of a lyophilized extract of <i>Juniperus pseudo-fructus</i> : 1.2 g/kg vs. controls	Thermal stimuli: analgesic response of 178%	Results extracted from a screening program
Male rats Male mice (Hänsel <i>et al.</i> 1993)	Lyophilized extract of <i>Juniperus pseudo-fructus</i> : topical application of 5 mg in 0.05 ml 0.9% NaCl or 750 mg/kg	Neither local anaesthetic activity, nor lowering of spontaneous motoric activity	
Gram + and Gram - bacteria, yeast, yeast-like fungi, yeasts and dermatophytae (Pepeljnjak <i>et al.</i> 2005)	Essential oil from Juniper cone berries, concentrations expressed as MIC	Gram + / -: MIC: 8-70% (V/V) Fungicidal activity against <i>Candida</i> : MIC: 0.78-2% (V/V) Dermatophytes MIC: 0.39-10% (V/V)	No comparator tested. The antibacterial concentrations vary considerably. The highest concentrations are not relevant in a therapeutic context.
Microbial organisms <i>Staphylococcus aureus</i> <i>Escherichia coli</i> <i>Enterobacter aerogenes</i> <i>Pseudomonas aeruginosa</i> (Rossi <i>et al.</i> 2000)	Essential oil distilled from aerial parts of <i>J. communis</i> spp. <i>alpine</i> Concentrations 0.03-2% (V/V) in agar	Inhibition zones for <i>S. aureus</i> and <i>E. coli</i> : controls < <i>J. communis</i> < antibiotics (ciprofloxacin, penicillin G)	Concentrations tested are within acceptable limits.
Gram-negative and gram-positive bacteria, fungi and <i>Candida albicans</i> (Glisic <i>et al.</i> 2007)	Essential oil fractions distilled from cone berries	Diameter inhibition zone components (8.75 µg) > antibiotics (gentamycin, tetracycline, erythromycin, vancomycin, clindamycin, streptomycin, ampicillin, penicillin: 6-30 µg)	No comparator for fungi and <i>Candida</i>
Antioxidant activity: ferric thiocyanate, thiobarbituric acid models	Methanol extracts from the <i>pseudo-fructus</i> of <i>Juniperus communis</i> L. ssp. <i>hemisphaerica</i> vs.	Activity of methanol extracts: Ferric thiocyanate: > 90% Butylated hydroxytoluene:	Approximative results given as a histogram Antioxidant activity

SPECIES (references)	PREPARATIONS & INTERVENTIONS	RESULTS	COMMENTS
(Emami <i>et al.</i> 2007)	Vitamin E and butylated hydroxytoluene Concentrations: 0.02%	> 80% vs. positive controls	with specific substrate.
Antioxidant activity: Difenylpicrylhydrazine (= DPPH) Desoxyribose degradation (Emami <i>et al.</i> 2007)	Essential oil of fruit	Concentration-response relationship * DPPH: Juniper fruit oil << vitamin C < quercetin * Desoxyribose <i>Juniper</i> fruit << quercetin	Antioxidant activity with specific substrate: should not be extrapolated
MCF-7/AZ breast cancer cells (Van Slambrouck <i>et al.</i> 2007)	Aqueous extracts of fruit Concentration rate: 0 – 180 µg/ml	Dose-dependent growth inhibition by extracts: ≥ 60 µg/ml: significant inhibition (P < 0.05) Invasion by MCF-7/AZ cells: significantly inhibited by <i>Juniper pseudo-fructus</i> extract (P < 0.05) Phosphorylation significantly inhibited by 50 µg/ml (P < 0.05)	No positive controls used
Human blood platelets 12(S)-Lipoxygenase inhibition (Schneider <i>et al.</i> 2004)	<i>Juniperi communis pseudo-fructus</i> (1) Methylene chloride (2) Ethyl acetate extract	Inhibition of 12-HETE biosynthesis (P<0.05) at 100 µg/ml: (1) 66.2 ± 4.03% (2) 76.2 + 3.36%	Quantification fractionation on Sephadex LH-20 and GC-MS

12-HETE = 12-OH-eicosatetraenoic acid

HSV-1 = Herpes simplex virus 1

i.v. = intravenous

MCF-7/AZ = mammal carcinoma cell line

MIC = minimal inhibitory concentration (= no growth)

p.o. = per oral

vs = versus

Assessor's overall conclusions on pharmacology

The earliest experimental evidence for a diuretic activity goes back more than 70 years. Rats were mostly used as subjects. The p.o. way of administration corresponds to traditional use in humans. The extracts are mostly prepared from whole cone berries, but also the essential oil and terpinen-4-ol are

used. The diuretic activity cannot be characterized as only aquaretic, i.e. increasing the volume of water excreted by the kidneys, as several authors found also an increased excretion of an organic component (mainly chloride). In one study, the whole extract of the cone berries seemed to be more potent as compared to the essential oil, but in this study the rats were pretreated with antidiuretic hormone. It should be mentioned that the diuretic activity is not always consistent and obtained with relatively high doses if converted to human conditions (when recalculating the number of berries to be taken, this leads to more than 100 berries/day). There are no systematic investigations reported about the possible beneficial consequences of the diuretic activity. Only one study with total extract intravenously administered to anaesthetised normotensive rats mentioned a lowering effect on blood pressure without any link to increased diuresis.

In contrast with the traditionally claimed indication, there is no experimental evidence for use in dyspeptic complaints.

Juniper pseudo-fructus preparations had a hypoglycaemic activity in streptozotocin pretreated mice and rats. It should be taken into account that streptozotocin quickly leads to high glucose levels and that the results cannot be extrapolated to human diabetic conditions.

Other activities include an anti-inflammatory (*in vivo* and *in vitro*) effect, antimicrobial activity towards some viruses (HSV-1), bacteria (*E. coli* and *S. aureus*) and *Candida albicans*. The antimicrobial and anti-inflammatory activity may underpin the traditional claim of urinary infections (see comment on the high concentrations). Most of the experiments were carried out with the essential oil or its components. However, extrapolation of *in vitro* results to *in vivo* conditions remains difficult, due to the sometimes high concentrations of oil used and the direct contact with micro-organisms which may result in cytotoxic rather than antimicrobial effects.

Furthermore antioxidant and antitumoral activity is reported in some experimental *in vitro* models. Extrapolations of these activities remain speculative.

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

No data were found about absorption, distribution, metabolism, elimination and pharmacokinetic interactions with other medicinal products.

Assessor's overall conclusions on pharmacokinetics

No data are available. The complex phytochemistry of Juniper cone berries makes it difficult to conceive any representative pharmacokinetic study.

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

Acute toxicity

LD₅₀ of a lyophilized water extract of Juniper pseudo-fructus in male mice: 3000 mg/kg intraperitoneally. Juniper is considered as a mild toxic agent (Hänsel *et al.* 1993).

Acute toxicity was tested on 10 Wistar rats of a standardised 80% ethanolic extract of Juniper pseudo-fructus (2.5 g/kg) during 7 days. No side effects were reported. All animals survived. A dose of 3 g/kg induced hypothermia and mild diarrhoea in 10-30% of animals (Hänsel *et al.* 1993).

Other sources mention an oral LD₅₀ of the herbal substance or Juniper pseudo-fructus: 6.28 g/kg or at least 5 g/kg in rats (De Smet *et al.* 1993).

Reproductive and developmental toxicology

Doses of 300 and 500 mg (p.o.) of an of *Juniperi communis pseudo-fructus* extract (extraction solvent 50% ethanol) was administered to 10 Swiss albino female rats from day 1 to 7 of pregnancy. On day 10 the implantation was controlled by laparotomy. In the 300 mg/kg group 5 out of 10 and in the 500 mg/kg 8 out of 10 animals had no implantation. Another series of doses was administered on day 14, 15 and 16, to the rats which showed implantation. On day 18 the rats were again laparotomized in order to control abortifacient activity. The number of embryos developing was lower in the intervention group as compared to the rats receiving vehiculum only: in rats which showed implantation sites (pregnant), no pups could be delivered.

In another experiment, three of the rats without implants on day 10 were allowed to mate with males after 2 months of rest. Although mating was successful, no implantations were reported.

Based on the results of the preceding experiments, the investigations concluded that *Juniperi communis pseudo-fructus* extract had antifertility and abortifacient effects in rats. This type of experiment cannot be used to evaluate teratogenicity as the study was not adapted for teratogenicity (Agrawal *et al.* 1980; Hänsel *et al.* 1993; De Smet *et al.* 1993; ESCOP, 2003; Barnes *et al.* 2007).

Genotoxicity

There are no genotoxicity data available for *Juniperus communis* or preparations thereof. In the tar of *Juniperus oxycedrus* (cade oil) benzpyrenes were found in the nanogram/g range, but this does not apply to *J. communis*.

According to one source, the chemical composition of *J. communis* oil and *J. communis pseudo-fructus* extract is considered as similar when genotoxicity is considered (Anonymous, 2001). However, the difference in composition between the oil and water extracts of *Juniperi pseudo-fructus* must be taken into consideration.

Assessor's overall conclusions on toxicology

There is no serious concern about possible acute toxicity of the *Juniperi pseudo-fructus*. No data on carcinogenicity and genotoxicity exist. Incomplete investigations concerning reproductive toxicity point to antifertility and abortifacient effects of the preparation tested. The antifertility testing cannot be used to conclude on teratogenicity because the design of the study is not appropriate.

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

There are no data available on human pharmacodynamics.

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

There are no data available on human pharmacokinetics.

4.2. Clinical Efficacy

4.2.1. Dose response studies

Not available.

4.2.2. Clinical studies (case studies and clinical trials)

Not available.

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

Not available.

4.3. Overall conclusions on clinical pharmacology and efficacy

Not applicable.

5. Clinical Safety/Pharmacovigilance

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

Not applicable.

5.2. Patient exposure

Historically, the cone berries were used in a diuretic wine recommended by Cato the Ancient in his book '*De re rustica*' (Leclerc, 1966). The use of Juniper cone berries can be considered as a century-long standing practice.

On the other hand, there is a lack of systematically obtained subacute clinical safety and toxicity data for Juniper, creating the need for safety update reporting. Standard references give contradictory information, mostly based upon interpretation by the authors and not on clinical data.

Schilcher & Heil are not convinced of the renal toxicity of *Juniperus* oil because quite a lot of sources may just have copied the doubtful renal side effects (Schilcher & Heil, 1994; ESCOP, 2003).

Nevertheless, the German Commission E only considered dyspepsia as the only therapeutic indication. The use of essential oil is questioned by some authors (Bruneton, 1999). A quote supported by Duke (1988): "...*this drug is no longer recommended for various kidney disorders by the medical profession. Since much safer and more effective diuretic and carminative drugs exist, the use of Juniper in folk medicine should also be abandoned...*". The author does not refer to case studies or causality reporting. Not all German sources limit the use of Juniper. Weiss & Fintelman (1999) consider the cone berries of *Juniperus communis* as valuable '*aquaretica*'. They include the following conditions for traditional use: unspecific dysuria, sensitive bladder ('Reizblase') and prophylaxis of relapsing urolithiasis and urinary infections.

Juniper berry oil was given GRAS (Generally Recognised as Safe) status by the Flavouring Extract Manufacturers Association (FEMA) in 1965 and is approved by the U.S. Food and Drug Administration for food use. Juniper berry was included in the Council of Europe list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product (De Smet *et al.* 1993).

5.3. Adverse events and serious adverse events and deaths

Most handbooks warn for renal damage when *Juniperus communis* preparations are used for their aquaretic properties. Although the monograph is conceived for the pseudo-fructus, some reporting on the essential oil is included as well. This must allow for comparisons with pseudo-fructus starting from the oil content.

Renal damage has been reported after long-term use (several months). Overdosing with the essential oil leads to renal damage. Cramp-like pain and bleeding of the uterus has been mentioned (Hänsel *et al.* 1993).

The most detailed study is made by Schilcher & Heil (1994) mentioning that ancient sources do not warn for renal complications in humans. Massive doses that were much higher than the 400-500 mg essential oil Raphael (1894, cited by Schilcher & Heil 1994) and Gmeiner (1904, cited by Schilcher & Heil 1994) tested on themselves. Furthermore, starting from cone berries it will be impossible to reach massive dose equivalents: the weight of 100 cone berries is 16 g. The weight of a daily dose of 15 cone berries is 2500 mg. With a 1% content of essential oil, the oil equivalent will be 25 mg. There have been no adverse events mentioned after the use of broiled cone berries, although it must be specified that this preparation is a residual product of cone berries from which the essential oil has been removed (Schilcher & Heil, 1994).

According to Semon (1844; cited by Schilcher & Heil 1994), *Juniperus* oil increases the renal circulation and dose-dependent damage can occur (stranguria, dysuria, hematuria and ischuria). The activity of *Juniperus* oil was formerly compared with turpentine oil. Most probably the findings for turpentine oil were copied to *Juniperus* oil without factual analysis. Also Potter (1898; cited by Schilcher & Heil, 1994) mentioned *Juniperus* cone berries in his *Materia Medica*: "...may set up renal irritation, in large doses producing strangury, priapism, hematuria, suppression of the urine and uremic convulsions...", a wording taken over by the German literature.

Although the volatile oil is reported to be generally non-sensitising and non-phototoxic, dermal irritation has been recognized with Juniper and positive patch test reactions have been documented. The latter are attributed to the irritant nature of the Juniper pseudo-fructus extract. Burning, erythema, inflammation with blisters and oedema have been reported after external application of the essential oil (Barnes *et al.* 2007).

Of 26 patients examined for suspect plant dermatitis, 14 showed positive patch test reactions to Juniper pseudo-fructus extract (nature of extract not specified) (Mathias *et al.* 1979).

Seizures and kidney damage have been reported in individuals who took more than 10 g of Juniper per day or who took high doses of Juniper for longer than 4 weeks. The way and form of administration is however not specified. Also the exact dose ("...more than 10 g...") is not mentioned. The same source recommends a maximal daily dose of 10 g of dried Juniper pseudo-fructus. However the source is not scientifically documented, which brings uncertainty about this information (<http://www.rxlist.com/Juniper/supplements.htm> last visit on 2 July 2009). If such reactions occur, they can be caused by contamination of the oil (Schilcher *et al.* 2007).

Serious adverse events and deaths

None reported.

5.4. Laboratory findings

No data are available.

5.5. Safety in special populations and situations

Safety in special populations and situations

The use of *Juniperus communis* is contra-indicated in case of inflammation of the kidney, nephritis and pyelitis (Commission E, 1984; De Smet *et al.* 1993; ESCOP, 2003).

Intrinsic (including elderly and children)/extrinsic factors

No data available. Because of the tighter dose margin, a restriction to adults is recommended.

Drug interactions

There is limited evidence from preclinical studies that Juniper may influence glucose levels in diabetes (ESCOP, 2003; Barnes *et al.* 2007).

Use in pregnancy and lactation

There are no data available about use during pregnancy and lactation.

Overdose

In case of prolonged use and overdose, urine will smell of violets. There may be renal irritation and pain in and near the kidney, strong diuresis, albuminuria, haematuria, purplish urine, gastrointestinal upsets, accelerated heartbeat and blood pressure. Rarely symptoms of central stimulation like convulsions occur as well as metrorrhagia and abortion (Wichtl, 1994; Duke, 1988; Barnes *et al.* 2007).

Drug abuse

No data available.

Withdrawal and rebound

No data available.

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

No data available.

5.6. Overall conclusions on clinical safety

With the use of cone berries serious adverse events are improbable as the amount of substance to be ingested before problems occur will be high. Issues of safety monitoring are related to:

- the preparation: the concentrating effect on the compounds depends upon the solvents and the way of extraction; as both the cone berries and the essential oil have a possible antioxidant affect, respecting the original composition is recommended
- the patients: apart from preclinical data on reproductive toxicology, little is known about possible groups at risk and interactions with other medication
- it can be expected that the kidney will be the first target organ

6. Overall conclusions

The traditional use of *Juniperus communis pseudo-fructus* and preparation thereof should be limited to the stimulation of renal water excretion and to dyspeptic disorders. The former is sustained by tradition and by experimental evidence, the latter only by tradition.

There is a need for systematic pharmacovigilance reporting in order to address the issue of subacute safety when using different preparations of Juniper.

Benefit-risk assessment

Juniper berries as well as the essential oil are described in the European Pharmacopoeia. The macroscopic identification of the berries can be done easily. Adulteration and contamination remain possible: unripe berries should not be used. Essential oil should only be prepared from ripe berries, without any needles or wood from the tree. Contaminated oil can indeed affect the renal function, so quality should be proven. However, reports on cases of overdose or prolonged use are vague and of questionable quality, not meeting the pharmacovigilance criteria. Pharmacokinetics of Juniper components are not known.

As genotoxicity and carcinogenicity are not studied, a list entry in the 'Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products' cannot be established.

The therapeutic indications do not relate to life threatening conditions and they are supported by traditional use evidence. There are more potent conventional medicines with known benefits based on well-established use. Groups at risk can be defined as constitutional: elderly, pregnant and breastfeeding mothers and children. There are no reports on drug interactions, but combining Juniper with diuretic compounds is not recommended. Although there is experimental evidence for a blood glucose lowering effect, there are no reports on clinical consequences of combining *Juniperus* with blood glucose lowering medicines. There are no clinical trials on Juniper berries and Juniper oil, but European tradition goes back to more than 2000 years for both.

Annex

List of references