EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/HMPC/12401/2010
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Juniperus communis* L., aetheroleum

Based on Article 10a of Directive 2001/83/EC as amended (well-established use)

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)	*Juniperus communis* L., aetheroleum
Herbal preparation(s)	Essential oil
Pharmaceutical forms	Herbal preparations in liquid dosage forms for oral and cutaneous use
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1. Introduction

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

- Herbal substance(s)

Not applicable.

- Herbal preparation(s)

The essential oil is obtained by steam distillation from the ripe, non-fermented berry cones of Juniper (*Juniper communis* L.). A suitable antioxidant may be added (Ph. Eur. 2008; Hänsel *et al.* 1993).

Juniper berries (*Juniperi pseudo-fructus*) are mentioned in the European Pharmacopoeia 6.0. It is described as 'dried ripe cone berry of *Juniperus communis* L'. Juniper belongs to the family of the *Cupressaceae*, and the class of the *Gymnospermae* (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 are needles occurring in whorls of three on the branches. The berry-like fruits are open on the apex with a triradiate mark and depressions that 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).

Four subspecies of *Juniperus communis* occurre in Europe: ssp. *alpine* (NEILR.) CELAK; ssp. *communis*; ssp. *hemisphaerica* (J. et C. PRESL), ssp. *nana* (Willd.) Syme (Hänsel *et al.* 1993).

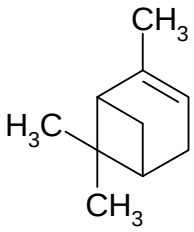
Other species of *Juniper* mentioned in the literature are *Juniperus oxycedrus*, *Juniperus phoenicea* and *Juniperus virginiana*. Their oils are used as fragrance ingredients in cosmetics (Anonymous, 2001).

The ESCOP monograph refers to the 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).

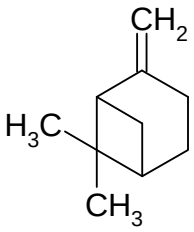
The following constituents were identified:

The composition of the essential oil varies depending upon the source but consists mainly of monoterpene hydrocarbons, principally monoterpenes (about 58% of the essential oil) (ESCOP 2003):

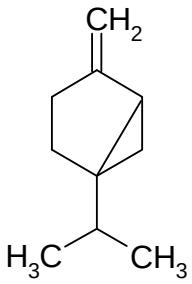
- α-pinene (24.1-55.4%) (range Ph. Eur. 2008 = 20-50%)
- β-pinene (2.1-6.0%) (range Ph. Eur. 2008 = 1.0-12%)
- β-myrcene (7.3-22.0%) (range Ph. Eur.2008 = 1.0-35%)
- sabinene (1.4-28.8%) (range Ph. Eur. 2008 = less than 20%)
- limonene (2.3-10.9%) (range Ph. Eur. 2008 = 2.0-12%)
- terpinene-4-ol (0.7-17.0%) (range Ph. Eur. 2008 = 0.5-10%)
- α-terpineol (up to 1.7%)
- α-thujene (0.6-1.9%)
- caryophyllene (1.3-2.3%) (Ph.Eur. 2008 for β–caryophyllene = less than 7.0%)



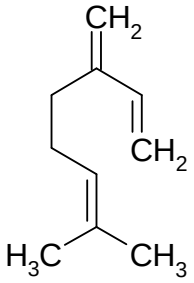
α-pinene



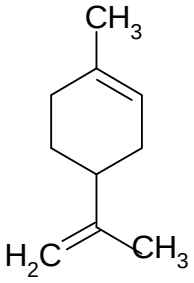
β-pinene



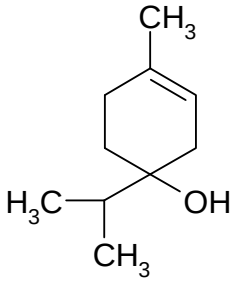
sabinene



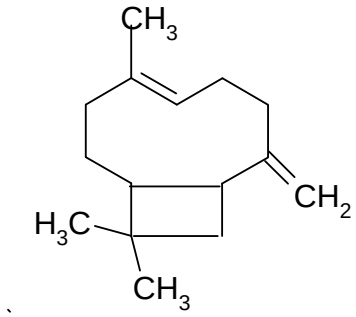
β-myrcene



limonene



Terpinen-4-ol



β-caryophyllene

The qualitative composition of the oil is constant, but as already mentioned, the percentage of the components analysed with GC-MS may vary considerably. Apart from the terpenes mentioned above, some other terpene compounds occur in lower concentrations (essential oil from Italian origin) (Hänsel *et al*. 1993):

- γ-muurolen (7.6%)
- humulen (2.1%)
- α-muurolen (1.1%)
- β-elemen (1%)
- β-farnesen (0.9%)
- α-cubeben (0.9%)
- 4-thujanol (0.8%)
- α-cadinol (0.8%)
- γ-cadinen (0.7%)
- aromadendren (0.6%)
- α-copaen (0.4%)

- bornylacetate (0.4 %) (range Ph.Eur. less than 2.0%)
- camphen (0.3%)
- campholenaldehyd (0.2%)
- p-cymene (0.2%)
- verbenon (0.2%)

Additionally the Ph.Eur. limits the concentration of α–phellandrene to less than 1.0%.

- 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.

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

Regulatory status overview

Member State	Regulatory Status				Comments (not mandatory field)
Austria	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Preparations with essential oil authorized
Belgium	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	Mixed preparations with essential oil authorized
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Denmark	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	Mixed preparations with essential oil authorized
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Only food supplements
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Germany	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Preparations with essential oil authorized
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No information
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	No authorized or registered preparations
Slovak Republic	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	Mixed preparations with

Member State	Regulatory Status				Comments (not mandatory field)
					essential oil authorized
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No authorized or registered preparations
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ 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.

Details about preparations

Country	Specifications	Classification
Austria	Juniper *oil* • Soft gelatin capsules with 20 mg essential oil • Increasing the amount of urine • Posology: 1 capsule 3 x daily Numerous combination products are on the market; indications: oral use – increase of the amount of urine; cutaneous use: rheumatic complaints.	Authorized product > 1993
Belgium	Juniper oil only combined with other essential oils or substances from essential oils (eucalyptol, eugenol, gaultheria oil, cajaput oil, menthol, *Mentha piperita* oil) for upper respiratory tract affections.	Authorized preparations
Denmark	1. Aetheroleum Juniper*i* 1g/100 gram Aetheroleum menthae piperitae 2. Combination product with peppermint oil, aetheroleum carvi, eucalypti oil and fennel oil	Authorized preparations
Estonia		All products containing Juniper oil are classified as non medical products.

Germany	Juniper oil - Bath oil Pharmaceutical form: bath additive, as bath additive Therapeutic indication: traditionally used to promote the blood circulation of the skin[1]. Posology: for use in adults and adolescents over 12 years; if necessary 3-4 x weekly: 15-20 ml bath additive/full bath for 10-20 min at 35-38°C; 6.993 g Juniper oil/100 g (approx. 94.5 ml) bath additive. Additional information There is a monopreparation that was marketed since 1978 until the end of the nineties: Wacholderöl=*Juniperi aetheroleum* 10 g/100 ml. The indication was "*Linderung von Rheumabeschwerden, Bandscheibenbeschwerden*" (mild symptoms of rheumatic diseases/discs). Juniper oil • Soft capsules • Dyspeptic complaints with minor abdominal cramps, flatulence and feeling of fullness • For oral use in adults and adolescents > 12y • Posology: 1 capsule with 100mg/day • Interaction: possible influence on blood glucose level in diabetics • Side effects: Long-standing use and overdose may cause renal impairment Juniper oil There are combination products with terpentine oil and *Juniperi oleum* the indication of which is in the field of rheumatic diseases.	Traditional $\geq$ 1976 Not any longer on the market. WEU $\geq$ 1976
Slovakia	Juniperi aetheroleum only combined with *Menthae piperitae aetheroleum*; *Caryophylli aetheroleum*; *Eucalypti aetheroleum*	Authorized preparation

[1] This wording was from the substance/indication list established by a German expert commission for the traditional medicinal products (with respect to the earlier German legislation). It was the strategy to have a reduced indication.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Leclerc (1966) mentions 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 Extra Pharmacopoeia Martindale (Todd, 1967) refers to the British Pharmaceutical Codex of 1949 when mentioning the essential oil of Juniper, as the oil distilled from the dried ripe fruits of *Juniperus communis*. According to this source juniper oil is carminative and antiseptic and has been used in flatulence and colics. During excretion it irritates the genito-urinary tract and may cause contraction of the uterus. It has been used as a diuretic but it should not be employed during pregnancy or in the presence of renal disease.

In Germany, Juniper oil is registered as an authorized preparation since 1976.

Soft capsules are used internally against dyspeptic complaints with minor abdominal cramps, flatulence and feeling of fullness. This indication is considered as a well established use.

It is also traditionally used as a bath additive to promote the blood circulation of the skin.

Kommission E considers Juniper only for 'Dyspeptische Beschwerden' or dyspepsia as a general complaint (Kommission E, 1984).

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 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, hypereamia of the glomeruli should stimulate the activity of the secretory epithelium (Wichtl 1994; Barnes *et al.* 2007).

Assessor's comments

Therapeutic indications for the essential oil of *Juniperus* are mostly related to diuresis and dyspepsia.

There is a lot of discussion about the safe use of *Juniperus*. Some sources refer to the hyperemic effect of terpenes in the essential oil fraction to explain the diuretic action. Their action should be based on hyperemia of the glomeruli which is considered as an irritative action. Experimental pharmacological and toxicological data will be important in a constructive therapeutic approach.

The indication for external use (promoting blood circulation in the skin) can be questioned as being too close to a health claim for cosmetics but no medicinal indication.

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

Doses used

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

Dose regimens for essential oil of *Juniperus* can be derived from the posology of the Juniper berries (*pseudo-fructus*). Some sources mention 2 to 4 drops per day (Van Hellemont 1985; Delfosse 1998).

Other sources recommend a daily dose of 20 to 100 mg (Hänsel et al. 1993). According to the Extra Pharmacopoeia Martindale (Todd, 1967) the dose can be 50 to 200 mg. It is not specified whether this dose is meant as a single or a daily dose. Most probably the upper daily limit is 200 mg.

In Germany soft capsules with 100 mg essential oil are registered as an authorized preparation. Posology is limited to 100 mg or one capsule orally per day. A bath additive with 6.993 g oil/100 g (approx. 94.5 ml) is used 3 to 4 times weekly: 15-20 ml bath additive/full bath for 10-20 min at 35-38°C.

Juniperus preparations should not be used for more than 4 weeks without medical advice.

Assessor's comments

There are some discrepancies as far as the dose is concerned. Doses up to 200 mg are mentioned with no clear reference to the daily dose regimen. It is recommended to stick to the reported doses of registered preparations. Therefore 60-100 mg per day is proposed to be taken in 1 to 3 single doses.

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

See section 1.2 and 2.2.

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 aetheroleum* studies with *Juniperi pseudo-fructus* are also included. In several studies, the essential oil as well as extracts are 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/100 g 0.04 IU/100 g 0.4 IU/100 g (Stanic *et al.* 1998)	p.o.: 5 ml/100 g body weight of (1) 10% aqueous infusion of *Juniper*us; or (2) 0.1% aqueous solution of Juniper 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%/24 h with (1) and (2) - 30%/24 h 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) Juniper oil 100 mg/kg/day (2) Juniper oil 333 mg/kg/day	No significant diuresis.	Essential oil did not give a positive result.

Species (references)	Preparation & intervention	Results	Comments
	Duration: 28 days		
Rats (Janku *et al.* 1957 ; Janku *et al.* 1960)	s.c. injection (1) Juniper oil: 1 ml/kg (2) NaCl solution (3) Terpinene-4-ol 0.1 ml/kg	Stimulation of diuresis after 4 /24 h with (3) 78.4 $\pm$ 7.1 / 157.6 $\pm$ 7.1% (1) 44.0 $\pm$ 6.9 / 85.3 $\pm$ 7.6% (2) 14.3 $\pm$ 4.1 / 43.8 $\pm$ 4.6%	Essential oil less active than pure compound terpinene-4-ol.

ADH = antidiuretic hormone (vasopressin) p.o. = peroral
i.p. = intraperitoneal s.c. = subcutaneous

Other activities

Species (references)	Preparations & interventions	Results	Comments
Rats: carrageenan used as a pro-inflammatory agent (Mascolo *et al.* 1987)	p.o. administered: (1) Ethanol extract (80%) of *Juniperi pseudo-fructus* (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.
Cell cultures (Hänsel *et al.* 1993; Barnes *et al.* 2007)	Extract of *Juniperi pseudo-fructus* prepared with hot isopropanol	DNA-replication of HSV-1 lowered in isolated amnion cells.	No cytotoxcitiy seen in a range of 1.5 to 7000 ng/ml Activity may be due to desoxypodophyl-lotoxin.
Gram + and Gram – bacteria, yeast, yeast-like fungi, yeasts and dermatophytae (Pepeljnjak *et al.* 2005)	Essential oil from Juniper cone berries, concentrations expressed as MIC	Gram + / -: MIC: 8-70% (V/V) Fungicidal activity against Candida: 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 *Staphylococcus aureus* *Escherichia coli* *Enterobacter aerogenes* *Pseudomonas aeruginosa* (Rossi *et al.* 2000)	Essential oil distilled from aerial parts of *J. communis spp. alpine* Concentrations 0.03-2% (V/V) in agar	Inhibition zones for *St. aureus* and *E.coli*: controls < *J.communis* < antibiotics (ciprofloxacine, penicillin G).	Concentrations tested are within acceptable limits.

Species (references)	Preparations & interventions	Results	Comments
Gram-negative and gram-positive bacteria, fungi and *Candida albicans* (Glisic *et al.* 2007)	Essential oil fractions distilled from cone berries	Diameter inhibition zone components (8.75 µg) > antibiotics (gentamycin, tetracycline, erythromycin, vancomycine, clincamycine, streptomycin, ampicylline, penicilline: 6-30 µg).	No comparator for fungi and *Candida*.
Antioxidant activity: Difenylpicrylhydrazine (= DPPH) Desoxyribose degradation (Emami *et al.* 2007)	Essential oil of pseudo-fructus	Concentration-response relationship * DPPH: Juniper fruit oil << vitamin C < quercetin * Desoxyribose Juniper fruit << quercetin	Antioxidant activity with specific substrate: should not be extrapolated.

HSV-1 = Herpes simplex virus 1 p.o. = perorally

MIC = minimal inhibitory concentration (= no growth)

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

There were no data found about absorption, distribution, metabolism, elimination, or pharmacokinetic interactions with other medicinal products.

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

Acute toxicity

Gavage of megadoses is mentioned in original literature sources: up to 5 or 30 g Juniperus oil for one rabbit (respectively Gmeiner 1904 and Senon 1844 cited by Schilcher & Heil 1994). Whereas the rabbits survived a dose of 15 g essential oil, a dose of 30 g killed all animals within 24 hours.

Acute toxicity of the essential oil intraperitoneally injected in mice resulted in a mean LD_{50} = 750 (range 685-815) mg/kg. Acute toxicity of the essential oil intraperitoneally injected in guinea-pigs was LD_{50} = 1200 (range 1170-1230) mg/kg (Anonymous 2001). A mean LD_{50} of 700 (range 654-746) mg/kg was reported for mice after intramuscular application. For guinea-pigs after subcutaneous application a mean LD_{50} of 1440 (range 1425-1455) mg/kg was reported (Anonymous 2001).

Cardiovascular and respiratory toxicity

The effect of Juniper oil (Juniper species not stated) on the cardiovascular and respiratory system was evaluated using 20 rabbits, anesthetized with urethane. When Juniper oil was administered intramuscularly as well as orally (concentrations 0.5%, 2.5% and 5% in corn oil: dose 1 mg/kg) a prolonged and slowly developing hypotonia occurred (Anonymous, 2001).

Skin irritation

Undiluted Juniper berry oil did not induce skin irritation when applied to the backs of hairless mice and swine. Moderate skin irritation occurred after the oil was applied to intact or abraded skin of rabbits for 24 hours under occlusive patches.

No phototoxicity effects were reported when the oil was applied to the skin of hairless mice and swine (Anonymous, 2001).

Reproductive and developmental toxicology

Experiments with Juniperus extracts were performed in several animal species. Abortifacient activity of Juniper has been observed in rats after oral administration of a 50% ethanolic extract at 300 mg/kg. (Agrawal et al. 1980, cited in ESCOP 2003)

There are no data about reproductive and developmental toxicology of Juniper oil.

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 Juniperus communis (Hänsel et al. 1993).

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

3.4. Overall conclusions on non-clinical data

Pharmacology

The earliest experimental evidence for a diuretic activity goes back more than 70 years. Rats were mostly used as subjects. The peroral 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 anorganic components (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 an 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. There are no systematic investigations reported about the possible beneficial consequences of the diuretic activity. Only one study with total extract intravenously administered to anesthetised normotensive rats mentioned a lowering effect on blood pressure without any link to increased diuresis.

Price & Price (2007) consider the diuretic properties as basic for Juniper: "… the property of *Juniperus communis* upon which all are agreed is its diuretic effect …".

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

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, although the concentrations used are not always physiologically relevant. 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 partially high concentrations of oil used in the assays 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.

Pharmacokinetics

The complex phytochemistry of Juniper essential oil makes it difficult to conceive any representative pharmacokinetic study. As a consequence no data are available.

Toxicology

Most reports of toxicity refer to the essential oil or essential oil components. No data on carcinogenicity and genotoxicity exist.

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

No data available.

5.2. Patient exposure

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 Kommission E only considered dyspepsia as the only therapeutic indication. The use of essential oil is questioned by some authors (Bruneton, 1999). Herewith 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.

In Belgium, only *Juniperus sabina* L. is prohibited to be used in food or food supplements. The cone berries of *Juniperus communis* L., *Juniperus procera* Hochst. and *Juniperus virginiana* L. are permitted, as notified ingredients of food supplements. Also the use of *Juniperus oxycedrus* L. is allowed (Anonymous, 1997).

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.

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).

According to Semon (1844; cited by Schilcher & Heil 1994), Juniper oil increases the renal circulation and dose dependent damage can occur (stranguria, dysuria, hematuria and ischuria). The activity of Juniper oil was formerly compared with terpentine oil. Most probably the findings for terpentine oil were copied to Juniper oil without factual analysis. Also Potter (1898; cited by Schilcher & Heil, 1994) mentioned Juniper 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 a *Juniperi pseudo-fructus* extract. Burning, erythema, inflammation with blisters and oedema have been reported after external application of the essential oil (Barnes *et al.* 2007).

Two irritation reactions were observed in 2 of 20 subjects patch-tested with Juniper berry oil for 24 hours. No skin irritations occurred when 8% Juniper berry oil was mixed with petrolatum and tested with closed patches for 48 hours. In another exposure test with the same mixture applied, no skin sensitization was seen (Anonymous, 2001). A patch test using full strength oil for 24 h produced two irritation reactions in 20 subjects. On the other hand a 48 h closed patch test in humans tested with 5% oil in petrolatum produced no irritation and no irritation and sensitization or phototoxic reactions were reported (De Smet *et al.* 1993). In a study including 86 patients with allergic reactions Juniper berry oil caused allergic reactions in 6 patients (Anonymous, 2001).

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 cone berries. However the source is not scientifically documented (http://ezinearticles.com/?Juniper---Uses-and-Side-Effects&id=1071369 last

access on September 13 2010). If such reactions occur, they may be caused by contamination of the oil (Schilcher *et al.* 2007).

It can be questioned whether the oil of Juniper, blamed for its renal toxicity was contaminated with terpentine oil. Some sources even use the term 'falsification'. By preference the concentration of α- and β-pinene ideally should be low, whereas the content of terpinene-4-ol should be high, the latter substance being considered as an active compound. Moreover, for such essential oils, the renal irritation should be minimal (Schilcher & Heil, 1994; ESCOP, 2003).

Serious adverse events and deaths

None reported.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

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

Intrinsic (including elderly and children) /extrinsic factors

No data available.

Drug interactions

There is limited evidence from preclinical studies that Juniper may influence glucose levels in diabetes. However, there will be no warning in the monograph, as the experimental data from different experiments are contradicting (ESCOP, 2003; Barnes *et al.* 2007).

Use in pregnancy and lactation

As the cone berries should not be used during pregnancy and lactation, use of essential oil in these conditions is also not recommended. It is generally accepted that Juniper should not be used by pregnant women as uretral contractions could occur (Duke 1988).

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).

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

Issues of safety monitoring of the essential oil of *Juniperus* are related to:

- the preparation: the effect depends on the concentration of compounds and thus on the solvents used and the way of extraction; as both the cone berries and the essential oil have a possible antioxidant effect, the original composition has to be considered;
- the patients: apart from preclinical data on reproductive toxicology, little is known about possible groups at risk and interactions with other medication;
- the physiological condition: it can be expected that the kidney will be the first target organ.

There seems to be confusion about the possible toxicity of Juniper oil and data obtained with terpentine oil. The findings reported by Semon (Semon 1844; cited by Schilcher & Heil 1994) have been copied several times without further analysis.

6. Overall conclusions

The traditional use of *Juniperus communis aetheroleum* 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 essential oil is described in the European Pharmacopoeia. 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 bad quality, not meeting the pharmacovigilance criteria. Pharmacokinetics of Juniper components are not known.

As genotoxicity has not been studied, a list entry cannot be granted.

The therapeutic indication for cutaneous use is close to a health claim for cosmetics and the status of a medicine in that context can be questioned. The therapeutic indications for oral use are far from life threatening and suitable for self-medication. They have to be considered within a traditional context. There are more potent conventional medicines with known benefits based on well established use. Standard groups of risk may be: elderly, pregnant mothers and children. There are no reports on drug interactions, but combining Juniper with diuretic compounds is not recommended. Although there is some experimental evidence for a blood glucose lowering effect with extracts of Juniper cone berries, the blood glucose lowering effect by the essential oil was not studied. There are also no reports on clinical consequences of combining Juniper oil with blood glucose lowering medicines. No clinical trials on Juniper oil are available; however, the European tradition is much older than 30 years.

Annex

List of references