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Committee on Herbal Medicinal Products (HMPC)

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

Draft – Revision 1

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Juniperi pseudo-fructus (galbulus)
Herbal preparation(s)	Traditional use i) Herbal substance Not applicable. ii) Herbal preparations a) Comminuted herbal substance b) Liquid extract (DER 1:1), extractions solvent 25% ethanol V/V c) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% V/V d) Soft extract (DER 1.7-1.8:1), extraction solvent water
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use. Herbal preparation in liquid dosage forms for oral use.
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Note: This draft revised assessment report is published to support the public consultation of the draft revised European Union herbal monograph on *Juniperus communis* L., galbulus (pseudo-fructus). It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft revised monograph.

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Abbreviations

BPH	British Herbal Pharmacopoeia
cDNA-RDA	Representational Difference Analysis of cDNA
ER	Endoplasmatic Reticulum
ESCC	Esophageal Squamous Carcinoma Cells
5-FU	5-FluoroUracyl
GC-MS	Gas Chromatography – Mass Spectrometry
IC50	Inhibitory Concentration 50%
STZ	Streptozotocin

For other abbreviations the reader is referred to the technical document EMA/HMPC/441838/2013 or the list of references.

Introduction

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

- Herbal substance(s)

In the first edition of the assessment report dd. 2012 the herbal substance is mentioned in the DAB 10 (1991), ÖAB 90 (1991), Ph. Fr. X (1996), Ph. Helv. VII (1987), BPH (1983) and the Ph. Eur. 6.0 (2008). It was described as 'dried ripe cone berry of *Juniperus communis* L.' containing not less than 10 ml/kg of essential oil, calculated with reference to the anhydrous drug and was formerly named as *Juniperus pseudo-fructus*. The plant part is now described as *Juniperi galbulus* in the most recent edition of the European Pharmacopoeia monograph. The English name is Common Juniper. Juniper belongs to the family of the *Cupressaceae* and the class of the *Gymnosperma* (Ph. Eur., 2019).

The plant is native in Europe northern Asia and North America. Leaves are needles occurring with three on the branches. The berry-shaped cone is globular, up to 10 mm in diameter, and violet-brown or blackish-brown, frequently with a bluish bloom. It consists of 3 fleshy scales. The apex has a 3-rayed closed cleft and 3 not-very-clearly defined projections. A remnant of peduncle is frequently attached at the base. The fleshy part is crumbly and brownish. It contains 3 or, more rarely, 2 small, elongated, extremely hard seeds that have 3 sharp edges and are slightly rounded at the back, acuminate at the apex. The seeds are fused with the fleshy part of the cone berry in the lower part on the outside of their bases. Very large, oval oil glands containing sticky resin lie at the outer surface of the seeds. (Bruneton, 1999; Wichtl, 1994, Ph. Eur., 2019).

Juniperus communis L. is included in the World Flora online as an accepted name in the genus *Juniperus* (family *Cupressaceae*). The same source mentions 64 records matching the search criterium *Juniperus communis* L. (Anonymus, 2022). 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, 2004).

Juniperus communis pseudo-fructus changed in *Juniperus communis galbulus* in the most recent monograph of the Ph. Eur. The *galbulus* is commonly named 'cone berries'. The cone berries contain a minimum of 10 mL/kg of essential oil (anhydrous drug; concentration to be considered as a requirement by the Ph. Eur.) (Ph. Eur., 2019). According to other sources, the amount of essential oil can be up to 3% (Chatzopoulou & Katsiotis, 1993). For the essential oil the following constituents are given, according to Ph. Eur. (% are requirements by the Ph. Eur.; not to be considered as the most possible range): α-pinene (20 to 50 %), sabinene (maximum 20%), β-pinene (1 to 12 %), β-myrcene (1 to 35 %), α-phellandrene (maximum 1.0 %), limonene (2 to 12 %), terpinen-4-ol (0.5 to 10 %), bornyl acetate (maximum 2.0 %), β-caryophyllene (maximum 7.0 %) (Ph. Eur., 2013).

ESCOP mentions as other constituents tannins (citing Schulz and Hermann 1980), flavonoids (citing Hiermann *et al.,* 1996; Lamer-Zarawska, 1980), diterpene acids, aldehydes and alcohols (citing De Pascual Teresa, 1973; De Pascual Teresa, 1977), fatty alcohols (citing De Pascual Teresa, 1977) (ESCOP, 2003). Further about 30% of glucose and fructose (Wichtl, 1984).

- 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. Search and assessment methodology

Search terms: *juniperus, juniper, oil, fructus, berry, pseudo-fructus*: from 2010 – May 2021.

Scientific databases: Medline, PubMed, Cochrane Database of Systematic Reviews, EMBASE.

Pharmacovigilance resources: Eudravigilance.

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form	Regulatory Status
Juniperi galbulus (*Juniperi pseudo-fructus*)	Digestive complaints with minor abdominal cramps, flatulence and feeling of fullness.	Herbal tea Adults and adolescents: SD 2.5 g DD 2.5-10.0 g No longer than 1 week without medical advice, if the acute symptoms do not improve.	1986, DE, German Standard Marketing Authorisation
soft extract from *Juniperi galbulus* (*Juniperi pseudo-fructus*) (1.7-1.8:1), extraction solvent: water	Traditional use to support the elimination function of the kidney.	Adults and adolescents: SD 0.57 g Used as a syrup	1976 until 04/2011, DE, TU
Juniperus communis L., *galbulus* (*Juniperi pseudo-fructus*); comminuted herbal substance	Traditionally used in mild urinary complaints and in mild gastrointestinal disorders like dyspepsia and bloating.	Comminuted herbal substance. 2 g infuse for 30 min in 150 ml of boiling water, drink 2 – 3 times daily. If the symptoms persist during the use of the infusion for	Present in register in 1955, medicinal use confirmed in 1959. National registration in Poland since 11.05.1993. TU 18.02.2014

Active substance	Indication	Pharmaceutical form	Regulatory Status
		longer than 2 weeks, please consult a doctor.	
Juniperus communis L., *galbulus* (*Juniperi pseudo-fructus*); comminuted herbal substance	Used in mild urinary complaints, insufficient urination and in mild gastrointestinal complaints like insufficient bile secretion and bloating.	Comminuted herbal substance. 2.5 g of the comminuted herbal substance infuse for 30 min in 150 ml, strain and drink 1 – 2 times daily.	Present in register in 1955, medicinal use confirmed in 1959. national registration in Poland since 1993.

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

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

Not applicable.

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

Not applicable.

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

Not applicable.

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

Historically, the cone berries were used to 'clean the kidneys' as written by Rembertus Dodonaeus, who cites Galenus (Dodnaeus 1608). 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.

Cone berries were traditionally used for dyspepsia (a.o. 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 quoting: Berger, 1952; BHP, 1983; Poletti et al., 1990; Schauenherg and Paris, 1977; Valnet, 1984) (Barnes et al., 2007 quoting: German Commission E; Tindle et al., 2005; Thomas et al., 2001; WHO, 2004).

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 (Commision E, 1984).

Besides for its diuretic action, sometimes Juniper was also reported to be used as a urinary antiseptic, an indication which is disputed. The activity should be mainly limited to water diuresis. Biochemical, pathological and histological investigations are questioning neither the juniper oil nor the terpinene-4-ol produced nefrotoxic effects, which were formerly thought to trigger the diuretic action (Schilcher and Leuschner, 1997).

In Belgium *Juniperus sabina* L. cannot be used in food or food supplements. Cone berries leaves and wood of *Juniperus communis* L., are allowed as notified ingredients of food supplements. When the berries are used, the following warnings have to be mentioned: no to be used during more than 6 weeks without medical advice, not to be used in case of renal dysfunction (Anonymus, 1997, updated in 2017).

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 BPH (1983) as a source. The BPH (1976) refers to five therapeutic actions: diuretic, antiseptic, carminative, stomachic and antirheumatic. The BPH 1996 only kept the diuretic action. It contains a shortened version of Juniper berry and no details are given about preparations. In this edition, the BPH 1983 is mentioned as the second consolidated edition comprising parts 1 (1976), 2 (1979) and 3 (1981).

All preparations are used orally. The dried herbal substance is used in a dose of 2 g with a maximum dose equivalent to 10 g per day. According to the most recent monograph of the European Pharmacopoeia, this posology corresponds at least with respectively 20 and 100 mg essential oil (Ph. Eur., 2019).

Some traditions (Sebastian Kneipp 1821-1897) recommend in case of a weak stomach 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 (Kneipp, 1891). The use of the whole berries has to be considered as an historical tradition. As there are no products on the market containing whole berries, their use is not any longer included in the monograph.

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

Schilcher & Heil estimated the approximate weight of 100 cone berries as 16 g (Schilcher & Heil, 1994). A dose of 10 g would correspond to approximately 60 cone berries. A daily dose of 10 g corresponds to a minimum of 0.1 ml essential oil, according to the Ph. Eur. (2019).

As a result of these considerations, for use as an infusion, a maximal dose of 2 g taken up to 4 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.

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

(Wichtl, 1984).

- 1:20 (W/V) with boiling water: 100 ml 3 times daily (Barnes *et al.,* 2007, citing the BPH, 1983).

The latter is more concentrated and most sources limit the single dose equivalent to 2 g. Therefore, an amount of 2 g 2 to 4 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 (BHP, 1983). As mentioned earlier there is indirect evidence for more than 30 years of medicinal use of the tincture. This preparation is kept in the monograph.

Tinctura Juniperi (Codex Français): 5 to 15 g to be enhanced and tapered progressively (cited by 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 (BHP, 1983).

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. For longer duration of use, medical advice should be sought.

Table 2: Overview of historical data

Herbal preparation	**Documented use / Traditional use**	**Pharmaceutical form**	**Reference**
Crushed berries	Traditional use as diuretic and urinary antisepticum.	Herbal tea: boiling water (ca. 150 ml) is poured over 2-3 g of the freshly crushed berries and after 10 min. strained 3 times daily	Wichtl, 1984
Liquid extract	Traditional use as diuretic	Liquid extract with 25% ethanol DER 1:1 W/V 2-4 ml 3 times daily	BPH, 1983 BPH, 1996
Tincture	Traditional use as diuretic	Tincture with 45% ethanol DER 1:5 W/V 3 times daily	BHP, 1983 BPH, 1996

2.3. Overall conclusions on medicinal use

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Comminuted herbal substance	Traditionally used in mild urinary complaints and in mild gastrointestinal disorders like dyspepsia and bloating.	2 g infuse for 30 min in 150 ml drink 2 – 3 times daily. If the symptoms persist during the use of the infusion for longer than 2 weeks, please consult a doctor.	PL since 1955
Comminuted herbal substance	Used in mild urinary complaints, insufficient urination and in mild gastrointestinal complaints like insufficient bile secretion and bloating.	2.5 g infuse for 30 min in 150 ml, strain and drink 1 – 2 times daily.	Present in register in 1955, medicinal use confirmed in 1959. National registration in Poland) since; 1993.
Comminuted herbal substance	Digestive complaints with minor abdominal cramps, flatulence and feeling of fullness.	2.5 g of the crushed or comminuted herbal substance in boiling water as a herbal infusion, 1 - 4 times daily	DE since 1986
Liquid extract (DER 1:1) with 25% ethanol v/v	Diuretic	2-4 ml 3 times daily	BHP, 1983
Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% v/v	Diuretic	1-2 ml 3 times daily	BHP, 1983
Soft extract (DER 1.7-1.8:1), extraction solvent water	Traditional use to support the elimination function of the kidney	0.57 g once daily	DE from 1976 until 04/2011

Based on the data in Table 3 the following therapeutic indications are proposed:

Indication 1)

Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary

tract in minor urinary tract complaints.

The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use.

Indication 2)

Traditional herbal medicinal product for symptomatic relief of digestive disorders such as dyspepsia and flatulence.

The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use.

As compared to the former edition of the monograph changes based on Table 3 were made in the revised version of the Monograph in section 4.1. and 4.2.

- Adjuvant has been deleted in therapeutic indication 1). 'Adjuvant' supposes a defined treatment to which the herbal treatment can be added. As there is no clear instruction in that way, the therapeutic indication is reduced, not any longer mentioning the use as adjuvant.
- All preparations have indication 1). On the contrary, indication 2) is only applicable to the comminuted herbal substance (see correct references in Table 3).
- The posology of the comminuted herbal substance has been adapted according to the introduction of a new herbal medicinal product.

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

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.

It should be noticed that mainly mice and rats are used and that the plant preparations are not always sufficiently documented. Only a part of the studies demonstrate a dose response relationship. A distinction should be made between an aquaretic and a salidiuretic effect.

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

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
(1) 10% aqueous infusion of Juniperus; (2) 0.1% aqueous solution of Juniper oil (with 0.2% of tween 20 solubilizer); (3) 0.01% solution of terpinen-4-ol; (4) control solution of water or water + 0.2% tween; (5) vasopressin dose response	One day experiment p.o.: 5 ml/100 g body weight of (1), (2), (3) or (4) (5) i.p.: 0.004 IU/100 g b.w., 0.04 IU/ 100 g b.w., 0.4 IU/ 100 g b.w.)	*In vivo*: female rats single dose after 24 h of fastening cumulative urine volume was measured during the first 5 h after oral administration of test solutions and again after 24 h	Stanic *et al.,* 1998	reduction of diuresis: - (1) and (2) comparable to 0.004 IU vasopressin/100 g bw - (3) comparable to 0.4 IU vasopression/ 100 g bw
(1) 10% aqueous infusion of Juniperus; (2) 0.1% aqueous solution of Juniper oil (with 0.2% of tween 20 solubilizer); (3) 0.01% solution of terpinen-4-ol; (4) control solution of water or water + 0.2% tween (5) 5 mg hydrochlorotiazide + 50 mg amyloride dissolved in 1250 ml water	3 day experiment p.o.: 5 ml/100 g body weight	*In vivo*: female rats cumulative urine volume continuously measured during first 5 h after each administration and again after 24 h, i.e. before the next dose	Stanic *et al.,* 1998	Day 1: (5) stimulation of diuresis (+51%) (3) reduction of diuresis (-30%) No significant action of (1) and (2). Day 2: (5) stimulation of diuresis (+74.5%) ($p<0.001$) (1) stimulation of diuresis (+43%) ($p<0.05$)

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
				No significant action of (2) and (3). Day 3: (5) stimulation of diuresis (+70%) ($p<0.01$) (1) stimulation of diuresis (+44%) ($p<0.05$) No significant action of (2) and (3).
Infusions of cone berries (no further information)	Infusion in 5 ml water and administered p.o. Doses of 8; 16; 32.5; 65; 125 and 250 mg plant equivalent or control (not described if amount per animal or per kg) Control: water	*In vivo*: adult rats	Hänsel *et al.,* 1993 citing Vollmer & Giebel, 1938	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).
Lyophilized water extract of *Juniperus pseudo-fructus* (no further information)	All animals received 25 ml/kg	*In vivo:* male rats	Lasheras *et al.,* 1986	Volume urine excreted after 6 h and excretion of Na+, K+ and

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
	(1) extract equivalent to *Juniperus pseudo-fructus*: 1000 mg/kg p.o.; or (2) the same volume of water			Cl- was not increased versus controls
Aqueous infusions of *Juniperus pseudo-fructus* (no further information)	p.o. administration of: (1) aqueous infusion equivalent to 125 mg of Juniper; or (2) same volume of water	*In vivo:* rats	Vollmer & Hübner, 1937	+ 36% diuresis with (1) + 119% chloride excretion with (1). Reduction of the effect in higher doses, according to the authors due to toxic effects.
Aqueous infusion of *Juniperus pseudo-fructus* (no further information)	p.o. administration of: (1) aqueous infusion equivalent to 750 mg; or aqueous infusion equivalent to 50 mg (mice); or (2) same volume of water	*In vivo:* rabbits and mice	Vollmer & Weidlich, 1937	+ 20% diuresis with (1) in rabbits + 38% diuresis with (1) in mice. Reduction of the effect in higher doses, according to the authors due to toxic effects.

3.1.2. Secondary pharmacodynamics

Bais *et al.* (2014) and Bais & Patel (2018) published phytopharmacological reviews on *Juniperus communis*. They described various activities like anticancer, hepatoprotective, antifungal activity, antioxidant, antidiabetic activity, antibacterial, anti-inflammatory activity, anti-microbial activity, anticataleptic activity, antimalarial activity, lipid lowering activity, neuroprotective, anti-arthritic activity and anti mycobacterial activity.

Hypoglycemic activity

In an *in vivo* study, adult male mice were treated with STZ (streptozotocin) 200 mg/kg and several plant extracts were tested a.o. *Juniperus communis pseudo-fructus*. Juniperus berries were homogenized in the solid food as 6.25% by weight of the diet, and at the same time Juniperus was supplied as an infusion of 1 g per 400 ml boiling water during 15 min. This preparation replaced the drinking water. The experiment lasted for 30 days. The basal plasma glucose in the treated group was significantly lower as compared to controls ($P < 0.05$). The negative influence on body weight and fluid intake was significantly less as compared to controls ($P < 0.05$). There was no influence on food intake and on residual plasma insulin by Juniperus. The findings belong to a screening of several plants. No further investigations were done (Swanston-Flatt *et al.,* 1990).

In another experiment rats were treated with STZ or not. During 24 days the rats received a decoction of juniper berries: the normal rats got a dose of 250 to 500 mg/kg, the STZ-treated rats got 125 mg/kg. In both groups, treated or non treated with STZ, glycemia was significantly lowered. The hypogycemic effect was attributed to an increase of peripheral absorption of glucose, independent from plasma insulin levels. (Sánchez de Medina *et al.,* 1994).

Gray and Flatt did not see an influence on glucose levels when STZ treated diabetic mice were treated with a preparation of juniper berries. There is a lack of information about the methodology and results (Gray & Flatt, 1997).

In a sealed dialysis tube the *in vitro* diffusion of a solution of glucose and NaCl (0.15 M) was measured in the external solution after infusion of a 1 g of powdered Juniper cone berries in 40 ml distilled water, heated until boiling and infused during 15 min. The dialysis of glucose decreased by 6% after application of 50 g/l plant material. There was no physiological action. The effect is mainly due to physicochemical properties. Juniper was the least active of all plants applied (Gallagher *et al.,* 2003).

A methanolic extract of *Juniperus communis* (MEJC) (100 mg/kg, 200 mg/kg, b.w) was administered orally in rats made diabetic with STZ-nicotinamide and compared with the standard group (Glibenclamide 10 mg/kg, b.w). Fasting blood glucose levels along with the different biochemical parameters were evaluated on 21st day by collecting blood through retro-orbital puncture. The extract showed significant ($P<0.01$) reduction in blood glucose levels along with the different lipid profile parameters (with increase in HDL levels) in diabetic rats. According to the authors the dose dependent and significant anti-diabetic and antihyperlipidemic property of the extract, providing the rationale behind its use as an effective drug against type-2 diabetes (Banerjee *et al.,* 2013).

Other activities

In vivo experiments

An ethanol (80%) extract of *Juniperus pseudo-fructus* (1:3) 100 mg/kg was p.o. administered in rats with paw inflammation wherein carrageenan was used as a pro-inflammatory agent. There was a reduction of the paw oedema with 60% as compared to the 45% reduction by indomethacin 5 mg/kg ($P<0.01$). Because only one dose was investigated, no dose-response relationship can be evaluated (Mascolo *et al.,* 1987).

Intravenous administration of 25 mg/kg lyophilized juniper *pseudo-fructus* extract to male anesthetized normotensive rats enhanced blood pressure in a first phase and lowered it with 27% in a second phase, as compared to initial values. The observations were part of a screening program of several plants (Lasheras *et al.,* 1986).

Intravenous administration of a lyophilized extract of *Juniperus pseudo-fructus*, 1.2 g/kg vs. controls, enhanced the analgesic response to thermal stimuli with 178%. These results came out of a screening program (Lasheras *et al.,* 1986).

Topical application of a lyophilized extract of *Juniperus pseudo-fructus*, 5 mg in 0.05 ml 0.9% NaCl equivalent to 750 mg/kg did not reveal any local anaesthetic activity, or lowering of spontaneous motoric activity in male rats and mice (Hänsel *et al*., 1993).

The analgesic activity of 100 mg/kg and 200 mg/kg of a methanolic extract of Juniperus pseudo-fructus was tested in adult albino mice *in vivo*. The effect of the extract and pethidine (10 mg/kg) i.p on the tail flick test was inhibited by naloxone (2 mg/kg) i.p. The extract showed a dose dependent and significant ($P<0.01$) inhibition of writhing response. In case of formalin test, the extract showed a prominent dose dependent inhibition in the late phase comparable to acetylsalicylic acid (100 mg/kg) ($P<0.01$). The tail flick test revealed the central activity of the extract mainly after 30 minutes of administration. This central analgesic activity was confirmed by the blocking effect of naloxone. The doses applied are in the supratherapeutic area (Banerjee *et al.,* 2012).

In vitro experiments

Antioxidant activity of the methanol extracts from the *pseudo-fructus* of *Juniperus communis* L. ssp. *hemisphaerica* was compared to Vitamin E and butylated hydroxytoluene (concentrations: 0.02%). The activity was studied in ferric thiocyanate and thiobarbituric acid models. The activity of methanol extracts was > 90% and the one of the butylated hydroxytoluene > 80% (Emami *et al*., 2007).

The dose-dependent inhibition of MCF-7/AZ breast cancer cells by aqueous extracts of juniper fruit was tested in a concentration range of 0 – 180 µg/ml. The effects were as follows: a dose-dependent growth inhibition which was significant from > 60 µg/ml ($P < 0.05$); a significant inhibition of the invasion by MCF-7/AZ cells by the extract ($P < 0.05$), as well as a significant inhibition of the phosphorylation by 50 µg/ml ($P < 0.05$). No positive controls were used (Van Slambrouck *et al*., 2007).

The inhibition of 12-HETE (12-OH-eicosatetraenoic acid) biosynthesis of methylene chloride (1) and ethyl acetate (2) extracts of *Juniperi communis pseudo-fructus* was tested in human blood platelets. Quantification of 12-HETE was done by fractionation on Sephadex LH-20 and GC-MS (Gas Chromatography-Mass Spectrometry). 12(S)-lipoxygenase was inhibited by 100 µg/ml: 66.2 + 4.03% by (1) and 76.2 + 3.36% by (2) (Schneider *et al*., 2004).

Variable concentrations of some fractions of a non-defined extract of *Juniperus communis* fruit (500, 1000 and 2000 µg/ml solutions) were used *in vitro* on urinary stones brought out from human kidney. Neutral (normal saline), positive (sodium bicarbonate) and negative (acetic acid) control groups were also prepared. Significant findings were obtained in urinary stones composed of calcium oxalate (50%), calcium hydrogen phosphate (20%), magnesium ammonium phosphate, (10%) and ammonium urate (20%). There was a dose-response relationship seen in de stone weight reduction with some fractions of the extract of *Juniperus* fruit (Barzegarnejad *et al.*, 2014).

Methanol, water and ethyl acetate of *Juniperus communis* berry extracts displayed moderate to potent growth inhibitory activity against bacterial triggers of rheumatoid arthritis, ankylosing spondylitis and multiple sclerosis. The methanol and water extracts displayed the broadest specificity, inhibiting the growth of all bacteria tested. The ethyl acetate extract also displayed antibacterial activity, inhibiting

the growth of 9 of the 13 bacterial strains (69%). The ethyl acetate was most effective at inhibiting the growth of *P. mirabilis, P. vulgaris* and *S. aureus*, each with MIC's $\leq$ 500 µg/mL. The methanol and water extracts also proved effective at blocking the proliferation of the colorectal cancer cell line CaCo2 and HeLa cervical cancer cell growth, with IC50 values in the 1300-2500 µg/mL range. The *Juniperus communis* berry extracts tested in the study all had LC50 values towards *Artemia franciscana nauplii* well in excess of 1000 µg/mL and were therefore deemed to be nontoxic. (Fernandez & Cock, 2016).

Lantto *et al.* (2012) studied the cell signaling processes by detecting proteins p53, Bcl-2 and p65 by Western blotting and defining the caspase 3 activity in cells. A pilot study for differences in gene expression between treated and untreated cells was carried out by the cDNA-RDA (representational difference analysis) method. The authors observed that quercetin and piceatannol - well-known compounds of plant origin - and juniper berry extract affected the caspase 3 activity and/or the amount and localization of p53 in cancerous cells. (Lantto *et al.,* 2012).

Lantto *et al.* (2016) investigated the influence of phenolic compounds on apoptotic cell death. The study dealt with the effects of a juniper berry extract (*Juniperus communis* L.) on p53 protein, gene expression and DNA fragmentation in human neuroblastoma SH-SY5Y cells. In addition, the phenolic composition of the extract was investigated. The authors found that juniper berry extract activated cellular relocalization of p53 and DNA fragmentation-dependent cell death. Differentially expressed genes between treated and non-treated cells were evaluated with the cDNA-RDA method at the early time point of apoptotic process when p53 started to be activated and no caspase activity was detected. Twenty one overexpressed genes related to cellular stress, protein synthesis, cell survival and death were detected. They included endoplasmic reticulum (ER) stress inducer and sensor HSPA5 and other ER stress-related genes CALM2 and YKT6 indicating that ER stress response was involved in juniper berry extract mediated cell death. Concentrations of 15 phenolic compounds were quantified. The main groups of them were flavones, flavonols, phenolic acids, flavanol and biflavonoid including glycosides of quercetin, apigenin, isoscutellarein and hypolaetin. The authors suggested that juniper berry extract induced the p53-associated apoptosis through the potentiation and synergism by several phenolic compounds (Lantto *et al.,* 2016).

An *in vitro* study aimed to control *Campylobacter jejuni* using an alternative strategy of low doses of *Juniperus communis* fruit preparations to target bacterial adhesion properties in the first step of biofilm formation. The anti-Campylobacter activity of a juniper fruit crude extract and its fractionated biflavonoids, flavone glycosides, and purified amentoflavone, of juniper fruit essential oil and of juniper fruit postdistillation waste material extract. For accurate quantification of adherent *C. jejuni*, the optimised digital Polymerase Chain Reaction (PCR) and quantitative real-time PCR was used for construction of standard curves and quantification. It was shown for the first time that juniper fruit formulations can effectively inhibit adhesion of *C. jejuni* to polystyrene. Furthermore, ≥94% of the antiadhesion activity of juniper fruit crude extract and juniper fruit essential oil remained under food-related conditions: modified culture medium with glucose, or a stainless steel surface, or mixed co-cultures of *C. jejuni* and *Listeria monocytogenes*. The authors indicate that addition of juniper fruit formulations can control growth and adhesion of *C. jejuni* and thus limit food chain transmission of campylobacters (Klančnik *et al.,* 2018).

A study examined which of the herbal infusions used in treatment and reduction of symptoms of UTIs have the greatest efficacy, and at which concentration levels (5.85 mg/mL; 0.59 mg/mL; 0.29 mg/mL). The results obtained suggest that the Microtox test can be successfully used to assess the healing properties of herbal infusions. The results of the experiments carried out using the Microtox test showed, that both, in preventative medicine, as well as in aiding treatment of UTIs, the biggest benefit is brought by herbal infusions of wild thyme extract and birch leaf (at all concentrations), and

also by infusions at higher concentrations (approx. 5.85 mg/mL) of agrimony, dwarf everlast flower, lingonberry leaf, artichoke herb, goldenrod, and juniper berry (Okragla *et al.,* 2017).

Lee *et al*. investigated the anti-cancer mechanisms of *J. communis* extract (JCo) on a human gingival squamous cancer cell line and evaluated the synergistic effects of JCo combined with 5-fluorouracil (5-FU). *Juniperus communis* fruit was freshly obtained from Nepal and underwent steam distillation to gain the product that divided two layers, one was aqueous layer and the other was lipid layer, which was *J. communis* extract (JCo extract). JCo extract inhibited oral cancer cell growth, and might be less cytotoxic to normal cells than to cancer cells. The IC50 of the OECM-1 cells exposed to JCo extract for 24 h was 46.20±2.71 µg/ml (no further details given of the DER of the extract). After JCo extract treatment, cell cycle arrest was observed at the G0/G1 phase. JCo extract also caused an increase in the sub-G1 phase and cell apoptosis via the intrinsic and extrinsic apoptosis pathways. JCo extract combined with 5-FU presented a synergistic effect to reduce cell viability. It can be concluded that JCo extract inhibited oral cancer cell growth by inducing cell cycle arrest and activating cell apoptosis, and that JCo extract significantly synergized with 5-FU (Lee *et al.,* 2020).

The *in vitro* bioactivity of the active ingredient in selected antimicrobial magistral drug formulations and plant extracts used in folk medicine were investigated comparatively. The active ingredients of magistrals such as; boric acid, balsam of Peru, zinc oxide, *Calendula* tincture, thymol, resorcinol, crystal violet were used as well as fruit or leaf extracts of *Juniperus excelsa* (Je), J. *sabina* (Js), J. *foetidissima* (Jf), *J. communis* ssp. Nana (Jcsn), and *J. oxycedrus* spp. *oxycedrus* ripe (Joso) to determine the antimicrobial activity against gram positive bacteria (*S. pyogenes, S. aureus, S. epidermidis, E. faecalis*), gram negative bacteria (*K. pneumoniae, H. influenza, P. aeruginosa, A. baumannii*, *E. coli*), and fungi (*Candida. albicans, C. tropicalis, C. parapsilosis, C.* The inhibition end point of the minimum inhibition concentrations (MICs) were determined as µg/mL. The active ingredient and plant extracts have shown antibacterial and antifungal activities with a MIC values of 1->128 µg/mL) (Muftah *et al.,* 2020).

In a study cytotoxic activity of *Juniperus communis* (JCo) extract (preparation and DER not described) against esophageal squamous carcinoma cells (ESCC) and its possible mechanisms was investigated. The major components of JCo extract, analyzed by gas chromatography-mass spectrometry (GC-MS) were: α-pinene (34.87%), citronellyl acetate (14.26%), limonene (10.72%), terpinolene (10.65%), p-cymene (6.21%), elemene (3.32%) and cadinene (2.12%). The JCo extract suppressed cell growth in ESCC and showed higher selection for ESCC cells than normal cells compared to the clinical drug 5-FU. The estimated IC50 values of JCo extract after 24–72 hr treatment were 68.41 ± 1.38–60.07 ± 2.18 µg/ml in CE81T/VGH cells (human esophageal squamous cell carcinoma) and 69.38 ± 0.95 and 36.10 ± 4.19 µg/ml in CE48T/VGH cells (human esophageal epidermoid carcinoma (VGH). JCo extract induced cell cycle arrest at the G0/G1 phase by regulating the expression of p53/p21 and CDKs/cyclins, triggering cell apoptosis by activating both the extrinsic (Fas/FasL/Caspase 8) and intrinsic (Bcl-2/Bax/Caspase 9) apoptosis pathways. Moreover, a combination treatment of JCo and 5-FU synergistically inhibited proliferation of ESCC cells (Li *et al.,* 2021).

An extract of juniper pseudo-fructus prepared with hot isopropanol was tested in cell cultures of isolated amnion cells to study the influence on the DNA-replication of HSV-1 (Herpes simplex virus 1). The replication was lowered and no cytotoxicity was seen in a range of 1.5 to 7000 ng/ml. The activity on the virus may be due to desoxypodophyllotoxin, but no cytotoxic activity of the extract was detected (Markkanen *et al.,* 1981).

3.1.3. Safety pharmacology

No data available.

3.1.4. Pharmacodynamic interactions

No data available.

3.1.5. Conclusions

The earliest experimental evidence for a diuretic activity goes back more than 80 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 antidiuretic effect of a orally administered 10% *Juniperus pseudo-fructus* infusion was comparable with a small dose of intraperitoneally administered ADH after 24h. In the same experiment diuresis was stimulated after the second application (after 48h) and especially after the third application (after 72h) of a 10% drug infusion and stronger than the essential oil solution and terpinen-4-ol. These results suggest that the diuretic activity of juniper berries cannot be attributed only to the essential oil but also to hydrophilic drug constituents.

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 anesthetised 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.

Secondary pharmacology with preparations of juniper berries deals with *in vitro* and *in vivo* activities such as antimicrobial, antioxidant, anti-inflammatory and plasma glucose lowering activity. There is *in vitro* investigation done on partial solubilising of kidney stones with juniper berry extract. However there is no clinical cofirmation of the usefulness of juniper berries in case of urolithiasis.

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. The complex phytochemistry of Juniper cone berries makes it difficult to conceive any representative pharmacokinetic study.

Tam *et al.* studied the ethnopharmacological relevance of *Rhododendron groenlandicum* (Bog Labrador tea), *Rhododendron tomentosum* (Marsh Labrador tea) and *Juniperus communis* (Juniper) as being used in medicinal teas by Canadian aboriginal cultures alone and in combination with conventional drug products. This study was initiated to examine the potential of medicinal teas to inhibit the major human drug metabolizing enzyme, cytochrome P450 3A4 (CYP3A4). Decoctions of *Rhododendron groenlandicum* and *Rhododendron tomentosum* leaves and *Juniperus communis* berries were examined in a microtiter fluorometric assay to examine their potential to inhibit CYP-mediated metabolism. The decoctions showed progressive inhibition towards CYP3A4 the longer the leaves or berries were brewed. *Rhododendron groenlandicum* and *Juniperus communis* (1 g in 250 ml of boiling water) may have the potential to inhibit CYP3A4-mediated metabolism. There was a nearly 100% inhibition of CYP3A4 after a boiling time of 60 minutes. The authors conclude that a decoction of Juniperus

communis has the potential to affect the safety and efficacy of other health and medicinal products. This study only examined CYP3A4 (Tam *et al.,* 2014).

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

3.3.1. Single dose toxicity

LD_{50} of a lyophilized water extract of Juniper pseudo-fructus in male mice: 3000 mg/kg intraperitoneally (Lasheras *et al.,* 1986).

3.3.2. Repeat dose toxicity

No data available.

3.3.3. 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*.

3.3.4. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

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. No evidence of teratology was observed (Agrawal *et al.,* 1980).

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 (Prakash *et al.,* 1985).

An acetone extract of juniper berries at a dose of 200 mg/kg had an anti-implantation activity of 60% in rats. The extract was administered from day 1 to 7 of pregnancy (Prakash, 1986).

Based on the results of the preceding experiments, it cannot be concluded that that *Juniperi communis pseudo-fructus* extracts has antifertility and abortifacient effects. Only one species, more particularly rats, was used and the experiments are not conform the guidelines for testing on reproduction (EMA, 2008).

3.3.6. Local tolerance

No data available.

3.3.7. Other special studies

No data available.

3.3.8. Conclusions

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. No conculsions can be made on teratogenicity.

3.4. Overall conclusions on non-clinical data

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

Specific data on pharmacokinetics and interactions are not available.

Non-clinical information on safety of juniper berry preparations is scarce. As no data on carcinogenicity and genotoxicity exist, no list entry can be considered. There are no appropriate investigations concerning reproductive toxicity.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

4. Clinical Data

4.1. Clinical pharmacology

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

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

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

No data available.

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

No data available.

4.4. Overall conclusions on clinical pharmacology and efficacy

There are no clinical studies published.

5. Clinical Safety/Pharmacovigilance

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

No data available.

5.2. Patient exposure

No data available.

5.3. Adverse events, serious adverse events and deaths

A search in the EudraVigilance database was done from 1996 until 2019. It resulted in 124 hits on 'juniper', most of them related to *Juniperus ashei*. Juniperus was solely mentioned in 5 cases and in 8 cases other agents were also involved. The cases were reported in European countries and Canada. The age of the patients varied from 35 to 90 years, without gender specification. The pharmacovigilance information obtained from the Eudravigilance Database does not reveal any need to change the monograph on *Juniperus communis galbulus* (pseudo-fructus) as safety is concerned.

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.

Both the BPH (1983) and the Commission E monograph (1984) indicate that juniper berries should be avoided in renal disease. Czygan reported that after continued use renal damage can arise (Czygan, 1987).

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. 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. 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). Moreover, these data are related to juniper oil and cannot be directly extrapolated to the berries. Furthermore, starting from cone berries it will be impossible to reach massive dose equivalents: The recommended single (daily) dose is equivalent to max. 4 g (12 g) of cone berries. With a 1-3% content of essential oil, the oil equivalent will be max. 120 mg (360 mg) if a 100% extraction is assumed. 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 terpentine oil. Most probably the findings for terpentine oil were copied to Juniperus oil without factual analysis. Also Potter (1898; cited by

Schilcher & Heil, 1994) mentioned 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.

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). In a quote by Tyler it reads: *"…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…."* (Tyler, 1982). 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 '*aquareticum*'. 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 (Opdyke, 1976, cited by De Smet *et al.,* 1993). 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 (Opdyke, 1976, cited by De Smet *et al.,* 1993). However, in Belgium labelling of food supplements with juniper berries must contain the following warning: *no long term use without professional advice (maximum 6 weeks). Not to be used in case of renal complications* (Anonymus, update 2017).

Positive patch test reactions have been documented with juniper. They were attributed to the irritant nature of the Juniper pseudo-fructus extract (Mathias *et al.,* 1979).

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).

Because no other case reports of allergic skin reactions could be identified, the sentences *'Allergic skin reactions have been reported. The frequency is not known'* which was under section 4.8. in the former edition has been deleted from the Monograph.

There are no serious adverse events and deaths reported.

If patients with known intolerance to *Juniperus communis*, or plants of the family are excluded, a traditional use is possible if administration follows the instructions as specified in the monograph. Nevertheless, a limitation of the period of use is included under subheading 4.2. *Posology and method of administration* of the Monograph: *If the symptoms persist longer than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.*

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

No data available. Due to the lack of adequate data, a restriction to adults is recommended. This condition is phrased in the monograph as: *the use in children and adolescents under 18 years of age has not been established due to lack of adequate data.*

5.5.2. Contraindications

Hypersensitivity to the active substance is mentioned as a standard term in the Monograph under section 4.3.

5.5.3. Special warnings and precautions for use

If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

For preparations containing ethanol, the appropriate labelling for ethanol, taken from the 'Guideline on excipients in the label and package leaflet of medicinal products for human use', must be included.

If complaints or symptoms such as fever, dysuria, spasms or blood in the urine occur during the use of the medicinal product, a doctor or a qualified health care professional should be consulted.

Not to be used in case of severe renal disease including infectious interstitial nephritis, pyelitis and pyelonephritis .(BPH, 1976; Commission E, 1984) By lack of clinical reports this information has been moved from section 4.3. (contra-indications) to section 4.4. under indication 1): not recommended to be used in case of severe renal disease including infectious interstitial nephritis, pyelitis and pyelonephritis.

It does not seem logical to combine juniper and synthetic diuretics, although by lack of reports about clinical interactions no warning is included in the monograph. In the former version of the Monograph 'adjuvant' is added in the therapeutic indication. However 'adjuvant' supposes a defined treatment to which the herbal treatment can be added. As there is no clear instruction in that way, the therapeutic indication is reduced, not any longer mentioning the use as adjuvant.

5.5.4. Drug interactions and other forms of interaction

Kaufmann *et al*. (2013) reported one case study on an unexpected decrease of the INR in a patient with phenprocoumon treatment during the intake of juniper berries. It was presented as an abstract during a conference of the European Society of Clinical Pharmacy in 2013. The intake of a daily amount of five to seven juniper berries required an increase in the phenprocoumon dose by 28 % from an average dose of 10.2 mg per week resulting in INR values between 1.7 and 2.3 to 13.1 mg per week (INR 1.7–2.1). The INR increase appeared after beginning with the intake of the juniper berries and INR slowly decreased when the intake had been stopped. There was no re-challenge. As the INR depend on many factors, other reasons for the decrease cannot be excluded. The Naranjo algorithm score is 3 which assessed the interaction between juniper berries and the INR decrease as ''possible''.

Kaufmann *et al.* (2013) refer to an Italian publication by Argento *et al.* (2000) who assumed that juniper berries contain a high amount of vitamin K. The source of this evidence is not clear and is not confirmed by other literature sources or references. The case described by Kaufmann *et al*. (2013) is well described, but it is up to now the only case reported. There is also no clear explanation for the effect. Therefore a warning based on this case was not included in the monograph.

5.5.5. Fertility, pregnancy and lactation

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

5.5.6. Overdose

Although some reference works cite toxic effects in case of overdose, there is a lack of clinical safety and toxicity data for juniper berries (Barnes *et al.,* 2007). When examining carefully the sources cited. there seems to be a confusion between the volatile oil and the berries. An additional aspect is the confusion between *Juniperus communis* and other species of *Juniperus.* For possible symptoms and effects caused by overdoses, the reader is referred to the assessment report on the essential oil of *Juniperus communis.* Therefore, the information in monograph section 4.9 has been revised to "No case of overdose has been reported".

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

No data available.

5.5.8. Safety in other special situations

No data available.

5.6. Overall conclusions on clinical safety

Clinical safety data are limited. However, up to now no serious side effects have been reported. Due to lack of adequate data, allergic skin reactions which was under section 4.8. in the former edition has been deleted from the Monograph.

The use in adolescence and children under 18 years of age has not been established due to lack of adequate data.

Related to Indication 1), the following warnings are included in the monograph: "If complaints or symptoms such as fever, dysuria, spasms or blood in urine occur during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. Because adequate fluid intake is required during treatment (see section 4.2. Posology and method of administration), *Juniperus communis galbulus* (*pseudo-fructus*) is not recommended for patients with conditions where reduced fluid intake is advised by a medical doctor."

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended

A search in the Eudravigilance Database (January 2020) does not reveal any concern the monograph on *Juniperus communis galbulus* (*pseudo-fructus*) with regard to contraindications, special warnings, fertility, pregnancy, lactation, ability to drive and use machines or undesirable effects. A report on a lowering effect on INR when juniper berries were taken together with a vitamin K antagonist does not trigger a warning in the monograph. More evidence would be needed to consider an interaction between juniper berries and its preparations, with vitamin K antagonists. Reports on cases of overdose or prolonged use are vague and of questionable quality.

6. Overall conclusions (benefit-risk assessment)

The traditional use of *Juniperus communis galbulus* (pseudo-fructus) and preparation thereof is limited to the stimulation of renal water excretion and to dyspeptic disorders. As a consequence, in the monograph the following therapeutic indications were granted, based upon traditional use:

- Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract in minor urinary tract complaints.
- Traditional herbal medicinal product for symptomatic relief of digestive disorders such as dyspepsia and flatulence.

A well-established use cannot be considered, because there are no published clinical studies with juniper berries or preparations thereof.

A search in the Eudravigilance Database (January 2020) does not reveal any need to change the monograph on *Juniperus communis galbulus* (*pseudo-fructus*) with regard to contraindications, special warnings, fertility, pregnancy, lactation, ability to drive and use machines or undesirable effects. Reports on cases of overdose or prolonged use are vague and of questionable quality.

As genotoxicity and carcinogenicity are not studied, a list entry in the 'European Unition list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products' cannot be established. No constituent with known therapeutic activity or active marker can be recognised by the HMPC.

Annexes

List of references