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SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Origanum majorana* L., herba

Final

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)	*Origanum majorana* L., herba
Herbal preparation(s)	Comminuted herbal substance Extract (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 96% V/V and white petroleum jelly.
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use. Herbal preparations in semi-solid dosage forms for cutaneous use.
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1. Introduction

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

- Herbal substance(s)

Origani majoranae herba consists of the dried flowering shoots of *Origanum majorana* L. containing not less than 5 ml/kg of essential oil (in the dried herbal substance) (Farmakopea Polska X, 2014). *Origanum majorana* L., Lamiaceae (synonymous with *Majorana hortensis*) is a tender, bushy perennial hairy herb, up to about 0.6 m; leaves are 5-20(-35) x 5-10(-15) mm, glabrous to tomentose, not papilose, ovate to ovate elliptic-spathulate, obtuse or acute, rounded or attenuate at base; flowers purple rarely white in compact heads, forming a terminal trichotomous panicle. It is native to the south-eastern Mediterranean region and Middle East (Fernandes and Heywood (1972)). Common name in English is sweet marjoram.

It is an aromatic plant with a distinctive tangy odour and a bitter taste. Contains up to 5% volatile oil (usually less than 1%), consisting primarily of terpinen-4-ol and (+)-*cis*-sabinene hydrate that are considered to be responsible for the typical aroma. α-Terpinene, γ-terpinene, *p*-cymene and terpinolene are also important constituents of the oil. Differently from other *Origanum* species oils (e.g. *O. vulgaris* or *O. virens* oils) thymol and carvacrol only occur in small amounts (Baratta *et al*., 1998; Baser, 1993; Novak *et al*., 2000).

Other compounds with ubiquitous occurrence, such as flavonoid glycosides, tannins, phenolic acids, diterpenoids and triterpenoids were identified (Baratta *et al*., 1998; Baser, 1993; Novak *et al*., 2000).

Rosmarinic acid is set by the Farmakopea Polska X (2014) as an analytical marker.

Aerial parts of *O. majorana* contain hydroquinone derivatives in low concentrations. Rychlińska *et al.,* (2012) quantified 0.99 mg of hydroxyquinone and 17.2 mg of hydroquinone-β-D-glucopyranoside (arbutin) in 1 g of dried plant material.

- Herbal preparation(s)

  a) Comminuted herbal substance as herbal tea for oral use.

  b) Extract (ratio of herbal substance to extraction solvent 1:5), extraction solvents: ethanol 96% V/V; and white petroleum jelly.

- 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

Relevant articles and references were retrieved from e-databases (PubMed and ISI Web of Science), book collections from libraries (Biblioteca das Ciências da Saúde da Universidade de Coimbra and Biblioteca Geral Universidade de Coimbra), Pharmacopoeias and monograph compilations using the keywords: *Origanum majorana; Majorana hortensis; marjoram; majorlain; mejorana; manjerona.*

Retrieved information was carefully analysed and only articles considered of interest to this Assessment Report were selected. Articles or information on the uses and activities of *O. majorana* essential oil were not considered.

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

According to the information provided by the National Competent Authorities in the overview of the marketed products, the following preparations have been marketed in the EU/EEA:

Table 1: Overview of data obtained from marketed medicinal products

POLAND

Active substance	Indication	Pharmaceutical form	Regulatory Status
Extract (ratio of herbal substance to extraction solvent 1:5), extraction solvents ethanol 96% V/V and white petroleum jelly. Preparation according Farmakopea Polska, (1995): two parts of comminuted *Origanum majorana* L., herba is moistened with one part of ethanol 96% and then warm extracted with ten parts of white petroleum jelly until ethanol evaporation	Traditional herbal medicinal product used in mild inflammatory states of nasal mucosa	Cutaneous use Children older than 1 year and adults: Small amount of the ointment spread around nostrils, 2-4 times a day	Traditional use registrations (2011, 2013, Poland)

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

Native to the Mediterranean and Eurasia, *Origanum* species have been cultivated and used by the ancient Egyptians and Greeks since classical times. Marjoram (*O. majorana)* was known as the herb of happiness to the Romans and it was believed to increase longevity. It is listed in Dioscorides' De Materia Medica (A.D. 78) and in the Hildegard of Bingen´s (1098-1179) compilation of medicines. Hippocrates (460-370 B.C.) used *O. majorana* as antiseptic agent (The Herb Society of America, 2005).

Traditional use in Europe is affirmed in several reference textbooks:

- Garnier *et al*., (1961), describe the use of the aerial parts with flowers, as powder for oral use or prepared as an infusion at 5% as an herbal tea, as spasmolytic and to help digestion.
- Fischer (1966) reports the stomachic and anti-catarrh proprieties of the infusion (single dose: 2-4 g).
- The monograph at Die Große Enzyklopädie der Heilpflanzen (Wurzer, 1994) (translation of "La grande enciclopedia delle erbe", 1977) reports its use in severe digestive, abdominal pain, neuralgia, colds and coughs, in a form of 1) infusion (1 g to 100 g of water) one or two small cups, as needed or 2) tincture (20 g to 100 ml of alcohol 30% V/V), 20 to 40 drops on a piece of sugar, as needed. The infusion of the blooming shoot tips (5 g per 100 ml of water) is indicated for external use for relief of pain in neuralgia and rheumatism.
- Hallard (1988) reports the use of the infusion (40-50 g/L, one cup a day, before meal) as spasmolytic, analgesic, anti-rheumatism, expectorant, diuretic and digestive.
- Font Quer, (1988) reports the use to treat digestive disorders, appetizer, carminative, aphrodisiac, diaphoretic, hypotensor, expectorant and sudorific. No further details on pharmaceutic form, mode of administration and posology are given.
- An ointment (*Unguentum majoranae = Herba majoranae*, *Spiritus, Adeps suillus, Cera flava* 2:1:20:1 in weight) is considered in a Regulation of the Minister of Health of Poland (Dziennik Ustaw, Rzeczypospolitej Polskiej, 1949). It is traditionally indicated in Poland "for relief of nasal rhinitis, suitable for cutaneous use in paediatric practice" (Bobowska *et al*., 1975). The ointment is described in the Farmakopea Polska (1995 and 2014) and corresponds to the extract (ratio of herbal substance to extraction solvent 1:5), extraction solvents: ethanol 96% V/V and white petroleum jelly, prepared as follows: two parts of comminuted *Origanum majorana* L., *herba* is moistened with one part of ethanol 96% and then warm extracted with ten parts of white petroleum jelly until ethanol evaporation.
- Alonso (1998) and Proença da Cunha *et al.* (2003), abridging other references, mention the digestive effects (aperitif, digestive anti-flatulence diuretic) and antiseptic and expectorant proprieties of the infusion (10 g/L, one cup before meals; a dessert spoon of comminuted marjoram for 1 cup, three cups a day). Proença da Cunha *et al.* (2003) reports also the use of the tincture (1:10), 50–100 drops, one or twice daily or the encapsulated powder 250 mg per capsule, 2 to 4 capsules per day.

- Bown (2001) reports the external use for chest congestion, muscle aches and arthritis and the infusion of sweet marjoram in warm olive oil as a remedy for ear infections. No further details on pharmaceutic form, mode of administration and posology were given.
- Teuscher (2003) describes the application of infusions (1 to 2 teaspoons of the drug/250 ml of water, 1 to 2 cups daily) for relief of stomach and intestinal problems, as diuretic and sudorific, in migraines, nervous headache and cough or in the form of hot ointment for external use for coughs, colds and neuralgia in folk medicine.
- Gruenwald *et al*. (2000, 2007) reports the use in cramps, depression, dizziness, gastrointestinal disorders, migraine, nervous headaches, neurasthenia, paralysis, paroxysmal coughs, colds or as diuretic, as an infusion [1 to 2 full teaspoons (2 to 4 g) for 250 ml of water, 1 or 2 cups throughout the day], as mouthwashes and poultices (5% infusion) or as an ointment (ratio of herbal substance to extraction solvent 1:5), extraction solvents: ammonia, wine spirit and petroleum jelly.
- An ethnopharmacological study in two Italian villages (guided interviews and survey, 328 people aged from 60 to 80 years) evidenced the traditional use of the infusion of *O. majorana* leaves for treatment of stomach pain, neuralgia and as sedative (Loi *et al.*, 2005).

Table 2: Overview of historical data

Herbal preparation	**Documented use / Traditional use**	**Pharmaceutical form**	**Reference**
Comminuted herbal substance	Spasmolytic and digestive	Infusion (40-50 g/L, corresponding to 6-7.5 g in one cup of 150 ml; one cup a day, before a meal)	Garnier *et al*., 1961; Hallard, 1988
Comminuted herbal substance	Stomachic and anti-catarrh Digestive, abdominal pain, neuralgia, colds and coughs Gastrointestinal disorders	Infusion (single dose 2-4 g). Infusion (1 g/100 ml of water); - one or two small cups, as needed; - one cup before meals; - Infusion: 1 spoon per cup, three cups per day. Infusion: 1 to 2 full teaspoons (2-4 g)/250 ml of water; 1 or 2 cups per day	Fischer (1966) Wurzer (1994) Alonso (1998) Proença da Cunha *et al.* (2003) Gruenwald *et al*. (2000)
Tincture (20 g to 100 ml of alcohol 30% V/V)	Digestive, abdominal pain, neuralgia, colds and coughs	20 to 40 drops of tincture in on a piece of sugar, as needed.	(Wurzer, 1994)
Comminuted herbal substance	Analgesic, expectorant, diuretic, anti-rheumatic	Infusion (40-50 g/L). Posology and duration of use not reported.	Hallard, 1988
Extract (ratio of herbal substance to extraction solvent 1:5), extraction solvents ethanol 96% V/V and white petroleum jelly. Preparation according Farmakopea Polska, (1995).	Used for relief of irritated skin around the nostrils	Ointment for cutaneous use. Suitable for adults and children older than 1 year. Small amount of the ointment spread around nostrils, two to four times a day.	Dziennik ustaw. Rzeczypospolitej. Polskiej, 1949; Farmakopea Polska, (1995); Traditional herbal medicinal product registered in

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
Original formula (Ointment): Herba majoranae, spiritus, adeps suillus, cera flava (2:1:20:1 in weight)			Poland since 2011; Bobowska *et al*., 1975

2.3. Overall conclusions on medicinal use

Literature supports the traditional use of *Origanum majorana* herba, for more than 30 years in EU with the following indications and posologies:

Indication 1)

- Traditional herbal medicinal product used for the symptomatic relief of mild spasmodic gastro-intestinal complaints such as bloating and flatulence.

  Single dose: 2-4 g of the comminuted herbal substance in one cup of boiling water as herbal infusion, once to twice daily, before meal;

  Daily dose: 2-8 g

Indication 2)

- Traditional herbal medicinal product used for relief of irritated skin around the nostrils. Small amount of the ointment spread around nostrils, two to four times daily.

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
a) Comminuted herbal substance for oral use as a tea	Symptomatic treatment of mild, spasmodic gastrointestinal complaints such as bloating and flatulence	Single dose: 2-4 g of the comminuted herbal substance in one cup (150 ml) of boiling water as herbal infusion Daily dose: 2-8 g of the comminuted herbal substance as herbal infusion	Fischer (1966) Wurzer (1994) Alonso (1998) Gruenwald *et al*. (2000)
b) Extract (ratio of herbal substance to extraction solvent 1:5), extraction solvents: ethanol 96% V/V and white petroleum jelly	Relief of irritated skin around the nostrils	Cutaneous use Small amount of the ointment spread around nostrils, two to four times daily	Dziennik ustaw. Rzeczypospolitej. Polskiej, 1949 Bobowska *et al*., 1975 Farmakopea Polska (1995, 2014) Poland, traditional registration 2011 and 2013

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

Gastroprotective and antiulcerogenic effects

In vivo

Ethanolic extract

The antiulcerogenic activity of the ethanol extract was evaluated in stress- and chemical-induced, ulcers and basal gastric acid secretion in pylorus ligated Shay rat-model. The dry extract (DER not given) obtained from an ethanol percolate (16.6% w/v), administered orally (250 and 500 mg/kg bw) significantly decreased the incidence of ulcers, basal gastric secretion and acid output. The extract also replenished the wall mucus and non-protein sulfhydryls (NP-SH) contents and lowered significantly the concentration of malondialdehyde. Ulcer preventing potential was confirmed by histopathological evaluation (Al-Howiriny *et al*., 2009).

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

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
Dry ethanol extract (DER = n.a.) Percolate (16.6% w/v)	Administered orally at doses of 250 and 500 mg/kg bw	In-vivo stress- and chemical-induced, ulcers and basal gastric acid secretion in pylorus ligated Shay rat-model. Chemical and histopathological evaluation	Al-Howiriny *et al*., 2009	Decreased incidence of ulcers, basal gastric secretion and acid output. Replenished wall mucus and non-protein sulfhydryls (NP-SH) contents. Significantly reduces the concentration of malondialdehyde Dose-dependent effects for several parameters A large margin of safety was proved from an acute toxicity test, in mice

Antimicrobial activity

In vitro

Methanolic extract

A 95% methanol extract prepared from the aerial parts of *O. majorana* (6.6% w/v, DER=not given) was tested *in vitro* on 14 clinical isolates and one ATCC strain Helicobacter pylori according the National Committee for Clinical Laboratory Standards protocol (NCCLS, 1999). Minimum Inhibitory concentrations ranged 50 to 100 µg/ml, depending of the Helicobacter strains. Authors concluded that

data provide a plausible mechanism of action for this traditional medicine, since Helicobacter pylori is an etiological agent responsible for dyspepsia, gastritis, peptic ulcer disease and gastric carcinoma (Mahady *et al*., 2005).

3.1.2. Secondary pharmacodynamics

Anti-platelet aggregation activity

In vitro

Methanolic extract

Yazdanparast *et al*. (2008) investigated *ex-vivo* the effects of the methanol crude extract of *O. majorana* on human platelet functions including platelet adhesion, aggregation and protein secretion.

Platelets treated for 60 min with the methanol extracts, at the concentration of 200 µg/ml, showed a sharp decrease in platelet adhesion to laminin-coated plates. In addition, the extent of platelet aggregation has also decreased. Results clearly indicate a dose-dependent inhibitory action. The adhesions have been decreased by almost 40%. The protein content released, determined by Lowry's method, showed a decrease by almost 30%. Hydroquinone derivatives can be responsible for these effects, since hydroquinone-D-glucopyranoside (arbutin) strongly inhibits platelet aggregation induced by different stimulating agents.

Other non-clinical studies: Anti-carcinogenic activity, antiproliferative, antioxidant and cytotoxic activities.

Kaliora *et al*. (2014) investigated anti-carcinogenic effect of the leaves and flowers infusion (3 g/250 ml of boiling water during 3 minutes, then dehydrated by lyophilisation) for their ability to scavenge free radicals, inhibit cell growth, decrease interleukin-8 (IL-8) levels and regulate transcription factor p65 subunit (p65) in epithelial colon cancer (HT29) and prostate (PC3) cancer cells. *O. majorana* was found to be very efficient against PC3 prostate cells growth, but not against HT29 colon cell growth.

Elansary and Mahmoud (2015) studied *in vitro* the antioxidant, antiproliferative and cytotoxic activities against different human cancer cells of *Origanum majorana L.* Aqueous infusion and methanol extract of *O. majorana* showed antioxidant activity [inhibitory concentration values (IC_{50}) of 9.3±0.4 µg/ml and 8.2±0.3 µg/ml, respectively] in DPPH assay. In the β-carotene–linoleic acid assay, methanol extract showed a higher inhibition than aqueous infusion (90.2%±0.9 compared to 81.1%±0.1). HeLa, MCF-7 and Jurkat cancer cells were used to test anti-proliferative activity and cytotoxicity. In a dose-dependent manner (200 mg extract/ml, 400 mg extract/ml), the leaf extracts exhibited a significant inhibition percentage for different cancer cells. Association among phenolic contents, antioxidant capacity and antiproliferative activity was suggested.

Al Dhaheri *et al*. (2013) investigated, *in vitro and in vivo,* the ability of *O. majorana* ethanolic extract to inhibit migration, invasion and metastasis of MDA-MB-231 cells evidencing anti-tumour effects. They studied also the *in vitro* effect of *Origanum majorana* ethanol extract on the survival of the highly proliferative and invasive triple-negative tumour protein p53 mutant breast cancer cell line MDA-MB-231. Authors found that extract is able to inhibit the viability of the MDA-MB-231 cells in a time-and concentration-dependent manner.

3.1.3. Safety pharmacology

O. majorana contains hydroquinone derivatives. Hydroquinone (an environmental contaminant) was reported as carcinogenic in animals and humans. Based in this reason the Commission E did not recommend the therapeutic administration (oral use) of marjoram (Blumenthal *et al*., 1998). Arbutin is a suppressor of melanin biosynthesis in human skin and it is used in treating skin discolorations such as melasma, freckles, hyperpigmentation or other disorders, as well as in the cosmetic industry (Hu *et al*., 2009). It cannot be excluded that topical application of products containing arbutin can lead to depigmentation of the skin. However, a large margin of safety was proved from an acute toxicity test, in mice (Al-Howiriny *et al*., 2009). In a critical approach to the literature outcomes, McGregor (2007), states that the evidence (and the database) for any genotoxic effect of hydroquinone, *in vivo,* is sparse.

3.1.4. Pharmacodynamic interactions

No data available.

3.1.5. Conclusions

The antiulcerogenic activity of the dry ethanol extract of *O. majorana* (DER=n.a., percolate 16.6% w/v), administered orally to Wistar albino rats at the doses 250 and 500 mg/kg bw was evidenced. However, considering the used doses, the Rapporteur cannot find relevance of these results when looking for positive effects on humans.

There is no direct non-clinical data available supporting the use of *O. majorana* herba for relief of irritated skin around the nostrils, apart from unspecific antimicrobial properties.

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

Herbal substance/herbal preparation

No data available on pharmakokinetic of *O. majorana* herbal substance/preparations.

Hydroquinone/arbutin

Concerning isolated hydroquinone, after oral treatment in rodents, hydroquinone is absorbed rapidly and completely, metabolized principally via glucuronidation and sulphatation (with a minor contribution from glutathione transferase), and excreted as metabolites into urine. Dermal absorption is “slow”, but systemic exposure is still considerable.

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

Data are insufficient to conclude on the safety of the use of *O. majorana,* herba.

3.3.1. Single dose toxicity

Herbal preparation

A single-dose toxicity test showed a large margin of safety of an *O. majorana* extract (ethanol 96%, DER not available). Single doses in a range of 2.5 to 15 g/kg bw did not produce apparent toxic effects. LD_{50} in mice was estimated in 10.625 g/kg bw (Al-Howiriny *et al*., 2009).

3.3.2. Repeat dose toxicity

Herbal substance/preparation

Specific data on repeated dose toxicity of *O. majorana* herbal substance/preparations are not available.

Hydroquinone

Concerning hydroquinone, NOEL for subacute toxicity after 13-week oral treatment of rats is 20 mg/kg bw per day (NTP, 1989; OECD SIDS, 2012).

3.3.3. Genotoxicity

Herbal substance/preparation

Specific data on genotoxicity of *O. majorana* herbal substance/preparations are not available.

Hydroquinone

Hydroquinone (HQ) causes genotoxicity or chromosomal aberrations in rodent bone-marrow cells. At least a portion, if not all, of the chromosomal effects is caused by interference by hydroquinone or its metabolites with chromosomal segregation, probably due to interaction with mitotic spindle proteins. However, the dose routes used to demonstrate these effects in almost all of the studies in vivo were intraperitoneal or subcutaneous injection. In five studies by the oral route, a mouse bone-marrow cell micronucleus test showed a weak, marginally positive response following a single oral dose of 80 mg/kg body weight, whereas the remaining oral route studies all showed no significant effect. Thus, the evidence (and the database) for any genotoxic effect in vivo is sparse and none has been observed in kidney (McGregor, 2007; Matsumoto *et al*., 2014).

The lacZ transgenic mutation assay was conducted according to OECD test guideline 488 to determine whether mutagenic mechanisms were involved in HQ-induced carcinogenesis. Male Muta™ mice were repeatedly administered HQ orally at dosages of 0, 25, 50, 100, or 200mg/kg bw per day for 28 days. Body weight gain was decreased in all treatment groups. No significant differences were observed in mutant frequencies in the liver, stomach, lung, or kidney between HQ-treated mice and the concurrent negative controls, whereas the significant induction of mutations was noted in the positive control, N-ethyl-N-nitrosourea. These results suggest that a mutagenic mechanism is not responsible for HQ-induced carcinogenesis (Matsumoto *et al*., 2014).

3.3.4. Carcinogenicity

Herbal substance/preparation

Specific data on genotoxicity of *O. majorana* herbal substance/preparations are not available.

Hydroquinone

Hydroquinone induced hepatocellular adenomas and forestomach hyperplasias in mice and renal tubular cell adenomas in male rats (NPT, 1989). Regarding renal toxicity and carcinogenicity, the following mechanism of action (MOA) seems plausible: hydroquinone or a metabolite can interact with the kidney of rats to exacerbate a spontaneous and common disease process, chronic progressive nephropathy (CPN), which is a rodent-specific condition. This disease includes regeneration in the form of simple tubule hyperplasia as well as degeneration and atrophy. Severe or end-stage CPN in particular is associated with the development of atypical hyperplasia, out of which adenomas can develop as a consequence of the regenerative component. McGregor concludes that the extensive

evidence available is consistent with this mechanism of action being irrelevant in human risk assessment (McGregor, 2007). Murine liver adenomas are generally regarded to be of little concern.

Further evidence that the above mentioned animal tumors are not due to genotoxicity of hydroquinone is provided by Matsumoto *et al*. (2014), mentioned above. Lack of increase in mutations in the kidney suggests that a direct mutagenic mechanism is not responsible for HQ-induced carcinogenesis (McGregor, 2007).

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

Data are insufficient to conclude on local tolerance of *O. majorana* considering depigmentation effects due to hydroquinone derivatives.

3.3.7. Other special studies

By means of an experimental no observed effect level value, a permitted daily exposure dose below which there is a negligible risk to human health was estimated in 100 µg/kg bw per day of free hydroquinone (Garcia de Arriba *et al*., 2013). The same authors estimated that the intake of the therapeutic recommended human daily dose of bearberry (*Arctostaphylos uva-ursi*) leaf extract (containing 420 mg hydroquinone derivatives calculated as anhydrous arbutin) liberates free HQ in urine at a maximum exposure level of 11 µg/kg bw per day. Considering that concentrations of hydroxiquinone derivatives in *O. majorana* (arbutine, 17.2 mg/g; hydroquinone, 0.99 mg/g) are considerable lower than in bearberry (arbutine, 98.4 mg/g; hydroquinone, 1.9 mg/g) (Rychlińska *et al*., 2012) it can be assumed that the daily exposure to hydroquinone derivatives from the therapeutic recommended human daily dose of *O. majorana* herba involves negligible risk to human health.

3.3.8. Conclusions

Specific toxicological data regarding the herbal substance/herbal preparation(s) of *O. majorana* are not available.

Concerning the contents of hydroquinone derivatives in *O. majorana* it can be assumed that the daily exposure from the therapeutic recommended human daily doses of *O. majorana* herbal preparations involves negligible risk to human health.

3.4. Overall conclusions on non-clinical data

Results from relevant experimental studies on *O. majorana* to support the proposed indications are very limited. However, documented effects are not considered contradictory to the traditional use for the symptomatic relief of mild spasmodic gastro-intestinal complaints such as bloating and flatulence. There are no specific pharmacological data to support the indication, “for relief of irritated skin around the nostrils”.

Specific data on pharmacokinetics of *O. majorana* preparations and interactions are not available.

Non-clinical information on the safety is scarce.

The use of *O. majorana* herba during pregnancy and lactation cannot be recommended since no tests on reproductive and developmental toxicity have been performed.

4. Clinical Data

4.1. Clinical pharmacology

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

Not applicable

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

In humans, pharmacokinetics of hydroquinone after oral administration has been inadequately studied, but some conclusions can be drawn from studies on arbutin. Absorption of hydroquinone is relatively rapid, it is metabolized extensively by glucuronidation, sulphation and glutathione conjugation and metabolites are excreted via urine. Half-life is short, probably few hours or less.

Following application of a cream containing 2% [14C] hydroquinone to the skin of volunteers, the in vivo bioavailability was about 45% of the dose at 24 hours (Wester *et al*., 1998). With the aid of timed skin wash and skin-stripping sequences, this study found that there was a rapid and continuous movement of hydroquinone into the stratum corneum. Both ipsi- and contra-lateral blood samples contained radioactivity within the first 30 min and maximal plasma concentrations occurred at about 4 hours. Most radioactivity was excreted in urine within 24 hours as glucuronide conjugate(s).

A physiologically based toxicokinetic (PBPK) simulation of hydroquinone PK after oral and dermal exposures (Gajewska *et al*., 2014) suggested that while maximum blood concentrations after dermal exposure were about 25% of the oral exposure, the overall AUC was at least 8 times higher after dermal exposure, probably because of sustained dermal penetration and a relative lack of presystemic metabolism (McGregor, 2007; Matsumoto *et al*., 2014).

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

No data available.

5. Clinical Safety/Pharmacovigilance

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

Not applicable

5.2. Patient exposure

No data available.

5.3. Adverse events, serious adverse events and deaths

None reported

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

No data available.

5.5.1. Use in children and adolescents

Marjoram ointments have a special tradition in Poland for use in paediatric patients for relief of skin inflammations around the nostrils.

5.5.2. Contraindications

Hypersensitivity to the active substance or to other plants of the Lamiaceae family.

5.5.3. Special warnings and precautions for use

When using ointment for relief of irritated skin around the nostrils the deep penetration of the ointment inside nostril should be avoided, as it can reduce the activity of the ciliary epithelium.

5.5.4. Drug interactions and other forms of interaction

None reported

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.

No fertility data available.

5.5.6. Overdose

No case of overdose has been reported.

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

No studies on the ability to drive or use machines have been performed.

5.5.8. Safety in other special situations

No data available.

5.6. Overall conclusions on clinical safety

The safety of use in defined conditions of *O. majorana* medicinal products can be derived from the basis of long standing use and experience. Apart from the medicinal use, *O. majorana* is also used as food. In relevant literature sources no adverse events are reported. There are no case reports on overdose, drug interactions, drug abuse, withdrawal and rebound, effects on ability to drive or operate machinery or impairment of mental ability.

On the basis of information on traditional use *O. majorana,* herba proves not to be harmful in the specified conditions of use. Regarding both indications mentioned in the monograph the use *O. majorana,* herba is considered appropriate for adults and elderly without the supervision of a medical practitioner. The use in children is limited to the indication 2). Furthermore, the use in children under 1 year of age has not been established due to lack of adequate data. The duration of use without medical advice is limited to two weeks for the first indication and to one week for the second indication as found in the monograph.

O. majorana preparations are contraindicated in patients with hypersensitivity to the active substance and to other plants of the Lamiaceae family.

Due to lack of scientific data, the use is not recommended during pregnancy and lactation.

6. Overall conclusions (benefit-risk assessment)

Based on the data documented in the assessment report, an EU herbal monograph is established on the traditional uses of several preparations of *Origanum majorana* L., herba. The traditional uses of Majoranae herba preparations fulfil the requirement for at least 30 years of medicinal use at a specified strength and specified posology, according to Directive 2001/83/EC. None of the data fulfil the requirements to demonstrate a well-established medicinal use with recognised efficacy for Majoranae herba preparations, thus the monograph is restricted to traditional uses. The efficacy is plausible on the basis of long-standing use and experience for the following indications:

Traditional herbal medicinal product used for:

1) symptomatic relief of mild gastrointestinal complains such as bloating and flatulence;
2) for relief of irritated skin around the nostrils.

Benefit/risk assessment: No adverse events, with a therapeutic posology of the herbal preparations, are reported in the literature. Intoxications due to the herbal preparations are not reported and no cases of overdose have been documented. There are no reports on drug interactions, effects on ability to drive or operate machinery or impairment of mental ability. A single-dose toxicity test of an *O. majorana* ethanol extract showed a large margin of safety. No data from investigations of repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance or other special studies of preparations from in *O. Majorana* is available. The herbal preparations should

not be used in patients with hypersensitivity to the active substance and to other plants of the Lamiaceae family. The duration of use is limited. If the symptoms persist longer than a two weeks (indication 1) or one week (indication 2) during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. Due to lack of scientific safety data, the use is not recommended in children under 1 year of age or by pregnant or lactating woman.

The therapeutic areas for browse search on the EMA website are “Gastrointestinal disorders” and ”skin disorders & minor wounds”.

No constituent with known therapeutic activity or active marker can be recognised by the HMPC. A typical analytical marker is rosmarinic acid.

Because the minimum required data on mutagenicity (AMES test) is not available for herbal preparations of *O. majorana* herba, an inclusion to the EU list of herbal substances, herbal preparations and combinations thereof for use in traditional herbal medicinal products is not recommended.

Annex

List of references