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EMA/HMPC/200431/2012
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Origanum dictamnus* L., herba

Final

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Origanum dictamnus</i> L., herba
Herbal preparation(s)	Comminuted herbal substance
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use Comminuted herbal substance (for preparation of an infusion or a decoction) for cutaneous use
Rapporteur	I. Chinou
Assessor(s)	I. Chinou



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1. Introduction

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

- Herbal substance(s)

Dittany of Crete consists of the dried flowering herb of *Origanum dictamnus* L. (Gennadios 1914; Liolios *et al.* 2010).

The plant is native to the island of Crete, in Greece. *Origanum dictamnus* L. (syn. = *Origanum pseudodictamnus* Sieber, *Amaracus dictamnus* (L.) Benthham) is a chasmophyte endemic of Crete. It is a short green white lanate shrub, with stems up to 35 cm. Its leaves are 13-25 x 12-25 mm, broadly ovate to orbicular, entire, lanate-hairy, with their veins raised and conspicuous. The lower leaves are shortly petiolate. Its spicules are in groups of 3-10, dense, ovoid or oblong, arranged in opposite reticulate pairs in lax panicles. The bracts are of 7-10 mm conspicuous, purple, and longer than the calyx. The upper lip of calyx is sub entire, the lower shallowly toothed. The corolla is pink, with its tube twice as long as the calyx tube (Fernandes & Heywood 1972; Polunin 1969; Ietswaart 1982; Kavadas 1956). It grows wild inside fissures of calcareous cliffs; usually it prefers shadowy places from 0 up to 1900 m above sea level (Turland 1995). Dittany is widely distributed along the Cretan island with more dense populations on the Western part, while it is doubtfully reported present in South West Asiatic Turkey (Rechinger 1943; Turland 1995; Greuter *et al.* 1986).

Origin of the names

Various names have been attributed to the plant in the ancient world, among them the name *dictamnus*, which survives till our days, probably derives from "*Dicti*" + "*thamnus*" *Dicti*" is the name of Cretan mountain where Zeus (Jupiter) was raised up by the goat Amalthea, and it was dedicated to him and "*thamnus*" means shrub in Greek (Skrubis 1979; Skoula & Kamenopoulos 1997). Ancient names like "veloulko, velotoko" probably derive from the ability to heal arrow wounds (Gennadios 1914) ("velos" = arrow in Greek) which *Origanum dictamnus* was strongly believed to possess. It is believed that *Origanum dictamnus* L. was called by the Sicilians *Amarakos*. Virgil refers to *Origanum dictamnus* as *Amaracon*. Korrais had proposed that it would be the same plant, which was called *Maioraca* by the Romans and *Maggiorana* or *Marjoram* by the Italians (Gennadios 1914). The plant had been classified under different names by various researchers until Linnaeus placed it under the genus *Origanum* and identified it botanically as the species *Origanum dictamnus*. Nowadays, the plant is widely known across the world with various vernacular names among which, the name "erontas", attributed to dittany by the local people of Crete, presents great interest because it probably derives from "Erotes", the ancient Greek god of love. *Origanum dictamnus* is offered to girls as an expression of love. Dittany grows wild, high in the mountains, in places difficult to be reached, thus it is believed that someone has to be fully in love in order to climb and gather the plant to be offered (Plimakis 1997; Fragaki 1969). Additionally, the name of the genus "*Origanum*", according to some researchers has its roots in the Greek words "oros" which means 'mountain' + "ganos" (like "ganimai-ganousthai") which means 'becoming bright'. This name probably originates and is closely associated with the natural growing environment of *Origanum* plants in the Mediterranean, which are the high mountains (Liolios *et al.* 2010). The name of dittany "*stamatochorto*", which literally means in Greek "stopping something herb" originates from the Greek words "*stamato*" (= 'to stop') and "*horto*" (= 'herb'), probably derives from the plant's property to stop bleeding. Also the name "*stomachohorto*", literally meaning "herb for the stomach", originates from the words "stomach" and "horto" and refers to its healing properties to cure stomach ache (Plimakis 1997; Skoula & Kamenopoulos 1997). Other names like "*maliarochorto*", which

means in Greek 'hairy herb', and "gerondas" (= 'old man') refer instead to the plant morphology as its aerial parts are covered by dense white hairs (Skoula & Kamenopoulos 1997; Liolios *et al.* 2010).

Chemical constituents according to existing references

- The lipid composition, as well as a variety of non-polar components such as fatty acids, lipids, sterols and essential oil has been identified (Komaitis *et al.* 1988; Revinthi-Moraiti *et al.* 1985).
- Polyphenolic components, flavonoids and coumarins have also been isolated and identified from methanol extract of aerial parts of the plant (Skaltsa & Harvala 1987; Harvala & Skaltsa 1986; Møller *et al.* 1999) such as: p-coumaric acid (13.9%), ferulic acid (0.34%), hydrated catechin (0.5%) or catechin (0.22%) (Proestos *et al.* 2006). From the polar extracts of the aerial parts of cultivated *Origanum dictamnus* have been isolated one new depside, to which the name salvianolic acid P was given, in addition to the known depsides rosmarinic acid and rosmarinic acid methylester; two monoterpenes: thymoquinone and thymoquinol 2-O- β -glucopyranoside; two simple phenolic acids: oresbiusin A and E-caffeic acid; six flavonoids: apigenin, kaempferol, quercetin, eriodictyol, taxifolin, narigenin; and two alicyclic derivatives: 12-hydroxy jasmonic acid and its 12-O- β -D-glucoside (Chatzopoulou *et al.* 2010).
- Triterpenes such as oleanolic and the rare 21 α -OH oleanolic acid, ursolic acid and a new 21 α -OH ursolic acid and also ouvaol (Piozzi *et al.* 1986).
- Essential oil: for *Origanum dictamnus* the major components of its essential oil are the monoterpenes: carvacrol, γ -terpinene and p-cymene (Liolios *et al.* 2010; Liolios *et al.* 2009; Chorianopoulos *et al.* 2004; Daferera *et al.* 2000; Figueredo *et al.* 2006; Economakis *et al.* 2005; 2002; 1999; Sivropoulou *et al.* 1996; Harvala *et al.* 1987; Skrubis 1979; Schaden & Hesse 1976; Skoula *et al.* 1999; Kokkini *et al.* 1997).

- Herbal preparation(s)

The monograph describes the uses of the comminuted herbal substance.

- 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.

This monograph refers only to *Origanum dictamnus* herba.

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

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Belgium	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Bulgaria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Czech Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Denmark	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
France	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Germany	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Herbal teas marketed since at least 1970
Hungary	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Liechtenstein	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Lithuania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Luxemburg	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Malta	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
The Netherlands	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Norway	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Poland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Portugal	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Romania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Spain	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Sweden	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
United Kingdom	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

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

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

1.3. Search and assessment methodology

Search terms: *Origanum dictamnus* L., Dittany of Crete herba

Databases: Pubmed, Medline, HealLink, Scopus.

Libraries: University of Athens, Laboratory of Pharmacognosy and
Chemistry of Natural Products of the University of Athens

2. Historical data on medicinal use

The herb of dittany of Crete consists of the dried or fresh aerial parts of *Origanum dictamnus*, which are collected during the early summer. More specifically, wild dittany is collected while in full bloom (Fragaki 1969).

Ancient mythology states that the plant was dedicated to the ancient Cretan goddess Diktyinna, thus its name Dittany. Moreover, both Artemis and dittany were believed to magically cure arrow wounds. This relation explains why Artemis is often represented with *Origanum dictamnus* crown on her head (Skoula & Kamenopoulos 1997). Excavations in Knossos palace (near Heraklion city, Crete), Zacros (east coast of Crete, south of Palaikastro), and the Royal palace of Mycenae as well as in the palace of Pylos (North East and South Peloponnese respectively), revealed seeds of different kinds of aromatic plants like *Origanum dictamnus*, *Artemisia absinthium*, *Salvia triloba* and others (Diapoulis 1949). Since ancient times, dittany was considered as “panacea”, which means a drug against every illness. So it was thoroughly used for stomach disorders, gastric ulcers, generally for the peptic system, spleen, against rheumatism, to facilitate childbirth and against gynaecological disorders. The power of the plant has been extolled by at least twenty-four writers from antiquity up to the fourth century A.D. Homer (9th century B.C.) reported that dittany roots were a cure against gastric ulcers. Euripides (5th century B.C.) stated that it induced (facilitated) childbirth. Hippocrates (5th - 4th century B.C.) used it on Cos island for gastric complaints, tuberculosis and in poultices on wounds. The most interesting referral to the medicinal power of *Origanum dictamnus* comes from Aristotle, who stated that wild goats of Mount Ida (Crete) struck by poisoned arrows would eat aerial parts of *Origanum dictamnus*, causing the arrows to leave their bodies and their wounds to heal (Historia Animalium); Theophrastus (4th – 3rd century B.C.) repeated the previous statement of his master (Thanos 1994). Cicero (2nd - 1st century B.C.) and Virgil (1st century B.C.) attributed many virtues to *Origanum dictamnus*; specifically in the work of Virgil, Aphrodite used the Cretan *Origanum dictamnus* to heal the wounds of Aeneas (Virgil, Aeneid 12.412). Dittany is also mentioned by Pliny (Gaius Plinius Secundus 23 – 79 A.D.) and Celsus (Aulus Cornelius Celsus 1st century B.C.), who suggest that four sips of NH₃ or water solution of the plant are needed in order to have the desired effects (Med. 5.25.13). Later on, Plutarch (1st - 2nd century A.D.) and Dioscorides (1st century A.D.) in his work “De Materia Medica” (Codex Vindobonensis, book 3, 23) attributed to dittany similar properties than those attributed by Aristotle. Finally, Galen attributed healing properties to dittany (Berendes 1902; Liolios *et al.* 2010).

During the middle ages, the plant is recorded in the code of Carlomagnum (742-814 A.D.) about 795 A.D. “...diptamnum, sinape, satureiam, sisimbrium, mentam, mentastrum...” (chapter LXX.). Linnaeus (1707-1778 A.D.) fully identified *Origanum dictamnus* botanically much later (1753 A.D.) (Linnean Herbarium 2003). Dittany was also widely used in liqueurs Benedictine and Trappistine of the Benedictines and Trappistines monks, respectively. Even in our days, dittany is used in distilleries, as vermouth for example is flavoured with this very aromatic plant (Skrubis 1979; Baumann 1996).

Dittany is a species with significant commercial interest since it is widely used for herbal teas, not only in the local markets of the island of Crete but all around Greece in traditional or modern shops and open-air market stalls (Skoula & Kamenopoulos 1997; Hanlidou *et al.* 2004; Liolios *et al.* 2010). In the past, the demand for plant material was covered only by the collection of wild populations, a fact which led to their rapid decrease and extinction from several areas of the island.

The collectors of wild dittany were organised groups of local people called "Erontades", "Atitanologi", "Botanologi" or "Mazoctades" which travelled across the island in order to collect enough plant material. Climbing accidents, which occurred often during the collection, and the increasing demand for plant-material, drove the locals towards the cultivation of the plant since 1920. Nowadays, the cultivated plants maybe the main source of plant-material used. Wild populations are given legal protection as a vulnerable species under the Revised Appendix 1 of the Bern Convention (2002) (Baden 1991; Turland 1995). Around 1920 started the systematic cultivation of *Origanum dictamnus* in several villages of Crete. After 1935, there was a rapid increase in its cultivation reaching a peak of 10 tons/year of total production. Right after 1945, the production reached 50 tons/year. Eighty-five percent of the product is exported (mainly to Italy, France, Germany and Japan), while 15% of the total production is absorbed by the Greek market (Skoula & Harborne 2002).

2.1. Information on period of medicinal use in the Community

Common names of the plant

Greece: Dictamos, Adichtamos, Atitamos, Dictami, Erontas, Levanochorto, Malliarochorto, Stathori, Stamatochorto, Stomachohorto, Titamos, Attitamos, Simpsychi, Gerontas, Diapsychos, wild *Origanum*, Kefalochorto

England: Dittany of Crete, Dictamna hops, Dictamnus, Winter Sweet, Dittany, Hop Marjoram, Hop Plant

Turkey: Mangirotu

Germany: Diptamdsten, Kretadiptam, Dictamno, Kreta-Majoran, Majoran, Kreta (Schaden & Hesse 1976)

Italy: Origano de Creta, Dittamo di Candia, Dittamo Cretico (De Vincenzi *et al.* 2004; Skrubis 1979)

France: Dictame de Crête (Fournier 1947; Havakis 1978; Liolios *et al.* 2010).

Herbal use

Nowadays, as in the past, dittany is widely used in Crete as a traditional medicine. The aerial parts of the plants are being used in various preparations against almost every illness and for the maintenance of good health. The following data refer to the most common uses of these preparations according to the local villagers and ethnographic literature (Plimakis 1997; Skoula & Kamenopoulos 1997; Havakis 1978; Spyrou 1972; Fragaki 1969; Steinmetz 1954).

Infusion: 20-50 g of plant material in 1 l hot water, (or 3-7 g in 150 ml of hot water) 2-3 cups (150-200 ml each) daily. Oral use. (Plimakis 1997; Skoula & Kamenopoulos 1997; Havakis 1978; Spyrou 1972; Fragaki 1969; Steinmetz 1954). Uses: against tonsillitis, cold, cough, sore throats, digestive, spasmolytic, against stomach discomfort and mild gastric disorders (Liolios *et al.* 2010; Anassis 1959; Bazaios 1982; Platakis 1975).

Also infusion: 3-7 g in 150 ml of hot water, or chewed crude plant parts against gingivitis and cough and cold as well as against mild gastric disorders (Skoula & Kamenopoulos 1997).

Decoction: 1.5-5 g of dried dittany in 150 ml (about one cup) of water. The plant should not be left for long into the boiling water (around 2-4 min is enough). The decoction called 'brastari' in Crete should be used within 24 h after its preparation (Plimakis 1997; Skoula & Kamenopoulos 1997; Havakis 1978; Fragaki 1969). Dosage: 2-3 cups per day (150-200 ml each).

Uses: for gingivitis and sore throat, common cold and against cough. The decoction has been also used for digestion, stomach-aches and mild gastric disorders.

Tincture: 15-30 g of dried or fresh herb in 1 l wine or "raki" traditional Cretan drink or white wine (or 25% ethanol dilution) (Liolios *et al.* 2010).

Uses: similar to the decoction 5 ml 1-2 times per day.

Cutaneous use (used externally): compresses of the infusion or the decoction (30-75 g/l of herbal substance) (Liolios *et al.* 2010; Lampathianaki-Papadaki 1982; Anassis 1959; Bazaios 1982; Platakis 1975; Zaharopoulos 1980).

Uses: antiseptic, anti-inflammatory, against bruises and ulcerations, for wound healing (Anassis 1959; Bazaios 1982; Platakis 1975; Zaharopoulos 1980). Dosage: 2-5 times per day.

Additionally a recent ethnopharmacological study, considering the herbs traded in the local markets of Thessaloniki, reported the following therapeutic uses for the aerial parts of the herb applied either as an infusion for oral use or as an external application (cutaneous use as compress or washing): *Gastrointestinal disorders* - spasmolytic, stomach ulcer, *Skin disorders* - antiseptic, antibacterial activities, aphrodisiac (Hanlidou *et al.* 2004).

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

According to the overview of the European market, there are no herbal preparations containing *Origanum dictamnus* herba except in Greece where it is used widely since at least the last 40 years (according to existing references); the comminuted herbal substance is found in literature references and the period of its use is longer than 30 years.

Therefore for *Origanum dictamnus* herba a period of at least 30 years of medicinal use, as requested by Directive 2004/24/EC for qualification as a traditional herbal medicinal product is fulfilled. The evidence on traditional medicinal use is confirmed by a large number of publications providing consistent information.

Literature: Steinmetz 1954; Anassis 1959; Fragaki 1969; Platakis 1975; Havakis 1978; Zaharopoulos 1980; Bazaios 1982; Hanlidou *et al.* 2004; Plimakis 1997; Skoula & Kamenopoulos 1997.

The monograph describes the use of the comminuted herbal substance as a herbal tea for oral use and its use for preparation of an infusion or a decoction for cutaneous use.

The indications recommended in the monograph are:

1. Traditional herbal medicinal product used for the relief of cough associated with cold.
2. Traditional herbal medicinal product used for the relief of mild gastrointestinal disorders.
3. Traditional herbal medicinal product used for the relief of minor skin inflammations and bruises.

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

Posology

Indications 1) and 2)

Adults and elderly

Single dose

Herbal tea: 3-7 g of the comminuted herbal substance in 150 ml of boiling water as a herbal infusion, 3 times daily.

Daily dose 9-21 g

Or

Single dose

Herbal tea: 1.5-5 g of the comminuted herbal substance in 150 ml of water as a decoction, 3 times daily.

Daily dose 4.5-15 g

The use in children and adolescents under 18 years of age is not recommended.

Indication 3)

Adolescents, adults and elderly

Comminuted herbal substance for infusion or decoction preparation for cutaneous use: 30-75 g of the comminuted herbal substance in 1 l of water.

The use in children under 12 years of age is not recommended.

Duration of use

Indication 1)

If the symptoms persist longer than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Indications 2) and 3)

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.

3. Non-Clinical Data

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

In vitro experiments

Antimicrobial ability

Origani dictamni herba and preparations

The water extracts of *Origanum dictamnus* and other plants from the Lamiaceae family have been tested against the yeast *Yarrowia lipolytica*. Dittany extracts (concentration of 5 g extract/l of water) presented the greater lag time and the greater inhibition activity against *Yarrowia lipolytica* from all the other tested extracts (Karanika *et al.* 2001).

There is a traditionally known use of the plant against gastrointestinal disorders (Fournier 1947; Berendes 1902). In an *in vitro* test, an aqueous 70% methanolic extract was tested against one reference strain of *Helicobacter pylori* and 15 clinical isolates of *Helicobacter pylori* (from antral biopsies). *Origanum dictamnus* and its close relatives, *Origanum vulgare* and *Origanum majorana* proved very active against the used *Helicobacter* strains. The minimal inhibition concentration (MIC) was also identified for the extract (around 2.50 mg/ml) (Stamatis *et al.* 2003).

Moreover the methanol extract and especially the isolated polar compounds from *Origanum dictamnus* (salvianolic acid, rosmarinic acid methyl ester, thymoquinone, thymoquinol 2-O- β -glucopyranoside, oresbiusin A, caffeic acid, eriodictyol, taxifolin, naringenin and 12-hydroxyjasmonic acid) showed MIC values 0.012-0.22 millimol/ml; they have been proved active against the Gram-negative clinical strains *Acinetobacter haemolyticus*, *Empedobacter brevis*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* (Chatzopoulou *et al.* 2010).

Antioxidant activity

Origani dictamni herba and preparations

Studies conducted for various plants of the Lamiaceae family and among them *Origanum dictamnus*, by the Umezawa method, have shown that its methanol extract has antioxidant action identical with α -tocopherol (the antioxidant activity in relation to α -tocopherol is estimated in α -tocopherol units according to the ratio ΔA sample/ ΔA tocopherol where ΔA sample is the absorption of the control – absorption of the sample solution and ΔA tocopherol is the absorption of the control – absorption of the solution containing tocopherol) (Couladis *et al.* 2003).

Extracts of dittany of different ΔA polarities have been tested: (i) with electron spin resonance (ESR) spectrometry (16.5 μ l extract/ml corresponding to 0.413 mg of dried spice/ml), for their efficiencies as scavengers of free radicals and (ii) by measurement of oxygen depletion (12.5 mg dried spice/ml) in a methyl linoleate emulsion, for their efficiencies as chain breaking antioxidants. The water extracts showed high efficiency for both tests. The methanol extract was of medium efficiency, whereas the acetone extract showed less activity in both assays. The methanol and water extracts are rich in phenolic derivatives, contrary to the acetone extracts and that is why they have greater efficiency as antioxidants (Møller *et al.* 1999; Lionis *et al.* 1998).

The non-polar extracts of dittany have also been tested with positive results. The cyclohexane extract has reported antioxidant efficiency as well as the ability to suppress the mutagenicity of Trp-P-2, a common dietary carcinogen. Also, in the unsaponified fraction of dittany have been determined all the four known tocopherols (alpha-, beta-, gamma- and delta- tocopherols), whereas the concentration especially of gamma-tocopherol was significantly higher. Total tocopherol content ranged from 288 to 672 ppm (Liolios *et al.* 2010).

In a study comparing the antioxidant scavenging activity against DPPH (2,2-diphenyl-1-picrylhydrazyl) between the non-polar and the polar extracts of *Origanum dictamnus* (0.1 ml of extracts), Kouri *et al.* (2007) showed that the most polar ethanol extract presented the highest activity (at concentration of 200 ppm), followed by the diethyl ether extract and the ethyl acetate extract, while the petroleum ether extract exerted a weak activity.

Cytotoxic activities

Origani dictamni herba and preparations

Based on preliminary bio-assays for the isolation of potentially cytotoxic compounds various extracts of *Origanum dictamnus* were submitted to pharmacological investigations. The dichloromethane residue showed an important *in vitro* cytotoxic activity, while ethanol and water extracts were proved almost inactive. The dichloromethane extract was tested according to NCI (National Cancer Institute) procedures and proved to be active *in vitro* ID₅₀ = 8 and 14 μ g/ml against murine leukemia P388 and human bronchial epidermoid cancer NSCLC-N6 (non-small cell lung cancer) cell lines, respectively (Chinou *et al.* 2007).

Ursolic acid

The bioassay-directed fractionation of the dichloromethane extract led to the isolation and characterisation of ursolic acid (Chinou *et al.* 2007). Ursolic acid exhibited a high activity *in vitro* against murine leukemia P388 and human bronchial epidermoid cancer NSCLC-N6 ($ID_{50} = 3.5$ and $9 \mu\text{g/ml}$).

In vivo experiments

Ursolic acid

Experiments in nude mice (two-month-old BALB/c x DBA/2F1 30 male mice, 20 to 22 g) on murine ascite leukemia P388 exhibited a marginal anti-leukemic activity (T/C = 125% at 50 mg/kg) for ursolic acid (Chinou *et al.* 2007).

Essential oil

The oil of the plant when given to rats induces the activity of glutathione S-transferase (GST) in some tissues. This particular enzyme is considered to possess a protective role against chemical mutagens (Lam & Zheng 1991).

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

No data on dittany herb preparations/extracts have been found or reported.

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

Single-dose and repeated-dose toxicity studies

Origanum dictamnus is characterised as safe for consumption as a spice (CFR 2009).

Genotoxicity studies

No data on genotoxicity carried out on dittany of Crete herb, was found in the scientific literature, while the toxicity of the monoterpene carvacrol (main constituent of its essential oil) towards human HepG2 and Caco2 cell lines is rather modest (Zeytinoglu *et al.* 2003). In another study, chromosomal aberrations in bone marrow cells from carvacrol were demonstrated. In this study, several short-term microbial and mammalian *in vitro* assays were used to evaluate cytotoxicity and genotoxicity of certain plant volatiles among which carvacrol. All inhibited proliferation of Hep-2 cells in a dose-dependent manner. IC_{50} ranged up to 0.2 mM (for carvacrol) in the proliferation test. The morphological analysis suggested an involvement of apoptosis in the case of carvacrol, while at non-toxic doses, carvacrol increased the number of revertants in the Ames test by 1.5 ± 1.7 times, regardless of metabolic activation. In the SOS-chromotest, carvacrol did not cause DNA damage at non-toxic doses (Stammati *et al.* 1999; Liolios *et al.* 2010).

Carcinogenicity studies

No carcinogenicity studies carried out on dittany of Crete herb in the scientific literature.

Reproduction and developmental toxicity studies

No reproductive and developmental toxicity studies carried out on dittany of Crete herb was found in the scientific literature.

The safety of dittany of Crete herb during pregnancy and lactation has not been established. In accordance with general medical practice, the herbal medicinal products (herbal teas and other finished products) should not be used during pregnancy and lactation.

3.4. Overall conclusions on non-clinical data

Origanum dictamnus is an endemic plant of Greece, growing wild and also cultivated since the last century in the island of Crete in Greece, very well known since antiquity but also in many references in the last century as a herbal remedy, in the form of infusion traditionally used for the relief of cough associated with cold (Plimakis 1997; Skoula & Kamenopoulos 1997; Havakis 1978; Spyrou 1972; Fragaki 1969; Steinmetz 1954; Liolios *et al.* 2010; Anassis 1959; Bazaios 1982; Platakis 1975; Zaharopoulos 1980; Hanlidou *et al.* 2004), for the relief of mild gastrointestinal disorders and topically (Anassis 1959; Bazaios 1982; Platakis 1975; Zaharopoulos 1980) and for the relief of minor skin inflammations and bruises (Bazaios 1982; Platakis 1975; Zaharopoulos 1980; Lampathianaki-Papadaki 1982). It has been used as a traditional remedy without safety problems for more than 50 years mainly in Greece.

The published data referring to the indications and preparations is limited, but existing data on the above-mentioned pharmacological activities support the traditional use, for relief of cough associated with cold, of *Origanum dictamnus* L., herba.

Moreover the traditionally known use of the plant against gastrointestinal disorders (Fournier 1947; Berendes 1902) is considered, together with the results from an *in vitro* test of a water-methanol extract against one reference strain of *Helicobacter pylori* and 15 clinical isolates of *Helicobacter pylori*. In this study, the methanolic extract from *Origanum dictamnus* was proved active against the used *Helicobacter* strains (Stamatis *et al.* 2003).

The traditional use for the relief of minor skin inflammations and bruises is well known traditionally; in a case report study (Paulsen *et al.* 2012) where a woman patient had bought and used *Origanum dictamnus* for ulcerative lesions on her arms during a stay in Crete, the treatment was considered as very effective.

Due to the lack of tests on genotoxicity, a Community list entry cannot be established.

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

No data available.

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

No data available.

4.2. Clinical Efficacy

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

No data available.

There is a lack of clinical research, assessing the effects of dittany of Crete herb and rigorous randomised controlled clinical trials are required.

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

None reported.

4.3. Overall conclusions on clinical pharmacology and efficacy

The uses are made plausible by the long-standing use and experience (having regard also to existing *in vitro* and *in vivo* pharmacological data).

5. Clinical Safety/Pharmacovigilance

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

There is a lack of clinical and non-clinical safety and toxicity data for dittany of Crete herb and further investigation of these aspects is needed.

5.2. Patient exposure

One recent case was reported (Paulsen *et al.* 2012). A 60-year-old non-atopic woman was referred by her general practitioner with suspected impetigo in October 2010. Her past medical history included ulcerative colitis, which was treated with tincture of opium only, and a transient itchy dermatitis on her arms and trunk in the previous year. She was clinically diagnosed with secondarily infected nummular dermatitis on the arms, nape of the neck, trunk, and legs, and the diagnosis was confirmed by a skin punch biopsy. The patient had bought and used the ointment for ulcerative lesions on her arms during stays in Crete in June and August, and the treatment was very effective. The main ingredients of this herbal remedy were organically grown dittany of Crete (*Origanum dictamnus*), organic extra virgin olive oil and organic beeswax. Dittany of Crete is known for its wound-healing properties, and as this seems to be the first report on contact allergy, the sensitising potential of *Origanum dictamnus* is probably low, even though the possible contact allergy in a control may suggest underreporting of sensitisation to the genus.

5.3. Adverse events and serious adverse events and deaths

No data available.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

Special patient population

No data on the oral use in children and adolescents are available, therefore dittany of Crete herb can be intended only for adults and elderly.

For the cutaneous use, the use in adolescents, adults and elderly is supported by the long-standing use, information on marketed products and the preparation's safety profile.

Fertility, pregnancy and lactation

No fertility data available.

In the absence of data available and in accordance with general medical practice, it is recommended not to use traditional herbal medicinal products containing dittany of Crete herb during pregnancy and lactation.

Overdose

No cases of overdose have been recovered in the scientific literature.

Drug abuse

No information in the literature search.

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

No data in the literature search.

5.6. Overall conclusions on clinical safety

In the absence of adequate data on the use in children and adolescents, the oral use of dittany of Crete herb is intended only for adults and elderly.

In the absence of data available and in accordance with general medical practice, it is recommended not to use traditional herbal medicinal products containing dittany of Crete herb during pregnancy and lactation.

No fertility data available.

One case of contact dermatitis was recently reported (Paulsen *et al.* 2012) where a 60-year-old non-atopic woman was referred by her general practitioner with suspected impetigo in October 2010. This seems to be the first report on contact allergy, the sensitising potential of *Origanum dictamnus* is probably low, even though the possible contact allergy in a control may suggest underreporting of sensitisation to the genus.

Moreover no adverse effects have been reported, showing enough safety data for the proposed traditional use of herbal medicinal products containing *Origanum dictamnus* herba, in the conditions for a safe use found in the monograph.

6. Overall conclusions

The positive effects of dittany of Crete herb on the relief of symptoms of cough associated with cold as well as for the relief of minor skin inflammations and bruises have been recognised empirically. There

is also a long-standing traditional use in part of Europe of the plant for the relief of gastrointestinal disorders.

The uses are made plausible by the long-standing use and experience, having regard also to existing *in vitro* and *in vivo* pharmacological data. There is a lack of controlled clinical studies with preparations containing *Origanum dictamnus*.

In conclusion, dittany of Crete and its preparation (comminuted herb) can be regarded as traditional herbal medicinal products in the following indications:

1. Traditional herbal medicinal product used for the relief of cough associated with cold.
2. Traditional herbal medicinal product used for the relief of mild gastrointestinal disorders.
3. Traditional herbal medicinal product used for the relief of minor skin inflammations and bruises.

In the absence of adequate data in adolescents and children, the oral use of preparations containing *Origanum dictamnus* L., herba is intended only for adults and elderly. The cutaneous use for the third indication is accepted in adolescents, adults and elderly.

In the absence of available data and in accordance with general medical practice, it is recommended not to use traditional herbal medicinal products containing dittany of Crete herb during pregnancy and lactation.

Due to the lack of genotoxicity tests, a Community list entry cannot be established.

Annex

List of references