12 July 2011
EMA/HMPC/96910/2010
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Commiphora molmol* Engler, gummi-resina

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Commiphora molmol* Engler, gummi-resina
Herbal preparation(s)	Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 90 % (V/V)
Pharmaceutical forms	Liquid dosage forms for oromucosal or 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)

Gumresin, hardened in air, obtained by incision or produced by spontaneous exudation from the stem and branches of *Commiphora molmol* Engler and/or other species of *Commiphora*, complying with the monograph of the European Pharmacopoeia (01/2008:1349).

Commiphora myrrha (Nees) Engler is a synonym of *Commiphora molmol* Engler. Other species which may be acceptable as sources of myrrh are *Commiphora abyssinica* (Berg) Engler and *Commiphora schimperi* (Berg) Engler (ESCOP 2003).

- Herbal preparation(s)

Myrrh tincture (1:5; extraction solvent: ethanol 90% V/V), Ph. Eur. monograph (01/2008:1877).

- 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.

Combination products can be found in the EU: see section 1.2.

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

According to the information provided by the National Competent Authorities:

Austria: Myrrh is present in combination products (as ethanolic extracts) used as bitters for stomach problems. Myrrh tincture (reported as magistral/officinal formula) is used in phytotherapy for inflammations of the gingiva.

Czech Republic: No single active ingredient products available, but several combination products („Schwedenbitter") containing myrrh, used as adjuvants in mild gastrointestinal complaints, are available.

Denmark: Some MAs (from 1980) containing myrrh tincture, either alone or in combination products. Used as local astringent and anaesthetic in the mouth.

Estonia: One combination product registered.

Germany: Myrrh tincture (1:5; extraction solvent: ethanol 90% V/V) and a dry extract (4-6:1; extraction solvent ethanol 60% m/m) available in combination products. Myrrh tincture as single active ingredient is available as a product with a German standard marketing authorisation.

Slovenia: No single active ingredient products available, but several combination products („Schwedenbitter") containing myrrh, used as adjuvants in mild gastrointestinal complaints, are available.

United Kingdom: Myrrh tincture (British Pharmaceutical Codex) is available as a product first approved in 1972. The indications are: 1) Ulcers in the mouth and pharynx; 5 ml directly applied as required or

diluted with water to 20 ml and used as a gargle as required - 2) Flatulence; 2.5-5 ml 3 times daily as required. The product is not recommended for children under 12 years of age.

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	Combination products
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combination products
Denmark	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combination products
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Slovenia	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	Combination product
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
United Kingdom	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

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

PubMed was searched on 27 January 2010 using the terms [myrrh OR commiphora molmol OR commiphora mol mol OR commiphora myrrha]. One hundred twenty two references were retrieved. The abstracts were screened manually and all articles deemed relevant were assessed and included in the list of references.

2. Historical data on medicinal use

Myrrh appears to be one of the oldest medicines. Its use was recorded in the recipes from ancient Rome and in the texts of Hippocrates. Myrrh is also mentioned in both the Bible and the Koran (Madaus 1938).

2.1. Information on period of medicinal use in the Community

Myrrh has been used within the European Union for more than 30 years (Madaus 1938, Moritz 1967, Braun 1968). The herbal preparation mainly used seems to be the tincture (Todd 1967, Bradley 1992, Blumenthal 2000 (Commission E monograph dated 1987, BAnz Nr 193. 15.10.1987), ESCOP 2003, Barnes 2007, Ph. Eur. 2008).

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

The current use of myrrh in the form of tincture (1:5, extraction solvent ethanol 90% V/V) for oromucosal treatment of minor ulcers and inflammation in the mouth (stomatitis and gingivitis) is well-documented in recent handbooks (e.g. Bradley 1992, Blumenthal 2000, ESCOP 2003, Barnes 2007). The use of undiluted myrrh tincture to dab the affected areas in the mouth is also well-documented (Hänsel 1992, Blumenthal 2000, Information from UK).

Another current use of myrrh tincture is the topical application to minor wounds, abrasions, furuncles and skin inflammations (Bradley 1992, Hänsel 1992, ESCOP 2003, Barnes 2007).

Historically, myrrh (tincture) has had a medicinal use to relieve various gastrointestinal disorders, such as indigestion and intestinal infections (Madaus 1938, Todd 1967, Hänsel 1992, Bradley 1992, Information from UK), but this use seems to have declined (Hänsel 1992, Bradley 1992, ESCOP 2003, Barnes 2007). The oral use of myrrh tincture in combination products is still in practice within the Member States (Information from e.g. Austria, Czech Republic, Denmark, Estonia, Germany, Slovenia, UK).

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

Recommended posology for oromucosal use of myrrh tincture (1 g = 65 drops; 0.8194 g/ml; 0.02 ml/drop) as a gargle:

- 30-60 drops (0.6-1.2 ml) of tincture in a glass of warm water (Blumenthal 2000).
- 5 ml of tincture in a glass of water 3 times daily (Bradley 1992).
- 5 ml of tincture in 15 ml of water (Information from UK).
- 1-5 ml of tincture in a glass of water several times daily (ESCOP 2003).
- 20-30 drops (0.4-0.6 ml) of tincture in a glass of water several times daily (Madaus 1938).

- 2.5-5 ml in a glass of water several times daily (Barnes 2007).

Based on this information, the following posology appears well founded in European tradition:

0.5-5 ml of myrrh tincture in a glass of water 3 times daily.

Recommended posology for direct oromucosal application of myrrh tincture:

- Apply the undiluted tincture to the affected areas on the gums or the mucous membranes of the mouth. Dab with a brush or swab, 2-3 times daily (Blumenthal 2000).
- Dab the affected areas 2-3 daily with undiluted tincture (Hänsel 1992).
- Apply undiluted tincture directly as required (information from UK).

Recommended posology for topical use of myrrh tincture on the skin:

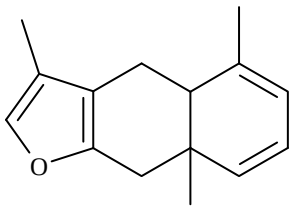
- Apply undiluted tincture (Bradley 1992).
- For use on skin, dab 2-3 times daily with diluted or undiluted tincture (ESCOP 2003).
- For skin, diluted or undiluted (Barnes 2007).

3. Non-Clinical Data

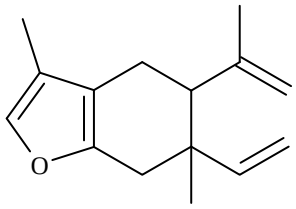
3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Constituents:

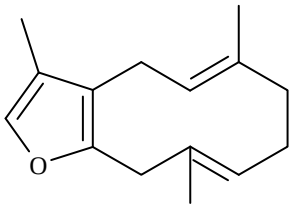
Volatile oil, resin and gum. The main constituents of the volatile oil are furano-sesquiterpenes with furanodesma-1.3-diene as the main component (structure: see below). Important components of the resin are α-, β- and γ-commiphoric acids, α- and β-heerabomyrrhols, heeraboresene, commiferin, burseracin, various terpenes. Also present are the steroids campesterol, cholesterol and β-sitosterol (Wichtl 1989, Hänsel 1992, ESCOP 2003).



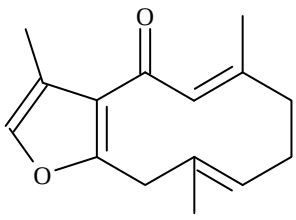
Furanodesma-1,3-diene



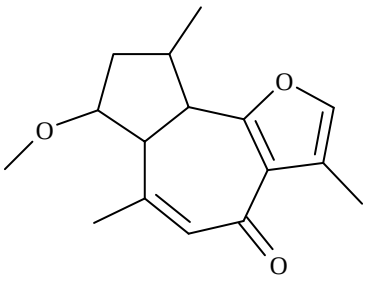
Curzarene



Furanodiene



Furanodiene-6-one



Methoxyfuranoguaia-9-ene-8one

Isolation of furano-sesquiterpenes not mentioned in the above cited handbooks is described by Maradufu (1982, 1988).
A review of myrrh, including products from other *Commiphora* species than the ones accepted as sources of myrrh, is published by El Ashry (2003).
The sesquiterpenes furanodesma-1.3-diene, curzarene, furanodiene, furanodiene-6-one and metyhoxyfuranoguaia-9-ene-8-one have been found to have antibacterial, antifungal, analgesic and local anaesthetic effects, see pharmacological effects below (Dolara 1996a, 1996b and 2000).
Two new furano-sesquiterpenes were isolated from *Commiphora myrrha* Engler (= *C. molmol* (Nees) Engler) and their structures determined (Zhu 2001).
Six aromatic sesquiterpenes were isolated from *Commiphora myrrha* Engler. One was a new furano-sesquiterpene and one was identified as a new natural aroma previously not found in the genus *Commiphora*. The others were isolated for the first time from *Commiphora myrrha* Engler (Zhu 2003).
The sesquiterpenes cadina-3-en-15-ol (myrracadinol A),7,8-seco-2,5-dihydroxy-12-acetoxycalam-8-ene (myrracalamene A), 7,8-seco-2,3,5-hydroxy-12-acetoxycalame-8-ene (myrracalamene B), 7,8-seco-cadin-3,8-dien-2β,12-diol (myrracadinol B), 7,8-seco-12-hydroxycalam-8-ene (myrracalamene C), 7, 8-seco-cadin-3,7(12)-dien-5α,10α-diol (myrracadinol C) along with a known compound triacont-1-ene were isolated from *Commiphora myrrha* (Nees) Engler and their structures elucidated on the basis of spectral and chemical analyses (Ahmed 2006).
The octanordammaranes mansumbinone and 3.4-seco-mansumbinoic acid as well as the sesquiterpenes β-elemene and T-cadinol were isolated from the oleo-resin of *Commiphora molmol* Engler (Rahman 2008).
A review of the constituents found in myrrh and frankincense has been published by Shen (2008).
The watersoluble gum fraction of myrrh (40% w/w) has been found to comprise a mixture of proteoglycans with dominating amounts of uronic acid rich polymers (Wiendl 1995).

Pharmacological effects relevant to traditional use:

Antibacterial and antifungal effects
A fraction from an n-hexane extract of myrrh containing a mixture of furanodiene-6-one and methoxyfuranoguaia-9-ene-8-one had antibacterial effect against *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escherichia coli* as well as antifungal effect against *Candida albicans* with minimum inhibitory concentrations (MIC) of 0.18-2.8 µg/ml (Dolara 2000).
The crude chloroform extract of the oleo-resin of *C. molmol* displayed potentiation of ciprofloxacin and tetracycline against *Staphylococcus aureus*, several *Salmonella enterica* strains and two *Klebsiella pneumoniae* strains. The antibacterial activity of the terpenes mansumbinone, 3.4-seco-mansumbinoic acid, β-elemene and T-cadinol was determined against a number of *Staphylococcus aureus* strains: SA1199B, ATCC25923, XU212, RN4220 and EMRSA15 and MIC values were found to be in the range of 4-256 µg/ml. The highest activity was observed by 3.4-seco-mansumbinoic acid with a MIC of 4 µg/ml against SA1199B, a multidrug-resistant strain which over-expresses the NorA efflux transporter, the major characterised antibiotic pump in this species. This activity compared favorably to the antibiotic norfloxacin with a MIC of 32 µg/ml. This compound also displayed weak potentiation of ciprofloxacin and tetracycline activity against strains of *Salmonella enterica* serovar Typhimurium SL1344 and L10 (Rahman 2008).

Assessor's comments: Myrrh contains terpenes with fairly potent antibacterial effect against several bacteria including the most common wound pathogen S. aureus. The antibacterial effect has been shown in vitro and the mechanism of action is not known.

Local anaesthetic activity
A fraction from myrrh containing a mixture of furanodiene-6-one and methoxyfuranoguaia-9-ene-8-one, in approximately equivalent amounts, had local anaesthetic activity ($p<0.01$) when administered in eye drops (2% DMSO + phosphate buffer) at a concentration of 280 µg/ml in the conjunctival sac of male New Zealand albino rabbits. The vehicle was used as control. The effect was about half that of procaine at 100 µg/ml. The local anaesthetic effect of the terpene mixture was shown to be due to inhibition of sodium inward currents in excitable mammalian membranes (Dolara 2000).

Assessor's comments: Myrrh contains terpenes exhibiting local anaesthetic activity in animal experiments.

Anti-inflammatory effects
An ethanol extract of the oleo-gum resin of *Commiphora molmol* in an intraperitoneally (i.p.) dose of 400 mg/kg bodyweight (bw) reduced the size of xylene-induced ear oedema in mice by 50-53% ($p<0.05$). In rats, an oral dose of 400 mg/kg bw significantly ($p<0.05$) reduced the weight of cotton pellet granuloma (Atta 1998).

In rats, a petroleum ether extract (25:1) of the oleo-gum resin of *Commiphora molmol* produced significant inhibition of carrageenan induced inflammation and cotton pellet granuloma in rats at an oral dose of 500 mg/kg bw (Tariq 1985).

Assessor's comments: The oral doses required for anti-inflammatory activity are comparatively high. No information is available concerning possible anti-inflammatory effects following topical application.

Analgesic effects
In mice, a suspension of ground myrrh in saline at an oral dose of 1 g/kg bw significantly ($p<0.01$) increased the latency of pain reaction (paw licking) when placed on a 52°C metal plate. The sesquiterpenes furanoeudesma-1.3-diene and curzarene, isolated from myrrh, were found to be analgesic to mice in this test at an intracerebro-ventricular dose of 1.25 mg/kg bw, whereas a third sesquiterpene -furanodiene- was ineffective. Furanoeudesma-1.3-diene, at an oral dose of 50 mg/kg bw, had the same effect. This oral dose also considerably reduced the number of writhes in mice after i.p. administration of 0.6% acetic acid. This effect was completely reversed by naloxone. Furanoeudesma-1.3-diene displaced concentration-dependently the specific binding of the opioid (^{3}H)diprenorphine to brain membranes (Dolara 1996a, 1996b).
Administered orally to mice, an ethanol extract of myrrh had a significant and dose-dependent analgesic effect in the acetic-acid writhing test at 200 mg/kg bw ($p<0.05$) and 400 mg/kg bw ($p<0.01$) (Atta 1998).

Assessor's comments: In high doses, orally administered myrrh and isolated terpenes have an analgesic effect in animal experiments. The effect can be blocked with naloxone, which indicates an interaction with brain opioid mechanisms.

Other reported pharmacological effects:

Antipyretic effect
After oral administration to hyperetic mice of either an ethanol or a petroleum ether extract of myrrh (25:1) at a dose of 500 mg/kg bw, a significant antipyretic effect ($p<0.001$) was demonstrated (Mohsin 1989, Tariq 1985).

Stimulation of phagocytosis
Mice inoculated with *Escherichia coli* were treated i.p. with either a dried ethanol extract or the unsaponifiable fraction of myrrh, as solutions in aqueous ethanol (10% V/V) at 50 mg/kg bw (1 mg per

20 g animal). Both treatments stimulated phagocytosis in over 80% of the mice compared to controls (Delaveau 1980).

Cytoprotective effect

Oral administration of myrrh to rats at 250, 500 and 1000 mg/kg bw provided significant and dose-dependent protection to the gastric mucosa against the ulcerogenic effects of various necrotising agents: 80% ethanol, 25% sodium chloride, 0.2 M sodium hydroxide, indometacin 30 mg/kg and combined ethanol 80%-indometacin 2.5 mg/kg ($p<0.05$ to $p<0.001$, depending on the dose). The same suspension significantly and dose-dependently protected against ethanol-induced depletion of gastric wall mucus ($p<0.05$ at 500 mg/kg; $p<0.001$ at 1000 mg/kg) (Al-Harbi 1997).

Protective effect against liver oxidative damage and genotoxicity

The effect of lead acetate in the diet (0.5% w/w) on reduced glutathione (GSH), activity on phase II metabolising enzyme glutathione S-transferase (GST), lipid peroxidation in liver homogenate and bone marrow chromosomes of mice, simultaneously supplemented with 1% myrrh powder for 8 weeks was investigated. Compared with negative control (only diet), GSH decreased in both positive control (diet + lead acetate) and treated group (diet + lead acetate + myrrh). GST decreased in positive control but increased in the treated group compared to both negative and positive control. Lipid peroxidation was reduced by 45% in the treated group compared to both positive and negative control. Lead genotoxicity was confirmed through significant reduction in the number of dividing cells, increased total number of aberrant cells and increased frequency of chromosomal aberrations. The genotoxicity was significantly reduced by treatment with myrrh (El-Ashmawy 2006).

Antitumour and cytotoxic effects

The anticarcinogenic potential of *Commiphora molmol* (oleoresin) was studied in Ehrlich solid tumour-bearing mice. Treatment with *C. molmol* (250 and 500 mg/kg bw/day) was found to be cytotoxic in Ehrlich solid tumour cells. The anti-tumour potential of *C. molmol* was comparable to that of the standard cytotoxic drug cyclophosphamide. This effect of *C. molmol* was less pronounced after 50 days of treatment than after 25 days (Al-Harbi 1994).

Oral doses of 125, 250 and 500 mg/kg bw of an aqueous suspension of myrrh given to mice for 7 days had no effect on the incidence of micronucleated polychromatic erythrocytes (PCE) in the bone marrow but in comparison to the control groups, there was a statistically significant decrease in the PCE/NCE ratio (NCE = normochromatic erythrocytes), indicating the cytotoxic potential of myrrh, which was found to be comparable to that of cyclophosphamide. The levels of DNA and protein in hepatic cells were not affected by treatment with myrrh but there was a significant decrease in their RNA content, comparable to that caused by cyclophosphamide. In Ehrlich ascites carcinoma (EAC) cell-bearing mice, oral doses of 500 mg/kg bw of the myrrh suspension caused significant reductions in the DNA ($p<0.05$), RNA ($p<0.01$) and protein ($p<0.01$) contents of the EAC cells and in their viability ($p<0.05$). An increased survival rate of the animals was also observed (Qureshi 1993).

The furano-sesquiterpenoid rel-1S,2S-epoxy-4R-furanogermacr-10(15)-en-6-one exhibited weak cytotoxic activity against a MCF-7- breast tumour cell line in a clonogenic assay (Zhu 2001).

Effects in gingival cells

Through their production of cytokines such as interleukin IL-6 and IL-8, human gingival fibroblasts and epithelial cells act as accessory immune cells, thereby contributing to peridontal destruction. The cytotoxicity of the essential oil from myrrh (*Commiphora molmol*) (MO) to human gingival fibroblasts and epithelial cells and the effect on IL-1β-stimulated production of IL-6 and IL-8 has been determined. Cell viability and cytotoxicity were determined by metabolic reduction of a tetrazolium salt to a formazan dye (MTT assay) and by release of lactate dehydrogenase (LDH) from membrane damaged cells (LDH release assay), respectively. Based on the MTT assay, 24 and 48 h exposures to ≤0.001% MO had little effect on fibroblast and epithelial cell (24 h only) viability. At 48 h, 0.0005-

0.001% MO decreased epithelial cell viability 30-50%. After 24 and 48 h, MO, at ≥0.005%, maximally decreased viability of all cell lines. In the LDH release assay, exposure to ≤ 0.0001% MO caused <10% cytotoxicity to all cells. At 24 h, ≥0.0025% MO caused maximal cytotoxicity; ≤0.001% MO caused 10-70% cytotoxicity. At longer exposure times, epithelial cells were more susceptible to cytotoxic effects of MO. There was little or no detectable IL-1β-stimulated production of IL-6 or IL-8 by cells exposed to ≥0.0025% MO, probably reflective of loss of viability. At subtoxic MO levels (0.00001-0.001%), there was a significant reduction of IL-1β-stimulated IL-6 and IL-8 production by fibroblasts, but not by epithelial cells (Tipton 2003).

The effect of MO on IL-1β-stimulated PGE(2) production and NF-κB activation in gingival fibroblasts and epithelial cells was determined. Cells were preincubated with MO, exposed to IL-1β, cytoplasmic and nuclear fractions were isolated, and activated NF-κB was measured using an ELISA-based assay. IL-1β increased nuclear activated NF-κB levels in fibroblasts and epithelial cells [10-and 2.5-fold over controls, respectively ($p=0.0001$)], and these increases were not significantly affected by MO. PGE(2) was measured in cell supernatants by ELISA, after preincubation with MO and exposure to IL-1β. MO inhibited IL-1β-stimulated PGE(2) production by fibroblasts ($p=0.001$), but not epithelial cells. The data suggest that gingival epithelial cells and fibroblasts may differ in the magnitude of NF-κB activation after IL-1β stimulation, and that MO inhibition of IL-1β-stimulated IL-6 production in fibroblasts is due in part to inhibition of PGE(2), but not NF-κB activation (Tipton 2006).

Hypoglycaemic effects

Intragastric treatment of normal and diabetic rats with a 5% w/v aqueous extract of myrrh (extracted with boiling water then filtered) daily for one week at 10 ml/kg bw lowered fasting blood glucose levels in both groups and, in the oral glucose tolerance test, significantly increased glucose tolerance in both normal ($p<0.02$) and diabetic animals ($p<0.05$) (Al-Awadi 1987).

Oral administration of two fractions (200-250 mg/kg bw) and two pure furano-sesquiterpenes (150-175 mg/kg) from myrrh (*C. myrrha*) to obese diabetic mice produced significant reductions in blood glucose at 27 hours post-dose ($p<0.005$ in all cases). One active fraction at 200 mg/kg reduced blood glucose by 50% ($p<0.0001$), compared to a 41% reduction with the oral antidiabetic metformin at 250 mg/kg (Ubillas 1999).

Antithrombotic activity

Powdered myrrh (*C. molmol*), administered orally at 100 mg/kg bw, provided 86% ($p<0.05$) protection against ADP/adrelanine-induced thrombosis in mice, comparable to the 94 % ($p<0.05$) protection by acetylsalicylic acid at 20 mg/kg (Olajide 1999).

Antischistosomal activity

In several experimental studies in mice, the antischistosomal activity of a purified extract of myrrh (Mirazid®) has been investigated. Some studies have concluded that the efficacy is promising, whereas others have been unable to confirm this result (Hassan 2003, Massoud 2004a, Massoud 2004b, Massoud 2005, Hamed 2005, Botros 2004).

Assessor's overall conclusions on pharmacology

Myrrh is a gum-resin with complicated chemistry. Best investigated are the components of the volatile oil, which are dominated by furano-sesquiterpenes, some of which have pharmacological activity.
A number of pharmacodynamic effects in animal experiments have been described for the resin as well as for isolated terpenes. Of relevance for the traditional indications gingivitis, stomatitis, wounds and furuncles are the reported antibacterial, local anaesthetic and anti-inflammatory effects, and possibly, the antifungal and the analgesic effect. The traditional use involves a direct application of the tincture

to the affected areas in the mouth or on the skin, so there is a reasonable plausibility that the experimentally observed effects may be clinically relevant.

In Egypt, myrrh is used for treatment of bilharzia and several Egyptian investigations have demonstrated antischistosomal activity of oral preparations of the herbal substance. This activity could, however, not be confirmed by other investigators. The potential antischistosomal activity of myrrh remains controversial.

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

No information.

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

Single dose toxicity
In mice, no visible signs of toxicity and no mortality were observed at oral doses of resin ≤ 3 g/kg bw (Rao 2001).

In rats, the acute oral LD50 value of myrrh oil is reported as 1.65 g/kg bw (1.40-1.90 g/kg) (Opdyke 1976).

Repeat-dose toxicity
Myrrh resin was administered to mice via the drinking water at a dose of 100 mg/kg bw/day during 3 months. No toxic symptoms were observed. The weight gain in the myrrh group was significantly ($p<0.05$) higher than in the control group. After treatment the average weight of the vital organs and conditions of the viscera were normal and comparable to that of the control animals. The weight of testes, caudae epididymides and seminal vesicles was significantly ($p<0.05$) higher in the myrrh group as compared to the control. Biochemical studies showed no significant differences as compared to the control. Haematological studies revealed a significant ($p<0.05$) rise of RBC and haemoglobin levels in the myrrh group as compared to the control (Rao 2001).

Myrrh resin given daily to 6 months-old goat kids (0.25, 1 and 5 g/kg bw/day) resulted in death between day 5 and 16 in the doses 1 and 5 g/kg bw/day. The lowest dose (0.25 g/kg bw/day) was apparently not toxic (Omer 1999).

Genotoxicity
Oral administration of a fresh aqueous suspension of myrrh to mice for 7 days at 125-500 mg/kg bw/day showed no mutagenicity in the micronucleus test. The levels of DNA and protein in hepatic cells were not affected but there was a significant decrease in their RNA content, comparable to that of cyclophosphamide (Qureshi 1993).

Myrrh reduced the genotoxicity produced by lead acetate in mice (El-Ashmawy 2006).

In rats, a preparation of myrrh (Mirazid®) caused a non-significant increase in the incidence of chromosomal aberrations at an oral dose of 500 mg/kg bw/day for 6 weeks. This dose had no hepatotoxic effect (Omar 2005).

Carcinogenicity
No information.

Reproductive and developmental toxicity
No information.

Local tolerance
No irritation, sensitisation (in 21 volunteers) or phototoxicity was found for myrrh oil (Opdyke 1976).

In tests of myrrh in the local lymph node assay (LLNA) in mice, a dose-dependent cell proliferation was observed. The stimulation index in the radioactive LLNA was more than 3, indicating that myrrh has a dermal sensitising potential. Flow cytometric analysis of the B- and T-cell populations in the local lymph nodes indicated that myrrh is a weak sensitiser (Lv 2009).

Assessor's overall conclusions on toxicology

Non-clinical data on the toxicity of *Commiphora molmol* Engler, gum-resin is incomplete.

Limited genotoxicity tests (micronucleus test in mice) have been performed, which indicated no genotoxic potential. Due to the antibacterial effect of myrrh, no results from Ames' test are to be expected.

There are no reports on reproductive and developmental toxicity.

There are some reports in the literature about tests of the local tolerance of myrrh. An old report from 1976 in human volunteers indicated no irritating or sensitising effects, whereas a very recent study in the LLNA indicated a weak sensitising potential. The LLNA is a validated OECD[1] test, and attention should be given to the sensitising potential of myrrh.

The analgesic effect following high doses of myrrh and the isolated terpenes furanodesma-1.3-diene and curzarene on oral administration is noteworthy as it seems to involve an opioid effect. No signals of abuse of myrrh have, however, been retrieved from the scientific literature.

3.4. Overall conclusions on non-clinical data

Antibacterial, local anaesthetic and anti-inflammatory effects of myrrh extracts and isolated terpenes have been shown in experimental models. These pharmacological effects make the traditional medicinal uses of myrrh and myrrh tincture plausible in the indications a) minor ulcers and inflammation in the mouth (stomatitis and gingivitis) and b) minor wounds and furuncles.
There is also a historical medicinal use of myrrh and myrrh tincture for gastrointestinal disorders. This use possibly has some support by the experimental data on opioid and cytoprotective effects of myrrh. The oral use of myrrh (tincture) as single active ingredient seems to have declined during the last decades (Barnes 2007), and is not included in recent handbooks like Commission E (Blumenthal 2000) and ESCOP (2003).

4. Clinical Data

4.1. Clinical Pharmacology

No information available.

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

No information available.

[1] Organisation for Economic Co-operation and Development

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

No information available.

Assessor's overall conclusions on clinical pharmacology: No information on clinical pharmacology is available.

4.2. Clinical Efficacy

4.2.1. Dose response studies

No information available.

4.2.2. Clinical studies (case studies and clinical trials)

No clinical studies on the efficacy related to the traditional indications are available.

A commercial extract of myrrh – Mirazid®, marketed for treatment of schistosomiasis, has been subject to several clinical studies in Egypt but – in analogy with the pharmacodynamic studies of this preparation (see above) – the results are controversial. Two open studies, comprising a total of 212 patients, reported an excellent cure rate (92%) of an oral dose of 10 mg/kg bw/day for 3 days (Sheir 2001, Soliman 2004).
This result could not be confirmed in two other open studies. In one of these (Barakat 2005), Mirazid® was given to 45 patients in a dose of 2 capsules/day for 3 days and the effect compared to a dose of 40 mg/kg of praziquantel given to 38 other patients. The cure rate obtained with Mirazid® was 15.6%, compared to praziquantel (73.7%). Also a second treatment with Mirazid® gave a very low cure rate. In the second study (Botros 2005), a total of 1131 patients (459 school children and 672 household members) were randomly assigned to two groups. One group was given 300 mg/day of Mirazid® for 3 consecutive days and the second received praziquantel at a single dose of 40 mg/kg bw. Mirazid® showed cure rates of 9.1% and 8.9% in *Schistosoma mansoni*-infected school children and household members, respectively, compared with cure rates of 62.5% and 79.7% respectively, in those treated with praziquantel.

The effect of myrrh for treatment of the zoonotic disease fascioliasis, caused by *Fasciola*, a liver fluke that infects sheep, goats and cattle for which humans act as an accidental host, has been investigated. 7 patients who were passing *Fasciola* eggs in their stools were treated with a formulation consisting of 8 parts of resin and 3.5 parts of volatile oils, all extracted from myrrh. The dose was 12 mg/kg bw/day for 6 consecutive days in the morning on an empty stomach. Patients were followed for 3 months. The therapy proved to be effective, with pronounced improvement of general condition and amelioration of all symptoms and signs. A dramatic drop in the egg count was detected at the end of treatment. Eggs were no longer detectable in the faeces 3 weeks after treatment and after a follow-up period of 3 months. High eosinophilic counts, elevated liver enzymes and *Fasciola* antibody titers returned to nearly normal. No signs of toxicity or adverse effects were observed (Massoud 2001).

Good cure rates were reported in an open study on treatment of human fascioliasis (liver fluke) with Mirazid® (Abo-Madyan 2004).

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

No information.

4.3. Overall conclusions on clinical pharmacology and efficacy

No studies of clinical efficacy related to the traditional indications are available.

There is no doubt that myrrh has a long-standing use. As mentioned in the introduction, myrrh was used as a medicine as far back as the ancient Greeks and Romans. Particularly the use in treatment of wounds and mouth infections is documented in the classical times. Myrrh and myrrh tincture have then been included and remained in many pharmacopoeias over the centuries and is still included in the most recent edition of Ph. Eur. On the basis of long-standing use and experience, the efficacy of myrrh must be seen as plausible in the traditional indications a) minor ulcers and inflammation in the mouth (stomatitis and gingivitis) and b) minor wounds and furuncles.

The results on antischistosomal effect and effect on liver fluke infection are controversial and require further studies before any firm conclusions can be made. There are no signals that myrrh has had a systematic use in these indications within the European Union.

5. Clinical Safety/Pharmacovigilance

Myrrh is listed by the Council of Europe as a natural source of favouring and may be added to foodstuffs in small quantities (Barnes 2007).

Myrrh and the essential oil have been evaluated by the Committee of Experts on Cosmetic Products of the Council of Europe and have been classified into Category A "Plants and plant preparations that can be used in cosmetic products". Myrrh and the essential oil have cosmetic uses in *e.g.* toothpastes, mouthwashes and in fragrances (Council of Europe 2001).

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

No information available.

5.2. Patient exposure

No information available.

5.3. Adverse events and serious adverse events and deaths

Allergic contact dermatitis caused by the Chinese orthopaedic solution tieh ta yao gin was demonstrated to be due to the content of myrrh and mastic (Lee 1993a, 1993b).

Two cases of contact dermatitis due to plasters containing myrrh for treatment of wrist tendonitis have been reported (Gallo 1999).

Strong allergy to myrrh solution and myrrh powder, resulting from application of the products for wound healing, is reported (Al-Suwaidan 1998).

5.4. Laboratory findings

No information available.

5.5. Safety in special populations and situations

Drug interactions: A case of interaction with warfarin has been reported. The anticoagulant effect of warfarin was reduced after the patient had taken an aqueous extract of boiled roots of *Commiphora molmol* as a treatment for bronchitis (Al Faraj 2005).

Assessor's comment: This report on boiled aqueous root extract of C. molmol is of limited relevance for the use of myrrh resin (tincture).

5.6. Overall conclusions on clinical safety

Very little clinical safety information is available. Apparently, there is a widespread cosmetic use of myrr and the essential oil, and the Council of Europe has approved this use. Nevertheless, there are a few reports on allergic skin reactions in the literature, and this is mentioned in the monograph.

6. Overall conclusions

Sufficient data have not been retrieved from the literature to support any well-established medicinal use according to provisions of Article 10a of Directive 2001/83/EC.

Myrrh and its tincture have a very long history and tradition of medicinal use. The required 30 years of medicinal use (including 15 years within the European Union) must be considered fulfilled.

The main areas of traditional medicinal use of myrrh and myrrh tincture have been treatment of infections/inflammation and pain in the mouth, infected wounds and other skin infections, and as a remedy for various gastrointestinal disorders.

The oral use for gastrointestinal disorders appears to have declined very much in the last 30 years and does not seem to be common practice today according to several authoritative handbooks of recent dates. The uses that still exist today appear to be limited to myrrh tincture as an ingredient in multi-component recipes. It is not recommended to include myrrh tincture for oral use in the Community herbal monograph.

The oromucosal use of myrrh tincture for oral infections/inflammations is currently in practice. For safety reasons, it appears reasonable to limit the use in self medication to the indications minor ulcers and inflammation in the mouth, such as stomatitis and gingivitis. These conditions are normally expected to benefit from an improved oral hygiene and the experimentally shown antibacterial, local anaesthetic and anti-inflammatory activity of myrrh tincture may contribute to that. The posology recommended in different handbooks is overall in agreement. It should be noted in the product information that the use of myrrh tincture as a gargle in gingivitis cannot be used as a substitute for careful teeth-brushing.

The cutaneous use of myrrh tincture for treatment of infected wounds and skin inflammations has a long tradition. Again, the experimentally shown antibacterial, local anaesthetic and anti-inflammatory activity of myrrh tincture makes this use sensible. The content of 90% ethanol in the tincture will most certainly also contribute to an antimicrobial effect. The alcohol may, however, also cause a considerable pain when applied to a large wound. This is perhaps also part of the traditional use. For reasons of safe self medication, it appears reasonable to limit the use to minor wounds and small boils (furuncles). These conditions are normally self limiting in character and normally do not require a consultation of a physician.

The risks involved in oromucosal and cutaneous use of myrrh tincture are generally estimated to be low. A few clinical case reports in the literature and results from tests in mice point to a possibility of allergic skin reactions. Myrrh is, however, acceptable for use in both food and cosmetic products according to evaluations made by the Council of Europe.

Overall, a monograph on myrrh (tincture) is recommended with the following therapeutic indications:

a) Traditional herbal medicinal product for treatment of minor ulcers and inflammation in the mouth (stomatitis and gingivitis).

b) Traditional herbal medicinal product for treatment of minor wounds and small boils (furuncles).

with the statement that 'The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use'.

In the absence of adequate tests on genotoxicity, no Community list entry can be established.

Annex

List of references