



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Tanacetum parthenium* (L.) Schulz Bip., herba

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)	<i>Tanacetum parthenium</i> (L.) Schulz Bip., herba
Herbal preparation(s)	Powdered herbal substance
Pharmaceutical forms	Herbal preparation in solid dosage forms for oral use.
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1. Introduction

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

- Herbal substance(s)

Tanacetum parthenium herba consists of the dried, whole or fragmented aerial parts of *Tanacetum parthenium* (L.) Schultz Bip. It contains no less than 0.20% of parthenolide (C₁₅H₂₀O₃; Mr 248.3), calculated with reference to the dried drug. It has a camphoraceous odour (Ph. Eur. 6th edition 2008).

The genus *Tanacetum* includes about 50 species, of those only *T. santolinoides* (D.C.) grows in Egypt (El- Shazly et al. 2002).

T. parthenium (L.) Schulz Bip., also known as feverfew, is a member of the *Compositae* family (*Asteraceae*). It is an aromatic, hardy annual herb with chrysanthemum-like leaves and daisylike flowers that grows prolifically in gardens and other open spaces. It is indigenous to South-East Europe, as far East as the Caucasus, but commonly found throughout Europe and the United States of America (WHO monograph 2004).

The leafy, more or less branched stem has a diameter of up to 5 mm. It is almost quadrangular, longitudinally channelled, and slightly pubescent. The leaves are ovate, 2 to 5 cm long, sometimes up to 10 cm, yellowish-green, petiolate and alternate. They are pinnate or bipinnate, deeply divided into five to nine segments, each with a coarsely crenate margin and an obtuse apex. When present, the flowering heads are 12 to 22 mm in diameter with long pedicels (Ph. Eur. 6th edition 2008). Beneficial properties have been associated with consumption of the leaves or aerial parts.

Overview on main active compounds and common qualitative/quantitative characterisation

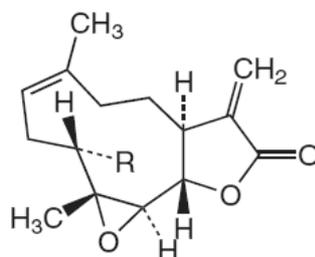
Sesquiterpenes

The most significant components present in feverfew leaves are a complex series of sesquiterpene α -methylenebutyrolactones which are stored in the glandular trichomes on leaves, flowers and seeds. Some of the detected sesquiterpene lactones are known to have biological actions such as cytotoxicity, growth regulation and antimicrobial effects and they cause allergic contact dermatitis. An exocyclic α -methylene function of the sesquiterpene lactones, which may react with sulphhydryl groups of proteins, seems to be responsible for these activities (Milbrodt et al. 1997). The predominant sesquiterpene lactone present in feverfew is a germacranolide, **parthenolide (PN)**, which has been indirectly linked to the anti-migraine action of feverfew preparations (Figure 1). This compound appears to have been first isolated from *T. parthenium*. Later, the same compound, initially named champakin, was also isolated from the roots of *Michelia champaca*. It has been supposed that PN is produced by feverfew as a defensive compound. This compound is located in glands on the underside of the leaves in growing plants, in which position it can express its antimicrobial properties. PN contains a highly electrophilic α -methylene- γ -lactone ring and an epoxide residue capable of interacting rapidly with nucleophilic sites of biological molecules. More recent studies have revealed that it also has anti-microbial, anti-inflammatory and anticancer activities, which may depend on a wide range of PN-stimulated intracellular signals (Won et al. 2004; Pajak et al. 2008).

Feverfew leaf from parthenolide-free sesquiterpene lactone chemotypes has never been clinically tested for effectiveness in migraine prophylaxis (Dennis & Awang 1998). Levels of PN in the dried leaves can be as high as 1%. The remaining sesquiterpene lactones are generally present in much smaller quantities, typically <1 mg/kg. During the growth of *T. parthenium* the percentage of PN is the highest at an early stage (just before the formation of stems). The yield of PN in the plant gradually

increases until the plant is in full bloom. However, PN is present in the leaves and flower heads, but not in the stems.

Drying at ambient temperature and lyophilisation seems to have no negative influence on the yield of PN.



parthenolide R = H
3β-hydroxy parthenolide R = OH

Figure 1. Chemical structure of parthenolide (from WHO monograph).

Since the PN content greatly varies depending on the part used and the season, it has been proposed to distinguish two qualities of feverfew: A) *Tanacetum parthenium* folium (feverfew leaf), harvested at an early stage before the formation of the stems and B) *Tanacetum parthenium* herba (feverfew herb), harvested at full bloom, with a minimum PN content of 0.50% and 0.20% respectively, calculated on a dry weight basis (Hendriks et al. 1997).

The aerial parts of feverfew contain a rich mixture of mono- and sesquiterpenes compounds. Sesquiterpenes contained in the aerial parts are germacrene D, β-farnesene and camphor (the most abundant monoterpene in feverfew). In the roots, β-farnesene and bicyclgermacrene are present. The aerial parts contain also smaller amounts (<10 mg kg⁻¹) of chrysanthenyl acetate, the epimeric cis-chrysanthenol (plus the derived acetic, angelic and isovaleric esters), the isomeric cis-verbenol (an oxidized relative), 4,β-acetoxy-chrysanthenone, bornyl acetate and the corresponding angelate ester. Non-terpenoid spiroketal enol ethers are other substances that are present in small quantities in the aerial parts (Knight 1995).

The presence of different sesquiterpene lactones depends on the habitat of the plant (Milbrodt et al. 1997).

Parthenolide metabolites

Other reported germacranolides are PN metabolites: 3β-hydroxy parthenolide, costunolide (common component of the Compositae), 3β-hydroxycostunolide, artemorin and 3β-hydroxy anhydroverlotrin. They are probably formed by epoxidation and/or allylic oxidation of PN. Related epoxides are represented by epoxyartemorin and anhydroverlotrin-4α,5β-epoxide. Costic acid methyl ester and reynosin have also been found in small quantities. Some sesquiterpenes belong to the biosynthetically closely related guaianolide family: 8α-hydroxyestafiatin, with the corresponding isobutyl and angeloyl esters.

Other compounds

The roots of *T. parthenium* contain the coumarinic compound isofraxidin (Kisiel & Stojakowska 1997).

Melatonin was identified in four samples from feverfew leaves and a commercial preparation was tested by Murch. The authors of the study suggested that melatonin in plant tissues may explain the antimigraine effects of feverfew (Murch et al. 1997).

Lipophilic flavonoids in the leaf and flower of *T. parthenium* were identified as methyl ethers of the flavonols 6-hydroxykaempferol and quercetagenin. A number of other flavones such as apigenin, luteolin and chrysoeriol and their glucuronides, and glycosides such as apigenin 7-glucuronide, luteolin 7-glucuronide, luteolin 7-glucoside and chrysoeriol 7-glucuronide in feverfew extracts have been found. Apigenin and two flavone glucuronides are present in glandular trichomes on the lower epidermis of the flowers. The vacuolar flavonoids are dominated by the presence of apigenin and luteolin 7-glucuronides. Other substances found are tanetin (previously thought to be a new structure and now formulated as the known 6-hydroxykaempferol 3,6,4'-trimethyl ether (Williams 1995)) and the other three flavonol methyl esters as respective 6-O-methyl ethers instead of 7-O-methyl ethers (Williams 1999) and two closely related flavonols, jaceidin and centaureidin (Long et al. 2003). The major flavonol and flavone methyl ethers inhibit the major pathways (cyclo-oxygenase and 5-lipoxygenase) of arachidonate metabolism in leukocytes (Williams et al. 1999).

Moreover, antioxidant polyphenolic acids were isolated and characterised as 3,5-, 4,5- and 3,4-di-O-caffeoylquinic acids (Wu et al. 2007).

Feverfew oil

The analysis of feverfew oil showed the presence of many monoterpenes as α -pinene, camphene, β -pinene, sabinene, myrcene, α -felandrene, α -terpinene, p-cymene, γ -terpinene, terpinolene, terpinen-4-ol and α -terpineol. Among them, the oxidized monoterpenes are very well represented especially camphor, trans-chrysanthenyl acetate, linalool, linalyl acetate and bornyl acetate. The essential oil is mostly composed of camphor and trans-chrysanthenyl acetate amounting up to 70% of the whole oil content. These are the main components of the oil. Among other monoterpene components, there is a greater amount of p-cymene (4.77%), linalool (2.28%) and camphene (1.96%). Sesquiterpenic lactones are not qualitatively or quantitatively present as monoterpenes. Among the sesquiterpenic compounds there are: β -caryophyllene (1.96%), trans- β -farnesene, germacrene (1.49%) and δ -cadinene. The phenyl propanic compound eugenol is also present (1.09%) (Kalodera et al. 1997).

- Herbal preparation(s)

The powdered herbal substance is yellowish-green and is widely used (Ph. Eur. 6th edition 2008).

Herbalists and naturopathic doctors in the UK favoured the use of the tincture and extracts of feverfew. Feverfew extract with a standardized PN content of at least 250 micrograms per daily dose has been recommended for the treatment and prevention of migraine.

Researchers also paid attention to the other chemical components of feverfew leaf as possible responsible agents for feverfew's anti-migraine effect. Dutch researchers of feverfew leaf extract, evidently focusing on its essential oil, suggested that the content of trans-chrysanthenyl acetate might be significant (De Weerd 1996; Hendricks 1996). This constituent declines markedly during the extraction process from 0.25% to just 0.017%; the relevance of this difference has not been determined. Trans-chrysanthenyl acetate and camphor, in contrast, are monoterpenes that are regarded as characteristic constituents of *T. parthenium*, whose content in the essential oil has not shown to vary significantly.

PN was found to be the main constituent of the biologically active sesquiterpene lactones in ethanol and aqueous extracts of feverfew. The sesquiterpene lactone content of ethanol extracts (ca. 0.5%) were higher than those of the aqueous ones (ca. 0.3%) (Gromek et al. 1991).

Commercial preparations of feverfew leaves are known to vary widely in the PN content, as shown by various authors. Feverfew products from the European markets have been simultaneously analysed by HPLC, NMR and biological methods and all were consistent in showing a high variability of the PN content (Heptinstall et al. 1992). Mean PN levels of commercial preparations of feverfew leaves exhibited a range from non-detectable to $1.68\% \pm 0.97$ (per dry weight) based on HPLC-UV-MS (Cutlan et al. 2000).

Nelson et al. (2002) studied the PN content in capsules containing 25 to 500 mg of feverfew leaf, available to consumers, by means of HPLC. The quantity of feverfew leaf in each capsule was similar to that declared on the label. However, the PN content per dosage form varied 150-fold (from 0.02 to 3.0 mg), while percentage of PN varied 5.3-fold (from 0.14% to 0.74%). Therefore, if a person consumes the daily dose recommended on the label, the intake of dried feverfew leaf would range from 225 to 2246 mg/day, a 10-fold variation, while intake of PN would range from 0.06 to 9.7 mg/day, a 160-fold variation.

Taking into consideration the large variations observed in the PN contents and daily intake as recommended by labelling in commercial feverfew products, as well as that therapeutic efficacy has only been shown for preparations of feverfew that contain PN, it is suggested that manufacturers of feverfew products should use measurements of PN for standardization and quality control (Heptinstall et al. 1992). Among the proposed references for establishing quality control of feverfew preparations, a minimum level of 0.2% PN in dried leaves was adopted by the Ph. Eur. and the French Ministry of Health.

Possible differences in physico-chemical properties of extracts from different sources were investigated in the USA on selected formulations of several commercial feverfew extracts. Flowability, hygroscopicity, compressibility and compactibility were studied in order to develop and validate a suitable extraction method. HPLC was used to determine the PN content of several commercial feverfew extracts. The results of the investigation showed that the extracts exhibited poor to very poor flowability. Hygroscopicity and compactibility varied greatly with the source. Moreover, no extracts contained the PN content labelled. Even different batches from the same manufacturer showed a significantly different PN content (Jin et al. 2007).

Another investigation was conducted by the same group of researchers with the aim to evaluate the stability of PN in feverfew solutions versus powdered feverfew (solid state). They further explored the compatibility between commonly used excipients and PN in feverfew. Feverfew extract solution was diluted with different pH buffers to study the solution stability of PN.

Powdered feverfew extract was stored at 40°C/0% to 75% relative humidities (RH) or 31% RH/5 to 50°C to study the influence of temperature and relative humidity on the stability of PN in feverfew solid state. In addition, binary mixtures of feverfew powdered extract and different excipients were stored at 50°C/75% RH for excipient compatibility evaluation.

The degradation of PN in feverfew solution appeared to fit a typical first-order reaction. PN is comparatively stable when the environmental pH is in the range of 5 to 7, but becomes unstable when pH is less than 3 or more than 7.

PN degradation in feverfew in the solid state does not fit any obvious reaction model. Both moisture content and temperature play important roles affecting the degradation rate. After 6 months of storage, PN in feverfew remains constant at 5°C/31% RH. However, ~40% PN in feverfew can be degraded if stored at 50°C/31% RH. When the moisture changed from 0% to 75% RH, the degradation of PN in feverfew increased from 18% to 32% after 6-month storage at 40°C. The authors concluded

that PN in feverfew exhibits good compatibility with commonly used excipients under stressed conditions in a 3-week screening study (Jin et al. 2007). Since the active constituents are unknown, it is recommended that preparations containing the whole leaf (dried or fresh) should be used. Since the PN stability can vary with storage conditions, feverfew should be stored in a cool, dry environment and in a well-closed container, protected from light and humidity (Heptinstall et al. 1992).

- 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 have been designed and their effects on migraine prophylaxis studied.

A study with a daily dose of riboflavin 400 mg, magnesium 300 mg and feverfew 100 mg was conducted. Authors concluded that no significant positive effects were observed (Maizels et al. 2004).

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

Regulatory status overview

Member State	Regulatory Status				Comments (not mandatory field)
Austria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No licensed HMPs
Belgium	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Food supplements (multicomponent herbal tea)
Bulgaria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Czech Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No licensed HMPs
Denmark	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Single preparations and combination authorised in the past. MAs withdrawn by the Companies.
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No licensed HMPs
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No licensed HMPs
France	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input checked="" type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Single preparations and fixed combination
Germany	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No licensed HMPs
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Hungary	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	A single preparation on the market from 1993 to 2005
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Food supplements
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Food supplements

Member State	Regulatory Status				Comments (not mandatory field)
Liechtenstein	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Lithuania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Food supplement (capsules containing Tanacetum herba, Vitis vinifera et Zingiberis officinale extract)
Luxemburg	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Malta	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
The Netherlands	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No licensed HMPs
Norway	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Poland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products available on the market
Portugal	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No licensed HMPs
Romania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No licensed HMPs
Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No licensed HMPs
Spain	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Single preparation and fixed combinations
Sweden	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No licensed HMPs
United Kingdom	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Feverfew products are currently available for the following indication: "A traditional herbal medicinal product for the prevention of migraine headaches based on traditional use only". The hard capsules contain as active ingredient powdered feverfew.

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

This assessment report reviews the scientific literature data available for *T. parthenium* and from the WHO monograph, European Pharmacopoeia monograph, PubMed, EMA library, internet as well as available information on products marketed in the European Community, including pharmaceutical forms, indications, posology and methods of administration.

The keywords "*Tanacetum parthenium*", "Tanaceti herba", "*Chrysanthemum parthenium*", "feverfew", "parthenolide" in all text fields were used.

Clinical studies conducted on the effects of parthenolide or other single active principles were excluded.

2. Historical data on medicinal use

Feverfew has been described since ancient times as having beneficial medicinal effects and has been recommended for centuries for its medicinal properties.

The herb has also been known under other names such as *Matricaria parthenium* (L.), *Leucanthemum parthenium* (L.) Gren. and Gordon, *Pyrethrum parthenium* (L.), *Chrysanthemum parthenium* (L.).

The origin of the term *parthenium* is not certain. According to the ancient Greek author Plutarch, following an incident occurred in the 5th century, feverfew was used to save the life of a person fallen from the Parthenon during its construction. Another explanation is based on the Greek word *parthenios* meaning 'virgin', probably because of the reputation of the herb as an antidote for women's ailments (Groenewegen et al. 1992).

Feverfew is derived from the Old English name 'febrifuge' from the Latin 'febrifugia', pointing to one of its benefits in reducing fever. In some other European countries this herb is referred to as 'motherherb' for example, 'Mutterkraut' in Germany, indicating its acclaimed beneficial properties in various women's conditions. Other names for feverfew include featherfoil, flirwort and bachelor's buttons.

The use of feverfew as a medicinal plant can be traced back to the Greek herbal 'Materia Medica' by Dioscorides and was successively described by Dodoens in 1619, by Gerard in 1636 and Culpeper in 1650.

It has been used for 'intermittent fevers' and for a variety of other conditions and disorders including toothache, rheumatism, psoriasis, insect bites, asthma, stomach ache, menstrual problems and treatment of miscarriage. During the 17th century, it was also used for aiding the ejection of after births and still births, cleansing the kidneys and bladder, strengthening the womb as well as for the treatment of vertigo, spots, wind, colic, and for the treatment of disturbances due to the excessive use of opium. Other uses recommended in the ancient times were the alleviation of St. Antoine's fire, inflammatory processes and hot swellings (Knight 1995).

Ancient uses of feverfew may be categorized broadly into three main groups:

1. treatment for fever, headache and migraine;
2. women's conditions such as difficulties in labour, threatened miscarriage, and regulation of menstruation;
3. relief of stomach ache, toothache and insect bites (Groenewegen et al. 1992).

Bibliographic evidence for a traditional use of feverfew for migraines and headaches are partially traceable in monographs and old texts on herbals (Table 1).

Table 1. Monographs on feverfew

Source	Indications	Dose	Dried herb equivalent/day
BHP 1990	Migraine prophylaxis	n/s	-
BHP 1996	Migraine prophylaxis	n/s	-
Barnes et al. 2007	<i>Traditional uses</i> migraine vertigo tinnitus arthritis fever menstrual disorders difficulty during labour stomach ache toothache insect bite <i>Modern uses</i> prevention and treatment of migraine	- Leaf (fresh) 2.5 leaves daily - Leaf (freeze-dried) 50 mg daily - Aerial parts (dried) 50- 200 mg daily equivalent to 0.2-0.6 mg parthenolide daily	- ≈125 mg* - 50 mg - 50-200 mg
ESCOP 2003	Prophylaxis of migraine	Adult daily dose: 50-120 mg of powdered feverfew	50-120 mg

BHP= British Herbal Pharmacopoeia

ESCOP= European Scientific Cooperative on Phytotherapy

n/s = not stated

The uterine stimulant effect may explain the folk uses of the plant as abortifacient, emmenagogue and in certain labour difficulties but conflicts with the folk use of the drug in threatened miscarriage (Rateb et al. 2007). This contradictory information supports the common warning of the producers avoiding use of feverfew during pregnancy.

2.1. Information on period of medicinal use in the Community

T. parthenium has a long history of usage in Europe to prevent headache and migraine, for relief in arthritis and for treatment of psoriasis. In recent years, it has become popular also in the United States of America.

Because of all its folk fields of application, feverfew has been long referred to as a 'medieval aspirin'. In 1772 John Hill claimed that 'in the worst headache this herb exceeds whatever else is known' (Heptinstall 1988).

Today's use started in late 1970s when the British press reported that a group of migraine sufferers from Wales had found relief from attacks after taking the leaves of the plant for some time. Studies carried out reported that patients were successfully using the herb in the prophylaxis of both migraine and arthritis (Knight 1995). Thus the interest in feverfew grew quickly, bringing it back into the limelight from obscurity since the Middle Ages. A number of investigations have now been carried out on the plant's *in vitro* biological actions and the chemical components responsible for these actions.

Following the success of feverfew in migraine, the herb was also tried in many other conditions and it has now been claimed (but not scientifically proven) to be effective in arthritis, psoriasis and stress, among others (Groenewegen et al. 1992).

Feverfew products have been widely available in the UK as herbal remedies exempt from licensing under section 12 (2) of Medicines Act 1968. Since April 2007 hard capsules containing 100 mg of powdered feverfew herb have been registered according to the new traditional herbal medicinal products registration scheme according to art. 16c of the directive 2001/83/EC as amended.

Feverfew products are currently available in the UK as herbal remedies for oral use for the following indication: "A traditional herbal medicinal product for the prevention of migraine headaches based on traditional use only". They can be bought without prescription from pharmacies and other outlets. The hard capsules contain as active ingredient powdered feverfew.

Between the early 1970's and 1988, feverfew products held product licenses in the UK. This information was obtained from the MHRA under a Freedom of Information Act enquiry. Information on indication and posology was not available as these details for "product licenses of right" are not held on the MHRA electronic database (Table 2).

Table 2. Licensed feverfew HMPs since the early 1970s in the UK (data from MHRA).

Licence no.	Product name	Date granted	Date cancelled
PLR 00250/5674	Liquid Extract Feverfew Herb	Assumed to be the early 1970's	13/02/1977
PLR 00250/5843	Tincture Feverfew	Assumed to be the early 1970's	27/05/1975
PLR 0076/5631	Feverfew Liquid Extract	Assumed to be the early 1970's	28/10/1976
PLR 01252/5448	Chrysanth. Parthen. Liquid Extract	Assumed to be the early 1970's	11/05/1979
PLR 02167/5183	Feverfew Extract	Assumed to be the early 1970's	17/07/1979

In Spain, the powdered herbal substance is registered as a traditional herbal medicinal product since 1991, in form of capsules both as a single preparation and in fixed combinations containing 200 mg of *T. parthenium* and 100 mg of *Anthemis nobilis* or 150 mg of *T. parthenium* and 150 mg of *Artemisia*.

In France, the powdered herbal substance has been authorised as a traditional medicinal product since 1991, the dry extract (solvent: ethanol 30% V/V, DER 4.5-5.5:1) since 1994 and the comminuted herbal substance was authorised from 1996 to 2000.

In Denmark, medicinal products containing Tanacetum extracts (0.1-0.2 mg) quantified to PN (0.1-0.2 mg) in form of tablets were on the market from 1990 to 2004.

An extract corresponding to 0.1 mg of partenolide had been authorised as a medicinal product from 1993 to 2002 and an extract containing 0.2 mg of PN had been authorised from 1997 to 2004. As a fixed combination with *Achillea millefolium herba* and *Populus tremula*, the extract corresponding to 1 mg of PN had been authorised from 1993 to 2000. No further information on the type of the above mentioned extracts is available. All these products were withdrawn by the Companies and no information about their possible presence on the EU market as food supplements is available.

In Hungary capsules containing 50 mg of feverfew herb (*Chrysanthemi parthenii herba*) quantified to 0.4% parthenolid content were on the market from 1993 to 2005.

Food supplements are on the market in Italy, Latvia and Lithuania. In Belgium, an herbal tea containing 11 herbal components is on the market as a food supplement; however that will have to undergo a revision phase according to the new directive 2004/24/EC on THMPs.

In the light of the above evidences, it can be concluded that feverfew herbal medicinal products for migraines have been available for more than 30 years in the European Union and the medicinal use of feverfew for migraine and headaches in Europe is documented since centuries.

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

The powdered herbal substance is registered in the UK as "a traditional herbal medicinal product used for the prevention of migraine headaches based on traditional use only" (ATC code N02CX), in Spain as "a traditional herbal medicinal products used in case of headache". In France single preparations containing the comminuted or powdered herbal substance or the dry extract (ethanol 30% V/V, DER 4.5-5.5:1) are authorised as medicinal products traditionally used in the prevention of headaches. A fixed combination with *Artemisia vulgaris* was authorised from 1995 to 2007 as a medicinal product traditionally used in painful periods.

In Hungary, capsules containing feverfew herb are used to reduce the frequency of migraine headaches, to relieve the associated symptoms (pain, nausea, vomiting and vision disturbances) and to relief of headaches occurring prior or during menstruation.

In Denmark, the extract corresponding to 0.1 mg or 0.2 mg PN were authorised as an herbal medicinal product for the prevention of milder forms of migraine, when a doctor has excluded other reasons for the condition (ATC code N02CX). The fixed combination of the *Tanacetum* extract containing 0.1 mg PN plus *Achilleae millefolii herba* and *Populus tremula* (Gitadyl) was authorised as a non-steroidal anti-inflammatory drug (ATC code M01A).

Feverfew is used mainly for migraine, arthritis, rheumatic diseases and allergies. It has also been used in the treatment of tinnitus, vertigo, fever, difficult labour, toothache, insect bites and asthma.

In folk medicine, feverfew has been used for cramps, as a tonic, a stimulant, a digestive substance, blood detoxicant, migraine prophylaxis, intestinal parasites and gynecological disorder. The herb is also used as a wash for inflammation and wounds, as a tranquilizer, an antiseptic and as a mouthwash following tooth extraction. It is used externally as an antiseptic and insecticide.

The herbal infusion has been used for dysmenorrhea. In postpartum care, it has been used to reduce bleeding (lochia) (PDR monographs 2007).

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

Feverfew has been administered in a variety of ways, both for internal and external use.

It has been used as a dried powder taken with honey (presumably because of its bitter taste), or as a bath using decoction made with wine (for the women's conditions) or as syrup. In most cases, it was advised to use the leaves, but for some conditions it was suggested to use the flowers (Groenewegen et al. 1992).

Feverfew is supplied as whole or fragmented herbal substance for decoction or infusion or powdered or as extracts in capsules, tablets, tinctures and drops.

Herbal tea as an infusion: 2 teaspoons of the herbal substance per cup, brew for 15 minutes. Three cups to be taken daily for dysmenorrhea (PDR monograph 2007).

A stronger infusion, made with doubled amount and allowed to steep for 25 minutes, is used for washes (PDR monograph 2007).

It is commonly taken orally in tablets or capsules, often with food to disguise its bitter taste. The stated amounts of feverfew per tablet or capsule for different products generally vary from 25 to 250 mg (Heptinstall 1988).

The daily dose of feverfew has not been clearly defined yet. Jin et al. (2007) suggests a daily dose of 50-250 mg feverfew dried leaf containing at least 0.2% PN and not exceeding the equivalent of 4 mg PN daily.

For the treatment of migraine, 200 to 250 mg daily (standardized on 0.2% PN content) is used or 25 mg of freshly dried powdered feverfew extract that corresponds to 0.1 mg of sesquiterpene lactones (PDR monograph 2007). Positive effects were recorded in a few clinical studies with the posology of about 100 mg daily of feverfew extract.

The powdered herbal substance for oral use is administered in form of capsules. The recommended dosage in the UK is 1 capsule containing 100 mg to be taken once daily for three months, in Hungary two capsules containing 50 mg 2 times daily for two months, in France 1 capsule containing 260 mg 3 times daily and in Spain 1 or 2 capsules containing 200 mg/capsule up to 3 times daily.

The comminuted herbal substance had been used in form of herbal tea; in France the posology was 1 to 2 sachets daily (1 sachet containing 1.35 g).

The dry extract (ethanol 30% V/V, DER 4.5-5.5:1) is administered in capsules containing 200 mg/caps, 1 to 2 daily (FR).

An extract corresponding to 0.1 mg PN was orally used in Denmark in tablets, 2-3 times daily together with the meals. Another extract corresponding to 0.2 mg PN was administered in tablets for oral use 1-2 times daily together with the meals (DK).

The recommended dosage for the fresh material varies from 1 to 3 leaves (25 to 75 mg) once or twice daily (Heptinstall 1988).

Feverfew leaves are used mainly in the prophylaxis both of migraine and arthritis but sometimes in single high doses to control the migraine attacks. The estimated period of use as a prophylactic agent varies from instant relief to over a period of months in case of migraine. An average of 7 days is claimed for the relief of arthritis pain and an average of 14 to 28 days to reduce the inflammation and improve the mobility (Groenewegen et al. 1992).

3. Non-Clinical Data

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

Feverfew has been largely investigated for its traditional uses in medicine such as treatment of fever, headache, migraine, stomach ache, insect bites, bronchitis, arthritis, cold, as an abortifacient, and for alleviating menstrual cramps (Rateb et al. 2007).

The main active constituent in feverfew is the sesquiterpene lactone PN that contains a highly electrophilic α -methylene- γ -lactone ring and an epoxide, which are able to readily interact with nucleophilic sites of biological molecules (Won et al. 2004).

PN inhibits platelet aggregation and serotonin release from platelets granules and it is a well documented inhibitor of the transcription factor NF- κ B. The inhibition of NF- κ B in cancer cells has

become one of the major strategies in anticancer therapy. According to numerous data, PN is also the inhibitor of I κ B kinases complex (IKC), with the sustained cytoplasmic retention of NF- κ B (Zhang et al. 2009).

Pharmacodynamics

This section is constituted of three separate paragraphs on studies describing effects of PN, extracts and essential oil activity.

3.1.1. Studies on parthenolide

Studies on PN have shown that this compound possesses several biological properties such as antitumoral, anti-microbial and anti-inflammatory activities. PN exerts effects also on smooth contractile activity and it has been also studied for its antimigraine properties.

3.1.1.1. Antitumoral activity

PN has been shown to withdraw cells from cell cycle or to promote cell differentiation and finally to induce programmed cell death. Recent advances in molecular biology indicate that this sesquiterpene lactone might evoke the above-mentioned effects by indirect action on genes. In particular, it has been shown that PN inhibits NF- κ B- and STATs-mediated anti-apoptotic gene transcription. The pro-apoptotic activity of PN seems to be associated with stimulation of the intrinsic apoptotic pathway with the higher level of intracellular ROS (reactive oxygen substances) and modifications of Bcl-2 family proteins (conformational changes of Bak and Bax, Bid cleavage). On the other hand, PN also amplifies the apoptotic signal through the sensitization of cancer cells to extrinsic apoptosis, induced by TNF- α . These properties suggest that PN could be further studied as a promising metabolic inhibitor to retard tumorigenesis and to suppress tumor growth (Pajak et al. 2008).

Glioblastomas are difficult to treat and frequently aggressive and fatal. Treatment of glioblastoma cells with PN resulted in rapid apoptosis through caspase 3/7 without a suppression of NF- κ B activity. On the basis of these results and due to its apparent potential for crossing the blood brain barrier for the treatment of migraines, it has been suggested that PN or its derivatives may represent a new class of compounds that will be useful in the treatment of brain tumors (Anderson & Bejcek 2008).

PN inhibits cell growth irreversibly at concentrations above 5.0 μ M and an exposure time of 24 h. At lower concentrations the effect is reversible; PN acted as a cytostatic over multiple cell generations for mouse fibrosarcoma (MN-II) and human lymphoma (TK6) cell lines (Ross et al. 1999).

Transcription factors such as NF- κ B provide powerful targets for drugs to use in the treatment of cancer. PN, inhibitor of NF- κ B activity, markedly increases the degree of human leukaemia HL-60 cell differentiation into monocytes via the inhibition of NF- κ B activity and evidence has been provided that inhibition of NF- κ B activation can be a pre-requisite to the efficient entry of promyelocytic leukaemia cells into a differentiation pathway (Kang et al. 2002).

The anticancer property of PN was tested in an UVB-induced mouse skin cancer model. The authors examined the cancer chemopreventive property of PN using a combination of *in vivo* and *in vitro* approaches. First, the anticancer effect of PN in an UVB-induced skin cancer model was tested. Mice fed with PN (1 mg/day) showed a delayed onset of papilloma incidence, a significant reduction in papilloma multiplicity (papilloma/mouse) and sizes when compared with the UVB-only group. The molecular mechanism(s) involved in its anticancer effects using cultured JB6 murine epidermal cells were next investigated. Non-cytotoxic concentrations of PN significantly inhibited UVB-induced activator protein-1 DNA binding and transcriptional activity. In addition, PN pre-treatment also inhibited c-Jun-N-terminal kinase (JNK) and p38 kinase activation. Impaired AP-1, JNK and p38

signalling led to the sensitization of JB6 cells to UVB-induced apoptosis. These data confirmed the anticancer property of PN in an animal model and provided evidence that the inhibitory effects on AP-1 and mitogen-activated protein kinases could serve as one of the underlying mechanisms for the cancer chemopreventive property of PN (Won 2004).

Another research demonstrated that PN is able to induce robust apoptosis in primary human acute myeloid leukemia (AML) cells and blast crisis chronic myeloid leukaemia (CML) cells while sparing normal hematopoietic cells. Furthermore, analysis of progenitor cells using *in vitro* colony assays as well as stem cells using the nonobese diabetic/severe combined immunodeficient xenograft model showed, that PN also preferentially targets AML progenitor and stem cell populations. Notably, in comparison to the standard chemotherapy drug cytosine arabinoside (Ara-C), it was observed that PN is much more specific to leukemia cells. The molecular mechanism of PN mediated apoptosis is strongly associated with inhibition of nuclear factor KB (NF-κB), proapoptotic activation of p53, and increased reactive oxygen species (ROS). On the basis of these findings, the authors proposed that the activity of PN triggers leukemia stem cells (LSC)-specific apoptosis (Guzman et al. 2005).

To investigate PN anticancer activity in ultraviolet B (UVB)-induced skin cancer in SKH-1 hairless mice, the role of protein kinase C (PKC; the subtypes novel PKCδ and atypical PKCζ) in the sensitization activity of PN on UVB-induced apoptosis has been studied. The results have demonstrated that PN sensitizes UVB-induced apoptosis via PKC-dependent pathways (Won et al. 2005).

The effects of PN induced apoptosis in pre-B acute lymphoblastic leukemia (ALL) lines, including cells carrying the t(4; 11) (q21; q23) chromosomal translocation were investigated. PN induced rapid apoptotic cell death distinguished by loss of nuclear DNA, externalization of cell membrane phosphatidylserine and depolarization of mitochondrial membranes at concentrations ranging from 5 to 100 μM. Using reactive oxygen species (ROS)-specific dyes, an increase in nitric oxide and superoxide anion was detected in the cells by 4 h after exposure to PN. Parthenolide-induced elevation of hypochlorite anion was observed only in the two (4; 11) lines. Data suggest that PN may have potential as a potent and novel therapeutic agent against pre-B ALLs (Zunino et al. 2007).

Parada-Turska et al. (2007) determined the effect of PN on proliferation of three human cancer cell lines: human lung carcinoma (A549), human medulloblastoma (TE671), human colon adenocarcinoma (HT-29) and human umbilical vein endothelial cells (HUVEC) *in vitro*. Cell proliferation was assessed by means of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. PN inhibited proliferation of all three types of cancer cells (A549, TE671, HT-29) and HUVEC with the following IC50 values (in μM): 4.3, 6.5, 7.0 and 2.8 respectively.

The inhibitory activity of PN and golden feverfew extract against two human breast cancer cell lines (Hs60ST and MCF-7) and one human cervical cancer cell line (SiHa) was determined *in vitro*. Feverfew ethanolic extract inhibited the growth of all three types of cancer cells with a half-effective concentration (EC50) of 1.5 mg/ml against Hs60ST, 2.1 mg/ml against MCF-7, and 0.6 mg/ml against SiHa. Among the tested constituents of feverfew (i.e., PN, camphor, luteolin and apigenin), PN showed the highest inhibitory effect with an EC50 against Hs60ST, MCF-7 and SiHa of 2.6 μg/ml, 2.8 μg/ml and 2.7 μg/ml, respectively. Interactions between PN and flavonoids (apigenin and luteolin) in feverfew extract were also investigated to elucidate possible synergistic or antagonistic effects. The results revealed that apigenin and luteolin might have moderate to weak synergistic effects with PN on the inhibition of cancer cell growth of Hs60ST, MCF-7 and SiHa (Wu et al. 2006a).

Studies of intensive immunotherapy revealed several metabolic inhibitors, such as cycloheximide, actinomycin D, anisomycin, harringtonine and other metabolic inhibitors, which are able to modulate the resistance of various cancer cells to cytokine induced cell death. However, the clinical use of several tumor cell death promoting agents is limited, because they act non-specifically and are often

cytotoxic. In turn, due to its low toxicity PN seems to be the ideal agent in future anti-cancer immunotherapy.

3.1.1.2. Anti-inflammatory activity

The protein tyrosine kinase (PTK) inhibitors radicicol and herbimycin A inhibit the expression of the mitogen-inducible cyclooxygenase (COX-2) and proinflammatory cytokines. Radicicol and herbimycin A possess polarized double bonds which can conjugate sulphhydryl groups of proteins. PN contains α -methylene- γ -lactone (MGL) and an epoxide in its structure. These moieties can interact with biological nucleophiles such as a sulphhydryl group. Hwang et al. (1996) showed that PN inhibits the expression of COX-2 and proinflammatory cytokines (TNF α and IL-1) in lipopolysaccharide (LPS)-stimulated macrophages. The structure-function relationship indicates that the MGL moiety confers the inhibitory effect. PN suppressed LPS-stimulated protein tyrosine phosphorylation in the murine macrophage cell line (RAW 264.7). This suppression was correlated with its inhibitory effect on the expression of COX-2 and the cytokines.

Excessive nitric oxide production by inducible nitric oxide synthase (iNOS) in stimulated inflammatory cells is thought to be a causative factor of cellular injury in inflammatory disease states. Compounds inhibiting iNOS transcriptional activity in inflammatory cells are potentially anti-inflammatory. It has been demonstrated that PN exerts potent dose-dependent inhibitory effects on the promoter activity of the iNOS gene in THP-1 cells. PN suppressed iNOS promoter activity at concentrations higher than 2.5 mM, with an IC₅₀ of about 10 mM. A tumor-promoting phorbol ester, 12-O-tetradecanoylphorbol-13-acetate (TPA), significantly increased the iNOS promoter-dependent reporter gene activity, and the TPA-induced increase in iNOS promoter activity was effectively suppressed by PN, with an IC₅₀ of approximately 2 mM. These findings may further explain the anti-inflammatory property of PN (Fukuda et al. 2000).

In order to identify the molecular mechanisms of parthenolide's anti-inflammatory activity, a PN affinity reagent was synthesized by Kwok et al. (2001) and shown to bind directly to and inhibit I κ B kinase L (IKKL), the kinase subunit known to play a critical role in cytokine-mediated signalling. Mutation of cysteine 179 in the activation loop of IKKL abolished sensitivity towards PN. Moreover, the authors showed that parthenolide's *in vitro* and *in vivo* anti-inflammatory activity is mediated through the K-methylene Q-lactone moiety shared by other sesquiterpene lactones. According to the authors, PN targets this kinase complex providing a possible molecular basis for the anti-inflammatory properties.

The NO donor glyceryl trinitrate (GTN) provokes delayed migraine attacks when infused into migraineurs and also causes iNOS expression and delayed inflammation within rodent dura mater. Sodium nitroprusside, a NO donor as well, also increases iNOS expression. As inflammation and iNOS are potential therapeutic targets, Reuter et al. (2002) examined transcriptional regulation of iNOS following GTN infusion and the consequences of its inhibition within dura mater. They show that intravenous GTN increases NO production within macrophages, iNOS expression is preceded by significant nuclear factor kappa B (NF- κ B) activity, as reflected by a reduction in the inhibitory protein-I κ B α (I κ B α) and activation of NF- κ B after GTN infusion. I κ B α degradation, NF- κ B activation and iNOS expression were attenuated by PN (3 mg/kg). These findings suggested that GTN promotes NF- κ B activity and inflammation with a time course consistent with migraine attacks in susceptible individuals. Based on results with this animal model, the authors concluded that blockade of NF- κ B activity can provide a novel transcriptional target for the development of anti-migraine drugs.

Pharmacological control of interleukin-12 (IL-12) production may be a key therapeutic strategy for modulating immunological diseases dominated by type-1 cytokine responses. Kang et al. (2001) showed that PN potently inhibited the lipopolysaccharide-induced IL-12 production in a dose-

dependent manner. The authors suggested that PN-induced inhibition of IL-12 production in macrophages may explain some of the biological effects of PN including its anti-inflammatory activity.

The massive hyperplasia of synovial fibroblasts is one of the most striking features of rheumatoid arthritis. The effect of PN on the proliferation of rabbit synoviocytes cell line HIG-82, rheumatoid arthritis fibroblast-like synoviocytes (RA-FLS) and human skin fibroblasts (HSF) *in vitro* was investigated. Cell proliferation was assessed by means of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide and 5'-bromo-2'-deoxy-uridine methods. PN inhibited proliferation of HIG-82 and human RA-FLS, whereas the proliferation of HSF was inhibited less effectively (Parada-Turska et al. 2008).

3.1.1.3. Antimicrobial activity

PN showed significant activity against the promastigote form of *L. amazonensis* with 50% inhibition of cell growth at a concentration of 0.37 µg/ml. For the intracellular amastigote form, PN reduced by 50% the survival index of parasites in macrophages when it was used at 0.81 µg/ml. The purified compound showed no cytotoxic effects against J774G8 macrophages in culture and did not cause lysis in sheep blood when it was used at higher concentrations that inhibited promastigote forms. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis with gelatin as the substrate showed that the enzymatic activity of the enzyme cysteine protease increased following treatment of the promastigotes with the isolated compound. This finding was correlated with marked morphological changes induced by PN, such as the appearance of structures similar to large lysosomes and intense exocytic activity in the region of the flagellar pocket, as seen by electron microscopy. These results provided new perspectives on the development of leishmanicidal activities of PN (Tiuman et al. 2005).

3.1.1.4. Antioxidant activity

A study was performed to investigate the protective effect of PN against oxidative stress-induced apoptosis of human lens epithelial (HLE) cells and the possible molecular mechanisms involved. HLE cells (SRA01-04) were incubated with 50 µM H₂O₂ in the absence or presence of different doses of PN (10, 20 and 50 µM). The expression of caspase-3 and caspase-9 induced by H₂O₂ in HLE cells was significantly reduced by PN both at the protein and mRNA levels, and the activation of caspase-3 and caspase-9 was also suppressed by PN in a dose-dependent manner. The authors concluded that PN prevents HLE cells from oxidative stress-induced apoptosis through inhibition of the activation of caspase-3 and caspase-9, suggesting a potential protective effect against cataract formation (Yao et al. 2007).

3.1.1.5. Effects on smooth muscle contractility

Extracts of feverfew and PN inhibit smooth muscle contractility in a time-dependent, non-specific and irreversible manner. The hypothesis that this toxic effect is caused by the presence of the potentially reactive α -methylene function in the sesquiterpene lactone was tested on rabbit isolated aortic ring preparations. The α -methylene functions in PN were chemically inactivated by reaction with cysteine. The results showed the characteristic smooth muscle inhibitory profile for PN but not for the compound lacking this functional group or by cysteine inactivated compounds. Thus the α -methylene function is critical for this aspect of the toxic pharmacological profile of the sesquiterpene butyrolactones (Hay et al. 1994).

3.1.1.6. Antimigraine effects

Although migraine is a complex neurovascular disorder, serotonin based mechanisms are central to its pathophysiology. Antimigraine drugs interact predominantly with receptors of 5-HT₁ and 5-HT₂

classes. 5-HT_{2B} and 5-HT_{2A} receptor antagonists such as methysergide, cyproheptadine, and mianserin have been shown to be effective in migraine prophylaxis. PN at a concentration of 1×10^{-5} mol/L was observed to be a potent inhibitor of neuronal release of 5-HT but without any significant direct effect on 5-HT_{2B} and 5-HT_{2A} receptor sites in both fundus, and ileum when the tissues were incubated for 30 min. Increasing the incubation time to 1.5 h resulted in a potent inhibition of both responses to exogenous 5-HT and neuronal release of 5-HT via d-fenfluramine. At a higher concentration (5×10^{-5} mol/L), PN followed a similar trend as with 30-min incubation but its antiserotonergic effect was much more striking when a 1.5-h incubation period was provided. The above results indicate that the antagonism at the 5-HT receptor sites is very slow (Mittra et al. 2000).

In another report by Bejar et al. (1996) no 5-HT_{2B} blocking action was noted with PN (1×10^{-5} mol/L), whereas a significant inhibition of neuronally released 5-HT was seen.

3.1.2. Studies on extracts

Extracts of *T. parthenium* (L.) showed antimicrobial, analgesic, anti-inflammatory, antipyretic, antispasmodic, antithrombotic, antioxidant and uterine-stimulant activities in addition to the *in vitro* cytotoxic effects. The effect of extracts on vessels and smooth muscle cells and antimigraine properties has also been studied.

3.1.2.1. Antimicrobial activity

The activity of crude extracts, fractions and PN (pure compound) obtained from *T. parthenium* against two forms of the parasite *Trypanosoma cruzi* was investigated. One thousand grams of dried aerial parts were sequentially extracted by exhaustive maceration in ethanol/water 9:1. The powder resulting from lyophilization, soluble in water, was termed the aqueous crude extract (WCE). The residue was dissolved in ethanol or ethyl-acetate. Activity against epimastigote forms was observed for aqueous (WCE), ethanolic (ACE) and ethyl-acetate (ECE) crude extracts, fractions and PN, and a progressive increase in the antitrypanosomal effect was observed in the course of the purification process. These extracts were assayed for their activity against epimastigote forms of *T. cruzi*. At 1000 µg/ml, all the crude extracts showed similar effects inhibiting more than 90% of the parasites' growth. At low concentrations, ACE was the most effective extract. The pure compound showed IC₅₀/96h and IC₉₀/96h of 0.5 µg/ml and 1.25 µg/ml, respectively. The cytotoxic effect of PN in LLMCK2 cells was 3.2 µg/ml (CC₅₀/96h) and the selectivity index was 6.4. No haemolysis was detected for the pure compound. The internalization index of *T. cruzi* in LLMCK2 cells was reduced to almost 51% at the concentration of 2 µg/ml of PN and 96.6% at 4 µg/ml. Scanning and transmission electron microscopy permitted observation of morphological modifications and ultrastructural alterations (Izumi et al. 2008).

Other investigations showed that the ethanolic extracts possess high activity against all Gram positive bacteria, on some Gram negative bacteria and on some fungi (Kalodera et al. 1997).

3.1.2.2. Anti-inflammatory, analgesic and antipyretic activities

The alcoholic extracts of flowers and leaves and PN showed significant analgesic, anti-inflammatory and antipyretic activities which confirmed the folk use of feverfew herb for treatment of headache, fever, common cold and arthritis. These effects are attributed to the sesquiterpene lactones and flavonoids present in the leaves and/or flowers (Milbrodt et al. 1997). The roots showed no or mild biological activities due to the absence of sesquiterpene lactones and flavonoids; thus confirming the hypothesis of these compounds as active constituents.

Feverfew inhibits human blood platelet aggregation and secretion induced by a number of agents *in vitro* and this may be related to the beneficial effects in migraine. The inhibitory activity of PN was compared with that of crude feverfew leaves extract by Groenewegen & Heptinstall (1990). The effects of both on [¹⁴C]5-HT secretion from platelets and on platelet aggregation induced by a number of different stimulants were determined. The activating agents studied included the phorbol ester PMA, ADP, arachidonic acid, collagen, the thromboxane mimetic U46619, the calcium ionophore A23187, the diacylglycerol analogue OAG and adrenaline. Powdered leaves were stirred with chloroform (feverfew, 50 mg/ml⁻¹, chloroform) for 30 min. The dried extract was re-suspended in an equal volume of PBS (phosphate-buffered saline) to obtain a final solution concentration 50 mg/ml⁻¹ PBS as derived from feverfew. The results show that there are marked similarities between the effects of feverfew extract and of PN on both [¹⁴C]5-HT secretion and platelet aggregation, which is consistent with the effects of feverfew extract on platelets caused by PN or similar compounds in the extract.

The effect of feverfew as a whole plant on an aqueous extract equivalent to 20 mg dried plant per ml, has been examined on both cyclo-oxygenase and lipoxygenase activity in rat leucocytes *in-vitro*. At 10-25 µg ml⁻¹ feverfew had no effect on the formation of arachidonate metabolites; while at the highest concentrations (50-200 µg ml⁻¹) it inhibited both cyclooxygenase and lipoxygenase metabolic products (Capasso 1986).

A feverfew extract produced a dose-dependent inhibition of histamine release from rat peritoneal mast cells stimulated with anti-IgE or the calcium ionophore A23187. The extract was obtained by extraction of 1 g of air-dried leaves using chloroform (20 ml). Greater inhibition of anti-IgE-induced histamine release was achieved with feverfew compared with the inhibition of A23187-induced release. Inhibition of anti-IgE-induced histamine release by feverfew extract was observed when the drug was added simultaneously with anti-IgE and the inhibitory activity increased only slightly when the drug was pre-incubated with the cells for 5 min before anti-IgE stimulation. In this respect feverfew differs from cromoglycate and quercetin. Feverfew extract inhibited anti-IgE-induced histamine release to the same extent in the absence and or the presence of extracellular glucose. The authors concluded that feverfew extract contains a novel type of mast cell inhibitor (Hayes & Foreman 1987).

Crude chloroform extracts of fresh feverfew leaves (rich in sesquiterpene lactones) and of commercially available powdered leaves (lactone-free) produced dose-dependent inhibition of the generation of thromboxane B₂ (TXB₂) and leukotriene B₄ (LTB₄) by ionophore- and chemoattractant-stimulated rat peritoneal leukocytes and human polymorphonuclear leukocytes. Approximate IC₅₀ values were in the range 5-50 µg/ml, and inhibition of TXB₂ and LTB₄ occurred in parallel. Isolated lactones (PN, epoxyartemisinin) were also inhibitory, with approximate IC₅₀ values in the range 1-5 µg/ml, as were crude extracts treated with cysteine (to neutralize reactive α-methylene butyrolactone functions of the sesquiterpenes). Inhibition of eicosanoid generation appeared to be irreversible but not time-dependent. The authors concluded that feverfew contains a complex mixture of sesquiterpene lactone and non-sesquiterpene lactone inhibitors of eicosanoid synthesis of high potency, and that these biochemical actions may be relevant to the claimed therapeutic activity of the herb (Sumner et al. 1992).

The bioactivity of feverfew leaf extracts has been analysed by use of a human polymorphonuclear leukocyte (PMNL) bioassay to assess the relative contributions of solvent extraction and PN content to the biological potency of the extract. Extracts prepared in acetone-ethanol contained significantly more PN (mean ± s.d. 1.3 ± 0.2% dry leaf weight) than extracts in chloroform-PBS (phosphate-buffered saline; 0.1 ± 0.04% dry leaf weight) or PBS alone (0.5 ± 0.1% dry leaf weight). Extract bioactivity was measured as inhibition of phorbol 12-myristate 13-acetate-induced 5-amino-2,3-dihydro-1,4-phthalazinedione (luminol)-enhanced PMNL chemiluminescence. Extracts inhibited phorbol 12-myristate 13-acetate-induced oxidative burst by amounts which, if solely attributable to PN, indicated PN concentrations for the respective solvent systems of 2.2 ± 0.6%, 0.2 ± 0.1% and 0.9 ± 0.1% dry

leaf weight. The mean ratio of PN concentration to the PN equivalent/PMNL-bioactivity value for acetone-ethanol and PBS extracts were both 1:1.7. The results indicated that PN, although a key determinant of biological activity for *T. parthenium* leaf extracts based on the PMNL-bioassay, seems not to be the sole pharmacologically-active constituent. The identical and elevated bioactivity-PN ratios for both organic and aqueous-phase leaf extracts suggested that a proportion of the other bioactive compounds have solubility similar to that of PN (Brown et al. 1997).

Oral administration of a water feverfew extract (composition unknown) led to significant anti-nociceptive and anti-inflammatory effects against acetic acid-induced writhing in mice and carrageenan-induced paw edema in rats, respectively. These responses were dose-dependent (10, 20, 40 mg/kg, p.o.). PN (1.2 mg/kg i.p.) also produced anti-nociceptive and anti-inflammatory effects. Naloxone (1 mg/kg i.p.), an opiate antagonist, failed to reverse feverfew extract and PN-induced anti-nociception. Feverfew extract in higher doses (40, 60 mg/kg p.o.) neither altered the locomotor activity nor potentiated the pentobarbitone-induced sleep time in mice. It also did not change the rectal temperature in rats. Feverfew extract exerted anti-nociceptive and anti-inflammatory effects without altering the normal behaviour of animals (Jain & Kulkarni 1999).

Both crude ethanol feverfew extracts and purified PN were examined for their ability to modulate adhesion molecule expression in human synovial fibroblasts. Pre-treatment of synovial fibroblasts with either feverfew extracts or purified PN could inhibit the expression of intercellular adhesion molecule-1 (ICAM-1) induced by the cytokines IL-1 (up to 95% suppression), TNF- α (up to 93% suppression) and, less strongly, interferon- γ (up to 39% suppression). Inhibition of ICAM-1 was dose and time dependent; as little as a 30-min pretreatment with feverfew resulted in inhibition of ICAM-1. The decrease in ICAM-1 expression was accompanied by a decrease in T-cell adhesion to the treated fibroblasts. The modulation of adhesion molecule expression may be an additional mechanism by which feverfew mediates anti-inflammatory effects (Piela-Smith & Liu 2001).

Chen & Leung (2007) tested three different feverfew extracts to check possible differences in gene response of human cells. The standard reference extract (SRE) was obtained by extraction of 2 g of dried leaf powder with 20 ml of 90% ethanol under mild conditions (sonication for 30 min with no evaporation or exposure to the air). A carbon dioxide supercritical fluid extract was prepared under conditions giving a spectrum of components similar in ratio of concentration to the SRE which contains most of the volatile components of feverfew including camphor, chrysantenylacetate and PN. A negative control extract was prepared with the same extraction solvent and DER but under stress condition (extraction for 19 days, moderate heat up to 50°C and evaporation). Both, a standard reference ethanolic extract and the carbon dioxide supercritical fluid extract of feverfew exhibited blockade on lipopolysaccharide-mediated TNF- α release. Extracts effectively suppressed also CCL2 (also known as monocyte chemoattractant protein 1, MCP-1), suggesting that CCL2 is a potential cellular target for feverfew's antimigraine effects.

3.1.2.3. Effects on vessels and smooth muscle cells

Barsby et al. (1992) showed that samples prepared from chloroform extracts of fresh leaves of feverfew strongly inhibited responses of rabbit aortic rings to phenylephrine, 5-hydroxytryptamine, thromboxane mimetic U46619 (9,11-dideoxy-11 α ,9 α -epoxy-methano-PGF_{2 α}), and angiotensin II. In contrast, the inhibition of potassium induced depolarization was much less pronounced. The inhibition was concentration- and time-dependent, non-competitive, irreversible and also occurred in endothelium-denuded preparations. The feverfew extracts also caused a progressive loss of tone of pre-contracted aortic rings and appeared to impair the ability of acetylcholine to induce endothelium-dependent relaxations of the tissue. These effects were mimicked by PN, obtained from the extract. The results suggest a non-specific and potentially toxic response to feverfew on the vessels.

Thakkar et al. (1983) demonstrated that phospholipase A activity, measured in homogenates and acid extracts of smooth muscle cells from rat aorta and mesenteric artery, was inhibited by an extract from the leaves of feverfew plant.

The effects of a chloroform feverfew extract of fresh leaves on potassium currents in smooth muscle were studied by Barsby et al. (1993). The currents were recorded from single cells dissociated from the rat anococcygeus and the rabbit ear artery using the whole-cell patch-clamp technique. When applied to cells isolated from the rat anococcygeus, the extract reduced the inactivating voltage-dependent potassium current in a concentration-related manner, with an IC₅₀ value of 56 µg/ml⁻¹. A complete block of the current occurred at 1 mg/ml⁻¹. In addition to reducing the peak current, feverfew decreased the time to peak of the current and increased the rate of delay of the current. These effects could be explained by the feverfew extract blocking open potassium channels. In single cells isolated from rabbit ear artery, the feverfew extract again reduced the voltage-dependent potassium current, whilst at the same time having no effect on the spontaneous ion of calcium-dependent potassium channels. These results suggest that chloroform extracts of feverfew leaf contain an as yet unidentified substance capable of producing a selective, open-channel block of voltage-dependent potassium channels.

3.1.2.4. Antithrombotic activity

Chloroform and water extracts of feverfew inhibited secretory activity in blood platelets and polymorphonuclear leucocytes (PMNs). Release of serotonin from platelets induced by various aggregating agents (adenosine diphosphate, adrenaline, sodium arachidonate, collagen, aM U46619) was inhibited. Platelet aggregation was consistently inhibited but thromboxane synthesis was not. Feverfew also inhibited release of vitamin B12-binding-protein from PMNs induced by the secretagogues formyl-methionyl leucyl-phenylalanine, sodium arachidonate and zymosan-activated serum. Feverfew did not inhibit the secretion induced in platelets or PMNs by the calcium ionophore A23187. The pattern of the effects of the feverfew extracts on platelets was different from that obtained with other inhibitors of platelet aggregation. The effect on PMNs was more pronounced than that has been obtained with very high concentrations of non-steroidal anti-inflammatory agents (Heptinstall et al. 1985).

Loesche et al. (1988) demonstrated that chloroform feverfew leaves extract inhibits aggregatory and secretory responses in human platelets and granulocytes, and such inhibition may be relevant to the beneficial effects. It has been suggested that feverfew extracts inhibit platelet behaviour via effects on platelet sulphhydryl groups. In another study, researchers found evidence that feverfew inhibits uptake as well as liberation of arachidonic acid into/from platelet membrane phospholipids.

The same group studied the effect of feverfew on the interaction of platelets with different types of collagen immobilized plastic as well as on the integrity of endothelial cells monolayer in perfused rabbit aorta. Feverfew leaves were dried in air, powdered and extracted with chloroform (20 ml/g leaves). The extract was dried under nitrogen and the residue dissolved in phosphate-buffered saline. Feverfew extract inhibited in a dose-dependent way deposition of platelets and inhibited the formation of surface-bound aggregates. The results of the study indicate that feverfew extract may have antithrombotic potential (Loesche et al. 1988).

Chloroform/methanolic and water extracts of the herb were found to inhibit mitogen-induced tritiated thymidine ([³H]-TdR) uptake by human peripheral blood mononuclear cells (PBMC), interleukin 2 (IL-2)-induced [³H]-TdR uptake by lymphoblasts and PGE₂ release by interleukin 1 (IL-1)-stimulated synovial cells. Both crude organic and aqueous extracts and PN proved cytotoxic to mitogen-induced PBMC and IL-1 stimulated synovial cells, the cytotoxic effect being functionally indistinguishable from

the inhibitory effects. The authors suggest that pharmacological properties of feverfew may thus be due to cytotoxicity (O'Neill et al. 1987).

3.1.2.5. Antioxidant activity

A PN-depleted extract of feverfew (PD-feverfew), which was free of sensitization potential, was found to possess free radical scavenging activity against a wide range of reactive oxygen species and with greater activity than Vitamin C. *In vitro*, PD-feverfew restored cigarette smoke-mediated depletion of cellular thiols, attenuated the formation of UV-induced hydrogen peroxide and reduced pro-inflammatory cytokine release. *In vivo*, topical PD-feverfew reduced UV-induced epidermal hyperplasia, DNA damage and apoptosis. In a clinical study, PD-feverfew treatment significantly reduced erythema versus placebo 24 h post-UV exposure. The authors suggested that through the ability to scavenge free radicals, preserve endogenous antioxidant levels, reduce DNA damage and induce DNA repair enzymes, which can help repair damaged DNA, PN-depleted extract of feverfew may protect skin from the numerous external aggressions encountered daily by the skin and reduce the damage to oxidatively challenged skin (Martin et al. 2008).

In another study, the antioxidant activities of an ethanolic feverfew extract and its bioactive components were determined in terms of their free radical-scavenging activities against the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical and their Fe²⁺-chelating capacities. In addition, the bioactive constituents in feverfew were determined by GC-MS and HPLC-UV. Feverfew powder extracted by 80% alcohol contained camphor, PN, luteolin and apigenin in 0.30 ± 0.08%, 0.22% ± 0.03%, 0.84% ± 0.10% and 0.68% ± 0.07%, respectively. Total phenolic content of the feverfew extract was measured in 21.21 ± 2.11 µg gallic acid equivalent per mg dry material. The feverfew alcoholic extract possessed a strong DPPH free radical-scavenging activity of 84.4% and moderate Fe²⁺-chelating capacity of 53.1%. Luteolin also showed strong DPPH scavenging activity of approximately 80% at 0.52 mg/ml. PN exhibited weak DPPH scavenging activity of 15% and moderate Fe²⁺-chelating capacity of nearly 60%. Similar moderate Fe²⁺-chelating activity (approximately 60%) was observed for luteolin and apigenin at 2 mg/ml (Wu et al. 2006).

3.1.2.6. Antimigraine effects

To study the mechanism of antimigraine activity of *T. parthenium*, its extracts and PN were tested for their effects on 5-HT storage and release, and stimulation of 5-HT_{2B} and 5-HT_{2A} receptors. Dichloromethane feverfew extracts (containing 1×10⁻⁵ mol/L PN and a number of other mono- and sesquiterpenes) showed a potent inhibition of neuronally released 5-HT via d-fenfluramine. In rat fundus and ileum incubated with the extract for 30 min, the 5-HT_{2B} and 5-HT_{2A} receptors were blocked in a manner similar to cyproheptadine (a predominantly 5-HT_{2B} receptor blocker) and risperidone (a 5-HT_{2A/2C} receptor blocker) (Mittra et al. 2000).

Tassorelli et al. (2005) studied the biological effects of different *T. parthenium* extracts and purified PN in an animal model of migraine based on the quantification of neuronal activation induced by nitroglycerin. The methanolic extract enriched in PN significantly reduced nitroglycerin-induced Fos expression in the nucleus trigeminalis caudalis. Purified PN inhibited nitroglycerin induced neuronal activation in additional brain nuclei and significantly, the activity of nuclear factor κB. These findings suggest that PN is the component responsible for the biological activity of *T. parthenium* as regards its antimigraine effect and provide important information for future controlled clinical trials.

3.1.3. Studies on the essential oil

The essential oil showed bactericidal and fungicidal activity. Gram positive species demonstrated a significantly lower sensitivity than the Gram negative ones, moulds, the dermatophytes and some fungi. Regarding the Gram positive species, the essential oil has a strong bactericidal effect only on the *Bacillus* species, while this effect is negligible on other species (*Sarcina flava*, *Staphylococcus aureus*, *Enterobacter* sp.). The oil has a strong bactericidal effect on many of the Gram negative species: *Escherichia coli*, *Klebsiella oxitoca*, *Salmonella*, sp., *Shigella sonnei*, *Serratia marcescens* and *Citrobacter freundii*. On *Candida tropicalis*, *C. pseudotropicalis* and *C. apicola*, the essential oil has a strong fungicidal effect. The microbicidal effect on moulds (*Aspergillus flavus*, *A. ochraceus*, *A. niger*) and dermatophytes (*Microsporum gypseum*, *Trichophyton mentagrophytes* and *Epidermophyton floccosum*) has also been determined (Kalodera et al. 1997).

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

No data available.

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

Single/repeat dose toxicity, genotoxicity, carcinogenicity and local tolerance studies have not been performed.

Reproductive toxicity

Yao et al. (2006) carried out a preliminary screen of a commonly used formulation of feverfew in order to determine its potential for reproductive toxicity. The recommended human dose is 1 g/day. The extract of feverfew used consisted of a commercial preparation of the dried leaf of the feverfew plant extracted in 60% ethanol in a 1:2 dilution, giving a final concentration of 200 mg/ml feverfew standardized to 0.7 mg/ml of PN. The reported teratogenic threshold of ethanol is 2 g/kg in the Long-Evans rat, used in the study. The upper dose of the ethanol content of the feverfew concentrate was therefore limited to 1.98 g/kg. This meant that the maximum dose of feverfew that could be delivered to the rat was 839 mg/kg/day or 58.7 times the recommended human dose. Treated rats were dosed with 12.8 ml/kg/day of a 65.2 mg/ml feverfew solution. Control rats received either 12.8 mg/kg of distilled water or 20% (v/v) ethanol. Five female rats were orally dosed with 839 mg/kg feverfew daily on either gestation days (GD) 1-8 or 8-15. Two pregnant rats became very sick (exhibited piloerection, reduced mobility, reduced response to stimuli) before the 8 days of feverfew treatment were completed. On GD20, rats were sacrificed and fetuses, placentae and ovaries were collected. The fetuses were weighed and examined for malformations. While maternal weight gain appeared to be reduced, ANCOVA analysis suggested that the difference was due to the litter size, rather than treatment. Pre-implantation loss appeared increased but this was not statistically significant in the feverfew GD 1-8 group. Fetuses exposed to feverfew from GD 8-15 were smaller than ethanol controls perhaps as a result of the increased frequency of runts in treated litters. Feverfew induced toxicity when GD 10.5 embryos were cultured for 26 h in rat serum to which extract was added. The results of this preliminary study suggest that a comprehensive reproductive study of feverfew is warranted.

3.4. Overall conclusions on non-clinical data

Several non clinical investigations support feverfew traditional medicinal uses.

The sesquiterpene lactone PN containing an α -methylene- γ -lactone ring and an epoxide residue capable of interacting rapidly with nucleophilic sites of biological molecules is considered the main

active constituent. PN possesses anti-tumoral, anti-microbial, anti-inflammatory and antioxidant activities. It inhibits platelet aggregation and platelet serotonin release and it is also an inhibitor of NF- κ B and I κ B kinases complex.

The role of PN in the antimigraine effects of feverfew was investigated and antagonism of serotonin receptors and inhibition of neuronally released 5-HT have been suggested for the mechanism of action. Moreover, feverfew leaf extracts inhibit human blood platelet aggregation and secretion induced by a number of agents *in vitro* and this may relate to the beneficial effects in migraine.

Alcoholic extracts of flowers and leaves showed significant analgesic, anti-inflammatory and antipyretic activities. These effects are attributed to the presence of sesquiterpene lactones and flavonoids. Antioxidant activities of ethanolic feverfew extracts have also been shown.

Water, ethanolic and ethyl-acetate extracts of *T. parthenium* showed significant antimicrobial, anti-inflammatory, antinociceptive and antipyretic activity *in vitro*. Inhibition of histamine release and of phospholipase A2, cyclo-oxygenase and lipoxygenase activity has been suggested for the mechanism of action.

Chloroform extracts of fresh leaves of feverfew strongly inhibit responses of vessels to contracting agents and both chloroform and water extracts of feverfew inhibit secretory activity in blood platelets and polymorphonuclear leucocytes (PMNs) and release of serotonin from platelets induced by various aggregating agents.

Both feverfew and PN inhibit smooth muscle contractility in a time-dependent, non-specific and irreversible manner. The uterine stimulant effect of the plant agrees with the folk uses of the plant as an emmenagogue and in dysmenorrhea.

A preliminary study, to determine its potential for reproductive toxicity, was conducted in the rat. The dose of feverfew delivered daily corresponded to about 58.7 times the recommended human dose. Treatment induced both maternal and embryo toxicity, however, the same authors considered the study preliminary and suggested that a comprehensive reproductive study of feverfew is to be warranted.

The essential oil possesses bactericidal and fungicidal properties.

In conclusion, PN and different preparations of *T. parthenium* show biological activities *in vitro* and *in vivo* in experimental models. These findings support the traditional use in migraine prevention and in minor pain syndromes such mild articular pain.

4. Clinical Data

4.1. Clinical pharmacology

Migraine Prophylaxis

Migraine is a recurrent moderate-to-severe headache that can be unilateral and often is characterised by photophobia, phonophobia, nausea, vomiting, or aggravated by movement. Migraine is further classified into migraine without aura, migraine with aura, basilar-type migraine, familiar or sporadic hemiplegic migraine. These subtypes may be further classified as episodic or chronic.

Migraine is heterogeneous (among sufferers and between attacks) in frequency, duration and disability. Some migraineurs have less than one attack a month while others have one or more attacks a week. Some are quite disabled by their headaches, while others are not. Therefore, it is appropriate to stratify the care of the migraine population by headache frequency, severity and level of disability. Furthermore, prevention needs to be considered for those patients whose migraine has a substantial impact on their lives.

Migraine is considered a genetic disorder of neuronal hyper-excitability. The genesis of the attack is linked to neuronal activation. Migraine headache has an incidence of 6% in men and 15% to 17% in women (Bamford et al. 2009).

There are two ways to treat migraine headache: the acute therapy to terminate the headache when needed and the preventive therapy, in which treatment is given chronically to reduce attack frequency, severity and duration, to improve responsiveness to acute therapy, and to improve function and reduce disability (Bamford et al. 2009).

The aim of a preventive treatment for migraine is to prevent or reduce the frequency and/or to attenuate severity of new migraine attacks, to improve response to acute medications, to improve patient function and to reduce disability.

Prophylactic drug treatment of migraine should be considered and discussed with the patient when one or more of the following problems occur:

- quality of life, business duties, or school attendance are severely impaired;
- frequency of attacks per month is two or higher;
- migraine attacks do not respond to acute drug treatment;
- frequent, very long, or uncomfortable auras occur.

In summary, patients with high frequencies of migraine, high disability or impact from migraine, and frequent users of acute migraine medications merit migraine prophylaxis in the form of daily medication.

Migraine-preventive medications, at best, work in approximately half of patients to reduce migraine frequency by about 50%. A careful establishment of expectations with the use of headache diaries is crucial for determination of the therapeutic success. The treatment should be maintained for 2 to 3 months to evaluate effectiveness.

Medications with the best evidence for efficacy in the prevention of migraine are amitriptyline, propranolol, timolol, valproate, and topiramate. Options available include alternative and complementary therapies, optimized lifestyles with changes as necessary, dietary and substance changes and drug prevention (Taylor 2009).

Although all migraine preventive medications are non-specific and have multiple potential mechanisms for their effects, they often share a tendency to reduce central neuronal hyper-excitability by inhibiting excitatory neurotransmitters, such as glutamate and norepinephrine, increasing inhibitory tone via GABA, reducing the likelihood of cortical spreading depression or favorably altering channelopathies or mitochondriopathies thought to be intrinsic to migraine pathophysiology (Bamford et al. 2009).

Use of feverfew in the migraine treatment

Feverfew leaf extracts inhibit human blood platelet aggregation and secretion induced by a number of agents *in vitro* and this may relate to the beneficial effects in migraine. These effects are similar to those shown for drugs preventing migraine attacks (i.e. tryptans). On this basis, use of *T. parthenium* is not considered useful for acute therapy to terminate the headache but more suitable for the prevention (or prophylaxis) of migraine attacks. In conclusion, it can be given chronically to reduce attack frequency, severity and duration, to improve responsiveness to acute therapy, to improve function and reduce disability. Since feverfew appears to have a relatively benign side effect profile, it is considered as an option for migraine prophylaxis. Feverfew treatment has been assigned to 'class B recommendation' within guidelines on management of migraine in clinical practice differentiating between class A, B and C (Pryse-Phillips et al. 1998).

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

Feverfew has traditionally been used for fever, women's ailments, inflammatory conditions, psoriasis, toothache, insect bites, rheumatism, asthma and stomach-ache. During the last decades, it has also been used for headache and migraine prophylaxis.

Feverfew extract enables the release of serotonin (5-hydroxytryptamin) from platelets induced by a variety of aggregation agents. Moreover, both extracts of feverfew and pure PN inhibit the synthesis of prostaglandins (Sumner et al. 1992).

A role of the sesquiterpene lactone PN in migraine prophylaxis was supported by *in vitro* studies suggesting inhibition of serotonin release from blood platelets but this hypothesis is not commonly shared. PN also markedly interferes with both contractile and relaxant mechanisms of blood vessels. The pharmacological role of feverfew in the migraine pathophysiology is not completely understood.

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

The efficacy and safety of T. parthenium (feverfew) in migraine prophylaxis-a double-blind, multicentre, randomized placebo-controlled dose-response study

A study was designed with the primary objective to show a dose-response with a stable extract (MIG-99) reproducibly manufactured with supercritical CO₂ from feverfew. Furthermore, the study provided data on the safety and tolerability of MIG-99. In a randomized, double-blind, multicentre, controlled trial, the clinical efficacy and safety of three dosages of MIG-99 (2.08 mg, corresponding to 0.17 mg PN; 6.25 mg, corresponding to 0.5 mg PN; 18.75 mg, corresponding to 1.5 mg PN twice in a day) were compared with placebo. The patients (n=147) suffered from migraine with and without aura according to International Headache Society (IHS) criteria and were treated with one of the study medications for 12 weeks after a 4-week baseline period. During the active treatment period patients received either 2.08 mg MIG-99 (corresponding to 0.17 mg PN), 6.25 mg MIG-99 (0.5 mg PN), 18.75 mg MIG-99 (1.5 mg PN) or placebo. The primary efficacy parameter was the number of migraine attacks during the last 28 days of the treatment period compared with baseline. Secondary endpoints were total and average duration and intensity of migraine attacks, mean duration of the single attack, number of days with accompanying migraine symptoms, number of days with inability to work due to migraine as well as type and amount of additionally taken medications for the treatment of migraine attacks. The design of the study included a pre-planned adaptive interim analysis for patients with at least four migraine attacks within the baseline period. With respect to the primary and secondary efficacy parameter, a statistically significant difference was not found between the overall and the confirmatory intention-to-treat (ITT) sample in the exploratory analysed four treatment groups. The frequency of migraine attacks for the predefined confirmatory subgroup of patients (n=49) with at least four migraine attacks during the baseline period decreased in a dose-dependent manner (P=0.001).

The highest absolute change of migraine attacks was observed under treatment with 6.25 mg t.i.d. (mean ± SD = - 1.8 ± 1.5 per 28 days) compared with placebo (- 0.3 ± 1.9; P=0.02). Overall, 52 of 147 (35%) patients reported at least one adverse event.

The incidence of adverse events in the active treatment groups was similar to that in the placebo group, and no dose-related effect was observed in any safety parameter. MIG-99 failed to show a significant migraine prophylactic effect in general. Accordingly, in the ITT analysis a dose–response relationship could not be observed. MIG-99 was shown to be effective only in a small predefined subgroup of patients with at least four attacks during the 28-day baseline period, where the most favourable benefit–risk ratio was observed with a dosage of three capsules of 6.25 mg MIG-99 extract per day. Due to a low number of patients, these findings need to be verified in a larger sample. The incidence of adverse events was similar for all treatment groups. In conclusion, there were no statistically significant effects for either primary or secondary outcome measures. Accordingly, a dose–response relationship could not be observed. Subgroup analysis including patients with at least four migraine attacks during baseline evaluations (n=49) showed a significant effect when the 6.25-mg dose was compared with placebo (p=0.02) (Pfaffenrath et al. 2002) (Table 3).

4.2.2. Clinical studies (case studies and clinical trials)

Clinical studies with feverfew for prevention of migraine

- Efficacy of feverfew as prophylactic treatment of migraine.

A double blind placebo controlled trial including seventeen patients who already ate fresh leaves of feverfew daily as prophylaxis against migraine was carried out. Patients who had suffered from classical or common migraine for at least two years, with eight or fewer attacks per month, were allocated randomly to receive either feverfew (freeze-dried leaves) or identical placebo capsules in numbered packs. Diary cards were used to assess the frequency of migraine and the incidence of nausea and vomiting. Patients were instructed how to record the various visual symptoms, nausea, vomiting and headache (including times of onset and relief and any additional treatment) and to grade them according to severity on diary cards provided for each period. The severity of nausea or vomiting was recorded as: 0 = neither nausea nor vomiting; 1=nausea only; 2=vomiting, single episode; 3=vomiting, repeated episodes. Headache was scored: 0=no pain; 1=mild, unpleasant but not affecting work or recreational activities; 2=severe, reducing ability to work or carry out recreational activities; 3=incapacitating, unable to work or carry out recreational activities; 1=duration up to six hours; 2=duration between six and 24 hours; 3=duration greater than 24 hours. Presence of usual visual disturbance scored 1. Use of drugs was scored: 1=use of repeated doses of minor analgesics; 1=use of single dose of ergotamine; 2=use of repeated doses of ergotamine. The cards were reviewed at intervals of one to two months throughout the study. Patients were instructed to take two capsules every morning with food for six periods of four weeks. The mean daily dose of feverfew used by patients before entry to the study was 2.44 leaves (roughly 60 mg). Hence, it was decided that the dose of each capsule should be fixed at 25 mg and that each patient should receive two capsules daily. Eight patients received capsules containing freeze dried feverfew powder and nine patients received placebo. The results showed a significant (p<0.02) increase in the number of attacks per month in the placebo group (mean, 3.1; standard error [SE], 0.8) compared with baseline, while attack frequency remained constant in patients receiving feverfew (mean, 1.7; SE, 0.6). 42% and 79% of attacks were associated with nausea and vomiting in the feverfew and placebo groups, respectively (p<0.05). The incidence of bouts of nausea/vomiting was significantly (p<0.05) lower in the feverfew group than in the placebo group (39 and 116, respectively). The global assessment of efficacy by patients indicated a significant (p<0.01) difference in favour of feverfew: 6/8 patients in the feverfew group rated the overall treatment effect as moderately good to excellent, while this result was reported by only 3/9 patients in the placebo group. This provided early evidence that feverfew taken prophylactically prevents attacks of migraine (Johnson et al. 1985) (Table 4).

- Randomised double-blind placebo-controlled trial of feverfew in migraine prevention.

The use of feverfew for migraine prophylaxis was assessed in a randomised, double blind, placebo-controlled crossover study. After a one-month single-blind placebo run-in, 72 patients with common or classical migraine were randomly allocated to receive either one capsule of a chloroform extract of dried feverfew leaves a day or matching placebo for four months and then transferred to the other treatment arm for a further four months. There was no wash-out period between the treatment periods. Capsule weights ranged from 70 to 114 mg (mean 82 mg) and contained the equivalent of 2.19 (SD 0.63) μmol of PN per capsule. Frequency and severity of attacks were determined from diary cards which were issued every two months; efficacy of each treatment was also assessed by visual analogue scores. Sixty patients completed the study and full information was available in 59. The results suggested a significant ($p < 0.005$) difference in the number of attacks per 2-month period during feverfew treatment (mean, 3.6; SE, 0.2) compared with placebo (mean, 4.7; SE, 0.3). Among patients with classical migraine ($n=17$), the number of attacks per 2-month period was significantly ($p < 0.05$) lower with feverfew (mean, 2.9; SE, 0.4) than with placebo (mean, 4.3; SE, 0.5); among patients with common migraine ($n=42$), headache frequency was similar during the feverfew (mean, 3.9; SE, 0.3) and placebo (mean, 4.9; SE, 0.4) periods ($p = 0.06$). In the study population as a whole, the total number of attacks rated as severe or very severe was 178/424 (42%) with feverfew and 258/559 (46%) with placebo. Nausea and vomiting accompanied the attacks in 207/424 (49%) and 313/559 (56%) cases treated with feverfew and placebo, respectively ($p < 0.02$). The global assessment of efficacy, measured on a 100-mm visual analogue scale with 'worst ever' and 'best ever' as the two extremes, indicated a significant ($p < 0.0001$) difference in favour of feverfew compared with placebo (mean, 74; SE, 2 versus mean, 60; SE, 3, respectively). Among patients with classical migraine, global assessment scores were significantly ($p < 0.01$) higher during treatment with feverfew (mean, 78; SE, 4) than during treatment with placebo (mean, 57; SE, 5); among patients with common migraine, scores for the two treatment periods were similar (mean, 72; SE, 2 for feverfew and mean, 61; SE, 3 for placebo). In conclusion, treatment with feverfew was associated with a reduction in the mean number and severity of attacks in both two-month periods, and in the degree of vomiting, while the duration of individual attacks was unaltered. Visual analogue scores also indicated a significant improvement with feverfew. There were no serious side-effects (Murphy et al. 1988) (Table 5).

- Herbal medicines in migraine prevention: Randomized double-blind placebo-controlled crossover trial of feverfew preparation.

De Weerd et al. (1996) assessed 50 patients diagnosed according to the criteria of the International Headache Society (IHS 1988). Patients suffering from migraine with or without aura received daily either one capsule of an alcoholic feverfew extract (143 mg) or placebo in a randomised crossover trial. The extract was obtained subjecting feverfew powder to 19 days of prolonged exposure to 90% ethanol, moderate heat (up to 90°C) and evaporation. A 1-month placebo run-in phase was followed by 2-month treatment periods. There was no wash-out period between the treatment periods. The investigators reported that no significant effects on the number or severity of headaches were observed (Table 6).

- Feverfew (*T. parthenium*) as a prophylactic treatment for migraine: A placebo-controlled double-blind study.

The crossover trial conducted by Palevitch et al. (1997) included 57 patients with migraine diagnosed by medical examination (diagnostic criteria not specified). During the preliminary, open phase of the trial, each patient received 100 mg feverfew daily for 2 months. The PN content of the dried leaves was 0.2% as determined by HPLC. 50 mg of fine powdered leaves was packed in small gelatin capsules. Powdered dry leaves of parsley (*Petroselinum crispum*), were prepared in the same way and

served as the placebo control. Thereafter, in the double-blind crossover phase, one group received placebo for 30 days, while the other continued taking feverfew. Patients in the active treatment group were then transferred to the placebo arm and vice versa. There was no wash-out period between the treatment periods. The severity of migraine attacks was measured by patients on a numerical scale of 0 ('no pain') to 10 ('most severe pain') and the severity of nausea and vomiting was assessed using a numerical analogue scale and a questionnaire. The results of the preliminary, open phase showed a significant decrease in migraine severity after treatment with feverfew compared with baseline ($p < 0.001$). In the first crossover phase there was a further reduction of migraine severity in the feverfew group (mean, 1.5; SE, 0.7) and an increase in severity in the placebo group (mean, 1.6; SE, 0.9) ($p < 0.01$). In the second phase of the crossover, these trends continued: migraine severity decreased among patients taking feverfew (mean, 4.0; SE, 1.1) and increased among patients taking placebo (mean, 1.4; SE, 1.1). In addition, there was a significant ($p < 0.001$) difference in the severity of nausea and vomiting in favour of feverfew (Table 7).

- Efficacy and safety of 6.25 mg t.i.d. feverfew CO₂-extract (MIG-99) in migraine prevention, a randomized, double-blind, multicentre, placebo-controlled study.

The efficacy and tolerability of a CO₂-extract of feverfew (MIG-99, 6.25 mg t.i.d.) for migraine prevention were investigated in a randomized, double-blind, placebo-controlled, multicentre, parallel-group study. Patients (N=170 intention-to-treat; MIG-99, N=89; placebo, N=81) suffering from migraine, according to the International Headache Society criteria, were treated for 16 weeks after a 4-week baseline period. The primary endpoint was the average number of migraine attacks per 28 days during the treatment months 2 and 3 compared with baseline. Predefined secondary efficacy parameters were the number of migraine attacks during each 28-day period of therapy, the clinical global impression of efficacy (very good, good, moderate, none), change of migraine intensity, the total duration of migraine attacks, mean duration of the single attack, number of migraine days, number of attacks with confinement to bed or inability to work or accompanying migraine symptoms per 28 days, number of migraine attacks with aura per 28 days, type and amount of analgesics and migraine preparations taken and number of drop-outs due to insufficient efficacy. Safety parameters included adverse events, laboratory parameters, vital signs and physical examination. The migraine frequency decreased from 4.76 by 1.9 attacks per month in the MIG-99 group and by 1.3 attacks in the placebo group ($P = 0.0456$). Logistic regression of responder rates showed an odds ratio of 3.4 in favour of MIG-99 ($P = 0.0049$). Adverse events possibly related to study medication were 9/107 (8.4%) with MIG-99 and 11/108 (10.2%) with placebo ($P = 0.654$). The authors concluded that MIG-99 is effective and shows a favourable benefit-risk ratio (Diener et al. 2005) (Table 8).

Table 3. Efficacy of feverfew as prophylactic treatment of migraine

Authors	N° subjects	Randomization and control	Endpoints
Johnson et al. 1985	17 patients with migraine. 8 patients active treated 9 patients treated with placebo	Randomization Placebo Double blind	Frequency and severity of headache, nausea and vomiting.
	Posology and Duration of treatment	Statistical analysis	Efficacy

Authors	N° subjects	Randomization and control	Endpoints
	The mean daily dose of feverfew used by patients before entry to the study was 2.44 leaves (roughly 60 mg). 25 mg of freeze-dried powdered feverfew leaves twice/day for six periods of four weeks	Yes	Those who received placebo had a significant increase in the frequency and severity of headache, nausea and vomiting with the emergence of untoward effects during the early months of treatment with respect to the period before the treatment with feverfew.

Table 4. Randomised double-blind placebo-controlled trial of feverfew in migraine prevention

Authors	N° subjects	Randomization and control	Endpoints
Murphy et al. 1988	60 patients with history of common or classical migraine of at least 2 years' duration	Randomization Placebo Double blind Cross-over	Duration, frequency and severity of attacks. Visual analogue score.
	Posology and Duration of treatment	Statistical analysis	Efficacy
	About 82 mg (from 72 to 114 mg) a day of a chloroform extract of dried feverfew leaves for four months	Yes	Reduction in the mean number and severity of attacks in each two-month period and in the degree of vomiting; duration of individual attacks was unaltered.

Table 5. Herbal medicines in migraine prevention: Randomized double-blind placebo-controlled crossover trial of feverfew preparation

Authors	N° subjects	Randomization and control	Endpoints
De Weerd et al. 1996	50 patients with migraine	Randomization Placebo Cross-over	Frequency and severity of migraine attacks
	Posology and Duration of treatment	Statistical analysis	Efficacy
	143 mg daily of an ethanolic extract	Yes	No significant effect in number or severity of attacks

Table 6. Feverfew (*Tanacetum parthenium*) as a prophylactic treatment for migraine: A placebo-controlled double-blind study

Authors	N° subjects	Randomization and control	Endpoints
Palevitch et al. 1997	57 patients with migraine Phase 1: open-labelled trial. Two groups (A and B) both received a daily dose of 100 mg feverfew for 60 days. Phases 2 and 3: double-blind controlled randomized cross-over trial. Group A (n=30) received feverfew for an additional 30 days and then shifted to placebo treatment for 30 days (100 mg daily of ground parsley).	Randomization Placebo Double blind Cross-over	Severity of migraine attacks
	Posology and Duration of treatment	Statistical analysis	Efficacy
	100 mg feverfew powdered leaves daily for two months	Yes	Decrease of severity of attacks both in the open labelled phase and in the controlled phases.

Table 7. The efficacy and safety of *Tanacetum parthenium* (feverfew) in migraine prophylaxis-a double-blind, multicentre, randomized placebo-controlled dose-response study

Authors	N° subjects	Randomization and control	Endpoints
Pfaffenrath et al. 2002	147 patients treated in four parallel groups	Randomization Placebo Double blind	Primary parameter: number of migraine attacks during the last 28 days of the treatment period vs baseline period. Secondary endpoints: total and average duration and intensity, mean duration of migraine attacks, mean duration of the single attacks.
	Posology and Duration of treatment	Statistical analysis	Efficacy
	MIG-99 (2.08 mg; 6.25 mg; 18.75 mg three times daily) for 12 weeks	Yes	MIG-99 was shown to be effective only in a small predefined subgroup of patients with at least four attacks during the 28-day baseline period where the most favourable benefit-risk ratio was observed with a dosage of three capsules of 6.25 mg MIG-99

Authors	N° subjects	Randomization and control	Endpoints
			extract per day.

Table 8. Efficacy and safety of 6.25 mg three times daily feverfew CO₂-extract (MIG-99) in migraine prevention, a randomized, double-blind, multicentre, placebo-controlled study

Authors	N° subjects	Randomization and control	Endpoints
Diener HC et al. 2005	MIG-99, N=89; placebo, N=81	Randomization Placebo Double blind	Primary endpoint: average number of migraine attacks per 28 days during the treatment months 2 and 3 vs baseline.
	Posology and Duration of treatment	Statistical analysis	Efficacy
	MIG-99 6.25 mg; three times daily) for 16 weeks	Yes	The migraine frequency decreased from 4.76 by 1.9 attacks per month in the MIG-99 group and by 1.3 attacks in the placebo group ($P=0.0456$). Logistic regression of responder rates showed an odds ratio of 3.4 in favour of MIG-99 ($P=0.0049$).

Reviews on clinical studies with feverfew for prevention of migraine

The first systematic review on feverfew as a preventive treatment for migraine was published by Vogler et al. in 1998. Only randomized, placebo-controlled, double-blind trials were included. The methodological quality of all trials was evaluated using the Jadad score.

Main results:

Five trials met the inclusion/exclusion criteria. The majority favoured feverfew over placebo. Three studies reported positive results in favour of feverfew. In total, 216 patients were included, both men and women suffering from classical and/or common migraine. The author concluded that the effectiveness of feverfew in the prevention of migraine has still not been established beyond reasonable doubt (Vogler et al. 1998).

Ernst published in the year 2000 a systematic review on the efficacy and safety of feverfew. Only randomized, placebo-controlled, double-blind trials of feverfew mono-preparations for the prevention of migraine in human subjects were included. Six trials met the inclusion/exclusion criteria. The majority favoured feverfew over placebo. The data also suggested that feverfew is associated with only mild and transient adverse effects and few other safety concerns. The author concluded that feverfew is likely to be effective in the prevention of migraine and that there are no major safety problems (Ernst & Pittler 2000).

A Cochrane review on feverfew for preventing migraine was released in 2004. The aim of the review was to systematically evaluate the evidence from double-blind randomised controlled trials (RCTs) assessing the clinical efficacy and safety of feverfew versus placebo for preventing migraine.

Publications describing (or which might describe) double-blind RCTs of feverfew extract for migraine were considered. Randomised, placebo-controlled, double-blind trials assessing the efficacy of feverfew for preventing migraine were included. Trials using clinical outcome measures were included. Trials focusing exclusively on physiological parameters were excluded. There were no restrictions regarding the language of publication.

Five trials (343 patients) met the inclusion criteria. Results from these trials were mixed and did not convincingly establish that feverfew is efficacious for preventing migraine. Only mild and transient adverse events were reported in the included trials (Pittler & Ernst 2004).

The authors concluded that there is insufficient evidence from randomised, double-blind trials to suggest an effect of feverfew over and above placebo for preventing migraine. It appeared from the data reviewed that feverfew presents no major safety problems. It has been suggested that the lack of efficacy may be due to the absence of the therapeutic constituents in the granulated feverfew leaves, which were either not sufficiently extracted, or perhaps degraded during the preparation.

Another explanation suggests only a secondary role for serotonin in the etiology of migraine. Assuming that whole-leaf preparations are effective, it would direct the attention towards feverfew constituents other than PN (Awang 1998).

Another hypothesis suggests that an essential oil constituent of feverfew, chrysanthenyl acetate, may be important. This component inhibits prostaglandin synthetase *in vitro* and seems to possess analgesic properties. Other investigators agree that PN is not the only pharmacologically active constituent in feverfew.

A link between the relatively high concentration of melatonin in different feverfew varieties and a decrease in melatonin excretion during migraine attacks has also been suggested.

An alternative explanation for negative trial results is offered by the fact that some commercial preparations are under-dosed, possibly due to the instability of the active constituents in these extracts (Pittler & Ernst 2004).

Clinical studies with combination products

To determine the efficacy for migraine prophylaxis of a preparation containing a combination of riboflavin, magnesium and feverfew a randomized double-blind placebo-controlled trial of a compound providing a daily dose of riboflavin 400 mg, magnesium 300 mg and feverfew 100 mg was conducted. The placebo contained 25 mg riboflavin. The study included a 1-month run-in phase and 3-month trial. The protocol allowed for 120 patients to be randomized, with a pre-planned interim analysis of the data after 48 patients had completed the trial.

Forty nine patients completed the 3-month trial. For the primary outcome measure, a 50% or greater reduction in migraines, there was no difference between active and "placebo" groups, achieved by 10 (42%) and 11 (44%), respectively ($P=.87$). Similarly, there was no significant difference in secondary outcome measures, for active versus placebo groups, respectively: 50% or greater reduction in migraine days (33% and 40%, $P=.63$); or change in mean number of migraines, migraine days, migraine index, or triptan doses. Compared to baseline, however, both groups showed a significant reduction in number of migraines, migraine days and migraine index. This effect exceeds that reported for placebo agents in previous migraine trials.

Author's conclusion: riboflavin 25 mg showed an effect comparable to a combination of riboflavin 400 mg, magnesium 300 mg and feverfew 100 mg. The placebo response exceeds that reported for any other placebo in trials of migraine prophylaxis and suggests that riboflavin 25 mg may be an active

comparator. There is at present conflicting scientific evidence with regard to the efficacy of these compounds for migraine prophylaxis (Maizels et al. 2004).

Feverfew and *Salix alba* (white willow) either alone or in combination have been shown to inhibit binding to 5-HT_{2A/2C} receptors; feverfew failed to recognise 5-HT_{1D} receptors, whereas *S. alba* or the combination did. It was hypothesised that *S. alba* in combination with feverfew may provide superior migraine prophylactic activity compared with feverfew alone.

On this basis, a prospective, open-label study was performed in 12 patients diagnosed with migraine without aura. Twelve weeks' treatment with a combination product (feverfew extract standardised on PN ($\geq 0.2\%$) 300 mg plus *S. alba* extract standardised on salicin ($\geq 1.5\%$) 300 mg) twice daily was administered to determine the effects of therapy on migraine attack frequency (primary efficacy criterion), intensity and duration (secondary efficacy criteria), and quality of life, together with the tolerability for patients.

Attack frequency was reduced by 57.2% at 6 weeks ($p < 0.029$) and by 61.7% at 12 weeks ($p < 0.025$) in nine of ten patients, with 70% patients having a reduction of at least 50%. Attack intensity was reduced by 38.7% at 6 weeks ($p < 0.005$) and by 62.6% at 12 weeks ($p < 0.004$) in ten of ten patients, with 70% of patients having a reduction of at least 50%. Attack duration decreased by 67.2% at 6 weeks ($p < 0.001$) and by 76.2% at 12 weeks ($p < 0.001$) in ten of ten patients. Two patients were excluded for reasons unrelated to treatment. Self-assessed general health, physical performance, memory and anxiety also improved by the end of the study. The treatment was well tolerated and no adverse events occurred.

Author's conclusions: the remarkable efficacy of the combination product in this trial is not only reducing the frequency of migraine attacks but also pain intensity and duration. Further investigation of this therapy in a double-blind, randomised, placebo-controlled investigation involving a larger patient population is necessary (Shrivastava et al. 2006).

Guideline for the non-pharmacologic management of migraine in clinical practice

To provide physicians and allied health care professionals with guidelines for the non-pharmacologic management of migraine in clinical practice, a large full range and quality of non-pharmacologic therapies available for the management of migraine was analysed. The objective of the guidelines was the improvement in the non-pharmacologic management of migraine. The creation of the guidelines followed a need of assessment by members of the Canadian Headache Society and included a statement of objectives. Regarding the use of feverfew, two small randomized controlled trials were considered to show the efficacy of feverfew (herb) in migraine prophylaxis. According to the Canadian Headache Society, feverfew may be considered as an option for migraine prophylaxis because of its relatively benign side effect profile (occasional mouth ulceration and contact dermatitis). Feverfew treatment was assigned to class B recommendation, when differentiating between class A, B and C recommendations (Pryse-Phillips et al. 1998).

Feverfew in rheumatoid arthritis

- Feverfew in rheumatoid arthritis: a double blind, placebo controlled study.

Feverfew is reputed by folklore to be effective in arthritis. Forty one female patients with symptomatic rheumatoid arthritis received either dried powdered feverfew (70-86 mg) leaf (equivalent to 2-3 μmol PN) or placebo capsules once daily for six weeks. One capsule of feverfew corresponded to two medium sized leaves. Allocation was random and not known by patient or observer. Variables assessed included stiffness, pain (visual analogue scale), grip strength, articular index, full blood count, erythrocyte sedimentation rate, urea, creatinine, C reactive protein, complement breakdown products

(C3dg), rheumatoid factor titre, immunoglobulins (IgG, IgA, IgM), functional capacity, and patient and observer global opinions. One patient (placebo) withdrew after three days and was not included in the analysis. Treatment and placebo groups (20 patients each) were well matched at entry. No important differences between the clinical or laboratory variables of the groups were observed during the six week period. This study therefore shows no apparent benefit from oral feverfew in rheumatoid arthritis (Patrick et al. 1989).

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

- *Compositae* dermatitis from airborne parthenolide

Feverfew is a member of the European *Compositae* plant family that are suspected of causing airborne contact allergy. Its most important allergen is the sesquiterpene lactone PN. A study was designed to: (i) assess the allergenicity of feverfew-derived monoterpenes and sesquiterpenes and their oxidized products in feverfew-allergic patients, (ii) re-assess the role of PN and other sesquiterpene lactones in airborne contact allergy. Feverfew-allergic patients were patch tested with extracts and fractions containing volatile monoterpenes and sesquiterpenes as well as extracts of airborne particles from flowering feverfew plants, obtained by fractionation of ether extracts, dynamic headspace and high-volume air sampler (HIVAS) technique, respectively. Among 12 feverfew-allergic patients, 8 had positive patch-test reactions to a HIVAS filter extract, while 2 tested positive to a headspace extract. Subsequent analysis of the HIVAS extract by gas chromatography and mass spectrometry detected PN in a concentration of 510 mg ml⁻¹ in the HIVAS extract. Testing with a dilution series of PN showed positive reactions down to 8x1 mg in selected patients. None of the 12 patients tested positive to monoterpenes or sesquiterpenes, whether they were oxidized or not. The clinical results have proved that some feverfew-allergic patients are sensitive to airborne particles released from the plant and isolation of PN from the particle-containing HIVAS extract in allergenic amounts is strong evidence of PN as the responsible allergen (Paulsen et al. 2007).

4.3. Overall conclusions on clinical pharmacology and efficacy

Based on the totality of evidence, including clinical trials and systematic reviews, feverfew should not be considered as definitely effective (grade B evidence) nor as established safe in long-term use. Even though some studies are positive, we consider their results inadequate to substantiate well established use because the small number of patients, effects that were only lightly superior than placebo and the different dosages used.

5. Clinical Safety/Pharmacovigilance

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

Feverfew was well tolerated in the included trials, and adverse events were generally mild and reversible. Controlled studies have demonstrated no effect on blood pressure, heart rate or body weight after 6 months of regular consumption of encapsulated dried feverfew leaf (Johnson et al. 1985). Two studies (Johnson 1985; Murphy 1988) reported a higher incidence of adverse events during treatment with placebo than with feverfew. Feverfew did not appear to affect blood pressure, heart rate, body weight or haematological and biochemical safety parameters (Pittler 2004).

During the study conducted in 1985 by Johnson at the City of London Migraine Clinic, roughly 10% of patients who were switched to placebo after taking feverfew for several years appeared to experience a genuine "post-feverfew syndrome": a cluster of nervous system reactions including rebound of migraine symptoms, anxiety, poor sleep patterns along with muscle and joint stiffness (Johnson 1985).

It was a small study including seventeen patients that were already using the plant by eating fresh leaves of feverfew daily as prophylaxis against migraine in the period before the beginning of the clinical investigation.

In another study conducted by Pfaffenrath et al. (2002), the incidence of adverse events was similar for all treatment groups.

Chewing feverfew leaves produces sometimes a more general inflammation of the oral mucosa and tongue, accompanied by swelling of the lips and occasionally loss of taste. In Johnson's 1983 survey of 300 feverfew users, mouth ulceration (aphthous ulcers) from chewing fresh leaves was reported by 11.3% of users, prompting discontinuance of treatment by some. Mouth ulceration is a systemic reaction to *Tanacetum Parthenii* observed only in subjects chewing fresh leaves; it requires discontinuation of the product. Inflammation of the mouth and tongue with swelling of the lips appears to be a local reaction that may be overcome by using encapsulated herb products (WHO monograph 2004).

Abdominal pains and indigestion have been reported for feverfew users who chewed the leaves over a period of years. Although long-term toxicity data are presently unavailable, no serious side effects have been noted in patients taking the plant for several years. Digestive disturbances were experienced by 6.5% of respondents (Dennis 1998, Johnson 1983).

The frequency of chromosomal aberrations and sister chromatid exchanges was determined from lymphocyte cultures established from blood samples. Samples had been taken over a period of several months in 30 migraine patients who had daily taken leaves, tablets or capsules of feverfew for more than 11 consecutive months. They were compared to 30 feverfew non-user migraine patients who had been individually age and sex matched. Matched pairs were sampled on the same date for two-thirds of the cases, and the greatest difference in sampling time of the remainder was 20 days. Also, the mutagenicity of urine samples from 10 feverfew user migraine patients was compared to that from 10 matched non-user migraine patients using the Ames *Salmonella* mutagenicity test system. Paired samples were given on the same date. The mean frequency of chromosomal aberrations in the feverfew user group was lower than that in the non-user group, both in terms of cells with breaks (2.13% vs 2.76%) and in terms of cells with all aberrations (4.34% vs 5.11%). However, this difference was small and not significant. The mean frequency of SCE in the feverfew exposed group was lower than that in the control group (8.78 vs 8.80 SCE/cell), but this difference was not significant as determined by factorial analysis of variance ($P = 0.897$). There was a highly significant variance between the frequencies of SCE in the matched pairs of migraine patients, but this was not related to age, sex or feverfew exposure. The mean number of revertants in the Ames mutagenicity assay was greater for the urine of the feverfew user migraine patients than that of the non-user migraine patients, in both strains of bacteria, with or without the inclusion of an S-9 metabolizing system. However, the increases were small and insignificant. The data indicate that the prophylactic use of feverfew for the alleviation of migraine symptoms affects neither the frequency of chromosomal aberrations nor the frequency of SCE in the circulating peripheral lymphocytes. Also, the mutagenicity of urine from feverfew user migraine patients is unaffected compared to urine from non-user migraine patients detectable by the methods used in this study (Anderson et al. 1988).

5.2. Patient exposure

Feverfew has been ingested continuously by large numbers of people without indication of any chronic toxicity effects (Dennis 1998). Anderson et al. (1988) found no substantial differences in the frequency of chromosomal aberrations and sister chromatid exchanges in lymphocytes, or in the mutagenicity of urine, in tests comparing migraine patients who used feverfew leaves, tablets or capsules chronically with non-users of feverfew.

Sesquiterpene lactones such as the feverfew constituent and PN are also known to cause contact dermatitis (Dennis 1998, Johnson 1983).

5.3. Adverse events and serious adverse events and deaths

Allergy to *Tanacetum* and other plants from the *Compositae* family

Parthenium dermatitis, in its classical form, is known as airborne contact dermatitis and primarily affects the exposed areas and the flexures. Other clinical patterns are a seborrheic pattern, widespread dermatitis and exfoliative dermatitis.

The trend of the clinical pattern is changing. The classic airborne contact dermatitis may change to photodermatitis resembling chronic actinic dermatitis or mixed pattern dermatitis. The allergens responsible for contact dermatitis are sesquiterpene lactones and are present in the oleoresin fraction of the leaf, the stem and the flower, and also in the pollen. The allergens can be extracted in various solvents (such as acetone, alcohol, ether and water) and then used for patch testing. The acetone extract of *T. parthenium* is better than the aqueous extract in eliciting contact sensitivity. The treatment of *T. parthenium* dermatitis is mostly symptomatic. Topical steroids, antihistamines and avoidance of *T. parthenium* are the mainstay of treatment for localised dermatitis. Systemic corticosteroids and azathioprine are frequently needed for severe or persistent dermatitis (Sharma et al. 2007).

A case of specific, delayed hypersensitivity induced by repeated contact with a wild form of feverfew in a 63-year-old man who had suffered from recurrent dermatitis on his hands and forearms; most marked on the dorsal side and on his face, mainly around the eyes, was reported in 1983. Cross-reactions were elicited with 11 of 21 mostly *Compositae* plants containing chemically related sesquiterpene lactones (Hausen & Osmundsen 1983).

Compositae dermatitis occurred in a 9-year-old boy with a strong personal and family history of atopy.

A positive patch test reaction was found for feverfew and other *Compositae* plants. The eruption resembled atopic dermatitis morphologically but was prominent on the palms and face and dramatically spared the area of the boy's feet covered by his shoes (Guin & Skidmore 1987).

Around 80% of patients with prurigo nodularis are atopic, even in the absence of eczema, and in 20%, the condition starts after an insect bite. The association of contact dermatitis with prurigo nodularis was documented in a study of 32 patients, 25 of whom had positive patch tests, including to ragweed. Three case reports of prurigo-like lesions in contact dermatitis have been described. They were the first reports of prurigo-nodularis-like lesions in patients with parthenium dermatitis. Azathioprine was effective in both prurigo nodularis and parthenium dermatitis and was successful in 2 of the 3 patients (Sharma & Sahoo 2000).

A 45-year-old woman presented an eruption involving her scalp and face, including her eyelids and behind her ears. The eruption began at the end of August. It flared after she used a calming moisturizer containing feverfew.

A second patient, a 25-year-old woman, presented complaining of a 1 month history of an eruption around the eyes that started after she began using a moisturizer containing feverfew. Both patients were patch-tested with the North American Contact Dermatitis Group series, cosmetic and plant series and their own skin care products. The first patient had a + reaction to sesquiterpene lactone mix, a + reaction to *Compositae* mix, a + reaction to PN, a + reaction to *Tanacetum vulgare* and a + reaction to the calming moisturizer. Patient 2 had + reactions to sesquiterpene lactone, *Compositae* mix, and the

same calming moisturizer. It is thought that both of these eruptions are a result of contact dermatitis from the *Compositae* plant family (Killoran et al. 2007).

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

Occupational or direct exposure has caused eczema and allergic dermatitis.

Feverfew cross reacts with Tansy, Yarrow, Marguerite, Aster, Subflower, Laurel and Liverwort (PDR monograph 2007).

Withdrawal and rebound

Post-feverfew syndrome. About 10% of migraine patients who abruptly stop taking feverfew fresh leaves may experience rebound headache, insomnia, muscle stiffness, joint pain, fatigue and nervousness (PDR monograph 2007).

Drug interactions

Some theoretical potential risks have been suggested:

- feverfew inhibits platelet aggregation and it has been suggested that caution should be used in patients treated with other inhibitors of platelet aggregation such as aspirin and dipyridamole (PDR monograph 2007);
- moderate risk of bleeding may result by interactions with anticoagulants, low molecular weight heparins, thrombolytic agents and antiplatelet agents (PDR monograph 2007);
- moderate risk of adverse reactions (i.e. gastrointestinal, renal effects) may result by interactions with nonsteroidal anti-inflammatory agents (PDR monograph 2007).

However, no drug interaction has been reported in people taking feverfew.

Use in pregnancy and lactation

In view of its traditional reputation for emmenagogic effect and to affect the menstrual cycle (Herbal Medicines 2007), feverfew preparations should not be consumed by pregnant or lactating women.

Use in children and adolescents

Because of lack of information on the plant's effect, it has to be advised that children and adolescents should not be treated with feverfew.

5.6. Overall conclusions on clinical safety

Data from clinical studies show that feverfew is well tolerated and adverse events were generally mild and reversible. In view of its traditional reputation for emmenagogic effect, feverfew preparations are contraindicated in pregnant or lactating women. Because of the lack of data, feverfew treatment is not recommended in children and adolescents. Moderate risks may result from interactions with drugs or substances influencing blood coagulation and platelets aggregation. Rebound symptoms may appear after stop taking feverfew. Exposure to feverfew may cause eczema and allergic dermatitis.

6. Overall conclusions

Tanacetum parthenium, also known as “feverfew”, is a member of the *Compositae* family and it has been described since ancient times as having beneficial medicinal effects. The plant parts used for medicinal use are the dried leaves or the dried aerial parts.

Several investigations support feverfew’s traditional medicinal uses. Feverfew herbal medicinal products for migraines have been available for more than 30 years in the European Union and the medicinal use of feverfew for migraine and headaches in Europe is well documented for centuries. The sesquiterpene lactone parthenolide is considered the main active constituent. Parthenolide inhibits platelet aggregation and platelets serotonin release. It has also been shown that parthenolide has antiinflammatory effects through the inhibition of NF-κB and the IκB kinases complex.

Feverfew appears to be safe and well tolerated for the indication proposed and side effects are generally mild and reversible. Despite the wide use, no serious adverse reaction was reported. The analysis of data from clinical studies shows that side effects associated with its use such as nausea, heartburn, constipation, flatulence, abdominal bloating and diarrhoea are rarely reported and their frequency is similar to that of placebo. The occurrence of frequent mouth ulceration has been reported, but it has successively become clear that it is associated with chewing of feverfew fresh leaves. Such events are not reported from clinical studies in which feverfew was encapsulated. This may be plausible because such preparations do not come into contact with the Langerhans cells of the skin oral mucosa. Potential problems of sensitisation caused by allergens can be avoided by the use of capsules.

The proposed medicinal use for *Tanacetum parthenium* herba is:

“Traditional herbal medicinal product for the prophylaxis of migraine headaches”.

Due to the lack of sufficient data on long term use and based on the knowledge that prolonged intake can provoke rebound effects when feverfew is withdrawn, the duration of use of two months seems to be suitable for self-medication.

Annex

List of references