European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT ON
POLYPODIUM VULGARE L., RHIZOMA

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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I. REGULATORY STATUS OVERVIEW[1, 2]

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'

Member State	Regulatory Status				Comments[3]
Austria	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	Only traditional
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No MA
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No MA
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No MA
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No MA Not permitted in food supplement
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No MA
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No MA
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No MA
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No MA
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

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

[3] Not mandatory field

Member State	Regulatory Status				Comments[3]
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

II. ASSESSMENT REPORT FOR HERBAL SUBSTANCE WITH TRADITIONAL USE

***Polypodium vulgare* L., rhizoma**

BASED ON ARTICLE 16D(1) AND ARTICLE 16F AND 16H OF DIRECTIVE 2001/83/EC AS AMENDED

(TRADITIONAL USE)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Polypodium vulgare* L., rhizoma (Polypody rhizome)
Herbal preparation(s)	Comminuted herbal substance for tea preparation
Pharmaceutical forms	Herbal preparations in solid dosage forms for oral use
Rapporteur	Norway
Assessors	Gro Fossum Karl Egil Malterud Asefeh Moradi

II.1 INTRODUCTION

This assessment report was initially suggested to be on polypody root. However, according to the botanical description of *Polypodium vulgare* L., the correct designation for this plant part should be rhizome and not root. A root has two main functions: anchoring the plant in the soil and absorbing water and minerals. The absorption takes place only near the very tips of roots, through trichomes called root hairs, which are tiny extensions on root epidermal cells that generally increase the amount of root surface area (Nabors 2004). Rhizomes are horizontal stems that grow below ground as well, often near the surface soil. Superficially, they resemble roots, but to close examination will reveal scale-like leaves and axillary buds at each node, at least during some stage development, with short to long internodes in between. Adventitious roots are produced all along the rhizome, mainly on the lower surface. A rhizome may be a relatively thick, fleshly, food storage organ, or it may be quite slender, as in some ferns (Stern 1997). Hence, according to Stern (1997), rhizome is defined as "an underground stem, usually horizontally oriented, that may be superficially rootlike in appearance but that has definite nodes and internodes".
A similar definition of rhizome was used by Campbell and Reece (2002): "Rhizomes are horizontal stems that grow underground".

Although some articles and handbooks referred to in this assessment report refer to the polypody root, it is reasonable to assume that polypody rhizome is what is meant. Nevertheless, we have chosen to use both polypody rhizomes and roots as terms in this document, in order to cite the authors correctly.

II.1.1 *Description of the herbal substance(s)*

P. vulgare is a perennial fern growing to a height of 30 cm (1 ft). It has slender knotty rhizomes and curving fronds that are dotted with brown spores (sori) on their lower surface (Chevallier 1996).
P. vulgare is a small, winter green fern, and may grow into large colonies, forming extensive, dark green ground cover. They are rather thick, creeping and ramifying, scaly stems, and long stalked, usually 10-30 cm. long, glabrous, dull green, pinnatisect to pinnatifid leaves, borne alternately in two rows on the upper side of the stem. The stem scales are narrowly triangular, red-brown in colour, variable in size, usually up to 4 mm long. The blades are one to three times as long as the petiole. Their texture is firmly herbaceous to slightly leathery. The pinnae are entire, with entire or crenate margins, rarely more deeply serrate, and with round, brownish yellow to rusty brown sori in two rows on the underside, one on each side of the midrib, mainly in the upper half of the blade. The veinlets usually fork 2-3 times. These are deep reddish brown when the sporangium is yellow and mature, appearing as a thin brown line when seen with hand lens. The spores are strikingly yellow, bean-shaped, with a warty – folded surface 60-75 µm long. (Øllgaard and Tind 1993).
According to Shivas (1961), *P. vulgare* is a tetraploid, it is believed to have arisen by chromosome doubling of a sterile diploid hybrid between two species which are not known in Europe. One of the parent species may be the North American *P. virginianum*, or *P. glycyrrhiza*. Biochemical data point to a species from eastern Asia as the second possible parent. The name is derived from poly (many) and pous, podos (a foot) (Bown 2002; Grieve 1995). Hence, *Polypodium* means many-footed (Moran 2004). The rhizome has a distinctive taste, rather like liquorice (Ryvardsen 1993; Lid and Lid 2005)

Polypody root is used both fresh and dried, and the leaves are also sometimes used (Grieve 1995).

II.1.2 *Information on period of medicinal use in the Community regarding the specified indication*

P. vulgare has an ancient history as a medicinal herb. *P. vulgare* has been recommended by Dioscorides for chapped or dislocated hands, and by Culpeper as a laxative (Bown 2002).
The traditional use of polypody rhizome has been documented in several handbooks and in the scientific literature. The traditional medicinal use of polypody rhizome as a remedy for diseases of the air passages, such as coughs, colds, adenoids and a multitude of other purposes has been documented in handbooks such as The Swedish Pharmacopeia (1849), Madaus (1938), Frerichs *et al.* (1938), Høeg (1975) and Nielsen (1977).

Polypody has been used medicinally in Europe since ancient times. The Greek physician Dioscorides, writing in the 1st century AD, noted that polypody was used to purge phlegm and was an ingredient of a plaster applied to dislocated fingers and to sores that occur between the fingers (Chevallier 1996). The use of *P. vulgare* is also recorded among the American Indians. The Indians used root tea for the pleurisy, hives, sore throats, stomach-aches; poulticed root for inflammations (Foster 1990).

An old legend according to a source in Telemark in Norway tells that the polypody grew for the first time where Virgin Mary squirted some of her breast milk into a rock crevice. Hence the folk name "Mariebregne" (Mary fern), which is used in Danish also (Øllgaard and Tind 1993).

Polypody rhizome has been used as a taste substance in food. It has previously been a pharmacy assortment as a remedy against respiratory complaints and rheumatism. It has expectorant and laxative effect. The Indians in North America chewed the rhizome and swallowed syrups to relieve symptoms such as painful throat and cough, while the Sami people used the rhizome as sweets (Källman 2006).
The previous availability of polypody rhizome in pharmacies is reported by Øllgaard and Tind (1993), Källman (2006) and Ljungquist (2006).

According to Bown (2002), polypody is native to Europe, Africa, and eastern Asia, mostly in northern or upland areas. Polypody is a common species almost throughout Scandinavia, especially in the southern part of the area, and along the Atlantic coast of Norway nearly to the North Cape. The total area of the species is not well known according to the present delimitation. Several closely related species replace it in North America, and others may do so in eastern Asia. The species complex is of circumpolar distribution, with an odd outlier in southern Africa. In Europe the species is known from all countries, and is common throughout the area, except in parts of the Mediterranean (Øllgaard and Tind 1993).

II.2 NON-CLINICAL DATA

II.2.1 *Pharmacology*

II.2.1.1 Overview of available data regarding the herbal substance(s)

Compounds:

Polypody rhizome contains: ecdysteroids (Krishnakumaran and Schneiderman 1968; Chevallier 1996), phloroglucine derivatives (Chevallier 1996; Constantinescu *et al.* 1966), volatile oil, 8% fixed oil (Frerichs *et al.* 1938; Madaus 1938) and tannins (Chevallier 1996; Chiej 1988; Frerichs *et al.* 1938; Madaus 1938; Berger 1939). However, a search on Scifinder on 29 October 2007 on "tannins and *Poypodium vulgare"* gave only results on *Polypodium vulgare* leaves. The literature mentioning tannin content in polypody root may therefore not be accurate. The polypody rhizome contains both 5-ß-hydroxyecdysterone and ecdysterone (Heinrich and Hoffmeister 1967).
For two ecdysterones isolated from the polypody rhizome by Jizba *et al.* (1967), the names polypodine A and polypodine B were proposed. Polypodine A is identical with ecdysterone, while polypodine B is an ecdysone-like substance (Jizba *et al.* 1967).

Polypody root contains also 5% sugar (Madaus 1938; Frerichs *et al.* 1938; Chiej 1988), glycyrrhizin, mannitol (Madaus 1938; Frerichs *et al.* 1938; Chiej 1988; Berger 1939), protein, starch and carbohydrates (slime) and calcium maleate (Frerichs *et al.* 1938; Madaus 1938). According to Constantinescu *et al.* (1966), they found 0.6% glycyrrhizic acid in the polypody rhizome. In the study done by Constantinescu *et al.* (1966), they use rhizome filicis maris (*Aspidium filix mas* Swartz) as a comparison to consider the chemical content of polypody rhizome. According to IPNI (The International Plant Name Index), retrieved on 20 September 2007, *Aspidium filix mas* Swartz is a synonym for *Dryopteris filix-mas*. *Dryopteris filix-mas* belongs to *Dryopteridaceae* family, which is not in near relation to *P. vulgare* (which belongs to the *Polypodiaceae* family) (Smith *et al.* 2006), like the authors claim.
A study done by Umek *et al.* (1984) found no glycyrrhizic acid in *P. vulgare*. Neither did Jermstad *et al.* in 1949. Furthermore, an investigation on the presence of glycyrrhizinic acid in the polypody rhizome done by Vijver and Uffelie (1966), did not detect glycyrrhizinic acid in the rhizome of polypody. In addition, Jizba and Herout (1967) have not mentioned glycyrrhizic acid in their report which deals with isolation of constituents of polypody rhizomes.
The glycyrrhizin content is only mentioned in old handbooks and journal, and not cited in newer literature. Interestingly, it was reported by Berzelius in 1827 that the sweet principle in polypody root was different from glycyrrhizin (Berlin 1849).
The glycyrrhizin content in polypody root is not confirmed in newer literature.

Polypody rhizome yield essential oil containing butyric, hexoic, lauric and succinic acids (Chopra *et al.* 1956), methyl salicylate (Chopra *et al.* 1956; Foster 1990), butyric, isovaleric and α-methylbutyric esters; a fatty oil acting as an energetic purgative; a resin (Frerichs *et al.* 1938), another resin containing benzylic alcohol and its esters which is strongly anthelmintic (Chopra *et al.* 1956), a glucoside samambain (Chopra *et al.* 1956; Duke and Ayensu 1985) and saponins (Chopra *et al.* 1956; Chevallier 1996; Chiej 1988). According to Chopra *et al.* (1956) citing "Resin containing benzylic alcohol", it may seem that free phenol or benzylic alcohol is available in polypody root, which appears somewhat unlikely. Free phenol is reactive and toxic. Furthermore, a search on Scifinder on 29 October 2007 on "phenol" or "benzylic" and "*Polypodium vulgare*" gave no results.

The saponin osladin has been found in Polypody rhizomes, and is responsible for the sweet taste (Hostettmann and Marston 1995; Kinghorn 1998; Bown 2002). Osladin is glycosylated at C-3 and C-26 and is, therefore, a bidesmosidic saponin (Hostettmann and Marston 1995). In addition to osladin, another monodesmosidic saponin, polypodosaponin, has been isolated from the rhizomes (Hostettmann and Marston 1995; Jizba *et al.* 1971). Other closely related compounds have been isolated from the rhizomes of

Polypodium glycyrrhiza (liquorice fern). One of these, polypodoside A, is 600 times sweeter than 6% w/v sucrose solution (Hostettmann and Marston 1995). However, osladin is considered to be 500 times sweeter than sucrose (Yamada *et al.* 1992, Nishizawa and Yamada 1996). In 1996, Nishizawa and Yamada found out that the former structure of osladin was incorrect. The stereochemistry at C-22, 25, and 26 was revised.

According to Kroeber, a reference cited by Madaus (1938), a partial haemolytic effect of the saponins is established. Furthermore, a resin and a substance called polydin, up to 15 g dose, have shown a laxative effect within 10 hours (Madaus 1938). The structure of polydin (a glycoside) has been investigated by Uvarova *et al.* (1967).
According to Weinges and Wild (1970), polydin in polypody rhizome is (+)-catechin-7-L-arabinoside.
Another resin active against worms is also mentioned by Foster (1990).

A phytochemical examination done by Jermstad *et al.* (1949), of the rhizome of *Polypodium vulgare*, collected in Norway, showed the following constituents:

- K, Na, Ca, Mg in considerable quantities; Mn, Al, Fe, Ba, Sr in small amounts; and traces of Cu, Ag, Ni, and Co (the anions phosphate, sulfate, and chloride were identified chemically).
- Sugars (the Bourquelot method showed that the dried rhizome contained 7.62-8.20% sucrose, 85-1.90% invert sugar, and a small amount of pentoses).
- Organic acids: citric acid and malic acid, identified as hydrazides, caffeic acid or chlorogenic acid, and traces of ascorbic acid;
- Fatty oil, consisting of glycerol esters of palmitic, oleic, and linoleic acids;
- A glycoside m. 187- 188^{o}, claimed to be polydin.
- A phytosterol, m. 162-3^{o}, acetate m. 165-6^{o}.
- Rubber and resin.

In 1967, Jizba and Herout did an isolation of the constituents of polypody rhizome, and found saccharose (glucose and fructose), polypodine A and B, glucocaffeic acid, polydine, osladine, saponin I and II (saponin I being different from saponin II by the presence of a methoxyl group in its molecule), and samambaine.

Polypody rhizome is a rich source of tetra- and pentacyclic triterpenoids according to Berti *et al.* (1966).
A study done by Arai *et al.* (1989) showed that 5.90 g dried extract of Oo-ezodenda rhizome in Japan (which the authors claims appears to be the same species as the European *P. vulgare*, considering the many similarities in their chemical constituents) had a cycloartane triterpenoid having a new 33-carbon skeleton, named cyclopodmenyl acetate, together with various kinds of constituents such as:

Triterpenoid hydrocarbons (0.58 g):	Fern-9(11)-ene, neohop-13(18)-ene, fern-7-ene, hop-17(21)-ene, hop-22(29)-ene, serrat-14-ene, eupha- 7,21-diene, and α-polypodatetraene.
Fatty acid ester (1.94 g):	ß-sitosteryl palmitate, and linolates of 31-norcycloartanol, cycloartanol, cycloartenol, cyclolaudenol and cyclomargenol.
Acetates (0.40 g):	Acetates of cycloartanol, cycloartenol, cyclolaudenol, cyclomargenol and dryocrassol, and cyclopodmenyl acetate.
Glyceride (1.65 g):	Glycerides of oleic and linoleic acids.

In 1964, Berti *et al.* reported isolation of cyclolanostanic triterpenes from polypody root. Polypody root yielded 12% hydrocarbons, mainly fernene, cyclolaudenol and its 4-methyl homolog. A plant material called balatol was also examined, and found to be a mixture of cyclolaudenol and its 4-methyl homolog.

In 1991, Arai *et al.* isolated or identified additional triterpenoids from the Polypody rhizome including: 21αH-hop-22(29)-ene and dammara-17, 21-diene (the presence of the compound was confirmed, but its yield was unknown). Furthermore, Berti *et al.* reported a triterpenoid epoxide (m.p. 268-270^{o,} $[\alpha]_D^{28}$ + 47^{o} ($CHCl_3$), which analysed for $C_{30}H_{50}O$, in 1966. Although 1,2-epoxides derived from pentacyclic

triterpenoids had never been found in other plants, this was the second case of such a compound isolated from a fern (Berti *et al.* 1966). However, one year later, in 1967, Berti *et al.* concluded that the third compound most probably was serratene and its isomer isoserratene.

A study done by Ghisalberti *et al.* (1969) examined the triterpene components of polypody rhizome, and found cycloartanol, cyclolaudenol, 31-norcycloartanol and 31-norcyclolaudenol. This was corroborated by Arai *et al.* (1989). Nevertheless, Ghisalberti *et al.* (1969) identified 24-methylenecycloartanol and cycloeucalenol too.

In 1970, Davys isolated pollinastanol from the leaves and rhizomes of *P. vulgare.* Pollinastanol was identified as the crystalline compound by mass spectrometry.

Pharmacodynamics

***In vitro* experiments**
The following have been tested:

Antiviral activity
The antiviral properties of polypody rhizome have been tested by Husson *et al.* (1986). A biological test on cell culture (Buffalo Green Monkey) for measuring antiviral activity was tested with twelve different plant extracts. An extract of polypody root, 35 mg dried extract/ml were among the three results mentioned as interesting in this preliminary study. The positive result with polypody root is especially interesting as a search on Scifinder on 29 October 2007 on "gallotannins and *Polypodium vulgare*" gave only results on *P. vulgare* leaves. Hence, this is not corroborated by the scientific literature.
Furthermore, nothing in this report describes the content of *P. vulgare*, although this report claims that the selection of the plants was done with regard to the activity of the different substances in the plants, such as polyphenols, saponins and the indole alkaloids. According to the authors, the butanol phase of the extract had antiviral activity, and they claim that it is due to the polyphenols. This assumption is made by looking at the polarity of the phase, and it is, however, not confirmed that it is the polyphenols that actually have the antiviral activity.
According to Grzybek (1976), flavonols of polypody leaves were quercetin, rutin, nicotiflorin, and quercetin trioside. Chlorogenic acid and sucrose were also detected. Spores of *P. vulgare* contained carotenoids but not flavonoids. The tannin content of leaves was 4.1%.
Phenolic compounds in plants can produce inhibitory effects in many biological assays, and are often considered not of great interest as therapeutic agents due to their non-specificity (Wall *et al.* 1996).

Ecdysones
The effects of ecdysterone on moulting in arthropods have been tested by Krishnakumaran and Schneiderman (1968). Groups of experimental animals were selected in which spontaneous moulting was minimal, such as crayfish after the moulting season, and animals which moulted infrequently such as *Limulus polyphemus* (horseshoe crab) and spiders. Animals were observed for up to 6 weeks after treatment and examined for signs of moulting. Ecdysterone stimulated moulting in all of the arthropods examined. The response was proportional to dose. According to the authors, the ecdysones act topically on a wide variety of arthropods and may cause abnormal moulting and death, so ecdysone analogues may be useful not only as insecticides but also miticides.
Ecdysterone is present in high concentrations in polypody rhizomes (0.07-1% dry weight) (De Souza *et al*. 1970). According to Jizba *et al.* (1967), ecdysterone from polypody rhizome possesses higher physiological activity in comparison with ecdysone isolated from insects. The presence of a considerable high amount of ecdysterone (over 1% of dry drug) in polypody rhizome, indicates that compounds of the character of moulting hormone may be exogenous factors and that the insects receive them with the food.

In addition, three patents were found on Scifinder on 1 November 2007 describing the activity of *P. vulgare* ecdysterones on the skin.

***In vivo* experiments**

A study done by Mannan *et al.* (1989) with an aqueous extract of polypody root (prepared then by refluxing finely powdered dried root in distilled water (1:10 w/v) on water bath for 3 hours, and dried at 70°C) showed amongst other activities, CNS depressant effect of polypody root.
The following effects were tested by Mannan *et al.* (1989):

Neuro-psychopharmacological activity
Six mice and/or rats were given 100-300 mg/kg aqueous extract i.p. Observation made at 5, 15, 30, 60, 120, 240 and 360 minutes after administration showed decreased alertness, mild passivity and decreased locomotor activity in mice and rats. Respiratory rate was increased and there was piloerection. These effects were dose dependent. However, all animals survived even with the highest dose (1000 mg/kg).
Spontaneous motor activity
Administration of polypody root extract (100 mg/kg) caused reduction ($P < 0.02$) in motor activity. The average activity counts of 5 minutes duration during the first 8 hours were 10.4 ± 1.5 (n=6) and 2.3 ± 1.3 (n=6) in control and drug treated groups. According to Mannan *et al.* (1989), the reduction in spontaneous motor activity was seen at doses which were 10 times lower than those required to produce impairment of motor coordination. The authors conclude that the polypody root extract appears to be acting at subcortical centres rather than cortical.
Forced coordinated motor activity
Forced coordinated motor activity was measured in mice rotarod. Animals falling off within 5 minutes were considered as affected. The forced coordinated motor activity was affected with high doses (1000 mg/kg) only, where 33% animals developed impairment in motor activity between 1 and 2 hours post-administration.
Hypnotic potentiation
Administration of 300 mg/kg extract prior to pentobarbitone injection caused an early and prolonged sleeping time (50 and 98.3% in rats and mice) compared to control animals.
Anticonvulsant activity
Administration of 100 mg/kg polypody root extract in rats caused protection against supramaximal electroshock and pentylenetetrazol induced seizures. The antiepileptic activity is, according to the authors, due to CNS depression.
Hypothermic and antipyretic activity
300 mg/kg of the extract caused gradual fall in rectal temperature of rats from $100.4F \pm 0.66F$ to $95.3F \pm 1.0F$ (n=6, $P<0.001$) appearing in 5 minutes and lasting for 4 hours. Furthermore, administration of the extract in the same dose significantly prevented or reduced the pyrexial response of TAB injection in rabbits.
Analgetic activity
300 mg/kg increased the reaction time in rats from 10.73 ± 0.78 to 14.77 ± 0.98, 16.67 ± 1.52 and 2.23 ± 2.39 seconds at 30, 60 and 90 minutes post administration (n= 30, $P <0.001$).
Cardiovascular activity
10-60 mg/kg of the extract produced a fall in blood pressure in anaesthetized dogs, which was rapid in onset and short in duration. The effect was blocked by propranolol. In rats, the extract caused hypotension with smaller doses (10-50 mg/kg). However, a fall followed by a rise in blood pressure was observed with high doses (100 mg/kg and above). The authors claim that the hypotensive effect appears to be due to vasodilatation due to ß-adrenergic receptor stimulation. However, since the extract, in high doses, caused a rise in blood pressure in rats, piloerection and increased respiration, the authors suggest α-adrenoceptor stimulation as well.

It has been suggested that the activity mentioned above, may be caused by catechins. Catechins have been subjected to several studies in order to demonstrate their adverse effects, but catechins are only present in very low concentration in the herbal preparations described in the Polypodii rhizoma monograph. These studies are therefore not relevant as described below.

In the Mannan *et al.*(1989) study, the animals were given polypody root extract intraperitoneally, and this can therefore not be compared with oral administration as an herbal tea preparation. The extraction yield is not given in the study, therefore, a calculation based on this study cannot be given for our posology.

However, if we assume the extraction yield to be 10%, 10 mg/kg will correspond to 5 g for a 70 kg human given i.p. No literature indicates that such amounts can be achieved after oral administration.
In general, flavonoids are relatively non-toxic to higher animals, and seem to be devoid of teratogenic effects. As long as the diet is the sole source of flavonoids, the risk of becoming intoxicated seems small. Clinical trials with large doses of the flavonoid catechin (cyanidanol) have, however, showed serious side effects, probably due to immunological reactions. The dosages in these cases were more than 1 g/day. The acute LD_{50} for flavonoids tested in animal experiments normally seems to be above 1 g/kg body weight (Review: Meltzer and Malterud 1997). It seems reasonable to assume that the amount of catechin obtained from polypody by drinking the tea preparation is not likely to exceed 1 g/day.

An examination of newer literature in Scifinder did not indicate any toxic effect or adverse effect of catechins. For example, a study reported by Glei *et al.* 2003, where the aim was to comparatively investigate two whole foods for cytotoxicity, genotoxicity and protective effects in human colon cells, a catechin-rich green tea (GT1) and an anthocyanin-rich plant juice did not indicate any potential toxic effects of catechins under clinical circumstances.

According to Weinges and Wild (1970), polydin in polypody rhizome is (+)-catechin-7-L-arabinoside. A search on Scifinder on 10 March 2008 on polydin, gave only 10 results. None of them deal with the toxic effects or adverse effects of polydin, except a Rumanian article from 1985 dealing with the response of some endocrine glands to acute polydin therapy written by Chiricuta *et al.* (1985). In this article polydin is mentioned, but nothing in this article seems to be relevant to *Polypodium*. Polydin has also been used as a name for an antibiotic preparation based on iodine and povidone (polyvinylpyrrolidone), and it seems likely that this is the subject of the study by Chiricuta *et al.* (1985).

Based on the Jizba and Herout study from 1967, the polydin amount in dried polypody rhizome has been calculated. According to Jizba and Herouts article 2.36 kg plant material correspond to 13 g polydin, which means that polypody rhizome contains 0.5% polydin.

The highest amount of polydin intake for the cough and cold indication will be 100 mg/day when polypody is used as an herbal substance for tea preparation. According to newer literature this amount of catechins is not high enough to cause any adverse effects.

II.2.1.2 Assessor's overall conclusions on pharmacology

Polypody rhizomes investigated in a few pharmacological studies have shown psychopharmacological activity in animal studies. Some of the investigations are old and scarce, and the activities concerning the suggested indications are not tested. Hence, the data available are not directly relevant to the proposed indications.

II.2.2 *Pharmacokinetics*

II.2.2.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

No information available.

II.2.2.2 Assessor's overall conclusions on pharmacokinetics

Due to lack of data, no conclusions can be drawn.

II.2.3 *Toxicology*

II.2.3.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

Acute toxicity

No data found on polypody rhizome. It should be mentioned that a study done by Adrian-Romero *et al.* (1999) quantifying formaldehyde as formaldemethone in plants and plant-like organisms by using HPLC, found 1400 µg/g formaldehyde (as formaldemethone) in fresh samples of *P. vulgare*. However, the plant part used was not given in the article.

It should be mentioned that a search on Google.com on 20 November 2007 on "horny goat" (a complex Chinese mixture containing several herbs including *P. vulgare*, as a Viagra for men) and *Polypodium vulgare* gave 3 800 matches. However, only 2 matches were found on Pubmed.com and Scifinder on 20 November 2007 containing "horny goat". Both of them described adverse effects such as strongly oestrogenic effect, tachyarrhythmia and hypomania. The adverse effects are mainly attributed to the L-dopa content in the horny goat weed (Partin and Pushkin 2004) in the mixture. The effects reported do not appear to be related to known activities of *P. vulgare*.

No data on genotoxicity, carcinogenicity, reproductive and developmental toxicity is available on polypody radix/rhizome. However, polypody root may cause a rash, which is harmless according to Bown (2002).

II.2.3.2 Assessor's overall conclusions on toxicology

Polypody rhizome can be regarded as safe under normal conditions of use.
In cell cultures, polypody rhizome extracts have not been shown to have cytopathogenic effects (Husson *et al.* 1986).
No signals of polypody rhizome having any harmful effects have been identified. Since minimum required data on mutagenicity (Ames test) are not available, inclusion to the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products cannot be recommended.

II.3 CLINICAL DATA

II.3.1 *Clinical Pharmacology*

No data available.

II.3.1.1 Pharmacodynamics

No data available.

Pharmacodynamic interactions

No data available.

II.3.1.1.1. Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

No data available. Furthermore, no references to clinical studies are found through PubMed.

II.3.1.1.2 Assessor's overall conclusions on pharmacodynamics

Due to lack of data, no conclusions can be made.

II.3.1.2 Pharmacokinetics

No data available.

Pharmacokinetic interactions

No data available.

II.3.1.2.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

No data available.

II.3.1.2.2 Assessor's overall conclusions on pharmacokinetics

Due to lack of data, no conclusions can be drawn.

II.3.2 *Clinical Efficacy*[4]

Polypody rhizome is used in European, American and Ayurvedic traditions. The traditional use of polypody rhizome has been thoroughly documented in handbooks. The use of polypody rhizome is reported by Chopra *et al.* (1956) in the book Glossary of Indian Medicinal Plants and by Nadkarni in the book Dr. K.M. Nadkarni's Indian Materia Medica.
In addition, the use of *P. vulgare* is also mentioned in Chinese Medicines by Duke and Ayensu (1985), although the part of the plant used traditionally is not mentioned.

In Norway, polypody is a common species throughout the country (Høeg 1975, Nielsen 1977). A search on www.artsdatabanken.no confirmed this (a Norwegian website showing a map on the spreading of different plant species in Norway) 20 November 2007.

The use of polypody as a drug dates back to ancient Greece. The thick stems were earlier used as a remedy for diseases of the air passages, such as coughs, colds, adenoids, and a multitude of other purposes. The stem has a sweet taste like that of liquorice, as indicated in the Danish and Swedish names, but also an acrid after-taste (Øllgaard and Tind 1993). The use of polypody rhizome is also described by Høeg (1975), where the root was reported to be cooked in milk and sugar against the common cold, and root cooked with liquorice and candy-sugar as a cure against respiratory catarrhs. The use of polypody rhizome as a sweetener has also been reported (Svanberg 1998).

The fresh root used to be employed in decoction, or powdered, for melancholia and also for rheumatic swelling of the joints. It is stated to be efficacious in jaundice, dropsy and scurvy and combined with mallows removes hardness of the spleen, stitches in the side and colic. The distilled water of the roots and leaves was considered by the old herbalists good for ague, and the fresh or dried roots, mixed with honey and applied to the nose, were used in the cure of polypus (Grieve 1995).
Polypody root is described as a soothing, demulcent stimulant, influencing the mucous membrane of the alvine canal and respiratory organs. It is a laxative to the bowels and to the bronchi it is an expectorant. It is highly valuable in the treatment of coughs, consumption and chest diseases (Lyle 1932). The author also claims that polypody root has a proved tonic effect in dyspepsia and is alterative in skin diseases. The use of polypody root against bronchial catarrhs and as a cough remedy is also reported by Madaus (1938) and Christophersen (1960).

[4] In case of traditional use the long-standing use and experience should be assessed.

According to Det Beste (1984), the saponin in the fresh plant of polypody acts as a cough suppressant.
The expectorant and antitussive effects of saponins in general are explained by Hostettmann and Marston (1995):
"Saponins posess a general and non-specific ability to produce local irritation, especially of mucous membranes. This can take place in the nasal cavity, the throat, the bronchi, the lungs and in kidney epithelia."

"The irritation of the throat and respiratory tract probably increases respiratory fluid volume by drawing more water into the bronchial secretions, hence diluting the mucus and reducing its viscosity. Alternatively, the surface activity of the saponins may render the sputum less vicid, making it more mobile and easier to eject. Another possibility is that the amphifilic nature of saponins causes them to spread out as a monomolecular film at the back of the throat and subsequently aid elimination of mucus."

According to the Matthiolus, cited by Madaus (1938), polypody root was also used externally against nose polyps and damaged skin. In folk medicine, *P. vulgare* is used as an expectorant and a diuretic (Berger 1939; Madaus 1938), especially suited for bronchitis and tuberculosis (Madaus 1938). Furthermore, the importance of polypody root as a remedy against respiratory complaints, and as an expectorant is mentioned in the Swedish pharmacopeia from 1849. Bown (2002) mentions also that polypody rhizomes are used internally for dry cough, bronchial catarrh and chest infections.
However, according to Frerichs *et al.* (1938), the polypody rhizome is not often used as an expectorant and a diuretic, and that the use as an expectorant was introduced in Europe from Peru and Chile.

The American Indians used root tea for pleurisy, hives, sore throats, stomachaches; poulticed root for inflammations. Historically, root steeped in milk was used as a laxative for children. Det Beste (1984) also reports the use of polypody rhizome as a laxative.

Once, polypody was considered valuable for lung ailments and liver disease. Tea or syrup of whole plant was used for liver ailments, pleurity, worms. The root has a unique, rather unpleasant odour, and a sweet flavour at first, but then quickly becomes nauseating (Foster 1990).

<u>The following indications have been reported for polypody rhizome:</u>
Polypody root is a laxative (Potterton 1983). Traditionally, it has been used in Europe herbal medicine as a treatment for hepatitis and jaundice, and as a remedy for indigestion and loss of appetite. The rhizome was, at one time, used to adulterate the liquorice root. It is still used as a sweetener according to Chiej (1988).
The rhizome is also expectorant (Chevallier 1996; Nielsen 1977; Chiej 1988; Bown 2002), having a supportive and mildly stimulating effect on the respiratory system (Chevallier 1996). It may be taken for the relief of catarrh, bronchitis, and dry irritable coughs (whooping cough) (Reichborn-Kjennerud 1922; Chevallier 1996; Bown 2002), and affections of the lungs (Vijer and Uffelie 1966).

Polypody makes a safe treatment for constipation in children (Chevallier 1996). The use of polypody rhizome against constipation, especially in children, is also cited by Bown (2002).

Polypody root is stated to be valuable in the treatment of wide range of ailments, such as:

Rheumatism	Nielsen (1977); Grieve (1995); Bown (2002)
Worms	Nielsen (1997); Madaus (1938); Bown (2002)
Tuberculosis	Høeg (1975); Det Beste (1984)
Cholagogic	Chopra *et al.* (1956); Madaus (1938); Chiej (1988); Hegnauer (1962); Vijer and Uffelie (1966), Bown (2002).
Purgative	Chopra *et al.* (1956); Potterton (1983); Madaus (1938); Bown (2002); Vijer and Uffelie (1966).
Intestinal complaints	Potterton (1983); Det Beste (1984); Madaus (1938); Reichborn-Kjennerud (1922)

Diuretic	Det Beste (1984); Bown (2002); Swedish pharmacopeia (1849).
Laxative	Det Beste (1984); Grieve (1995); Madaus (1938); Chiej (1988); Reichborn-Kjennerud (1922)
Dyspepsia	Grieve (1995)
Fever	Duke and Ayensu (1985)
Gonorrhea	Duke and Ayensu (1985)
Mechanical injuries/healing	Duke and Ayensu (1985); Bown (2002)
Female "suffering"	Berger (1939)
Asthma	Christophersen (1960)

Evidence regarding the traditional use and posology:

Culpepper's Colour Herbal, Potterton 1983:

- *Traditional use* : Laxative
- *Oral dose*: Decoction: Boil ½ oz (14 g) of the root in 1 pt (568 ml) boiling water, and sweeten with honey. Dose: 2 fl. Oz (56 ml), three or four times a day. This remedy also acts as a digestive tonic, stimulating the appetite. It is also helpful in relieving coughs and respiratory infections.
- *Duration of use*: Not mentioned.

A Modern Herbal/ http://www.botanical.com/botanical/mgmh/f/ferns-08.html, Grieve 1995:

- *Traditional use*: Coughs and catarrhal affection, particularly in dry coughs: it promotes a free expectoration,
- *Oral dose*: Infusion prepared from 1/2 oz. of crushed root to a pint of boiling water and sweetened, is taken in teacupful doses frequently, proving valuable in the early stages of consumption. Fluid extract: dose, one drachm.
- *Duration of use*: Not mentioned.

Lehrbuch der Biologischen Heilmittel, Madaus 1938 (http://212.185.118.226/publlehrbuch/xml/Frame.asp?D=21982202.xml&S=POLYPODIUM):

- *Traditional use*: Cholagogue and purgative, bronchitis and tuberculosis.
- *Oral dose citing Leclerc*: 2-4 g powder, 1-3 g fluid extract.
- *Oral dose*: 0.75 g fresh rhizome
- *Oral dose as a laxative*: 3 teaspoons rhizome steeped in 1 glass of cold water for 8 hours. Filter off the rhizome, and put it in 1 glass of boiling water, let it poach for 10 minutes. Mix both infusions (hot and cold). To be taken during the day.
- *Duration of use*: Not mentioned.

The Swedish Pharmacopeia, Berlin 1849:

- *Traditional use*: "Respiratory complaints", diaphoretic, diuretic and as an expectorant.
- *Oral dose*: infusion; ½ -1 ounce (approx. 30 g) in 6 ounce colature, or as an extract-preparation.
- *Duration of use*: Not mentioned.

Meddelelser fra Norsk Farmaceutisk Selskab, Jermstad *et al.* 1949:
Citing Leclerc: Union Pharmaceutique 1921 (not available to us):

- *Traditional Use*: Laxative
- *Oral dose*: Extraction of polypody rhizome and Glycyrrhizae root:

Polypody rhizome conc.	20
Glycyrrhiz. root conc.	20[5]
Aqua dest.	200, to be taken in the morning before eating.

- *Duration of use*: Not mentioned.

Vilda Växter som Mat och Medicin, Källman 2006[6]:

- *Traditional use*: Cough, hoarseness, as an expectorant, and as a laxative.
- *Oral dose:* *As remedy for cough, hoarseness and expectorant*:
  Finely divided 20 cm of fresh rhizome (or 2 tablespoons dry root) in one deciliter hot (not boiling) water. Let this simmer for 15 minutes before filtering off the solids. This liquid is to be taken 3-4 times a day. To prevent osladin from disintegrating, a cold infusion can be made: Take 3 tablespoons finely divided rhizome in a glass of cold water. Let this steep in 10 minutes before filtering the infusion. 1.5 deciliter boiling water is to be poured over the remaining root-pieces, and this is to be steeped for 10 minutes. Mix the cold and the warm fluid, and divide it into three doses a day.
  As a laxative:
  Boil 20 cm of the fresh rhizome (or three tablespoons of dry and finely divided root) in 1.5 decilitre water for five minutes. Let it poach for 3 hours before filtering off the root-pieces.
- *Duration of use*: Not mentioned.

Legeplanter, Faarlund and Wendelberger 1981:

- *Traditional use*: Respiratory catarrhal affection and gout.
- *Oral dose*: Infusion prepared from three teaspoons rhizome steeped in 1 glass of cold water for 8 hours. Filter off the rhizome, and pour boiling water into it. To be taken in small doses frequently during the day.
- *Duration of use*: Not mentioned.

Considering the above mentioned traditional use of polypody rhizome, and the longstanding traditional use, the following traditional indication is proposed:

A) Traditional herbal medicinal product used as an expectorant in cough and cold.

B) Traditional herbal medicinal product for short-term use in cases of occasional constipation.

[5] Assessor's comment on ingredients: Leclerc´s oral recipe is referred to by Volmar and Reeb (1924) in Journal de Pharmacie and by Madaus (1938). Volmar and Reeb write 10 g glycyrrhizin root, and not 20 as Jermstad *et al.* (1949) have done, while Madaus has written 20 g polypody rhizome, 10 g glycyrrhiza root and additionally 5 g rad. angelicae (assumed to be *Angelica archangelica*). Although all three references have cited Leclerc, they have different recipes. Leclerc´s original paper is not available to us.

6 The reference on which Källman (2006) has based his posology is not given. Källman's book describes traditional use of herbs as food and medicine in the northern parts of the world, not only Sweden.

II.3.2.1 Assessor's overall conclusion on the traditional medicinal use

Traditional medicinal use of polypody rhizome as an expectorant in cough and cold and as a medicinal product for short-term use in cases of occasional constipation fulfils the requirement of medicinal use for at least 30 years (15 years within the Community) according to Directive 2004/24/EC.

We have no information on marketed products containing *P. vulgare* . The substance has been widely used, so possible marketing authorisation applications on products containing *P. vulgare* in the future cannot be excluded. According to the handbooks, the substance seems to be used by herbal practitioners (Lyle 1932).
A search on Scifinder on 1 November 2007 on *Polypodium vulgare*, refined by document type "patent" gave twelve patent results. Three patents concern *P. vulgare* rhizome. However, all three dealt with the activity of ecdysterone on the skin.

II.3.2.2 Dose response studies

There are no dose-response studies available.

The listed posologies from handbooks (se II.3.2) are variable and not consistent.
However, since polypody rhizome is generally recognised as safe, and no case report of safety concerning polypody rhizome is identified, an average dosage has been suggested in order to recommend a posology for discussion.

Posology
Adolescents over 12 years of age, adults, elderly

Herbal substance:
i) Dried polypody rhizome

Herbal preparations:
Comminuted herbal substance for tea preparation

A) Cough and cold:
Herbal substance for tea preparation
Dried polypody rhizome 4-5 g, 3- 4 times daily

B) Occasional constipation:
Herbal substance for tea preparation
Dried polypody rhizome14-30 g, daily

Assessor's comment on posology
The suggested posologies for indication A and B, are too similar to exclude the possible laxative effects when polypody rhizome is used for cough and cold. However, both indications are thoroughly documented in traditional literature.
The use of polypody rhizome as a laxative has been reported in handbooks such as Madaus (1938), Reichborn-Kjennerud (1922) and Jermstad *et al.* (1949) (Citing Leclerc: Union Pharmaceutique from 1921). Hence, the use of polypody rhizome for short-term use in cases of occasional constipation cannot be excluded.

The mild laxative effect may be seen as a minor adverse reaction when polypody rhizome is used in cough and cold, and it is suggested to be included under section 4.8 'Undesirable effects' in the monograph.
Duration of use

Due to the nature of the proposed indications, we suggest that the use of polypody rhizome should be limited to 1 week.

II.3.2.3 Clinical studies (case studies and clinical trials)

No information available.

II.3.2.4 Clinical studies in special populations (e.g. elderly and children)

None reported.

II.3.2.5 Assessor's overall conclusions on clinical efficacy

There are no clinical investigations available on polypody rhizome.

II.3.3 *Clinical Safety/Pharmacovigilance*

There are no risks (adverse reactions) reported by the Member States. However, according to a list issued by the Danish Food Agency, *P. vulgare* is not permitted in any amount in food supplements or herbal teas in Denmark. No further information is given from Danish authorities. Many countries have lists with plants that are not suitable for use in food, and the Danish listing of Polypody rhizome can be seen as part of national regulation for food supplements. The European Food Safety Authority (EFSA) has made one compendium of botanicals that have been used in food and one compendium of botanicals that have been reported by some European Member States to be of possible concern regarding safety. However, Polypody rhizome has not been mentioned in any of the documents on public consultation: "Safety assessment of botanicals and botanical preparations intended for use as food supplements" with deadline: 15/02/2008.

II.3.3.1 Patient exposure

None reported.

II.3.3.2 Adverse events

Bibliographic review of safety data of the traditional herbal medicinal substances
The following electronic databases were searched on 24 September 2007 with the search term "*Polypodium vulgare*, polypody root and rhizome"

Results:

Scifinder (refined search with the term "adverse"): no references obtained (this database covers both Chemical Abstracts and Medline).
Toxline: 6 references obtained
PubMed (refined with the term "adverse"): no references obtained

Out of these references, no case report of safety concern in connection with polypody root or rhizome was identified.

However, according to Chevallier (1996), polypody may cause a skin rash when applied externally. It is not mentioned which is the part of the plant that may cause a skin rash. According to Williamson (2003), polypody rhizome occasionally produces a rash after ingestion; the reason for this is unknown and it appears to be harmless, however, this is not confirmed in scientific literature.
A case report describes that an 18-year-old man was diagnosed with mild rhinoconjunctivitis and asthma to pollen, mites, and cat dander. Several months later, he began working at a fishmonger's, when he noted

worsening of his rhinoconjunctivitis. He also developed local pruritus and wheals after handling the fern fronds (*Polypodium vulgare*) used to decorate boxes of fish. In addition, Prick test with the fern was positive (538 mm wheal), while seven control subjects were negative. The authors state that this is the first known case of occupational rhinoconjunctivitis and contact urticaria caused by an ornamental fern (Rodriguez *et al.* 2001). This report on adverse effects is a case report of single patient. It is apparent that the leaves with fern-spore are the reason for this adverse reaction, and not the polypody root or rhizome.

There are no risks (adverse reactions) reported from the member states.
Mild laxative effect is reported as a traditionally used indication, and could therefore be mentioned as a minor adverse reaction when polypody rhizome is used in cough and cold, and it is suggested to be included in 4.8 'Undesirable effect's in the monograph.

II.3.3.3 Serious adverse events and deaths

None reported.

II.3.3.4 Laboratory findings

None reported.

II.3.3.5 Safety in special populations and situations

Children (younger than 12 years of age)
Reports on the use of polypody rhizome in children are lacking. However, in the Norwegian tradition, the use of polypody rhizome in children occurs due to the liquorice taste (Høeg 1975).

The use of polypody rhizome is not recommended in children younger than 12 years of age due to lack of adequate data.

II.3.3.5.1 Intrinsic (including elderly and children) /extrinsic factors

None reported. However, hypersensitivity to the active substance should be a contraindication.

II.3.3.5.2 Drug interactions

None reported. However, another *Polypodium* species, *P. leucotomos*, may inhibit psoralen-UVA induced phototoxicity. This is reported as a beneficial affect (Middelkamp-Hup *et al.* 2007). *P. vulgare,* however, has not been investigated for this.

II.3.3.5.3 Use in pregnancy and lactation

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

II.3.3.5.4 Overdose

No case of overdose has been reported.

II.3.3.5.5 Drug abuse

None reported.

II.3.3.5.6 Withdrawal and rebound

None reported.

II.3.3.5.7 Effects on ability to drive or operate machinery or impairment of mental ability

Not available.

II.3.3.6 Assessor's overall conclusions on clinical safety

There are no risks (adverse reactions) reported by the Member States. Polypody rhizome is generally considered as safe. However, due to lack of toxicity data, the use of Polypody rhizome cannot be recommended during pregnancy, breast-feeding or in children younger than 12 years of age.

II.4 ASSESSOR'S OVERALL CONCLUSIONS

Sufficient data are available to conclude that the traditional medicinal use of polypody rhizome fulfils the requirement of medicinal use for at least 30 years (15 years within the Community) according to Directive 2004/24/EC. Listed posologies from handbooks (se II.3.2) are variable and not consistent. However, since no signals of polypody rhizome having any harmful effects have been identified, an average dosage has been suggested in order to recommend a posology.

Since minimum required data on mutagenicity (Ames test) are not available, inclusion to the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products cannot be recommended.

Due to lack of available data, the use of polypody rhizome cannot be recommended during pregnancy, breast-feeding or in children younger than 12 years of age.

III. ANNEXES

III.1 COMMUNITY HERBAL MONOGRAPH ON *POLYPODIUM VULGARE* L., RHIZOMA[7,8]

III.2 LITERATURE REFERENCES

[7] According to the 'Procedure for the preparation of Community monographs for traditional herbal medicinal products' (EMEA/HMPC/182320/2005 Rev.2)

[8] According to the 'Procedure for the preparation of Community monographs for herbal medicinal products with well-established medicinal use' (EMEA/HMPC/182352/2005 Rev.2)