EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Aesculus hippocastanum* L., cortex

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Aesculus hippocastanum* L., cortex
Herbal preparation(s)	Powdered herbal substance
Pharmaceutical form(s)	Herbal preparation in solid dosage forms for oral use
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Table of contents

1. Introduction

The aim of this report is to assess the available preclinical and clinical data on Hippocastani cortex (horse chestnut bark) for preparing a Community herbal monograph.

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

- Herbal substance(s)

Horse chestnut bark. The bark is obtained from the young branches and dried.

The composition of horse chesnut bark is complex. The most characteristic compounds are coumarin derivatives (up to 7%) (Wichtl *et al.* 2003):

- Glucosides:

Esculin (6-(*β*-D-glucopyranosyloxy)-7-hydroxy-2*H*-1-benzopyran-2-one, or 6,7-dihydroxycoumarin 6-glucoside), a glucoside of esculetin (6,7-dihydroxy-2*H*-1-benzopyran-2-one, or 6,7-dihydroxycoumarin).

Fraxin (8-(*β*-D-glucopyranosyloxy)-7-hydroxy-6-methoxy-2*H*-1-benzopyran-2-one, or 7,8-dihydroxy-6-methoxycoumarin-8-*β*-D-glucoside), a glucoside of fraxetin (7,8-dihydroxy-6-methoxy-2*H*-1-benzopyran-2-one, or 7,8-dihydroxy-6-methoxycoumarin);

Scopolin (7-(*β*-D-glucopyranosyloxy)-6-methoxy-2*H*-1-benzopyran-2-one), a glucoside of scopoletin (7-hydroxy-6-methoxy-2*H*-1-benzopyran-2-one, or 7-hydroxy-6-methoxy-coumarin)

- Aglycones: esculetin, fraxetin and scopoletin

Other constituents are: tannins (up to 2 %) (Fournier 1948; Paris & Moyse 1981), flavonoids, anthocyanins (Bombardelli *et al.* 1996, catechins derivatives (Bombardelli *et al.* 1996; Wichtl *et al.* 2003), traces of aescin (Wichtl *et al*. 2003; Schneider 1978).

- Herbal preparation(s)

Powdered herbal substance

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable

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

Horse chestnut bark as single herbal substance is authorised in France, Poland and Spain.

The active substance is present on the market as:

- Herbal substance

Dried bark for decoction preparation for cutaneous use (Poland, over 15 years).

- Herbal preparation

Powder (France, 1982; Spain, 1991).

Dry extract (solvent water, DER 5-6:1) (France, 1994).

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only homeopathic products
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
France	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only in combination
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products; the herbal is on a list of herbal substances/herbal preparations allowed in food supplements
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
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:	No products
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products

Member State	Regulatory Status				Comments
Spain	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
Other: If known, it should be specified or otherwise add 'Not Known'
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

Online database were used to research available pharmaceutical, non-clinical and clinical data on horse chestnut bark or its relevant constituents.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Aesculus hippocastanum L. belongs to the *Hippocastanaceae* family. Native to Western India, today the horse chestnut is widely distributed all over the world and it grows in Iran, Northern India, Asia Minor, Europe and USA (Bombardelli *et al.* 1996). It is a 25-30 m high tree (Bézanger-Beauquesne *et al.* 1980). Different plant parts have been used, only the bark is described in this assessment report.

Horse chestnut bark has been traditionally used for the capillary weakness and the venous system (varicose veins and haemorrhoids) (Bézanger-Beauquesne *et al.* 1975).

It was described for the first time in 1565 by Mathiole and it appeared in France in 1615. During the 18th century, it spread into most parts of Europe (Bombardelli *et al.* 1996; Fournier 1948; Leclerc 1976).

It was used in 1720 as febrifuge, as substitute for cinchona and as astringent for diarrhoea. It was used for external use in decoction (50 g/1000 g) as antiseptic for ulcers and gangrenous wounds (Fournier 1948).

The bark has been used (Fournier 1948):

- as tonic: as decoction (30 to 50 g/l, 1 to 2 cups a day) or as powder (1 to 4 g)
- as febrifuge: powder: 15 to 50 g
- for haemorrhoids: medicinal wine: 30 to 60 g/l of white wine; tincture 250 g/l of alcohol (1 tablespoon /day)

Horse chestnut bark was mentioned in the French Pharmacopoeia in 1866.

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

The current indications are:

- In France [Cahiers de l'Agence n°3 (AFSSAPS 1998)]:

Traditionally used in the symptomatic treatment of functional disorders of cutaneous capillary fragility, such as ecchymosis, petechias, etc.

Traditionally used in subjective signs of venous insufficiency, such as heavy legs.

Traditionally used in haemorrhoidal symptoms.

- In Spain:

Relief of symptoms of discomfort and heaviness of legs related to minor venous circulatory disturbances.

Relief of the symptoms associated with haemorrhoids.

- In Poland:

Adjuvant in oedemas, small bruises, limited skin and subcutaneous tissue inflammations.

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

Posology for "traditional herbal medicines":

Oral use:

Powder: 300 mg 2 times daily (Spain)

275 mg 3-6 capsules (= 1650 mg) daily, if necessary (France)

Dry extract (solvent water, DER 5-6: 1): 200 mg of extract 2 times daily

Cutaneous use:

Warm compresses (decoction 4 g in 400-500 ml of water) (Poland)

3. Non-Clinical Data

Non-clinical strategy

Online databases were used to research the available non-clinical data on extract of bark of horse chestnut or its relevant constituents. Only few articles about the non-clinical properties (pharmacology, pharmacokinetics, toxicology) of 'horse chestnut bark extract' were found in Medline.

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

Pharmacodynamics

The main pharmacological activity of horse chestnut bark is its venotonic activity (Leung & Foster 1996; Fleurentin 2008). It can increase the vascular resistance and decrease the capillary permeability (Fleurentin 2008; Ollier 2000; Girre 1997; Bézanger-Beauquesne *et al.* 1980). It is also reported to have an anti-inflammatory activity (Leung & Foster 1996).

The pharmacodynamic properties of horse chestnut bark extract or some of its constituents were investigated in the published literature (see Table 1).

Table 1: Summary of pharmacodynamics studies

Study reference	Test preparation	Test system	Main findings
Felixsson *et al.* 2010	Dry hydroalcoholic extract (plant part not specified), Bernett, Milan	<u>Contraction of vessels</u> Rings of bovine mesenteric veins and arteries. Pre-incubation of horse chestnut extract (concentration range 0.1 – 10 mg/ml) with or without various inhibitors (COX inhibitor indomethacin, 5-HT_{2A} receptor antagonist ketanserin, α1-receptor antagonist prazosin, angiotensin AT1 receptor antagonist saralasin). <u>Platelet aggregation</u> Human platelet-rich plasma incubated with horse chestnut extract (one tested concentration: 1 mg/ml), with or without ketanserin or ADP.	<u>Contraction of vessels</u> Concentration dependent contraction of veins and arteries with veins being more sensitive than arteries. Significant inhibition of contraction in both veins and arteries only in presence of ketanserin. <u>Platelet aggregation</u> Reduction of ADP-induced platelet aggregation by horse chestnut extract. Further reduction in the presence of ketanserin. Comment on specificity (one concentration tested only)
Senatore *et al.* 1989	Petrol extract of branch bark of Horse Chestnut	<u>Rat paw oedema model</u> Carrageenan-induced oedema male Wistar rats Only one mentioned dose of horse chestnut Oral route	Oral administration of the petrol extract dissolved in 5% arabic gum inhibits development of carrageenan-induced oedema into the paw of rats and produced a 30% inhibition of control oedemas at dose of 100 mg/kg. => Anti-inflammatory activity

Study reference	Test preparation	Test system	Main findings
Tubaro *et al.* 1988	Esculetin (6,7 dihydroxycoumarin) extracted from the bark of Horse Chesnut	Croton oil ear test Induction of cutaneous inflammation by application of croton oil in acetone to the inner surface of the right ear of male CD-1 mice, left ear being the control. Esculetin dissolved in the inflammatory inducing solution and applied to the ear (0.84, 1.17 and 1.68 µmol/ear) Assessment of granulocytes infiltration by measuring peroxidase activity. Acetylcholine-writhing test i.p. injection of acetylcholine in mouse producing an abdominal constriction response as a basis for testing analgesic drug.	Croton oil ear test Significant concentration-dependant reduction in oedema after 6 and 24 hours. (qualified by author as 'dose'dependant') Lower neutrophil infiltration in esculetin-treated tissues. Acetylcholine-writhing test ID_{50} = 69 mg/kg
Sekiya *et al.* 1982	Esculetin (Sigma) Esculin (Tokyo Kasei Co.)	Inhibition of platelet cyclooxygenase and lipoxygenase in rat blood Preincubation of sonicated platelets from rat blood with esculin and then with [1-^{14}C]arachidonic acid. Analysis of radioactive metabolites. Metabolites identification by GC-MS.	Esculetin IC_{50} Lipoxygenase: 0.647 µM Cyclooxygenase: 447 µM Esculin IC_{50} Lipoxygenase: 287 µM Cyclooxygenase: >10^4 µM => Anti-inflammatory activity and inhibition of platelet aggregation may be due to inhibition of lipoxygenase. =>Inhibition of lipoxygenase and stimulation of cyclooxygenase by esculetin may be due to radical scavenging.

Study reference	Test preparation	Test system	Main findings
Ambrogini *et al.* 1995	Proanthocyanidin-A2 obtained from the bark of Horse Chestnut	<u>Observation of peripheral nerve regeneration</u> Four groups of SD male rats: - Non treated undenervated - Non treated denervated - Treated undenervated - Treated denervated i.p. administration of 20 mg/kg/day of Proanthocyanidin-A2 for 6 days a week from the day after surgery until the day before death for denervated rats and for 20 days from the 45th day of age for undenervated rats.	No difference in behaviour or body weight between control and treated groups. No difference in the time course of muscle reinnervation between control and treated groups. Increase in muscle mass in denervated and undenervated treated rats compared to controls and increase in their contraction force. => trophic effect on muscle
Kaneko *et al.* 2003	Esculin Esculetin (Aldrich)	TIG-7 cells cultured with Earle's solution containing LOOH and/or $FeCl_3$. Esculetin was concurrently added or cells were pretreated with esculin or esculetin (50 µM). Quantitation of 8-oxodG in DNA by electrochemical detection.	Cotreatment of the cells with esculetin suppressed the formation of 8-oxodG by LOOH and iron(III) ion. When TIG-7 cells were pretreated with esculetin, esculetin exhibited a suppressive effect on the formation of 8-oxodG in cells treated subsequently with LOOH and iron(III) ion. Esculin also had a suppressive effect on the increase in 8-oxodG content but the effect was not significant.

Study reference	Test preparation	Test system	Main findings
Cals-Grierson 2007	Extracts of Horse Chesnut tree bark (PA2 Affilene®, Indena SpA, Milan, Italy) (Solvent non mentioned)	Modulation of activity of the adipocyte aquaglyceroporin channel Induction of expression of aquaglyceroporin (AQP) in human and mouse adipocytes. Stimulation of release of glycerol by addition of adrenaline. Evaluation of glycerol elimination due to plant extracts (Horse chestnut bark: 4, 20 and 100 µg/ml)	No stimulatory effect on glycerol release. Slight inhibitory effect when co-stimulation with adrenaline (inhibition of 22%, 4% and 10% with 4, 20 and 100 µg/ml respectively).

Additionally, data from reviews are also available:

Bombardelli published a review in 1996 where pharmacological properties of some of horse chesnut extract constituents were extensively reported.

Proanthocyanidin A2 exerts a venotonic activity normalising conditions of impaired capillary permeability and fragility. It increased capillary resistance in comparison to control and trihydroxyethylrutoside-treated rats.

Proanthocyanidin A2 was demonstrated to stimulate the processes of healing; it had a stimulating activity on the healing process by measurement of wound scar resistance in mice. It also showed wound healing activity in prednisone-treated rats after a topical or oral administration.

It also has antioxidant and antienzymatic activity. *In vitro*, it was able to inhibit all the stages of the peroxidative phenomenon in a dose-dependent manner. It inhibited the activity of some proteolytic enzymes (β-glucuronidase, elastase, collagenase) (Bombardelli *et al.* 1996).

Esculin has vasoprotective effects. It improves capillary permeability and capillary fragility. The capillary resistance was increased in guinea pigs treated with 1 mg/day of esculin compared to those on a diet of gray oats plus ascorbic acid.

It inhibits enzymes like hyaluronidase and collagenase.

In mice and rats, esculin and esculetin showed analgesic and antipyretic activities. Esculin also possesses an anti-inflammatory activity in the UV-induced erythema in animals and humans (Bombardelli *et al.* 1996).

Esculetin is known as a 5-lipoxygenase inhibitor that inhibits the production of leukotrienes and 5-hydroxyeicosatetraeinoic acid through lipoxygenase pathway. It shows scavenging activity against ROS and inhibits lipoperoxidation in rat liver (Kaneko *et al.* 2003).

Esculetin and esculin in a lesser extent exhibited suppressive effect on the formation of 8-oxodeoxyguanosine (8-oxodG) (Kaneko *et al.* 2003).

Safety pharmacology

No data about safety pharmacology are available.

Herb-Drug interactions

Herbs with coumarins, salicylate or with antiplatelet properties are suspected to potentially interfere with warfarin because of a theoretical risk of potentiation of anticoagulant activity. No direct experimental or clinical evidence is available. However, it has been recommended that patients taking horse chestnut extracts concurrently with medications that have anticoagulant effects, such as warfarin, should be closely monitored for signs of symptoms of bleeding (Heck *et al.* 2000).

No clinical cases have been reported.

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

No information about pharmacokinetics of horse chestnut bark extract is available.

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

Acute toxicity

Acute toxicity of esculetin (6,7-dihydroxycoumarin) extracted from the bark of *Aesculus hippocastanum* was tested in mouse after an intraperitoneal and oral administration. The intraperitoneal LD_{50} was 1450 mg/kg and the oral LD_{50} was > 2000 mg/kg (Tubaro *et al.* 1988). Acute toxicity of esculin was tested intraperitoneally in mice. The LD_{50} was 1900 mg/kg (RTECS 2010).

Repeat toxicity

No data available.

Genotoxicity

Esculin was screened on 6 Ames strains (TA92, TA94, TA97, TA98, TA100 and TA102) at 4 concentrations ranging from 0.2 to 500 µg/plate with or without S9. It was not mutagenic (Uwaifo 1984).

It should be pointed out that, in the quoted study, esculin was extracted from a Nigerian medicinal plant, *Afraegle paniculata* (Uwaifo 1984). Therefore, the relevance of this study for the safe use of horse chestnut bark preparation is doubtful.

Carcinogenicity

No conventional carcinogenicity study is available.

3.4. Overall conclusions on non-clinical data

Very few studies about horse chestnut bark preparations were found in the literature. No representative preparation can be defined.

Pharmacology

Effects on blood vessels
Horse chestnut bark has a venotonic activity. It produces a dose-dependent contraction of veins and arteries but its action is more pronounced on veins, possibly through an action on 5-HT_{2A} receptors. It increases vascular resistance and decreases capillary permeability. This activity can be due to proanthocyanidin A2 and esculin.

Anti-inflammatory activity
In vivo, horse chestnut bark exerted an anti-inflammatory activity in the rat paw oedema model after oral administration of a petrol extract.

Esculetin extracted from horse chestnut bark demonstrated an activity in the croton oil ear test in mice and the acetylcholine-writhing test in mice.

Esculin is reported to have an anti-inflammatory activity in the UV-induced erythema.

The anti-inflammatory activity may be due to the inhibiting properties of esculetin and esculin toward lipoxygenase.

Effects on platelet aggregation
Horse chestnut extract decreases ADP-induced platelet aggregation but the experiment was conducted with a single concentration of horse chestnut bark. Therefore, the specificity of the reaction is doubtful.

It could be linked to the inhibition of lipoxygenase. Esculetin induced a stimulation cycloxygenase activity at low concentrations and inhibition at higher concentration. The mechanism remains unclear.

Anti-oxidant and anti-enzymatic activity
Constituents of horse chestnut bark preparation (proanthocyanidin A2, esculetin and esculin) are reported to have anti-oxidant properties through inhibition of the peroxidation and some enzymes activity (β-glucuronidase, elastase, collagenase, hyaluronidase, 5-lipoxygenase) or a scavenging activity against ROS.

Effects on healing
Proanthocyanidin A2 was demonstrated to have a trophic activity on muscle and to stimulate healing process.

No safety pharmacology data were available.

Pharmacokinetics

No pharmacokinetics data about horse chestnut bark preparation were available.

Toxicology

The acute toxicity of esculin and esculetin is low.

No other toxicity data was available.

In conclusion, the literature about non-clinical studies with horse chestnut bark preparation is sparse.

However, based on the data found, the venotonic activity of horse chestnut bark seems to be established.

No relevant non-clinical safety data are available.

4. Clinical Data

4.1. Clinical Pharmacology

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

No clinical pharmacodynamic data are available.

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

No clinical pharmacokinetic data are available.

4.2. Clinical Efficacy

The clinical efficacy is supported by the traditional use of the preparation. No clinical study or case study reports can be found to illustrate the clinical efficacy.

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

No clinical data are available. Only the use in folk medicine is mentioned in published literature.

- **Use as febrifuge**:

Horse chestnut bark was used in 1720 by 3 physicians with a posology of 8 g 3 or 4 times daily. More than 20 cases of intermittent fever recovery were published in 1763. However, its use as substitute of cinchona was ruled out (Cazin 1868).

The minor efficacy as febrifuge, with a high dosage of 15 to 50 g of powder /day as it was used in 1809, has been mentioned (Fournier 1948).

- **Use in venous circulatory disorders**:

Horse chestnut bark was effective for varicose veins, phlebitis and haemorrhoids, due to its vitamin properties, and it was used for capillary fragility (Boullard 2001).

Horse chestnut bark was very effective for the treatment of varicose veins and haemorrhoids. It soothed pain and stopped to spit blood from the internal varicose veins (Fournier 1948).

Horse chestnut bark contains flavonoids and coumarins (esculin); these constituents are active on capillary fragility (Paris & Moyse 1981).

Horse chestnut bark was very used as venous tonic and for the prevention of vascular disease (Paris & Moyse 1981).

Horse chestnut had an important vitamin P activity due to the presence of coumarins (esculin) (Bézanger-Beauquesne *et al.* 1980).

- **Use in diarrhoea**:

Horse chestnut bark was used for the treatment of diarrhoea due to its tannins content (powder 1 to 4 g daily, decoction, wine 30 to 60 g/l) (Garnier *et al.* 1961).

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

No data available.

4.3. Overall conclusions on clinical pharmacology and efficacy

Assessor's comment:

The clinical efficacy of *Aesculus hippocastanum* bark preparation relies only on the traditional use. No pertinent clinical efficacy data can be found in the literature to support the claimed indications. Only few publications mention the use of horse chestnut bark in folk medicine and contribute to demonstrate the plausibility of the traditional use given the link between its constituents and the attributed indications.

5. Clinical Safety/Pharmacovigilance

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

No data available.

5.2. Patient exposure

No data available.

5.3. Adverse events and serious adverse events and deaths

In terms of using horse chestnut in general by oral or intravenous route, three main types of side effects have been reported:

- Kidney failure: Kidney failure has been documented in children and adults after receiving injections of escin, and in adults after taking high doses of escin (Chandler 1993; Hellberg *et al.* 1975; Klose & Pistor 1976)
- Liver damage: Liver damage has been documented in one person after the intramuscular injection of a product containing horse chestnut (Tagegoshi *et al.* 1986)
- Allergic reactions: An allergic reaction has been documented in one person after the rectal administration of a product for the treatment of haemorrhoids that contained esculin (Comaish & Kersey 1980)
- There is one report of a person experiencing a severe allergic reaction (anaphylactic shock) after the injection of a horse chestnut extract (Farah *et al.* 2000)

Aesculin poisoning in humans is manifested by symptoms of muscle weakness, lack of coordination, dilated pupils, diarrhoea and vomiting, paralysis and stupor (Nagy 1973).

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

No specific data are available on use in pregnancy and lactation, overdose, drug abuse, withdrawal and rebound, effects on ability to drive or operate machinery or impairment of mental ability. However, as safety during pregnancy and lactation, and in children and adolescents has not been established, the use of horse chestnut bark in these special populations should be avoided.

5.6. Overall conclusions on clinical safety

The specific safety of *Aesculus hippocastanum* bark preparation cannot be established due to the lack of published data. Due to the presence of aesculin in the bark, it could be assumed that the described adverse events with the different preparations could apply. However, the long term traditional use of oral forms is in favour of their good tolerance in the target population and in the recommended range of dose.

Clinical safety data are very limited. However, no safety problems concerning the traditional use of horse chestnut or its preparations have been reported.

In addition, due to lack of data, the use during pregnancy and lactation, and in children and adolescents under 18 years of age is not recommended.

In other situations, horse chestnut bark preparations are not harmful when used in the recommended dosages for the specified indications.

6. Overall conclusions

In conclusion, due to its long-standing use and based on the available documentation, only a traditional use can be granted for horse chestnut bark. Only the preparation which has been used for at least 30 years including at least 15 years in the European Union is described in the monograph.

To be in compliance with the wording validated in other monographs (e.g. monographs on *Aesculus hippocastanum* L., semen; *Melilotus officinalis* L., herba; *Hamamelis virginiana* L., folium; *Ruscus aculeatus* L., rhizoma), the monograph information should remain limited to the traditional use to “relieve symptoms of discomfort and heaviness of legs related to minor venous circulatory disturbances” and “for symptomatic relief of itching and burning associated with haemorrhoids”.

As there are no clinical studies conducted with horse chestnut bark in children and adolescents under the age of 18 years, horse chestnut bark should not be used in this target population and should be limited to adults and elderly.

Given that no reproductive toxicity studies have been conducted and there are no data from the use of horse chestnut bark in pregnant women, section 4.6 of the monograph is adapted accordingly and in compliance with the wording validated in other monographs.

The therapeutic area of the two indications is: venous circulatory disorders.

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

Annex

List of references