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Evaluation of Medicines for Human Use

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**COMMITTEE ON HERBAL MEDICINAL PRODUCTS
(HMPC)**

**ASSESSMENT REPORT ON
HAMAMELIS VIRGINIANA L., CORTEX
HAMAMELIS VIRGINIANA L., FOLIUM
*HAMAMELIS VIRGINIANA L., FOLIUM ET CORTEX AUT RAMUNCULUS DESTILLATUM***

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I. REGULATORY STATUS OVERVIEW

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 ¹
Austria	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Medicinal products
Belgium	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combinations
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 Med. Products
Denmark	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Medicinal products
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No Med. Products
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No Med. Products
France	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Germany	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No Med. Products
Hungary	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No Med. Products
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Ireland	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Medicinal products
Italy	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Medicinal products
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combinations reg.
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 type="checkbox"/> Other Specify:	
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:	
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:	
Portugal	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Medicinal products
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:	
Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Spain	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Medicinal products
Sweden	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
United Kingdom	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> 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.

¹ Not mandatory field

Austria: Ointment containing per 1 g, 50 mg of liquid extract (1:1), extraction solvent ethanol 45% V/V; Aqua Hamamelidis cooling gel.

Belgium: For oral use (herbal tea), authorisation date 1961-1962; no clear indication
For rectal use (suppositories): authorisation date 1965 (combination with lidocaine, triclosan...): indication: hemorrhoids
For cutaneous use (ointments): authorisation date 1961-1962 (combination with *Aesculus*, local anaesthetic, antiseptic, *Viburnum*, ...) : indication : hemorrhoids, “protective” , bleeding nose..

Czech Republic: there is not registered any herbal medicinal product containing *Hamamelis*

Denmark: *Hamamelis virginiana* L., fresh leaf and twig distillate (water steam distillate) (1:1.6); 0.5 g extract (HEL)/100 g ointment

Estonia: No medicinal product containing hamamelidis folium is authorised in.

Finland: No herbal medicinal product containing *Hamamelis*.

Germany:

Hamamelidis folium: WEU (In the market at least since 1976).

For adults and adolescents over 12 years old.

- 1) Liquid extract (1:1), extraction solvent ethanol 45% V/V. Ointment, containing 50 mg of liquid extract per 1 g of ointment. For cutaneous use 1 string of ointment 2-3 times daily.
For treatment of small skin lesions and minor inflammation of the skin. For relief of disorders in the beginning of haemorrhoids disease.
- 2) Liquid extract (1:1), extraction solvent ethanol 30% m/m. Gel, containing 2.5 g liquid extract per 25 g of gel. For cutaneous use. 1 string of ointment several times daily. For supporting treatment of superficial skin lesions.
- 3) Liquid extract (1:2), extraction solvent ethanol 60% V/V. Suppositories, containing 400 mg of extract. For rectal use. 1 Suppository two times daily. For relief of disorders as: itching, burning, slight bleeding in haemorrhoids grade I and II.
- 4) Liquid extract (1:2), extraction solvent ethanol 60% V/V. Ointment, containing 200 mg liquid extract per 1g ointment. For cutaneous use: 1 string of ointment two times daily. For relief of itching, weeping and burning in the beginning of haemorrhoids disease as soon as inflammation (i.e.: anal-eczema) and superficial skin lesions in the anal region.
- 5) Liquid extract (1:2), extraction solvent ethanol 60% V/V. Suppositories, containing 400 mg of extract. For rectal use. 1 suppository two times daily, in case of heavy discomfort temporarily 1 suppository three times a day. For relief of: itching, weeping and burning in the beginning of haemorrhoids disease as soon as inflammation of mucosa in the anal region.

Risks: 1-5): In many cases a short irritation and slight burning is possible. Very seldom allergic reaction could occur.

The products are in the market as authorised products. No pharmacovigilance actions taken on medicinal products containing the herbal substance.

The Herbal substance (*Hamamelidis folium*) is only available in combination products. There are 6 authorised products 4 (2-3 ingredients); 1 (4-5) and 1 >5.

There is also 1 German Standard Marketing Authorisation product. A herbal tea (single ingredient) for the preparation of poultices, for gargling and for rinsing of the oro-pharynx. For supporting treatment in superficial skin lesion at minor inflammation of the skin and mucosa.

Hamamelidis destillatum: WEU (1-2) In the market since 2007; 3-5) at least since 1976). For adults and adolescents over 12 years old.

1-5) Distillate of fresh *Hamamelis virginiana* L. leaves and branches (1:1.12-2.08), distillation agent ethanol 6% m/m.

- 1), 2) and 4) Ointment, 100 g of ointment containing 6.25 g distillate, for cutaneous and mucosal use. Several times daily, thinly to the affected regions. Minor skin lesions, minor inflammation of skin and mucosa. For relief of disorders in the beginning of haemorrhoids disease.
- 3) Liquid, 100g (=102 ml) containing 25 g distillate. For cutaneous use: apply several times daily undiluted to the affected regions. For oromucosal use: In case of gums bleeding add 1 measuring spoon (=5 ml) liquid to the mouthwash. Minor skin lesions and inflammation of skin and gums.
- 5) Cream, 100 g containing 5.35 g destillate. For cutaneous and mucosal use. Apply several times daily at regular intervals thinly to the affected regions. Superficial skin lesions, minor inflammation of skin and mucosa.

Risks: 1-5): In many cases a short irritation and slight burning is possible. Very seldom allergic reaction could occur.

The products are in the market as authorised products. No pharmacovigilance actions taken on medicinal products containing the herbal substance.

There is also 1 product in combination (2-3 ingredients).

Hamamelidis cortex: WEU (1-2) In the market at least since 1976). For adults and adolescents over 12 years old.

- 1) Ointment, containing 129 mg dry extract per 10 g ointment. Dry extract (5-7.7:1), extraction solvent ethanol 30% m/m. For cutaneous use 1 string of ointment of 1-2 cm length, 2-3 times a day. For amelioration of disorders as itching, burning, slight bleeding in haemorrhoids disease, grade I and II and inflammation, and slight skin lesion at the anus.
- 2) Suppository, containing 66 mg dry extract. Dry extract (5-7.7:1), extraction solvent ethanol 30% m/m. For rectal use 1 suppository 3 times daily. For amelioration of disorders as itching, burning, slight bleeding in haemorrhoids disease grade I and II. Inflammation and slight skin lesion at the anus.

Risks: 1-2): In many cases a short irritation and slight burning is possible. Very seldom allergic reaction could occur.

The products are in the market as authorised products. No pharmacovigilance actions taken on medicinal products containing the herbal substance.

The Herbal substance (Hamamelidis cortex) is only available in combination products. There are 3 authorised products (2-3 ingredients).

There is also 1 German Standard Marketing Authorisation product. A herbal tea (single ingredient) for the preparation of poultices, for gargling and for rinsing of the oropharynx. For supporting treatment in superficial skin lesion at minor inflammation of the skin and mucosa.

Greece: There is not registered any herbal medicinal product containing *Hamamelis*

Hungary: No herbal medicinal product containing *Hamamelis*.

Ireland: Four products which contain hamamelis distillate of fresh *Hamamelis virginiana* L. leaves and branches (1:1.12-2.08), distillation agent ethanol 6% m/m. authorised as medicines in Ireland and one adverse reaction has been reported [i.e. conjunctivitis case associated]. No 'herbal' products have been authorised containing it though!

Italy: Cream, 100 g containing 5.35 g distillate (1:1,6); Distillate of fresh *Hamamelis virginiana* L. leaves and branches (1:1.12-2.08), distillation agent ethanol 6% m/m.

Latvia: Only combinations.

Spain: Cream, 100 g containing 5.35 g distillate (1:1,6); Distillate of fresh *Hamamelis virginiana* L. leaves and branches (1:1.12-2.08), distillation agent ethanol 6% m/m.

II. ASSESSMENT REPORT

Hamamelis virginiana L cortex
Hamamelis virginiana L., folium
Hamamelis virginiana L., folium et cortex aut ramunculus destillatum

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)	<p><i>Hamamelis virginiana</i> L., cortex (hamamelis bark) <i>Hamamelis virginiana</i> L., folium (hamamelis leaf) <i>Hamamelis virginiana</i> L., folium et cortex aut ramunculus destillatum (leaf and bark distillate and twigs distillate)</p>
Herbal preparation(s)	<p>Dried comminuted bark, for tea preparation Dried or fresh comminuted leaf, for tea preparation Hamamelidis distillate (1:1.6) ethanol 12%-15% Hamamelidis distillate (1:1.12-2.08) ethanol 6% m/m Tincture (1:10) ethanol 45% V/V (leaf) Liquid extract (1:1) ethanol 30% m/m (leaf) Liquid extract (1:1) ethanol 45% V/V (leaf) Liquid extract (1:1) ethanol 60% V/V (leaf) Liquid extract (1:2) ethanol 60% V/V (leaf) Tincture (1:10) ethanol 45% V/V (bark) Dry extract (5-7.7:1) ethanol 30% m/m (bark)</p>
Pharmaceutical forms	<p>Semi-solid herbal preparation for cutaneous or for rectal use. Suppositories liquid dosage forms for ocular use (eye drops) oromucosal use (gargle).</p>
Rapporteur	Gloria García Lorente

II.1 INTRODUCTION

The aim of this report is to assess the available information on the herbal substances of *Hamamelis virginiana* L., bark, leaf and twigs and preparations thereof for the categorisation as products under well-established use or traditional use and the establishment of the corresponding Community herbal monographs.

This report is based on a scientific systematic review of the literature (mainly on efficacy and safety) of *Hamamelis virginiana* L. and the documentation provided by the European Medicines Agency completed by additional searches in biomedical databases and the available articles from references included in monographs on *Hamamelis virginiana* L. (Commission E Monographs, 2001; ESCOP, 2003; WHO, 2002), as well as the information provided by Member States.

MEDLINE (1960-2005); TOXNET (Toxline; HSDB); Pubmed Excerpta Medica and Micromedex databases have been used mainly for bibliographic searches. Due to the limited number of references obtained, the final strategy for the search was: “Hamameli* or witch hazel”.

This assessment report refers to preparations of *Hamamelis virginiana* L. as a single ingredient, while studies performed with combinations are not discussed.

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

Hamamelis virginiana L. (synonym: witch hazel) is a plant of the *Hamamelidaceae* family. It is a deciduous, tall shrub, or small tree, branches highly branched, indigenous to the Atlantic coast of North America, found in damp woods ranging from Nova Scotia to Florida and as far west as Texas. It is cultivated on a small scale in Europe, though the material of commerce is obtained mainly from the eastern USA and Canada (Wichtl and Bisset, 1994).

The flowers, bark and leaves of the common, colourful American witch hazel shrub provided tonics and remedies to Native Americans. Today, natural witch hazel is considered as one of the few plant products that meet FDA standards for safety and effectiveness. The plants of the genus *Hamamelis* are unusual because they bear their blossoms and fruits together, at the very same time of the year, usually in autumn or winter. Flowers of *Hamamelis virginiana* L. are ribbon-like clusters of yellow, orange, or red petals; the adjacent seed capsules, from the previous year’s blossoms, which eject two black seeds when they burst.

According to Laux (1993), *Hamamelis virginiana* L. has the following synonyms: *Hamamelis macrophylla* Pursh, *H. androgyna* Walt, *H. coryfolia*, *H. dioica*, *Trilopus dentate*, *T. nigra*, *T. rotundifolia*, and *T. virginiana*.

Hamamelis bushes are very similar in appearance to the hazelnut (*Coryllus avellana*), which can also lead to confusion during harvesting period. The two plants can be distinguished anatomically and analytically.

• Herbal substances²

“Hamamelidis folium” consists of the dried or fresh leaves of *Hamamelis virginiana* L. It contains not less than 3% of tannins, expressed as pyrogallol (C₆H₆O₃; M_r 126.1) and calculated with reference to the dried drug. The material complies with the monograph of the European Pharmacopoeia 6.1, [monograph (04/2008:0909)]. Leaves are about 7 to 15 cm long, brittle, dark green or brownish-green, alternate, stipulate, broadly oval or rhomboid ovate; short-petiololed about 1 to 1.5 cm long, margin coarsely crenate or sinuate, apex acute or rounded, base cordate and unequal and venation pinnate, lateral veins straight,

³ According to the ‘Procedure for the preparation of Community monographs for traditional herbal medicinal products’ (EMA/HMPC/182320/2005 Rev.2) and the ‘Procedure for the preparation of Community monographs for herbal medicinal products with well-established medicinal use (EMA/HMPC/182352/2005 Rev.2)

prominent on the under surface, each ending in a marginal crenation; trichomes stellate, scattered or under surface, numerous on young leaves. Flowers thread-like, golden-yellow; appear in axillary clusters as leaves fall in autumn and at about the same time as fruits ripen from blossoms of the previous year.

“Hamamelidis cortex” consists of the dried bark from the stems, branches and twigs of *Hamamelis virginiana* L. (Fam. *Hamamelidaceae*), collected in spring. It contains not less than 4.0% of hide-powder precipitable tannins, expressed as pyrogallol (C₆H₆O₃; M_r 126.1) and calculated with reference to the dried drug.

Stems and fruits are present in small amounts; stems pale reddish-brown or greyish-brown, smooth or slightly warty and up to about 4 mm thick, with alternate leaf scars; fruit a woody capsule, about 15 mm long when mature, splitting at the apex into 2 halves each containing a single black seed. Odour is not marked; the taste is bitter and astringent.

“Hamamelidis ramunculus (twigs)” have structures called buds, leaf scars and bundle scars that can differ for different species. Hamamelis twig is the herbal substance used in the preparation of hamamelis water, or as Witch Hazel as described in USP monograph.

Chemical constituents of herbal substances

The leaf contains 3-10% tannins (a mixture of catechins, gallotannins, plus cyanidin and delphinidin type proanthocyanidins), mainly hamamelose (Wichtl, 1989); catechins, mainly (+)-catechin, (+)-gallocatechin, (-)-epicatechin gallate, (-)-epigallocatechin gallate; phenolic acids (caffeic and gallic acids); flavonoid galactosides and glucuronides; flavonoids such as kaempferol, quercetin, quercitrin, and isoquercitrin (Hänsel et al, 1993; ESCOP, 1997; Sagareishvili, TG. et al., 1999; Kaul, R et al. 2001). 0.01-0.5% volatile oil (Meyer-Buchtela, 1999; Wichtl, 1989), among which 40% are aliphatic alcohols, 25% carbonyl compounds, 15% aliphatic esters, and a maximum of 0.2% safrol (Wichtl and Bisset, 1994). According to Hager, the leaves contain a small amount of hamamelitannin. The “hamamelin” reported in the literature for witch-hazel leaf is a preparation obtained by precipitating a concentrated alcoholic extract of powdered leaves.

Witch hazel bark contains 8-12% tannins (minimum content recommended of 4% tannins). Cortex tannins are qualitatively similar to folium tannins, but have a higher content of hamamelitannin (1-7%), followed by monogalloylhamamelose, free gallic acid, condensed catechin tannins, and small amount of flavonols; approximately 0.1% volatile oil with a very complex composition (Hänsel et al, 1993; Wichtl, 1996; Meyer-Buchtela, 1999; Wang et al, 2003). The bark contains significantly higher levels of phenylpropanoids and sesquiterpenoids in the volatile fractions compared to the leaves, which contain higher amounts of monoterpenoids. The bark is richer in hydrolysable tannins and the leaves mainly contain condensed tannins.

• Herbal preparations

Herbal preparations are obtained from dried or fresh leaves and/or the dried bark of the trunk and twigs of *Hamamelis virginiana* L. (Fam. *Hamamelidaceae*). The following herbal preparations have been proposed by Member States or cited in the literature search:

Dried comminuted herbal substance, for tea preparation (decoction), official in the standard license monographs (Banz, 1998; Braun et al, 1997; DAC, 1986; Wichtl and Bisset, 1994) and German Drug Codex (1986). Herbal tea preparation (decoction) 5-10 g/250 ml or 2-3 g/150 ml (decoction 10-15 min).

Powdered herbal substance (a green to greenish-brown powder possessing the diagnostic microscopic characters, odour and taste of the crude drug as described in the European Pharmacopoeia).

Tincture (1:10; ethanol 60%)

Tincture (bark) (1:10; ethanol 45% V/V)

Tincture (leaf or bark) (1:10; ethanol 45% V/V)

Tincture (leaf) (1:10; ethanol 55% V/V)

Liquid extract (leaf) (1:1; ethanol 30% m/m).

Liquid extract (leaf) (1:1; ethanol 45% V/V).

Liquid extract (leaf) (1:1; ethanol 60% V/V).

Liquid extract (1:2; ethanol 60% V/V).

Liquid extract (leaf) (1:3), extraction solvent ethanol 62% V/V (Gracza, 1987)

Dry extract (cortex) (5-7.7:1; ethanol 30% m/m).

Hamamelis water (Hamamelis distillate): Aqua hamamelidis. Distilled Witch Hazel; Witch Hazel USP; Liquor Hamamelidis. Several preparations, similar but not equivalent, obtained from different processes and called with different names are referring to hamamelis water.

Leaves, bark and twigs collected in spring are used for the production of water distillates. Aqua hamamelidis is a clear colourless liquid; the odour is characteristic. Their acidity or alkalinity is neutral or slightly acid to litmus solution. Its weight per ml at 20°C is 0.976 g to 0.982 g. The residue on evaporation, not more than 0.025% w/v, the residue being dried to constant weight at 105°C. The alcohol content is from 13 to 15% v/v of ethyl alcohol, determined by the method included in BP Codex.

Preparations:

- Distillate of fresh *Hamamelis virginiana* L. (leaves and branches) (1:1.12-2.08), distillation agent ethanol 6% m/m. Used as an ointment with 100 g of ointment containing 6.25 g distillate.
- Distillate prepared from dried twigs (1:2; ethanol 14-15% v/v).

Chemical constituents of hamamelis preparations.

Polyphenols

Tannins are a broad class of complex phenolic compounds of molecular weight between 500 and 3000. The biological importance of tannins is attributed to their ability to bind and precipitate mainly proteins but also alkaloids. Tannins have been defined as “phenolic natural products that precipitate proteins from their aqueous solutions”. There are two types of tannins, the hydrolyzable tannins, which, upon acidic, alkaline, or enzymatic hydrolysis produce glucose and phenolic acids; and the condensed tannins (proanthocyanidins), which are flavan-3-ol polymers. Condensed tannins can occur as galloyl esters.

Hydrolyzable tannins are polyesters of glucose, and upon hydrolysis, they release the sugar, and either gallic acid, hexahydroxydiphenic acid, or both, the latter acid rapidly lactonizes to ellagic acid (which explains the traditional terminology of ellagitannins). Oligomer hydrolysis also yields compounds with three or four aromatic rings, whose structures vary depending on the nature of the bond between monomers.

Tannins are generally extracted with a water and acetone mixture. The polymeric proanthocyanidins and high molecular weight gallotannins remain in the aqueous phase.

The therapeutic activity of tannins is mainly due to the astringency, and result from their affinity for proteins. Externally, they waterproof the external layers of the skin and mucosae, thus protecting the underlying layers; they also have a vasoconstrictor effect on small superficial vessels. By limiting fluid losses, tannins enhance tissue regeneration in case of superficial burn or wound.

Generally speaking tannins are enzyme inhibitors. They block 5-lipoxygenase; they inhibit angiotensin converting enzyme, hyaluronidase activation, and the glucosyl-transferases of microorganisms involved in the formation of cavities; ellagitannins and complex tannins inhibit protein kinase C.

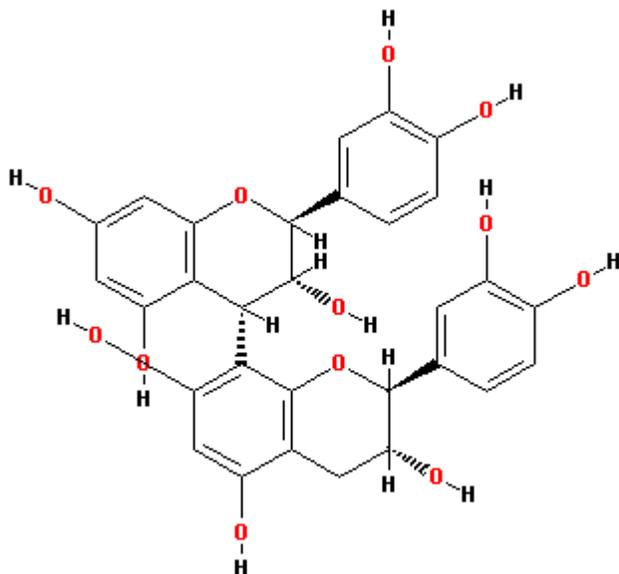
Tannins especially the hydrolysable ones inhibit the peroxidation induced by ADP and ascorbic acid in rat hepatic mitochondria. In vitro they are radical scavengers and inhibitors of superoxide ion formation, and some of them inhibit lipoxygenase in rat peritoneal granulocytes. (Bruneton 1999)

The main characteristic constituent of *Hamamelis virginiana* L. is hamamelitannin, a mixture of the α - and β - forms of (2', 5-di-O-galloyl-hamamelose), its molecular structure bears two gallate moieties and a sugar unit, hamamelose. Wang et al (2003) developed an HPLC method for the determination of hamamelitannin, catechins, and gallic acid from witch hazel bark, twig, and leaf. The concentrations in the bark for hamamelitannin, gallic acid, (+)-gallocatechin, and (+)-catechin were 4.77, 0.59, 0.22, and 0.39% (wt/wt), respectively. Hamamelitannin and catechins were also detected in the leaves at concentrations of < 0.04% (wt/wt).

Hamamelitanin

Proanthocyanidins are also present including: procyanidin dimers such as catechin-(4 α →8)-catechin, 3-O-galloyl-epicatechin-(4 β →8)-catechin and epicatechin-(4 β →8)-catechin-3-O-(4-hydroxy)benzoate; prodelfphinidins such as epigallocatechin-(4 β →8)-catechin, 3-O-galloyl-epigallocatechin-(4 β →8)-catechin and 3-O-galloyl-epigallocatechin-(4 β →8)-gallocatechin, and proanthocyanidin oligomers consisting of 4-9 catechin-gallocatechin units, some of which are 3-O-galloylated.

Other constituents include flavan-3-ols such as (+)-catechin, (+)-gallocatechin, (-)-epicatechin-3-O-gallate, and (-)-epicatechin-3-O-gallate, di- and tri-O-galloyl hamameloses and related 4-hydroxybenzoates, pentagalloylglucose, gallic acid and about 0.5% volatile oil. Hexen-2-ol, hexenol, α and β -ionones, eugenol, safrole and sesquiterpenes.



Epicatechin (4 β ->8) epicatechin (Procyanidin B2)

Polymeric proanthocyanidins were isolated from an acetone-water (7:3) extract from hamamelis bark in yields of about 5% by Dauer et al (2003), Touriño et al (2008). Terminal chain units were catechin and gallocatechin in a constant ratio of 95:5. All chain extension units were completely galloylated at position 0-3, while chain terminating units were not galloylated. Predominant interflavan linkages were 4→8-bonds.

According to Vennat et al (1992), proanthocyanidins, phenolic acids and flavonoids have been identified in leaf extracts. Ollivier et al (1992) studied on the biotransformation of polyphenols in *Hamamelis virginiana* L. leaves and had shown variations on the qualitative and quantitative determination of gallic acid and ethyl gallate in hamamelis leaves according to the extraction solvent used. In water, only gallic acid was present; both were found in solutions containing 10-70% of ethanol (m/m). For hydroalcoholic solutions up to 80% (m/m) their rate was negligible. Polyphenols are modified by conjugated action of enzymes and solvents. Gallic acid is produced by hydrolysis of tannins while ethyl gallate is an artifact obtained by esterification of gallic acid in hydroalcoholic solutions.

Hydroxycinnamic acids and flavonoids (e. g. myricetin, leucodelphinidin, quercetin, kaempferol, and gallic acid) are found mainly in the leaves of *Hamamelis virginiana* L. (Besset et al, 1986).

Phenolic compounds from leaves of *Hamamelis virginiana* L. were studied by Sagareishvili (1999), where kaempferol, quercetin, trifolin, kaempferol 3-O- β -D-glucuronide, quercetin 3-O- β -D-glucuronide were isolated.

Several pharmacological activities, including anti-phlogistic, antiviral (Erdelmeier et al, 1996), antimutagenic (Dauer et al, 1998) and cell proliferation stimulating effects (Deters et al, 2001) have been attributed to proanthocyanidins.

Volatiles

According to Engel et al, (1998), the composition of the volatile fraction obtained by water distillation from the leaves and bark of *Hamamelis virginiana* L., and determined in detail by GC-MS, consists in about 175 (leaves) and 168 (bark) identified compounds or at least partly characterized on the basis of a computerized database (SeKoMS). The dominating substances were represented by a homologous series of alkanes, alkenes, aliphatic alcohols, related aldehydes, ketones, and fatty acid esters. Significant differences in the terpenoid and phenylpropanoid patterns of the products obtained from the bark and leaves are apparent: whereas the product of bark distillation was found to typically contain phenylpropanoids and mainly sesquiterpenoids, that obtained from the leaves included some distinct monoterpenoids detected in comparably higher amounts. The chemical composition of the volatiles, when taken together with the absence of specific accumulation sites of lipophilics, emphasizes the definition "volatile fraction" rather than essential oil.

Reporting the same data, Engel et al (1998) stated "bark of young twigs" but Hartisch (1997) stated "young twigs tips were coarsely milled and then steam distilled". The volatile fraction (0.009% of the crude drug on the dry weight basis) contained about 160 compounds: aliphatic hydrocarbons (45.4% , of which nonacosane 6.9%, heptacosane 5.4%), sesquiterpenes (20.2% of which α -ylangene 11.1% , transnerolidol 2.73%) , monoterpenes (8.3%, of which linalool 2.0%), phenylpropanoids (7.5%, of which trans-anethole 3.3%, eugenol 2.4%), aldehydes (6.1%, of which nonanal 2.7%) and small amounts of many other compounds (British Herbal Compendium, 2006).

Literature data on the content of these components fluctuate between 0.01% and 0.5% referred to the leaf drug and 0.1% for the bark. Safrole was also found at a level of < 0.2% in hamamelis leaf oil.

The study of distilled water of *Hamamelis virginiana* L. permitted the identification of volatile components and relative changes under the effects of different storage conditions (Messerschmidt, 1971; Martelli et al, 1977, 1978 and 1979). Among identified compounds were phenylacetaldehyde, linalool oxide, guaiacol, and geranylacetone. Storage of the oil with addition of ethanol or storage at -20°C resulted in no changes in the oil.

- **Combinations of herbal substance(s) and/or herbal preparation(s)**

Hamamelis preparations are sometimes used in combinations with other herbal substances (herbal preparations), such as *Hydrastis canadensis* L., *Ruscus aculeatus* L., or *Aesculus hippocastanum* L.

This assessment report refers exclusively to the use of hamamelis preparations as single ingredient products.

- **Vitamin(s)**

Not applicable

- **Mineral(s)**

Not applicable

Pharmacopoeias' references

➤ *The European Pharmacopoeia (1997)*

There is a monograph on Hamamelidis folium in the European Pharmacopoeia (*Hamamelis leaf. Eur. Pharm 6.1, monograph 04/2008:0909*). The herbal substance consists of the whole or cut, dried leaf of *Hamamelis virginiana* L., containing minimum 3% of tannins, expressed as pyrogallol (C₆H₆O₃; M_r 126.1) (dried drug), and has the macroscopic and microscopic characters described under identification tests.

The leaf is green or greenish-brown, often broken, crumpled and compressed into more or less compact masses. The lamina is broadly ovate to obovate; the base is oblique and asymmetric and the apex is acute or, rarely, obtuse. The margins of the lamina are roughly crenate or dentate. The venation is pinnate and prominent on the abaxial surface. Usually, four to six pairs of secondary veins are attached to the main vein, emerging at an acute angle and curving gently to the marginal points where there are fine veins often at right angles to the secondary veins.

The powder is brownish-green, it shows fragments of abaxial epidermis with wavy anticlinal walls; abaxial epidermis with stomata mainly paracytic; star-shaped covering trichomes, either entire or broken, composed of four to twelve unicellular branches which are united by their bases, elongated, conical and curved, usually up to 250 µm long, thick-walled and with a clearly visible lumen with contents often brown in colour; fibres are lignified and thick-walled, isolated or in groups, and they are accompanied by a sheath of prismatic calcium oxalate crystals; small, cylindrical parenchymatous cells of palisade; irregular-shaped cells of spongy mesophyll; sclereids, frequently enlarged at one or both ends, 150 µm to 180 µm long, whole or fragmented; fragments of annular or spiral vessels; isolated prisms of calcium oxalate.

It may contain no more than 7% of stem pieces and maximum and not more of 2% of other foreign matter, determined on 50 g. Loss on drying, not more than 10.0%, determined on 2.000 g of powdered drug by drying in an oven at 100 °C to 105 °C for 4 h. Total ash, not more than 7.0%. Ash insoluble in hydrochloric acid, not more than 2.0%. Botanical identity must be confirmed by TLC as well as macroscopic and microscopic examinations. Assay: determination of tannins in herbal drugs. Action and use: Astringent.

➤ Real Farmacopea Española, 3ª ed. 3.0 (1997)

Hamamelis, hoja de, monografía 01/2005, 0909. (Ph. Eur. monograph 0909)

➤ British Pharmacopoeia (2007)

Hamamelis leaf. BP, 2007, Vol 1: 1007. (Ph. Eur. monograph 0909). Currently, there is no monograph for *Hamamelis water* in BP.

➤ British Pharmacopoeia (1932)

Hamamelis leaves. BP, 1932: 201

Extractum Hamamelidis Liquidum. BP, 1932: 170

1000 g of moderately coarse powder hamamelis and alcohol 45% V/V sufficient to produce 1000 ml. Exhaust the hamamelis by percolation with alcohol (45%), and reserve the first 850 ml of the percolate; remove the alcohol from the remainder of the percolate and evaporate the residue to a soft extract. Dissolve this in the reserved portion, and add the sufficient alcohol (45%) to produce the required volume. Set aside for not less than twelve hours; filter. Alcohol content 32 to 40% V/V of ethyl alcohol. Doses: 2 to 4 ml.

➤ German Drug Codex (1986)

Witch hazel is listed in the *German Drug Codex*, approved in the Commission E monographs, and the tea infusion is officially included in the standard license monographs (Banz 1998; Braun et al, 1997; DAC, 1986; Wichtl and Bisset, 1994). Witch hazel leaf and bark are used in some haemorrhoidal teas and antiphlebitis drugs. Several witch hazel mono-preparations and combinations products are available in various dosage forms, including ointments, suppositories, coated tablets, and tinctures.

Hamamelidis folium (*Hamamelisblätter*, DAC 86). The German Drug Codex requires for witch hazel leaf not less than 5.0% tannins, precipitated with hide powder (DAC, 1986; Wichtl and Bisset, 1994). The German standard license requires that the leaf comply with the quality requirements of the German Drug Codex monograph.

Preparations: Suppositoria Hamamelidis (Hamamelidis-Stuhlzäpfchen) EB 6: 'Aus 50T Hamamelisextrakt'. Hamamelis suppositories BPC 79.

Herbal tea preparation (decoction): 5-10 g /250 ml. 2-3 g/150 ml (decoction for 10 min).

Liquid extract (1:1) ethanol 45%, 3 times daily, 2-4 ml. Extractum hamamelidis EB 6: 0.1 g.; Extractum hamamelidis fluidum EB 6: 5.0 g, as an haemorrhoidal cream 10%.

Pharmacopoeial grade witch hazel bark consists of the dried bark from stems and branches of *Hamamelis virginiana* L. collected in spring. The bark is required a content of not less than 9.0 % tannins, precipitable with hide powder (DAC, 1986; Wichtl and Bisset, 1994), and not less than 20% ethanol (45%) soluble extractive.

Hamamelidia aqua (Hamamelisrindenwasser); Aqua Hamamelidis corticis (Monographiensammlungen: EB-6); Aqua Hamamelidis; Liquor Hamamelidis.

Preparations: Unguentum Hamamelidis (Hamamelissalbe, EB6)

The mother tincture (1:10) and liquid dilutions thereof, are also official in the German Homeopathic Pharmacopoeia (GHP), prepared from different plants of plants including the fresh leaves, the fresh bark from roots and branches, as well as the mixture of bark from the branches with tips of the shoots. The GHP also includes a monograph for an ethanolic decoction of the dried bark from stems and branches as pyrogallol (GHP, 1993).

➤ USP 31/NF 26 (2008)

Witch hazel is the clear, colourless distillate prepared from recently cut and partially dried dormant twigs of *Hamamelis virginiana* L. It is prepared by macerating a weighted amount of the twigs in water for 24 hours in about twice their weight of water. Then it is distilled until not less than 800 ml and not more of 850 ml of clear, colourless distillate is obtained from each 1,000 g of the twigs taken, which is followed by the addition of 150 ml of alcohol to each 850 ml of distillate, and thorough mixing. It has a tannins limit of 0.03 mg tannic acid per ml, a pH between 3.0 and 5.0, and alcohol content of 14.0-15.0% of ethanol, and is official in the current USP (USP-31- NF 26, 2008).

➤ Pharmacopoeia Helvetica VII (1987)

Hamamelidis Extractum Liquidum Normatum. Syn. Extractum Hamamelidis folium alcohol content 28-35% V/V. Quantified extract with a tannin content of 3.5-4.5%.

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

Witch hazel preparations have a long history of traditional use in North America. The bark aqueous infusion was used in aboriginal medicine to treat haemorrhages, inflammations and haemorrhoids (Millsbaugh, 1974). Pharmacopoeias and handbooks list the therapeutic uses as an astringent and anti-inflammatory product for the treatment of minor skin injuries, local inflammation of skin and mucous membranes; for bruises and localized inflamed swellings; to treat vascular disorders including hemorrhoids, varicose veins, phlebitis and other conditions associated with poor venous tone or congestion; menorrhagia and metrorrhagia; diarrhea; as a protective against oxidative stress and ultraviolet radiation. Mainly Hamamelidis aqua has been reported in medicinal use for many decades.

The decoction was used in poultices for painful swellings and tumours (Grieve, 1979). The alcoholic fluidextract form became official in the United States Pharmacopoeia in 1882 (Millsbaugh, 1974). Native Americans applied poultices of hamamelis leaves and barks as a remedy for haemorrhoids, wounds, insect bites, painful tumours and ulcers (Duke, 1985). Today, the external use of witch hazel is well known for the astringency associated with the tannin content of its leaves and bark. In Europe, tannin rich witch hazel extracts made from the leaf and bark are used.

K. Hering (1800-1880), a German doctor is thought as the first who has used *Hamamelis virginiana* L. in medical treatment in USA. At that time, a “Pond’s Extract” of hamamelis was already known, which T. Pond learned from an Oneida Indian tribe in 1840. This extract was sold under the name “Golden Treasure”. In the course of time Pond modified the production process, using an aqueous distillate of hamamelis twigs, known as “hazaline” (Laux, 1993).

In folk medicine, the drug is used in menorrhagia and dysmenorrhea as a haemostatic, and there are similar uses in homeopathy. Total extracts, such as hamamelis extracts or distillates from flowering branches freshly collected (“hazaline” witch hazel water), dry extracts of the leaves (“green hamamelin” and bark (“brown hamamelin”) are applied in the form of infusions, ointments, or suppositories, far more often than herbal teas made from the leaves or bark. Therapeutically, they are used for their astringent, antiseptic and haemostatic properties, and especially as venotonic, properties which have been demonstrated in animal experiments (Wichtl, 1994).

An hamamelis ointment containing a distillate of leaves and bark, has been commercially available in Germany since 1878 (Gäble, 1978).

The British Pharmacopoeia of 1932 included a monograph on *Extractum Hamamelidis Liquidum*. This liquid extract was obtained by percolation of 1000 g of moderately coarse powder hamamelis and alcohol 45%. The final ethanol content was 32 to 40% V/V and the recommended dose: 2 to 4 ml.

The medicinal use of hamamelis has been reported by Gathercoa & Wirth, 1936 (WHO monographs, 2002).

The herbal substance and some herbal preparations of hamamelis have also been mentioned in Hager’s Handbuch (List and Horhammer, 1969-1979).

The alcoholic fluid extract (Witch Hazel water distillate (1:2) became official in the United States Pharmacopoeia in 1882 (Millsbaugh, 1974). The FDA has approved as an OTC drug “witch hazel water”, made from the steam distillate of the twigs containing about 14-15% alcohol in water, with a small amount of the essential oil of the plant.

In USA witch hazel is used in several OTCs in astringent and haemostatic preparations in combination with Aloe.

An alcoholic tincture (1:10 w/v, in 55% ethanol V/V) of the bark, including the root bark, is classified in the Homeopathic Pharmacopoeia of the United States as an OTC Class C drug (HPUS, 1992), as well.

Witch hazel does not have GRAS status. However, it is freely available as dietary supplement in the USA under DSHEA legislation (1994 Dietary Supplement Health and Education Act).

Witch hazel has been defined as an astringent active ingredient in OTC skin protecting medical products, for relief of minor skin irritations due to insect bites, minor cuts, minor scrapes and in OTC anorectal products. These OTC products, in a suitable form for topical administration, are generally recognized as safe and effective. The FDA, however, advises “that based on evidence currently available, there is inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses” (USP 30/ NF 25, 2007).

Hamamelis virginiana L. preparations are used in cosmetics (skin lotions, nourishing creams, pre- and after-shaves etc) as well, while it is also used topically in veterinary medicine, as a solution or as an ointment in combination with other herbal preparations to promote wound healing of minor injuries of the skin, for treatment of skin inflammations, ulcerations and dermatoses. The medicinal products contain 2.5 to 10.8% (W/W) of an extract of the leaves and are applied 1 to 2 times daily for 2 to 3 days (CVMP Reports for *Hamamelis virginiana* L. mother tincture and dilutions thereof, which are intended for use in all food-producing animals, use in veterinary homeopathy, EMEA/MRL/358/98-final; and EMEA/MRL/689/99-final).

II.1.2.1 TYPE OF TRADITION, WHERE RELEVANT

American traditional medicinal use: Witch hazel distillate from twigs is official in the United States Pharmacopoeia- National Formulary (USP23-NF18, 1995- June 1999).

European traditional use: Witch hazel leaf is official in European Pharmacopoeia since 1997. ESCOP monographs, 2003.

II.1.2.2 EVIDENCE REGARDING THE INDICATION/TRADITIONAL USE

➤ Agencia Española de Medicamentos y Productos Sanitarios (AEMPS, 2007)

Hamamelidis distillate, 10%: “Temporary relief of eye irritation or discomfort due to various causes (smoky atmospheres, sustained visual effort, swimming in the sea or swimming baths, etc)”.

Hamamelidis distillate (1:1.6) 5% Ointment: “Temporary relief of haemorrhoids symptoms”

➤ Afssaps Avis aux fabricants... Bulletin officiel n° 86/20 bis (1986); (1990)

Hamamelis virginiana leaf (feuilles d’hamamélis, feuilles du noisetiere la sorcière): Listed in Médicaments à base de plantes.

N° 7: “Traditionally used in subjective symptoms of chronic insufficiency such as sensation of heavy legs and in haemorrhoids symptoms”.

N° 16: Traditionally used as a gargle in inflammation of the mouth and throat.

➤ Afssaps monograph : cahiers de l’Agence n° 3(1998)

Hamamelis virginiana leaf (feuilles d’hamamélis, feuilles du noisetierde la sorcière): Listed in Médicaments à base de plantes.

“Traditionally used in subjective symptoms of chronic insufficiency such as sensation of heavy legs and in haemorrhoids symptoms”.

“Traditionally used in the case of eye irritation or discomfort due to various causes (smoky atmospheres, sustained visual effort, swimming in the sea or swimming baths, etc)”.

➤ British Herbal Medicines Association, British Herbal Compendium Vol II (2006)

Hamamelis bark (Hamamelidis Cortex)

Indications: None adequately substantiated by pharmacological or clinical studies. Uses based on experience or tradition.

External: Small wounds, skin injuries and bruises, local inflammation of skin and mucous membranes; haemorrhoids and varicose veins complaints.

Internal: Diarrhoea, mucus colitis, haemorrhoids.

Regulatory status in UK: Medicinal products are accepted for general sale, internal or external use.

Permitted by Council of Europe as food flavouring, category N3 (this category indicates that there is insufficient information available for an adequate assessment of potential toxicity).

Hamamelis leaf

Indications: None adequately substantiated by pharmacological or clinical studies. Uses based on experience or tradition

External: Minor skin injuries, local inflammation of skin and mucous membranes, bruises; varicose vein complaints and haemorrhoids.

A hamamelis leaf extract (not defined) appears to be beneficial in the topical treatment of dermatitis atopica.

Internal: Diarrhoea, colitis.

Regulatory status in UK: Medicinal products are accepted for general sale, internal or external use.

Permitted by Council of Europe, as food flavouring, category N3.

Hamamelis water

The BPC 1973 monograph and the USP monograph for witch hazel water are broadly similar.

Indications: None adequately substantiated by pharmacological or clinical studies. Uses based on experience or tradition: hamamelis water is used to alleviate minor affections of the skin such irritation, roughness, or soreness. It has also been employed when diluted, as a constituent of eye lotions.

Topical use: Minor sores, inflammation or irritations of the skin such as cuts, grazes, insect bites, dermatitis, slight burns or scalds and sunburn; bruises and sprains, muscle pains; external haemorrhoids, varicose vein complaints; as a mouthwash for inflamed mucosa or bleeding gums; as a nasal plug for nosebleeds; as an eyewash for conjunctivitis and sore or tired eyes.

Regulatory status in UK: Medicinal products are accepted for general sale, internal or external use.

Food: Not used in foods. *Witch hazel is not on the UK General Sale List.*

➤ *British Herbal Pharmacopoeia (1983)*

Hamamelis leaf indications: Diarrhoea, mucus colitis, haematemesis, haemoptysis, haemorrhoids. Topical bruises, localised inflamed swellings.

➤ *British Pharmaceutical Codex (1973)*

Witch hazel leaf

Actions and Uses: hamamelis has astringent properties and its preparations are used in the treatment of haemorrhoids. It is used in toilet preparations.

Preparations: Hamamelis dry extract BPC; Hamamelis liquid extract BPC; Hamamelis ointment, BPC; Hamamelis suppositories.

Hamamelis water.

Uses: Hamamelis water is used to alleviate minor affections of the skin such irritation, roughness, or soreness. It has also been employed when diluted, as a constituent of eye lotions.

➤ *German Drug Codex (1986)*

Witch hazel is listed in the *German Drug Codex*, approved in the Commission E monographs, and the tea infusion is officially included in the standard license monographs (Banz, 1998; Braun et al, 1997; DAC, 1986; Wichtl and Bisset, 1994). Witch hazel leaf and bark have been used in some haemorrhoidal teas and anti-phlebitis drugs. Several witch hazel mono-preparations and combinations products are available in a variety of dosage forms, including ointments, suppositories, coated tablets, and tinctures.

Hamamelis herbal medicinal products are traditionally used in the form of herbal tea, as astringent in supportive therapy for acute diarrhoea, as a gargle in inflammation of the mouth and throat, especially when accompanied by inflammation of the gums.

In folk medicine the drug is used in menorrhagia as a haemostatic and in dysmenorrhoea, and there are similar uses in homeopathy. Extracts (of the leaves and bark) and distillates are applied in the form of infusions, ointments, or suppositories, far more often than teas, for their astringent, antiseptic and haemostatic properties, and especially for their ability to increase blood vessel tonus. It is used against haemorrhoids, varicose veins, local inflammation of the mucous membranes with swelling and superficial skin damage, and in body and face lotions (Bisset et al, 1994).

➤ USP 30/NF 25 (2007)

Witch hazel has been defined as an astringent active ingredient in OTC skin protectant drug products for relief of minor skin irritations due to insect bites, minor cuts, minor scrapes and OTC anorectal products. These OTC products in a suitable form for topical application are generally recognized as safe and effective. The FDA, however, advises “that based on evidence currently available, there is inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses”.

➤ ESCOP Monograph (ESCOP, 2nd ed. 2003)

Hamamelis water

Therapeutic indications:

External use: “Treatment of bruises, skin irritations, sunburn, insect bites, external haemorrhoids. Minor inflammatory conditions of the skin and mucosa”.

Hamamelis bark

Therapeutic indications:

Internal use: “Inflammations of mucous membranes of the oral cavity”.

“Short term symptomatic treatment of diarrhoea”

External use: “Haemorrhoids, minor injuries and local inflammations of the skin”

“Symptomatic treatment of problems related to varicose veins, such as painful and heavy legs”.

Hamamelis leaf

Therapeutic indications:

Internal use: “Symptomatic treatment of complaints related to varicose veins, such as painful and heavy legs, and of haemorrhoids”.

External use: “Bruises, sprains and minor injuries of the skin, local inflammations of the skin and mucosa, haemorrhoids, relief of symptoms of *neurodermitis atopica* and feeling of heavy legs”.

➤ Commission E Monograph (1985, correction 1990)

Witch hazel leaf and bark (Hamamelisblätter und –rinde)

Witch hazel leaf and bark are covered by positive Commission E monographs and both have the following applications: “Mild damage to the skin (minor skin wounds), local inflammation of the skin and mucous membranes, haemorrhoids and varicose veins.”

➤ WHO Monographs on selected medicinal plants. Volume 2 (World Health Organization, 2002)

Folium et Cortex Hamamelidis.

Medicinal uses supported by clinical data: Topically for minor skin lesions, bruises and sprains, local inflammation of the skin and mucous membranes, haemorrhoids and varicose veins.

Uses described in pharmacopoeias and in traditional systems of medicine: Topically as a haemostat.

Uses described in folk medicine, not supported by experimental or clinical data: Treatment of colitis diarrhoea, dysentery, dysmenorrhoea, eye inflammations, haematuria, kidney pains, neuralgia, nosebleeds and excessive menstruation, and as tonic.

➤ Martindale, The complete drug reference (35th edition, 2007)

Hamamelis, Witch hazel, Amamelide.

Hamamelis has astringent properties. It is used in preparations for the symptomatic relief of haemorrhoids. Hamamelis water is used as a cooling application and has been applied as a haemostatic.

Hamamelis from various parts of the plant is used in herbal or homeopathic preparations for a variety of disorders.

➤ *Non-prescription Product Therapeutics (2nd edition, 2006)*

Hamamelis water:

Includes references to different preparations of Witch hazel 50%, with glycerine, water, or aloe barbadensis, as astringent products suitable for external use in case of haemorrhoids.

A product for insect bites/stings which contains Witch hazel distilled 100% and some astringents, is used for the relief of pain and swelling caused by insect bites.

➤ *Handbook of Non-prescription Drug (15th edition, 2006)*

Therapeutic uses: Witch hazel has been used both externally and internally although it is currently recommended only for external use.

Dosage and Administration Guidelines: Witch hazel preparations are applied topically, as needed for the described disorders.

Safety: Oral use may cause stomach irritation and liver damage. Topical use may result in contact dermatitis.

Most commercially available Witch hazel preparations are mixture of alcohol 14% in water with only a trace amount of the volatile water.

Clinical evidence: Little clinical trial data are available. Witch Hazel's astringent effects are useful for treating minor skin injuries and relieving the itch, irritation, and pain of haemorrhoids and after anal surgery.

Table 1. Summary of Indications (short description)

	FOLIUM	CORTEX	AQUA/ DESTILLATUM
AEMPS			Haemorrhoids Eye irritation
AFSSAPS- (Avis 1986)	Haemorrhoids, Heavy legs, Gargle, mouth & throat Eye irritation		
AFSSAPS- (Cahiers 1998)	Haemorrhoids Heavy legs Eye irritation		
British Herbal Compendium	External use: Skin & mucous inflammation, small wounds / skin injuries, atopic dermatitis (extract not defined) Haemorrhoids Bruises, varicose veins, Internal use: Diarrhoea/ colitis	External use: Small wounds/skin injuries, Skin & mucous inflammation, Haemorrhoids, Bruises, varicose veins, Internal use: Diarrhoea/ colitis , Haemorrhoids	Skin irritation, roughness, soreness, cuts, wounds, insect bites, dermatitis, sunburns, Haemorrhoids, Bruises, varicose veins Gargle, mouth & throat Eyewash
British Pharmaceutical Codex	Haemorrhoids		Minor skin irritation Eyewash

British Herbal Pharmacopoeia	Skin inflammation, Local inflamed swellings Haemorrhoids, Bruises, Internal use: Diarrhoea/ colitis.		Minor skin irritation Eyewash
Commission E	Skin & mucous minor inflammation, minor skin injuries Haemorrhoids, varicose veins	Skin & mucous minor inflammation, minor skin injuries Haemorrhoids, varicose veins	
ESCOP	Internal use: Haemorrhoids, varicose veins, heavy legs External use: skin & mucous inflammation, minor skin injuries. Neurodermitis atopica Haemorrhoids, Heavy legs, Bruises	External use: Local skin inflammation Haemorrhoids, Heavy legs, Gargle mouth & throat Internal use: Diarrhoea	External use: Minor inflammation skin & Mucous membranes. Skin irritation, sunburns, Insect bites, Haemorrhoids Bruises
German Drug Codex	Local inflamed swellings. Damaged skin Haemorrhoids, Flebitis, varicose veins. Menorrhagia, dysmenorrhoea Gargle, mouth & throat Internal use: Diarrhoea	Local inflamed swellings Damaged skin Haemorrhoids, Flebitis, varicose veins. Menorrhagia, dysmenorrhoea Gargle, mouth & throat Internal use: Diarrhoea	
Martindale	Haemorrhoids	Haemorrhoids	Haemorrhoids
USP 30		Gargle, mouth & throat	Minor irritation skin Insect bites, cuts, Haemorrhoids,
WHO	Skin & mucous inflammation, Haemorrhoids, Heavy legs, Bruises Trad. Use: dysmenorrhoea Diarrhoea/colitis Eye irritation Nosebleeds	Skin & mucous inflammation, Haemorrhoids, Heavy legs, Bruises Trad. Use: dysmenorrhoea Diarrhoea/colitis Eye irritation Nosebleeds	Haemorrhoids

II.1.2.3 EVIDENCE REGARDING THE SPECIFIED STRENGTH /POSOLOGY

➤ Agencia Española de Medicamentos y Productos Sanitarios (AEMPS, information, 2007)

Hamamelidis distillate 10%, eye drops: Single dose 2 drops/each eye, 3-6 times a day.

➤ British Herbal Medicines Association, British Herbal Compendium Vol II (2006)

Hamamelis bark (Hamamelidis cortex)

External use: Semi-solid and liquid preparations containing the equivalent 5-10% of bark; as impregnated dressings, lotion or mouthwash, diluted tincture of hamamelis (1:10, 45% ethanol) or decoction of 5-10 g of bark to 250 ml of water.

Internal use: Tincture, 2-4 ml or an infusion of 2 g of dried bark, three times daily. In suppositories, an amount equivalent to 0.1-1 g of dried bark, up to three times daily.

Hamamelis leaf

External use, hamamelis ointment BPC 1973 (10% by weight of hamamelis liquid extract BPC 1973 in an ointment base); semi-solid and liquid preparations containing the equivalent 5-10% of leaf; for impregnated dressings and rinses, decoctions of 5-10 g of leaf to 250 ml of water, or 20 ml of tincture diluted to 100 ml.

Local use for mouthwashes: as a decoction of 2-3 g in 150 ml of water, several times daily.

Hamamelis suppositories BPC 1973 (200 mg of hamamelis dry extract BPC 1973 in a suitable base) or, more generally, suppositories containing the equivalent of 0.1-1 g of dried leaf.

Internal use, three times daily: dried leaf, 2 g or by infusion; hamamelis liquid extract BPC 1973 (1:1, 45% ethanol), 2-4 ml three times daily.

Hamamelis water

Topical use: undiluted hamamelis water for applications to cuts, grazes, insect stings, other skin complaints and haemorrhoids, as a mouthwash, and in a saturated cotton wool swab as a nasal plug for nosebleeds, or to place over eyelids; for compresses, undiluted or diluted 1:3 with water; in semi-solid preparations, 20-30%.

As an eyewash use diluted hamamelis water, 10 drops to an eyebath half-filled with water.

➤ German Drug Codex (1986)

Hamamelis folium (Hamamelisblätter. DAC 86; Wichtl and Bisset, 1994). Preparations: Suppositoria Hamamelidis (Hamamelidis-Stuhlzäpfchen) EB 6: 'Aus 50T Hamamelisextrakt'. Hamamelis suppositories BPC 79.

Herbal tea preparation (decoction) 5-10 g/250 ml 2-3 g/150 ml (decoction 10 min).

Liquid extract (1:1) Ethanol 45%, 3 times daily, 2-4 ml. Extractum hamamelidis EB 6: 0.1 g.; Extractum hamamelidis fluidum EB 6: 5.0 g, as a hemorrhoidal cream 10%.

Hamamelidia aqua (Hamamelisrindenwasser); Aqua Hamamelidis corticis (Monographiensammlungen: EB-6); Aqua Hamamelidis; Liquor Hamamelidis.

Preparations: Unguentum Hamamelidis (Hamamelissalbe, EB.6), according to Pharmacopoeial grade (DAC, 1986; Wichtl and Bisset, 1994)

➤ British Herbal Pharmacopoeia (1983)

Adults and elderly: Dried hamamelis leaf 2 g (or by infusion) three times daily.

Liquid extract 1:1 in 45% alcohol. Dose 2-4 ml.

Hamamelis water BPC for local application.

➤ ESCOP Monograph (ESCOP, 2nd ed. 2003)

Hamamelis water

For compresses: hamamelis water undiluted or diluted 1:3 with water; in semisolid preparations, 20-30%.

Apply as often as required.

For mucosa: hamamelis water undiluted or diluted with water, several times daily.

Hamamelis bark

Internal use: 2-10 g of the drug daily as a decoction, used as a mouthwash, or 2-3g daily as a tea.
2-4 ml of tincture, used diluted as a mouthwash 3 times daily.
Other preparations: the equivalent of 0.1-1g of the drug, 1-3 times daily
External use: 5-10 g of the drug as a decoction in 250 ml of water.
Extracts in semi-solid preparations corresponding to 20-30% of the drug.

Hamamelis leaf

Internal use: 2-3 g of the drug daily as a infusion, or 2-4 ml of liquid extract (1:1, 45% ethanol), three times daily.
External use: Extracts in semi-solid or liquid preparations, containing 5-10% of the drug.
Decoctions, 5-10 g of drug in 250 ml water, for compresses or washes.
Ointment containing 10% of liquid extract.

It has to be noted that the ESCOP Monograph considers only the available data on *Hamamelis virginiana* L. preparations as a single ingredient.

➤ Commission E Monograph (1998)

Internal use: (mucous membranes): Several times daily, corresponding to 0.1-1g of drug in preparations, or witch hazel water undiluted or diluted with water.

2-3 g of the drug daily as a infusion, or 2-4 ml of liquid extract (1:1, 45% ethanol), Three times daily.

External use: Water steam distillate (witch hazel water) undiluted or diluted 1:3 with water.

Extracts in semi-solid or liquid preparations, containing 5-10% of the drug.

Decoctions, 5-10 g of drug in 250 ml water, for compresses or washes.

Ointment containing 10% of liquid extract.

For poultices, 20-30% in semisolid preparations.

➤ WHO Monographs on selected medicinal plants. Volume 2 (World Health Organization, 2002)

External use: steam distillate, undiluted or diluted 1:3 with water to make poultices; 20-30% in semisolid preparations.

Extracts: in semisolid and liquid preparations corresponding to 5-10% of the crude drug. Decoctions, from 5-10 g of drug to 1 cup (250 ml) water for poultices and wound irrigation.

Rectal suppositories, 1-3 times daily the quantity of a preparation corresponding to 0.1-1.0g crude drug, Hamamelidis water undiluted or diluted 1:3 with water.

Other preparations, several times daily, corresponding to 0.1-1.0 g drug in preparations or witch hazel water undiluted or diluted with water.

Posology in children

Good tolerance and lack of adverse effects have been reported for hamamelis ointment (Hametum) for temporary relief of minor skin injuries such as diaper skin rash, nevertheless such kind of treatment should be monitored by medical supervision to avoid other clinical complications (Candida infections). There are not adequate clinical data on the paediatric use of other hamamelis preparations.

Elderly: Same posology as recommended for adults.

Table 2. Summary of recommended Posologies.

	FOLIUM	CORTEX	AQUA/ DESTILLATUM
AEMPS			External use: Distillate 10%, eye drops. 2 drops/each eye, 3-6 times daily
AFSSAPS- (Avis 1986)	-----		
AFSSAPS- (Cahiers 1998)	-----		
British Herbal Compendium	<p>External use: Hamamelis ointment (10% by weight of liquid extract BPC in an ointment base) Semisolid or liquid preparations corresponding to 5-10% leaf. Herbal tea (decoction): 5-10 g dried leaf for compresses and rinses, or 20 ml tincture diluted to 100 ml. Herbal tea (decoction): 2-3 g, several times a day for mouthwashes. Suppositories 200 mg hama. extract or equivalent to 0.1-1 g of dried leaf. Internal use: 2 g dried leaf, hama. liquid extract 1:1; 45% ethanol), 2-4 ml, three times daily</p>	<p>External use: Semisolid or liquid preparations corresponding to 5-10% bark. As compresses, lotion or mouthwash, diluted tincture (1:10; 45% ethanol), or herbal tea (decoction): 5-10 g dried bark up to three times a day Internal use: Tincture (1:10; 45% ethanol), 2-4 ml Herbal tea: 2 g dried bark up to three times a day,</p>	<p>External use: Hamamelis water undiluted or diluted 1:3 with water, in semisolid preparations 20-30% As an eyewash, 10 drops of diluted (with water) hamamelis water.</p>
British Pharmaceutical Codex	-----		-----
British Herbal Pharmacopoeia	2g herbal tea: 2 g, three times a day. Liquid extract (1:1, 45% ethanol) 2-4 ml		-----
Commission E	<p>Internal use: Preparations corresponding to 0.1-1 g dried leaf, several times daily. Herbal tea (infusion) 2-3 g drug daily 2-4 ml liquid extract (1:1, 45% ethanol) three times daily</p>	<p>Internal use: Preparations corresponding to 0.1-1 g dried leaf, several times daily. Herbal tea (infusion) 2-3 g drug daily 2-4 ml liquid extract (1:1, 45% ethanol) three times daily</p>	<p>External use: Hamamelidis water undiluted or diluted (1:3) with water</p>

	<p>External use: extracts in Semisolid or liquid preparations, containing 5-10% of the drug Herbal tea (decoction): 5-10 g/250 ml (compresses or washes). Ointment containing 10% of liquid extract Poultices: 20-30% in semisolid preparations</p>	<p>External use: extracts in Semisolid or liquid preparations, containing 5-10% of the drug Herbal tea (decoction): 5-10 g/250 ml (compresses or washes). Ointment containing 10% of liquid extract Poultices: 20-30% in semisolid preparations</p>	
ESCAP	<p>External use: Extracts in semisolid or liquid preparations, containing 5-10% of the drug Herbal tea (decoction): 5-10 g drug daily (for compresses or washes) Ointment 10% liquid extract drug daily 0.1-1 g herbal drug, 1-3 times daily</p> <p>Internal use: Herbal tea (infusion)2-3 g drug/ daily 2-4 ml liquid extract (1:1, 45% ethanol) three times daily</p>	<p>External use: Extracts in semisolid or liquid preparations, containing 20-30% of the drug Herbal tea (decoction): 5-10 g/250 ml</p> <p>Internal use: Herbal tea (infusion)2-3 g drug daily 2-4 ml tincture (diluted, mouth wash) 0.1-1 g herbal drug, 1-3 times daily</p>	<p>External use: Undiluted or diluted 1:3 with water; semisolid preparations, 20-30%, several times daily</p>
German Drug Codex	<p>External use: Ointment hamamelis extract BPC (10% by weight in an ointment base). Herbal tea (decoction): 5-10 g/250 ml or 2-3 g/150 ml, several times daily.</p> <p>Internal use: herbal tea: 2g x 3 times daily. Liquid Extract (1: 1, 45% ethanol), 2-4 ml x 3 times daily. Suppositories hamamelis extract BPC (200 mg extract in a suitable base) or containing equivalent to 0.1-1 g of dried leaf.</p>		<p>External use: Hamamelidis aqua (cortex) Unguentum Hamamelidis.</p>
Martindale	-----	-----	-----
USP 30		-----	-----

WHO	<p>External use: Semisolid or liquid preparations, containing 5-10% of the drug</p> <p>Herbal tea (decoction): 5-10 g/250 ml.</p> <p>Internal use: suppositories, corresponding to 0.1-1.0 g crude drug</p>		<p>External use: Undiluted or diluted 1:3 with water; semisolid preparations 20-30%, several times daily.</p>
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External use:

1. *Skin/mucosae (irritation/inflammation). Wounds. Insect bites.*
2. *Haemorrhoids*
3. *Heavy legs/varicose veins. Bruises*
4. *Gargle & mouth & throat*
5. *Eye irritation/eye lotion*

Internal use:

6. *Diarrhoea/colitis*
7. *Haemorrhoids*
8. *Heavy legs/varicose veins. Bruises*
9. *Menorrhagia. Dysmenorrhoea*
10. *Nosebleed*

II.1.2.4 EVIDENCE REGARDING THE ROUTE OF ADMINISTRATION

The oromucosal, cutaneous and rectal applications, have been proposed for hamamelis preparations in the recommended traditional indications.

II.1.2.5 EVIDENCE REGARDING THE DURATION OF USE

It is recommended not to take oral preparations for more than 1 month. In case of external application, it might be used for a longer time.

II.1.2.6 OVERALL CONCLUSION ON THE TRADITIONAL MEDICINAL USE

Based on the information obtained from Member States and the literature search, it can be concluded that the following extracts and uses fulfil the criteria for traditional use:

Hamamelis water:

- 1) Distillate prepared from fresh leaves and bark (1: 1.12-2.08; ethanol 6% m/m)
- 2) Distillate prepared from dried twigs (1:2; ethanol 14-15% v/v)

A) Traditional Herbal Medicinal Product for relief of minor skin inflammation and dryness of the skin. Distillates (1, 2) in a strength corresponding to 5-30% in semi-solid preparations, several times a day.

External use

B) Traditional Herbal Medicinal Product for the temporary relief of discomfort due to dryness of the eye or to exposure to wind and sun. Eye drops: Distillate (2) diluted (1:10), 2 drops each eye, 3 to 6 times a day.

Hamamelis bark:

- 1) Comminuted herbal substance for herbal tea
- 2) Tincture (1:10; ethanol 45% v/v) and corresponding dry extracts
- 3) Dry extract (5-7.7:1; extraction solvent ethanol 30% m/m)

External use

- A) Traditional Herbal Medicinal Product for relief of minor skin inflammation and dryness of the skin.
Tincture in a strength corresponding to 5-10% in semi-solid preparations, several times a day.
Dry extract in a strength corresponding to 1.3% in semi-solid preparations, several times a day.
- B) Traditional herbal medicinal product for symptomatic relief of itching and burning associated with hemorrhoids.
Tincture in a strength corresponding to 5-10% in semi-solid preparations, several times daily.
Comminuted herbal substance as decoction: 5-10 g / 250 ml, up to 3 times a day in impregnated dressings.
Suppositories containing 66 mg of dry extract (5-7.7:1; ethanol 30% m/m) One suppository, two or three times a day.
- C) Traditional Herbal Medicinal Product for (mouthwash and gargles) relief of minor inflammation of mucous membranes of the oral cavity. 2-3 g of herbal substance as herbal tea (decoction) for using as a mouthwash, up to three times a day.

Hamamelis leaf:

Dried comminuted herbal substance for herbal tea

- Tincture (fresh leaf) (1:10; ethanol 45% v/v)
- Liquid extract (fresh leaf) (1:1; ethanol 45% v/v)
- Liquid extract (dried leaf) (1:1; ethanol 30% m/m)
- Liquid extract (dried leaf) (1:2; ethanol 60% v/v)

- A) Traditional herbal medicinal product for relief of minor skin inflammation and dryness of the skin.
Tincture or liquid extracts (1:1) in a strength corresponding to 5-10% in semisolid or liquid preparations, several times daily.
Liquid extract (1:2; ethanol 60% V/V) in a strength corresponding to 20% as semi-solid preparation
- B) Traditional herbal medicinal product for symptomatic relief of itching and burning associated with hemorrhoids.
Tincture or liquid extracts in a strength corresponding to 5-10% in semisolid and liquid preparations, several times daily.
Liquid extract (1:2; ethanol 60% V/V) in a strength corresponding to 20% as a semi-solid preparation, several times daily.
Comminuted herbal substance as decoction: 5-10 g/250 ml, up to 3 times a day in impregnated dressing
Suppository containing 400 mg of liquid extract (1:2; ethanol 60% v/v), 2-3 times a day.
- C) Traditional Herbal Medicinal Product for (mouthwash and gargles) relief of minor inflammation of mucous membranes of the oral cavity.
2-3 g of comminuted herbal substance as herbal tea (decoction) for using as a mouthwash, up to three times a day.
Tincture (1:10) in 45% ethanol (diluted (1:3) with water) 2-4 ml, three times daily as gargle

II.2 NON-CLINICAL DATA

II.2.1 Pharmacology

Venotonic activity

Hamamelis has been used as vasoconstrictor substance but there are not well performed experimental tests to demonstrate this effect. Balansard et al (1970) described a method derived from the technique of Laewen-Trendelenburg. The method was not intended for the study of the venotonic activity since it was not possible to eliminate the arterioconstrictive activity typical of certain substances which manifest their effect simultaneously by increasing the venous tone and an arterial vasoconstriction. The method consists in perfusing at a constant pressure *via* the aorta the rear part of the rabbit a substance provided that it was soluble in water or in a water solvent mixture which does not precipitate in dextran. A catheter is introduced into the abdominal aorta and a second into the superior vena cava following heparinization (5 mg/kg/ i.v.). The arterial activity of the hamamelis fraction (condensed tannins) has been tested on an isolated aortic segment. The arterial vasoconstriction of the hamamelis fraction is weak and initial kinetics are very slow when compared with kinetics of the adrenergic type. A decrease in blood supply was observed after intra-arterial administration of the distillate. This effect was not influenced by concomitant administration of adrenergic, adrenergic, adrenolytic or myotonic drugs (Balansard, 1970, 1972).

The venotonic effects of leaf preparations (steam distillate, tincture or alcohol extract) were tested by measuring the blood supply to the rear paw of rabbits (Bernard, 1972).

Neugebauer (1948) studied the similarity of effects between *Hamamelis virginiana* and *Corylus avellana*. For monitoring the haemostatic effect determined the bleeding time for the rabbit ear according to the method of Fleisch and Tripod. The preparations studied had an ethereal oil content of 0.015% on average, and manufactured by distillation from fresh leaves previously treated with alcohol and water. Both the distillate and the ethereal oil produced a positive reduction in bleeding time and an acceleration of blood coagulation, as demonstrated by experiments with the hollow-bead capillary method of Schultz.

Vasoconstrictor activity

A randomized, placebo controlled study assessed the vasoconstrictive effects of an aqueous propylene glycol extract of hamamelis in 30 volunteers. The hamamelis extract used was a hydroglycolic extract (water/propylenglycol 50:50), obtained from hamamelis leaves. A thermometric method is proposed in this study. The extract produced a significant reduction in skin temperature as compared with the placebo (Diemunsch and Mathis, 1987).

Astringent activity

Hamamelis leaves and bark contain tannins. Although tannins may be responsible for the astringent and styptic properties, the distilled product contains almost no active tannins. Alcohol provides the astringent effect. When applied to broken skin or mucous membranes, hamamelis products induce protein precipitation that tightens up superficial cell layers and shrinks colloidal structures. This action, in turn, causes capillary vasoconstriction, decreasing vascular permeability and inflammation (Lamont Hume and Strong, 2006).

In vitro experiments

The phenolic constituents of hamamelis, particularly the tannins (e.g. hamamelitannin), aldehydes and oligomeric proanthocyanidins are responsible for its astringent activity. Similar to other astringent drugs, application of hamamelis preparations to the skin and mucosa in low concentrations sealed cell membranes and reduced capillary permeability. Higher concentrations precipitated proteins and thickened colloidal tissue, forming a thin membrane in the wound region, and slightly compressed the skin tissue

beneath it. Alcohol hamamelidis extracts showed strong astringent action, the bark extract is slightly superior to the leaf extract (Laux, 1993, Vennat 1988, Hänsel 1993)

The astringent effect of a tincture (1:3; 62% ethanol) prepared from fresh hamamelis bark was demonstrated with hide powder (Gracza, 1987)

In vivo experiments

The healing effect of hamamelis distillate was compared with hydrogen peroxide on skin damaged by application of dichlorodiethyl sulfide (mustard gas) in various animal models. The distillate was more effective than hydrogen peroxide in reducing the occurrence of pus in the affected skin areas. Furthermore, subsequent treatment of the purulent skin areas with a 20% Hamamelidis ointment reduced the incidence of suppuration as compared with hydrogen peroxide treatment.

Anti-inflammatory activity

Hamamelis extracts and isolated chemical constituents have shown anti-inflammatory activity *in vitro* and *in vivo*.

In vitro experiments

Anti-inflammatory effects of polyphenols isolated from hamamelis stem and twig bark were evaluated in human polymorphonucleocytes (PMNs) and human macrophages. With the exception of hamamelitannin, all the tested substances inhibited the synthesis of platelet activating factor (PAF) in human PMNs. Dimeric galloylated proanthocyanidins showed the strongest effects. The synthesis of leukotriene B₄ in PMNs was inhibited by the tested substances. Oligomeric proanthocyanidins had stronger activity than hamamelitannin, which had the weakest effect (Hartisch et al, 1996).

In the lyso-PAF: Acetyl-CoA acetyltransferase assay, hamamelitannin proved to be ineffective, but in the same assay other potent candidates are represented by the group of B-type proanthocyanidins. A range of compounds from hamamelis bark had an inhibitory effect on 5-lipoxygenase, hamamelitannin and the galloylated proanthocyanidins showed greater potency than other substances; With IC₅₀ values ranging from 1.0 to 18.7 μM. Structure-activity relationships regarding the *in vitro* inhibitory potency of the polyphenols in the biological assays were discussed (Hartisch et al, 1997).

According to Deters et al (2001), polysaccharides and proanthocyanidins from hamamelis bark could influence on human skin keratinocyte proliferation and differentiation of cultured human keratinocytes, and influence on irritated skin. While the polysaccharide fraction, consisting mainly of arabinans and arabinogalactans, did not have effect human keratinocytes, the proanthocyanidins strongly increased the proliferation of the cells, while the differentiation was not influenced significantly. Within a preliminary cumulative *in vivo* study on SLS-irritated skin, proanthocyanidins were proven to reduce trans-epidermal water loss and erythema formation. Furthermore, a clinical scoring indicated that procyanidins can influence irritation processes significantly.

In vivo experiments

Intra-peritoneal administration of a 70% ethanol extract of hamamelis leaf (200 mg/kg body weight) significantly inhibited the chronic phase of carrageenan-induced rat footpad oedema (Dowiejua et al, 1994).

A aqueous ethanolic extract of hamamelis bark (ethanol 70%) showed a significant anti-inflammatory effect (43% inhibition of oedema; p<0.05) in the croton oil ear oedema test in mice when applied topically at 250μg per ear. This effect was shown to be mainly due to proanthocyanidins of molecular weight ≥3kDa (69% inhibition at 250μg per ear; p<0.05) obtained from this extract subjected to ultrafiltration (UF) and identified by TLC, HPLC. Proanthocyanidins also exhibit significant antiviral activity against Herpes simplex virus type 1 (HSV-1). In addition, the UV-conc. displayed radical scavenging properties, inhibited α-glucosidase as well as human leukocyte elastase (HLE). With the exception of the antioxidant

potential and the inhibition of HLE-action the lower molecular fraction possessed weaker activities and contained mainly hamamelitannin, catechin, and unidentified constituents (Erdelmeier et al, 1996).

Studies by Brown and Dattner (1998), presented witch hazel preparations as useful in the treatment of atopic dermatitis or pruritus (Millikan et al, 2003).

The aqueous ethanolic extracts of *Polygonum bistorta* L., *Guaiacum officinale* L. and *Hamamelis virginiana* L. were screened for their anti-inflammatory activity. Administered (100 and 200 mg/kg body weight, p.o.) before the induction of carrageenan rat paw oedema, extracts of *P. bistorta* significantly suppressed both the maximal oedema response and the total oedema response, while *H. virginiana* was inactive and *G. officinale* was only active a 200 mg/kg. (Dowiejua et al, 1994).

In vitro Antibacterial activity

An aqueous extract of the leaves of hamamelis inhibited the growth of *Escherichia coli* (MIC 0.4 mg/ml), *Staphylococcus aureus* (MIC 0.4 mg/ml), *Bacillus subtilis* (MIC 1.1mg/ml) and *Enterococcus faecalis* (MIC 3.0mg/ml). Aqueous extracts of the bark inhibited the growth of *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Enterococcus faecalis* (MIC for all 10.0 mg/ml) (Brantner et al, 1994, WHO monograph).

The antimicrobial activity of a distillate of Aqua Hamamelidis (USP) (90%) and urea (5%) formulated as a topical dermatological preparation was studied in vitro by the agar diffusion test showed inhibition of *Staphylococcus aureus* and *Candida albicans*, among other organisms. Comparison with earlier studies of chlorhexidine digluconate and fuchsine, hamamelis distillate and urea were relatively weak. (Leyden et al, 1979).

Lauk et al (2003), studied the antibacterial activity of some medicinal plant extracts against periodontopathic bacteria, such as: *Porphyromonas gingivalis*, *Prevotella sp*, *Fusobacterium nucleatum*, *Capnocytophaga gingivalis*, *Veilonella parvula*, *Eikenella corrodens*, *Peptoscoccus micros* and *Actinomyces odontolyticus* among which the methanol extract of *H. virginiana* was shown to possess an inhibiting activity (MIC \geq 2048 mg/L) against all the tested species except for *Prevotella sp*.

Antiviral activity

Hamamelitannin and proanthocyanidins obtained from a hydroethanolic extract of *Hamamelis virginiana* L., bark subjected to ultrafiltration exhibited *in vitro* antiviral activity against Herpes simplex virus type 1 (HSV-1) in monkey kidney cells. After 2-3 days the ED₅₀ of hamamelitannin for antiviral activity was 26 µg/ml, compared to 6.3 µg/ml for a fraction consisting mainly of oligomeric to polymeric proanthocyanidins and 0.42 µmol/ml for acyclovir as positive control (Erdelmeier et al, 1996).

Radical scavenging effects

The activity of active-oxygen scavengers such as superoxide anion radicals, hydroxyl radicals, singlet oxygens and lipid peroxides in 7 plant extracts among which *Hamamelis virginiana* L. was examined in detail by both ESR spin-trapping and malondialdehyde generation. Furthermore, the active-oxygen scavenging activity of extract was evaluated using a murine dermal fibroblast culture system. *Hamamelis virginiana* L. extract was found to have strong active-oxygen scavenging activity of and protective activity against cell damage induced by active oxygen and it could be proposed as potent plant extract with potential application as anti-aging or anti-wrinkle material for the skin.

Hamamelitannin inhibited the production of superoxide anion radicals (IC₅₀ 1.38 µmol/l) and hydroxyl radicals (IC₅₀ 5.46 µmol/l) in murine dermal fibroblasts, as measured by electron spin resonance spectrometry and showed significant protective activity at minimum concentrations of 50 µM, while the corresponding figure for gallic acid was 100 µM. Pre-treatment of fibroblasts with hamamelitannin enhanced cell survival. The superoxide-anion scavenging activity of the compounds in terms of its IC₅₀

values, which represent the concentration giving 50% inhibition of active oxygens generated, was evaluated by ESR spin-trapping. Hamamelitannin and gallic acid protected murine dermal fibroblasts against damage induced by superoxide anion radicals ($IC_{50} = 1.31 \pm 0.06 \mu\text{M}$) and ($IC_{50} = 1.01 \pm 0.03 \mu\text{M}$) respectively, compared with 23.31 $\mu\text{mol/l}$ for ascorbic acid and Propyl gallate (1.41 μM). In hydroxyl radical scavenging, hamamelitannin gave the lowest IC_{50} value (5.46 μM) among the compounds treated, the values of gallic acid and propyl gallate were 78.04 and 86.46 μM , respectively. For singlet oxygen scavenging, the IC_{50} was 45.51 μM for hamamelitannin, 69.81 μM for gallic acid and 66.66 μM for propyl gallate. (Masaki et al, 1993, 1994, 1995)

Hamamelitannin exhibits potent superoxide-anion scavenging activity. Its high affinity for cells or membranes may be an important factor for protecting cells against active oxygen species. The author screened the active components using the superoxide dismutase like activity (SOD-like activity) as an indicator. The *Hamamelis virginiana* L. extract showed a strong SOD-like activity.

The extracts (leaf and bark) were extracted with ethanol 50%, and the bark extract showed higher activity than the leaf one. The study confirmed through further isolations procedures that the SOD-like activity was due to the hamamelitannin. Hamamelitannin showed also inhibitory activity on depolymerization of hyaluronic acid; synergistic activity on antioxidation of dl-alpha-tocopherol; protecting activity on cell injury induced by active oxygens and an in vivo suppressive activity on peroxidation in guinea pig skin. (Masaki et al, 1993, 1994, 1995).

Witch hazel (*Hamamelis virginiana* L.) bark extract and hamamelitannin, the major active component of witch hazel bark, were shown to possess a strong ability to scavenge peroxynitrite (ONOO-) and it was suggested that it might be developed as an effective peroxynitrite scavenger for the prevention of ONOO-involved diseases (Choi et al, 2002).

Touriño et al (2008) showed that *Hamamelis virginiana* L. bark is a rich source of tannins. They, by extraction and solvent fractionation, generated fractions rich in pyrogallol-containing polyphenols (proanthocyanidins, gallotannins, gallates).

The mixtures were highly active as free radical scavengers. The antiradical efficiency of the fractions was evaluated by the DPPH stable radical method (hydrogen donation and electron transfer) and HNTTM (electron transfer). These fractions were also able to reduce the newly introduced TNPTM radical, meaning that they included some highly reactive components. Witch hazel phenolics protected red blood cells from free radical –induced haemolysis and were mildly cytotoxic to 3T3 fibroblasts and HaCat keratinocytes. They also inhibited the proliferation of tumoral SK-Mel 28 melanoma cells at lower concentrations than grape and pine procyanidins. The high content in pyrogallol moieties may be responsible of its effects on skin cells. The authors hypothesize that the final putative antioxidant effect of polyphenols may be in part attributed to the stimulation of defense systems by mild prooxidant challenges provided by reactive oxygen species generated through redox cycling.

The abundance of pyrogallol groups appears to play a major role in the antioxidant/prooxidant effects of hamamelis phenolics (Touriño et al, 2008).

Tumour necrosis factor-alpha (TNF) inhibitory activity

The effect on TNF-mediated cell death of hamamelitannin and consequently *H. virginiana* extracts has been also reported (Habtemariam, 2002) by assessing the TNF-mediated EAhy926 endothelial cell death and adhesiveness to monocytes. One to 100 μM concentrations of hamamelitannin inhibited the TNF-mediated endothelial cell death and DNA fragmentation in a dose-dependent manner. 100% protection against TNF-induced DNA fragmentation and cytotoxicity was obtained for hamamelitannin concentrations higher than 10 μM .

The protective effect of hamamelitannin was comparable with that of a related compound epigallocatechin gallate while gallic acid was a weak protective agent (<40% protection). The cytoprotection assay (Habtemariam et al, 1997) has been used to study the effect of protective agents (hamamelitannin, gallate or epigallocatechin gallate) on TNF-mediated cytolysis. The order of potency in inhibiting the TNF-

mediated cytolysis was: hamamelitannin > epigallocatechin gallate > gallate. These data are in agreement with previous reports which revealed that compounds with catecholic functional moiety could inhibit the TNF-mediated apoptosis and cytotoxicity in the murine fibroblast, L929 cells. In parallel with the cytotoxicity results, the study suggests that hamamelitannin inhibited the TNF-induced DNA fragmentation in a concentration dependant manner. As shown for catechol and flavonoid compounds a post receptor mechanism of action: i.e. an action mediated neither through direct interaction with TNF nor with TNF receptors has been suggested. The study demonstrated that hamamelitannin inhibits the cytotoxic effects of TNF without altering its effects on endothelial adhesiveness. And these may inhibit the TNF-mediated apoptosis and cytotoxicity or its protective effect against UVB-induced cell damage but do not permit to establish the concrete mechanism of action and hence awaits further research. The observed anti-TNF activity of hamamelitannin may explain the haemostatic use of *H. virginiana* in traditional medicine and its claimed use as a protective agent for UV radiation. (Habtemariam et al, 2002).

Table. 3. Non-clinical studies

PHARMACOLOGY	FOLIUM	CORTEX	AQUA/ DESTILLATUM	
<i>Venotonic activity</i>	Bernard, (1972)		Neugebauer (1948)	Balansard (1970, 1972)(condensed tannins)
<i>Vasoconstrictor activity</i>				Diemunsch & Mathis (1987) (Aqueous propylene glycol extract)
<i>Astringent activity</i>		Gracza (1987) (tincture 1:3; 62% ethanol)		Laux et al 1993 (Hamamelitannin; folium & cortex extract)
<i>Antiinflammatory activity</i>	Duwiejua M et al (1994) (ethanolic extract 70%)	Hartisch et al (1996, 1997) (proanthocyanidins, hamamelitannin) Deters et al (2001) (proanthocyanidins, polysaccharides) Erdelmeier et al(1996) (ethanolic extract 70%)		Brown & Dattner (1998) Millikan et al (2003)
<i>Antibacterial activity</i>	Brantner et al (1994) (aqueous extract)	Erdelmeier et al (1996) (hamamelitannin, proanthocyanidins)		Lauk et al (2003)(methanol extracts)
<i>Radical scavenging effects</i>		Choi et al (2002) (hamamelitannin)		Masaki et al (1993,1994, 1995) (hamamelitannin)
<i>Tumour necrosis factor alpha (TNF) inhibitory activity</i>				Habtemariam et al (2002) (hamamelitannin)
<i>Antimutagenic activity</i>		Dauer et al (1998) (tincture (1:5) and a methanolic extract (1:5))		
<i>Genotoxic and antigenotoxic effects</i>		Dauer et al (2003) (tannins, catechin, hamamelitanin, proanthocyanidin low and high molecular fractions)		

Assessor's comments

Most of the tests have been performed on pure isolated components of hamamelis such as: hamamelitannin, polyphenols, proanthocyanidins and gallic acid.

Venotonic, astringent, antibacterial, antiviral, antioxidative and scavenging mainly in vitro activities have been reported.

The in vivo anti-inflammatory effects of two hydroethanolic extracts (ethanol 70% v/v), from the leaves and the bark respectively, have been also reported.

II.2.2 Pharmacokinetics

According to the definition of HMP, the total preparation (e.g: Hamamelidis destillatum) must be regarded as the active substance. This involves a mixture of numerous constituents. The active constituents have not yet been clearly defined and many compounds are only contained in very small concentrations or defy analytical detection due to their chemical structure or their ubiquitous occurrence (polymeric phenols) No single constituent has been defined as therapeutically active marker and consequently, no appropriate pharmacokinetic studies are available.

Witch hazel extracts locally applied in therapeutic amounts do not penetrate into the deeper layers of the skin because of the astringency of their ingredients, and they are therefore not absorbed into the blood circulation (Fachinfo Posterine ® Salbe, 1997)

II.2.3 Toxicology

Hamamelis virginiana L. distillate was one of the substances studied in the Carcinogenesis Bioassay Program by the National Toxicology Program of the National Cancer Institute in 1981; thus relatively reliable data on hamamelis can be found both in original articles and extensive analyses of this program (Haseman et al, 1984, 1987; Woodruff et al, 1985).

Acute and subchronic toxicity

The oral administration of 10-20 g (single dose) of hamamelis preparation (not specified) showed no toxic effect in mice and rats. The LD₅₀ (rats) on oral administration could not be found. A daily oral intake of 100 mg/kg body weight for three months produced no abnormalities in rats (Bernard et al, 1972).

The *i.v.* administration of different aqueous solutions of a liquid extract of Hamamelis (unknown declaration) 0.2-0.4 g extract/kg bw to dogs (8.5 kg) has shown a marked arterial hypotension, with lethal doses from 0.6 to 0.8 g/kg bw. The lethal dose after a slow administration in the intrafemoral arteria was of 0.5 to 1.2 g/kg bw (Mercier & Vignoli, 1936).

Genotoxicity

Mortelmans et al (1986) included data of *Salmonella* mutagenicity results of 270 coded chemicals, encompassing 329 tests performed by three laboratories under contract to the NTP. The *Salmonella*/mammalian microsome assay was used to test chemicals in up to five strains TA1535; TA1537; TA98; TA100 in the presence and absence of rat and hamster liver S9. Tests performed after Jan 1983 included the strain TA97 replacing TA1537. Hamamelis water was negative in all tests.

In a study by McGregor et al (1988), eighteen chemicals were tested for their mutagenic potential in the L5178Y tk[±] mouse lymphoma cell forward mutation assay. Cultures were exposed to the chemicals for 4h, and cultured for 2 days before plating in soft agar with or without trifluorothymidine (TFT), 3 µg/ml. The chemicals were tested at least twice. Witch hazel was not identified as a mutagen. [PMID: 3338442, PubMed - indexed for MEDLINE]

Witch hazel was evaluated for the induction of sex-linked recessive lethal mutations in *Drosophila melanogaster* by the National Toxicology Program. Canton-S wild-type males were treated with concentrations of the witch hazel that result in approximately 30% mortality. Following treatment, males were mated individually to 3 harems of Basc virgin females to produce 3 broods for analysis. The concentrations of witch hazel tested by injection (500 ppm) or feeding (500 ppm) were negative in this assay (Woodruff et al, 1985).

Carcinogenicity

The results of approximately 86 chronic studies in rodents were published as technical reports by Huff et al (1984, 1985). The studies consist in two years feeding or gavage experiments involving groups of 50 male and female Fischer -344/N rats and B6C3F₁ mice (Haseman et al, 1984, 1987).

Hamamelis water (68916-39-2) is considered as showing no carcinogenic effects after dermal application 50% or 100% in deionized water 5 d/wk. Witch hazel was tested at EGG and SRI and gave a reproducible dose response, EGG, EGG (+, -) and SRI, SRI (-,-). Both samples were returned to Radian Corporation for analysis and comparison with the parent repository sample where it was found that all three samples gave identical HPLC tracings. This ruled out the possibility of a mutagenic contaminant in the EGG sample. The possibility of a contamination or mislabeled samples was ruled out by the analysis of the remainder sample which gave negative results. Technical reports classified hamamelis as a non-carcinogen. However, the study was considered inadequate and no formal report was prepared.

Antimutagenic activity

In the Ames mutagenicity test, a tincture (1:5) and a methanolic extract (1:5) of hamamelis bark dose dependently inhibited 2-nitrofluorene-induced mutagenicity in *Salmonella typhimurium* TA98, by 60% and 54% respectively at 100 µl/plate. The mechanism of antimutagenic action was also studied. The proanthocyanidins did not act as bioantimutagens, but rather as direct-acting desmutagens. Tannin-free samples did not display any inhibition. It was demonstrated that the antimutagenic effect increased with increasing degree of polymerisation of proanthocyanidins, the most active fraction consisting of catechin and galocatechin oligomers with an average degree of polymerization of 9.2 (Dauer et al, 1998) .

Reproductive and development toxicity.

There is not information on reproduction toxicity.

II.2.3.1 OVERALL CONCLUSIONS ON TOXICOLOGY

Limited information is available on toxicology of herbal preparations of hamamelis. Details of the preparations used in the studies reported are usually lacking. There are only few studies with *Hamamelis virginiana* L. distillate, fractions of hamamelis preparations and isolated compounds such as hamamelitannin.

Reliable data from tests on genotoxicity are only available for Hamamelidis aqua preparations, which are devoid of genotoxic activity. Although the definite carcinogenicity NTP study has not been formally reported, it can be provisionally concluded that hamamelis water is not carcinogenic. Nevertheless, according to the studies of hamamelis water preparations, the external application of hamamelis water probably poses a very low or absent genotoxic or carcinogenic risk.

The safe use of hamamelis distillates has been accepted by the MLWP and HMPC, taking into account the data in the AR toxicology section (II.2.3) and all available data for the therapeutic indications for cutaneous use as well as the short-term duration recommended for treatments. As the requirements have been found to be fulfilled, a positive decision has been taken for the preparation of a List entry on hamamelis leaf and bark or twigs distillate.

II.3 CLINICAL DATA

II.3.1 Clinical Pharmacology

II.3.1.1 PHARMACODYNAMICS

Anti-inflammatory activity

Although *Hamamelis virginiana* L. has long been used in the traditional treatment of skin diseases, there are few controlled clinical studies defining the extent of its anti-inflammatory action.

Topical herbal drugs have for centuries been used for treating skin ailments. Although they are currently widely accepted by patients, their scientific esteem among dermatologists in particular is limited. In a review of the efficacy and safety of anti-inflammatory agents used in dermatology, with >100 references, a variety of herbal drugs for topical application were reviewed by Hoermann et al, (1994). Hamamelis preparations looked particularly well documented. While the final proof of efficacy in common dermatoses such as atopic dermatitis was found still lacking, the authors found fairly ample evidence for their activity against cutaneous inflammation in man, as may be deduced from experiments with normal volunteers and unwanted effects related to the drug are virtually absent. The authors concluded that in particular dermatitis and related disorders can be considered potential indications for topical herbal anti-inflammatory drugs (Hoermann et al, 1994).

In a randomized, placebo controlled study Sorkin (1980) assessed the vasoconstrictive effects of an aqueous propylene glycol extract of hamamelis in 30 healthy volunteers. The extract produced a reduction in skin temperature as compared with the placebo. The anti-inflammatory effects of a hamamelis ointment containing 25 g aqueous distillate /100 g ointment base (about 4 g of drug) were analysed in five patients with dermatoses and 22 healthy volunteers were examined. 44 fluvographic curves were obtained, of which 23 were recorded under the verum product under its ointment base.

Fluorography involves the measurement of the thermal conductivity of the skin, this being as a factor in linear proportion to skin circulation. Fluorography measurements indicated that in both groups the ointment reduced the thermal conductivity of the skin due to vasoconstriction, suggesting a mild anti-inflammatory activity. These data were confirmed by trans-cutaneous oxygen measurements.

The anti-inflammatory activity of hamamelis distillate has been evaluated with respect to drug concentration (0.64 mg/2.56 mg hamamelis ketone/100 g) and the effect of the vehicle (O/W emulsion with/without Phosphatidylcholine (PC) in an experimental study (two randomized double blind studies). The effects were compared with those of chamomile cream, hydrocortisone 1% cream and 4 base preparations. Erythema was induced by UV irradiation and cellophane tape stripping of the horny layer in 24 healthy volunteers and two tested experiences. Skin blanching was quantified by visual scoring and chromometry. Drug effects were compared with one another and with an untreated control area, as well as with any action due to the vehicle.

UV-induced erythema at 24h was best suppressed hydrocortisone cream and standard low dose hamamelis PC-cream while chamomile cream appeared inactive. Hydrocortisone appeared superior to both hamamelis vehicle, hamamelis cream (without PC) and chamomile extract. Though the cellophane tape stripping Seventy five µl of each test preparation was applied to five test areas in random order, and another remained untreated and served for control. Twelve subjects received the low dose hamamelis cream and the corresponding vehicle as well as chamomile cream (Group 1) and 12 volunteers received hydrocortisone cream, hamamelis PC-creams (low and high dose), the corresponding vehicle and O/W vehicle-2(Group 2). Skin colour was determined after 4, 8 and 24 h by chromametry. The erythematous reaction to the stripping of the horny layer faded rapidly. Thus, only the changes in the skin redness 4 and 8 hours after stripping and drug application were suitable for the analysis of drug effects. Comparing the effects of the active preparations, hydrocortisone appeared superior to PC-creams in 9 of 12 tests according to the visual scores and chromametry data ($p < 0.1$).

Erythema 4 to 8 h after the stripping of the horny layer was suppressed by hydrocortisone 1% ($P \leq 0.05$). Inflammation was also less pronounced following lower dose hamamelis PC-cream and chamomile cream.

As expected, the results have demonstrated the anti-inflammatory activity of hamamelis PC-cream, which appeared more active than hamamelis cream (Korting et al, 1993).

The anti-inflammatory efficacy of an aftersun lotion with 10% hamamelis distillate, the vehicle and a prior after sun formulation were tested in 30 healthy volunteers using a modified UVB erythema test as model of inflammation. The main indication for the lotion is the alleviation of the symptoms accompanying by mild sunburn. Chromametry and visual scoring were used to determine the degree of erythema in the treated fields and an untreated, irradiated control field 7, 24 and 48 h after irradiation. The erythema suppression in the test sites treated with hamamelis tended to increase with longer treatment times. The erythema suppression ranged from approximately 20% of 7 h to 27% at 48 h in the hamamelis fields. A suppression of 11-15% was recorded in the fields treated with the other lotions. Significant differences were noted between hamamelis and these lotions. Hamamelis distillate in a conventional O/W cream did not prove effective. The results provide evidence for the topical use of hamamelis distillate for the treatment of minor inflammatory skin diseases which do not need treatment with potent corticosteroids. The authors stated that, in particular the relief of the symptoms associated to the sunburn inflammation, is a suitable indication for aftersun lotion with hamamelis (Korting, 1993).

The anti-inflammatory activity of hamamelis in experimental irritation models were explored in 15 healthy volunteers. Irritation test caused by Sodium lauryl sulphate (SLS) on 4 test sites on both volar forearms. SLS was applied once a day for ½ hour. 4 symmetrical test sites were tested: a distillate of Aqua Hamamelidis (USP) (90%) and urea (5%) formulated as a topical dermatological preparation vs untreated; the product containing Hamamelidis Aqua vs the product without hamamelis; hamamelis extract USP vs extract and hydrocortisone 1% in the above mentioned speciality without hamamelis and hydrocortisone. Stratum corneum water content (corneometry), transepidermal water loss (TEWL, Tewameter), cutaneous blood flow (Laser Doppler), and skin redness (Chromameter, a *value) were determined at baseline and after at 7 days (Gloor et al, 2001).

Eighteen subjects underwent the dithranol (anthralin) irritation test for 3 days. An erythema was produced by application of 1% dithranol for 10 minutes. The product containing hamamelis against the product without hamamelis, and one site untreated. Cutaneous blood flow (Laser Doppler) and skin redness chromameter were determined at baseline and after 3 days.

In both irritation models, hamamelis produced significant reductions in cutaneous blood flow and skin redness compared with the vehicle. In the SLS irritation test, TEWL and stratum corneum water the effects were mainly due to the vehicle that contained both glycerol and urea. Hamamelis USP was ineffective on all measures. Hydrocortisone 1% had similar effect on cutaneous blood flow and had also significant hydrating effect. The vehicle in the formulation is fundamental for having an effective product. (Gloor et al, 2001).

Clinical trials data regarding the efficacy in eczema patients are conflicting (Swoboda et al, 1991; Korting et al, 1995). However it has been possible to demonstrate a beneficial effect of hamamelis preparations in inflammation induced by UV light (Korting et al, 1993, Hughes-Formella et al, 1998). The efficacy of three lotions with 10% hamamelis distillate obtained from different suppliers, two hamamelis free vehicles (vehicle 1: distillate replaced with 85% water and 15% ethanol and vehicle 2: hamamelis distillate replaced by water) and three comparators (dimethindene maleate 0.1% gel, hydrocortisone 1% cream and hydrocortisone 0.25% lotion) were tested in 40 volunteers (19-50 years of age), in a modified UV erythema test with three dosages (1.2, 1.4 and 1.7 MED, Individual minimal erythema dosage determined). Chromametric measurement of redness and visual assessment were performed 24, 48 and 72 h after the induction of erythema. The hydrocortisone formulations were most effective in erythema suppression. An anti-inflammatory effect was noted for all three hamamelis lotions as well as for the vehicles. In this study the best results for all three hamamelis formulations were found at 1.4 MED. Antihistamine dimethindene maleate 0.1% gel did not prove to be more effective than the hamamelis lotions as well as the vehicles, this failure observed was in accordance with the available literature since antihistamines have usually found to be ineffective in this model when applied after irradiation (Hughes-Formella et al, 2002).

Vasoconstriction

A randomized, placebo controlled study assessed the vasoconstrictive effects of an aqueous propylene glycol (water/propylenglycol 50:50) extract of hamamelis leaves in 30 volunteers in three arms. A thermometric method is proposed in this study. The extract produced a significant reduction in skin temperature as compared with placebo (Diemunsch & Mathis, 1987).

Antimicrobial activity

The antimicrobial activity of a distillate of *Hamamelis* (Aqua *Hamamelidis*), United States Pharmacopoeia (USP) 23, and urea (5%) formulated as a topical dermatological preparation was studied. The study was conducted in 15 healthy volunteers. In vivo, the occlusion and expanded flora tests produced consistent results. The occlusion and expanded flora tests were described by Leyden et al (1979). The occlusion test involved the application of a commercial water impermeable cling film, following the test solution application, having it in place for 24 hours and then the bacteriological test was performed. The expanded flora test involved 24-hour film treatment as described for the occlusion test but without prior test solution application.

The distillate showed significant antimicrobial activity on aerobes. The simple occlusion test showed the same tendency, but results were not significant. Formulations of hamamelis distillate and urea are mainly used for their anti-inflammatory, hydrating and barrier stabilizing effects in dermatitis maintenance therapy. The antimicrobial activity of such products is considered an added benefit. The antimicrobial activity is particularly welcome in the management of atopic dermatitis and intertrigo because the organisms involved in the pathogenesis of these conditions are susceptible to the hamamelis preparations (Gloor et al, 2002)

Anti-aging activity

Typical symptoms of skin aging are tautness and itching, which may eventually lead to exsiccation eczema. This study investigated the safety and efficacy of hamamelis ointment for skin care and symptom relief in patients with dry aging skin.

An open-label clinical study was performed with a hamamelis ointment for studying dry aging skin in 89 patients at a minimum age of 50 years. Patients were treated with Hametum ointment, applied twice daily for a period of four weeks. Primary variables of the study were sebumetric and corneometric measurements, secondary visual score of dryness symptoms such as tautness, roughness or itching. The outcome after a period of 4 weeks of application was a significant and clinically relevant improvement of skin sebum content and moisture. Improvement of symptoms was statistically significant for all tested variables. Pronounced effect was already present after 2 weeks of treatment. Scaling and fissures were clearly reduced and symptoms like tautness, roughness and itching improved. Skin tolerability was regarded as very good. Hametum wound healing ointment contains 6.25 mg distillate from fresh leaves and twigs of *H. virginiana* (1:1.6) as active ingredient. The effect could be attributed to the ointment base which protects the skin from moisture loss in the form of a superficial layer, but also to the healing-promoting action of the hamamelis distillate contained in the ointment. (Welzel et al, 2005; Hartmann, 2005)

Table 4. Clinical References

Author	Design(D)/ Indication(I)	Test substance	Test criterion	Posology/ Duration of use	Year
Sorkin B	(D): open against base, intraindiv. Comparison. Volunteers (N=20) (I): Atopic eczema (N=5)	Ointment	Blood flow in the skin (Fluovography)		1980
Diemunsch AM	D) Randomized, controlled Intraindividual comparison (I) Volunteers (N=30) (II)	Extract (water/propylene glycol)	Skin temperature Thermometric method		1987
Moore W James DK	(D): Double blind, randomized, placebo-controlled. (I) Postepisiotomy care (n=266)	Hamamelis water BPC	Pain swelling, oedema (Patient and doctor)		1989
Korting HC	D): Double blind, multiple control, intraindiv. comparison. (n=12) (I) Inflammation models in volunteers (cell stripping)	-phosphatidylcholine-containing ham. distillate (PC-Cream) or ham. ketone -cream without PC - hydrocortisone 1% - Chamomile extract	Visual appearance. (multiple sum score) Chromametry	4, 8, 12h test	1993
Korting HC	D): Double blind, multiple control, intraindiv. comparison. (n=24) (I) Inflammation models in volunteers (erythema UV irradiation)	-phosphatidylcholine containing ham. distillate (PC-Cream) or ham. ketone -cream without PC - hydrocortisone 1% - Chamomile extract	Visual appearance. (multiple sum score) Chromametry	24, 48h	1993
Korting HC	(D) Randomized, double-blind, placebo controlled. (I) Inflammation models in volunteers. UV induced Erythema (N=40)	aftersun Lotion 10% ham. distillate	Inflammation induced by UV light		1993

Gloor M	(N=18) Experimental irritation model: Dithranol (anthralin)	Hamamelidis Aqua + Urea		3 days	2001
Gloor M	(N=15) Experimental irritation model: Sodium Lauryl sulphate (SLS)	Hamamelis ointment; Base ointment; Hamamelidis extract USP Hydrocortisone 1%	Corneometry/ Transepidermal water loss/ Cutaneous blood flow/Skin redness (chromameter)	7days. SLS once a day for ½ hour + study products	2001
Gloor M	Occlusion and expanded flora tests	Hamamelidis Aqua + Urea	Dermatitis/Anti- septic effects	24 h	2002
Hughes- Formella BJ	Erythema suppression. antinflammatory effect Finn chamber (N=40)	Aftersun Lotion, ham. distillates, lotion base	Inflammation induced by UV light	24, 48, 72h	2002
Welzel J	(D) Open, clinical study (N=89)	Hamatum ointment	Dry aging skin	4 Weeks	2005

II.3.1.2 PHARMACOKINETICS

No data available.

II.3.2 Clinical Efficacy³

Eczema

Hamamelis preparations could be proposed in the maintenance therapy for atopic eczema, particularly as follow up to treatment with steroidal anti-inflammatory agents. The low toxicity of hamamelis and the absence of known undesirable effects, support a favourable risk/benefit ratio for this preparation containing hamamelis distillate. Hamamelis water led to a significant reduction in erythema compared to the vehicle ($p=0.00001$) and untreated irradiated skin ($p=0.00001$) (Hughes-Formella et al, 1998).

A randomized double blind comparison study assessed the efficacy of ointments containing either a standardized extract of the dried leaves or bufexamac in the treatment of 22 patients with bilateral, moderately or severe endogenous eczema. Patients were treated three times daily for an average of 17 ± 5 days (Treatment duration between 5 to 22 days). Comparison of the patients' forearms showed that both treatments reduced the severity of symptoms such as desquamation of the skin, redness, itching, infiltration and lichenification, with desquamation showing the highest reduction (55%). No differences were observed in the global assessment of the therapy or the severity of symptoms between treatments (Swoboda et al, 1991).

A randomized, double-blind, placebo controlled trial lasting 14 days compared the efficacy of three creams containing either a hamamelis distillate (5.35 g hamamelis distillate with 0.64 ketone/100 g) 0.5% hydrocortisone cream or a drug-free vehicle in 72 patients for the symptomatic treatment, and reductions in severe atopic eczema (Δ values of the sum scores) were evaluated. Effects were compared using

³ In case of traditional use the longstanding use and experience should be assessed.

Wilkinson's test. All treatments significantly reduced the incidence of itching, scaling and erythema after 1 week of treatment. Hydrocortisone proved superior to hamamelis distillate. The cream containing hamamelis distillate did not differ from the vehicle. The results showed that the therapeutic outcome using the hamamelis preparation was not better than following the base preparation (Korting et al, 1995).

A case of accidental skin injury caused by leakage of sodium hypochlorite solution from the rubber dam during root canal preparation is reported. The patient developed a skin rash followed by scab formation which required medical treatment with topical *Hamamelis virginiana* extract for 2 weeks, with full recovery (Ahmet et al, 2004).

The efficacy of two hamamelis ointments (differing only in the ointment base) containing 25 g aqueous distillate/100 g ointment base (equivalent to about 4 g drug), for the treatment of endogenous eczema (neurodermatitis) and toxic degenerative eczema (attrition eczema) was compared in a placebo controlled, double blind study (the placebo was not described) in 80 patients. Symptomatic improvements in itching, redness, burning sensation and desquamation of the skin were observed in 36 patients after 28 days of treatment with endogenous eczema with both hamamelis preparations after treatment for 39 days (Pfister, 1981).

In a pilot study of 37 patients with endogenous eczema a cream containing a hamamelis leaf extract was applied twice daily for two weeks. Following treatment, considerable improvement in symptoms like such as inflammation and itching was noted in 24 patients (Wokalek, 1993)

In a multicenter, prospective paediatric cohort study on the efficacy and tolerability of hamamelis ointment, children of different age groups (27 days to 1 year; 1 to 5 years; 6 to 11 years of age) suffering from superficial skin lesions/ diaper skin rash/ or other local inflammations of skin and mucous membranes were treated in a randomized manner at a ratio of 3:1 with either an hamamelis ointment and dexpanthenol. The recommended individual observation was 7 to 10 days; dosage was based on the recommendations of the treating physician.

309 patients were enrolled into the study (hamamelis ointment: 231; dexpanthenol: 78). Both therapeutic groups showed comparable initial values. The efficacy of both therapeutic treatments could be proven for all three diagnoses with statistically significant and clinically relevant improvement of the total score between the beginning and the end of treatment ($p < 0.0001$ in each case). Within the three age groups, the total score for the skin diseases investigated improved in both therapeutic treatments without statistically relevant differences between the comparative cohorts. In total, 83.5% of the doctors and 83.1% of the parents considered the efficacy of hamamelis ointment as excellent or good (Dexpanthenol: 83.3% and 80.7%). Tolerability of hamamelis ointment was assessed as excellent or good by 99.1% of the doctors and 98.2% of the parents (Dexpanthenol: 97.4% and 92.3%).

Hamamelis ointment could be considered effective and safe as a temporary treatment for certain skin disorders in children up to 11 years of age in minor skin injuries, diaper dermatitis, or localized inflammation of skin (Wolff et al, 2005). Regarding the safety in this study: 12 out of 309 children experienced adverse events, 1 out of 78 in the dexpanthenol treatment (conjunctivitis) and 11 out of 231 in the hamamelis treatment group (confusion, head lice, cough/allergic reaction, fungal infection/deterioration, otitis, erythema increased, rhinopharyngitis, burning sensation, super-infection, diaper candidiasis, and obstructive bronchitis). The authors considered only two adverse events as potentially drug related, i.e.: erythema and burning sensation. A series of physical, chemical, enzymatic and microbial changes related to diaper's holding of urine and faeces are considered responsible for diaper dermatitis. In this situation, antifungal and antibacterial products should be avoided and not to be used, as it is known that bacterial infection does not have a role in diaper dermatitis and the normal microflora should be preserved, while the antimicrobial activity of hamamelis preparations could be an explanation for some of these events.

Antihemorrhoidal efficacy

Witch hazel extracts, high in tannins and volatile oils, have a long therapeutic tradition and are used primarily for its astringent, anti-inflammatory and local haemostatic effects. In folk medicine hamamelis has been used for poor venous conditions, including the treatment of haemorrhoids. A few studies have shown that witch hazel water relieves itching, burning and other discomforts when applied to anorectal area. The substance is judged safe and effective in concentrations 10 to 50% (cream 50%); it can be applied after each bowel movement or up to 6 times daily (Zimmerman, 1993).

A randomized double blind three limb study, of 21 days duration, compared the efficacy of rectal ointments containing either a hamamelis liquid extract, bismuth subgallate or a local anaesthetic in the treatment of 90 patients with acute stage 1 haemorrhoidal symptoms. The local anesthetic was presented in two control ointments which also contained either policresulen or fluocinolone acetonide. After 21 days of treatment, all four ointments were equally effective in improving: pruritus, bleeding, burning sensation and pain. All three ointments proved highly effective. Both during the course of treatment and at the final examination; no major differences were to be found between the three groups (Knoch 1992; Barnes et al, 2007).

The study of Steinhart (1982) considered corticoid-free preparations suitable for conservative long-term treatment of symptoms associated to anorectal complaints such as haemorrhoids which may lead to bleeding, itching, burning and pain. The study compared the efficacy of Hamatum ointment to an hamamelis reference preparation in 70 patients of both sexes. After a four weeks treatment 60% of symptoms disappeared in the ointment group; in the reference group, this percentage was 30%.

Episiotomy pain

In a randomized clinical trial involving 300 mothers patients undergoing episiotomy, the efficacy of three topical agents (Epifoam, hamamelis water and ice) was investigated to determine their effects on pain, bruising and oedematous swelling. Data were collected in 266 women for immediate postnatal evaluation. The treatment tested were local application of a cream containing hamamelis water BPC 1973; a reference cream containing 1% hydrocortisone and a local anesthetic (Epifoam); and ice packs. All three agents were equally effective at achieving on the first day though one-third of the mothers derived not benefit from any agent. Ice had a tendency to be better considered. Whilst differences in the incidence resolution of bruising and oedema were demonstrated, these differences were not reflected in the mothers' perception of pain relief. Oral paracetamol and salt baths were also used as needed. The efficacy of all three treatments appeared to be equal (Moore et al, 1989).

East et al (2007) reviewed in Cochrane database the published and unpublished randomised or quasi randomised trials (RCTs) that compared localised cooling treatment applied to relieve pain related to perineal trauma sustained during childbirth. Seven published RCT were included, comparing local cooling treatment (ice packs, cold gel pads or cold/iced baths) with no treatment, hamamelis water, Pulse electromagnetic energy (PET), a hydrocortisone/pramoxine foam (Epifoam) or warm baths. The RCTs reported on a total of 859 women. Ice packs improved pain relief 24 to 72 hours after birth compared with no treatment. Women preferred the utility of the gel pads compared with ice packs or no treatment, although no differences in pain relief were detected between the treatments. None of the treatments resulted in differences detected in perineal oedema or bruising. Women reported more pain and used more additional analgesia following the application of ice packs compared with PET. There is only limited evidence to support the effectiveness of local cooling treatments.

Table 5. Clinical studies

Author	Design(D)/ Indication(I)	Test substance	Test criterion	Posology/ Duration of use
Pfister, 1981	(D): Double blind, randomized, reference controlled (I) Atopic eczema (N=36) Toxic Degenerative Eczema	25 g /aqueous distillate /100 g ointment base	Neurodermatitis Various skin symptoms	28/39 days
Steinhart, 1982	(D): Open, ref. controlled (I): Anorectal disorders (n=70)	Hametum ointment vs hamamelis reference product	Gen. Symptoms, rectal examination findings.	3 times daily 4 weeks
Moore, James, 1989	(D): Double blind, randomized, placebo controlled (I) Postepisiotomy care (n=266)	Hamamelis water BPC	Pain swelling, oedema (Patient and doctor)	
Swoboda, Meurer, 1991	D): Double blind, randomized, reference- controlled. (I)Atopic eczema (N=22)	Hametum ointment. (Standardized aqueous distillate) + Bufexamac	Neurodermatitis/ eczema Various skin symptoms	3 times daily 3 weeks
Knoch, 1991	D): Open; uncontrolled trial (I) Haemorrhoids (N= 75)	Ointment combination of fluid extract, base, bismuth gallate (corticoid free rectal ointment)	Acute stage I haemorrhoidal complaints: Bleeding, pain, itching, burning.	2 times daily 3 weeks
Knoch, 1992	D): Double blind, randomized, reference controlled, three arms study (I) Haemorrhoids (N= 90)	Ointment combination of fluid extract, base, bismuth gallate, local anesthetic (Eulatin N salbe)	Acute stage I haemorrhoidal complaints: Bleeding, pain, itching, burning.	21 days (3/7/14/21d) twice daily After 3 days, improvement of pruritus, bleeding., burning sensation and pain (p<0.001)
Wokalek, 1993	(I) Endogenous eczema. Inflammation/itching (N=37)	Cream Ham. leaf extract	Hamamelis leaf extract	2 times daily 2 weeks
Korting, 1995	(D) Randomized, double- blind, placebo controlled. (N=72)	Ham. distillate cream Ointment base 0.5% hydrocortisone (n=36 each group)	Moderate/severe atopic eczema. itching, scaling and erythema	2 weeks
Hughes- Formella, 1998		Hamamelis distillate	Erythema maintenance therapy	
Wolff, 2005	(D) Multicenter, prospective cohort study, (children) Arms: 27d-1yr; 1-5 yr; 6-11 yr. (N= 309)	Hamamelis ointment (N=231) / Dexpanthenol (N=78). Posology not reported	Superficial skin lesions/ local inflammations/ nappy rash	7 to 10 days

II.3.3 CLINICAL SAFETY

The special feature of *Hamamelis virginiana* L. is that the indications, mode of administration and the parts of the plant therapeutically used in preparations have always been the same. This simplifies the toxicological assessment and provides further evidence that hamamelis is effective and safe. A fact worth mentioning is that *Hamamelis virginiana* L. has been reported as of no toxicological importance.

II.3.3.1 PATIENT EXPOSURE

No exact data on patient exposure are available. Hamamelis products are widely used as safe ingredients in medicinal products and in cosmetics.

II.3.3.2 ADVERSE EVENTS

Witch hazel preparations are referred in Mayler's Side Effects of Drugs among the Agents known or believed to have caused immunological contact urticaria. The patch test concentration and vehicle is 10% alcohol distillate and the proposed frequency of sensitization is rare (reference SEDA 19, 162).

No significant adverse effects from the ingestion of witch hazel are expected. It may cause irritation of the stomach in a small number of susceptible individuals and topical application may cause contact allergy in rare cases (Mills and Bone, 2000).

Allergic contact dermatitis may occur in sensitive individuals. The type of contact reactions to witch hazel in the older literature is not clear, as patch test were not performed or not reported. Bruynzeel et al (1992) tested 1032 patients consecutively or randomly chosen, in 6 patch test clinics with a series of 5 popular ointments. The ointments elicited positive reactions in 11 patients among which 4 were found to react to an ointment containing 25% extract of hamamelis.

Grandlund (1994) reported a case of a 31 year-old non-atopic woman treated with 1% hydrocortisone-17-butyrate for dermatitis of the lower limbs. At the same time she started to use an eye gel, after which developed oedema around the eyes within one week. She stopped the use of the eye gel, but the oedema spread to the rest of the face and neck, and finally became eczema. The patient showed positive patch test reactions to the eye gel and to the ingredients: hamamelis distillate and cucumber extract.

Conjunctivitis has been reported by Ireland and Spain for eye drops (hamamelis distillate (1.6:1) the frequency is not known.

Contraindications (hypersensitivity and allergic potential to be both covered)

Hypersensitivity to the active substance.

II.3.3.3 SERIOUS EVENTS AND DEATHS

None known.

II.3.3.4 LABORATORY FINDINGS

No data available.

II.3.3.5 SAFETY IN SPECIAL POPULATIONS AND SITUATIONS.

Caution should be exercised with long term oral use due to the presence of tannins. In susceptible patients, irritation of the stomach may occur occasionally. In rare cases, witch-hazel tannins may cause liver damage (McGuffin, 1997)

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

None known.

II.3.3.5.2 Drug-drug interactions and other interactions

None reported for hamamelis preparations.

Tannins inhibit absorption of minerals and B vitamins.

II.3.3.5.3 Use in pregnancy and lactation

Safety during pregnancy and lactation has not been established definitely. In accordance with general medical practice and in absence of sufficient data, hamamelis preparations for internal use should not be used during pregnancy and lactation without medical advice (ESCOP, 2003).

II.3.3.5.4 Overdose

No case of overdose has been reported.

II.3.3.5.5 Drug abuse

None known.

II.3.3.5.6 Withdrawal and rebound

None known.

II.3.3.5.7 Effects on ability to drive or operate machinery

None known.

II.3.3.6 OVERALL CONCLUSIONS ON SAFE USE

The external application of hamamelis preparations can be regarded as safe, especially at the recommended doses.

Contact allergic dermatitis has been reported only in rare cases.

Some conjunctivitis cases have been reported during the use of eye drops containing hamamelis (dilution of hamamelis distillate (1.6:1)), while the frequency is not known.

In view of the results of the preclinical toxicological studies, clinical trials and several decades of experience of its use in human beings, as well as the degree of satisfaction expressed by the patients, the hamamelis preparations can be classified as safe and well tolerated medicines.

II.4 OVERALL CONCLUSIONS

As is the case for many other plant preparations, consistent scientific data supporting the efficacy of hamamelis preparations are still limited. Some controlled clinical trials have been performed, some of them showed positive outcomes but of weak statistical interpretation. The beneficial effect of hamamelis is primarily supported by traditional use.

Diluted preparations of hamamelis distillate virtually with no tannin content, 14-15% alcohol in water and a small amount of the essential oil of witch hazel have been widely used in many eye cleansing products. There are some products of Hamamelis aqua (water steam distillate) (1:1.6), authorised as medicinal products in different European countries (see I. Regulatory Status Overview), but this provides no rationale for recommending the use of this preparation under well established use (WEU).

In relation to the cutaneous use of hamamelis, some randomized, placebo controlled studies have been performed with products containing hamamelis distillate. The results of some of these clinical trials regarding the efficacy in eczema are conflicting (Hughes-Formella, 2002; Korting, 1995). However, in two separate laboratories the beneficial effect of hamamelis preparations in inflammation induced by UV light or tape stripping in human volunteers has been demonstrated (Hughes-Formella BJ, 1998; Korting,

1993). In both of these studies the anti-inflammatory potency was weaker than for hydrocortisone but significantly greater than for the vehicle. The efficacy has been demonstrated with concrete products and related mainly to the excipients used as carriers in the formulations. This is the rationale for not considering Hamamelidis aqua preparations for WEU.

The plausibility of the traditional cutaneous use of hamamelis distillate and its preparations (semi solid/solid preparations) is reinforced upon available (non-) clinical pharmacological experiences and based upon long-standing use, as well.

The assessor's final conclusion is to recommend only the traditional registration procedure for the preparations of hamamelis considered in this AR mainly for cutaneous use (skin and external mucosa), including products containing hamamelis water preparations which are considered as the most extensively studied.

The oral use of hamamelis preparations such as tincture (1:10) (leaf); tincture (1:10 w/v, in 55% ethanol V/V) (bark); Liquid extract (1:1) ethanol 45% v/v (leaf) which has been referred and supported by handbooks and hamamelis monographs (WHO, Commission E and ESCOP), is not recommended by the assessor, as there are not products in the market which comply with the conditions required for traditional herbal medicinal products.

The following extracts: Dry extract with ethanol 80% V/V (DER 5-8.5:1) and dry extract with ethanol 96% V/V (DER 6-9:1), have not been included in the monographs because no adequate information on the use of either of them was available to the assessor.

Period of traditional use (art. 16a(1)(d)), as laid down in (art. 16(1)(c)), has elapsed for the preparations included in the monograph. The traditional use outside and inside the European Union has been shown in detail for much more than 30 years.

Recommended indications for hamamelis leaf or bark for cutaneous use: Traditional herbal medicinal product for relief of minor skin, inflammation and dryness of the skin.

Recommended indications for hamamelis leaf or bark preparations for anorectal use: Traditional herbal medicinal product for symptomatic relief of itching and burning associated with haemorrhoids.

Recommended indications for hamamelis leaf or bark for oromucosal use
Traditional herbal medicinal product used as a mouthwash and gargle for relief of minor inflammation of mucous membranes of the oral cavity conditions of the oral mucosa.

Recommended indications for diluted hamamelis distillate/External use
Traditional herbal medicinal product for relief of minor skin inflammation and dryness of the skin.
Traditional herbal medicinal product for the temporary relief of discomfort due to dryness of the eye or to exposure to wind and sun.
The product is a traditional herbal medicinal product for use in specified indication exclusively based upon long-standing use.

Hamamelis bark (Hamamelidis cortex)

Recommended posology

External use:

Semi-solid and liquid preparations containing the equivalent 5-10% of bark, as often as required. As impregnated dressings, lotion or mouthwash, decoction of 5-10 g of bark to 250 ml of water.

For cutaneous use:

Tincture (bark) (1:10; ethanol 45% v/v) in a strength corresponding to 5-10% in semi-solid preparations, several times a day.

Dry extract (5-7.7:1; extraction solvent ethanol 30% m/m) in a strength corresponding to 1.3% in semi-solid preparations, several times a day.

For anorectal use:

Tincture in a strength corresponding to 5-10% in semi-solid preparations, several times daily.

Comminuted herbal substance as decoction: 5-10 g/250 ml, up to 3 times a day in impregnated dressings.

Dry extract (5-7.7:1; extraction solvent ethanol 30% m/m) in a strength corresponding to 1.3% in semi-solid preparations, several times a day.

For rectal use:

Suppositories containing 66 mg of dry extract (5-7.7:1; ethanol 30% m/m) One suppository, two or three times a day.

For oromucosal use (mouthwash and gargles):

2-3 g of herbal substance as herbal tea (decoction) for using as a mouthwash, up to three times a day.

Diluted tincture (1:10; ethanol 45% v/v), 2-4 ml, three times a day.

Hamamelis leaf (Hamamelidis folium)

For cutaneous use:

Tincture or liquid extracts (1:1) in a strength corresponding to 5-10% in semisolid or liquid preparations, several times daily.

Liquid extract (1:2; ethanol 60% v/v) in a strength corresponding to 20% as semi-solid preparation.

For oromucosal use:

Decoctions of 5-10 g of leaf to 250 ml of water (or 2-3 g in 150 ml), for impregnated dressings and rinses, several times daily.

Tincture (1:10) in 45% ethanol (diluted (1:3) with water) 2-4 ml, three times daily as gargle.

For symptoms associated with hemorrhoids:

Tincture or liquid extracts (1:1) in a strength corresponding to 5-10% in semisolid and liquid preparations, several times daily.

Liquid extract (1:2; ethanol 60% v/v) in a strength corresponding to 20% as a semi-solid preparation, several times daily.

Comminuted herbal substance as decoction: 5-10 g/250 ml, up to 3 times a day in impregnated dressing.

For rectal use:

Suppository containing 400 mg of liquid extract (1:2; ethanol 60% v/v), 2-3 times a day.

Hamamelis distillate (Hamamelidis destillatum)

For cutaneous use: distillates in a strength corresponding to 5-30% in semi-solid preparations, several times a day.

Eye drops:

Hamamelidis distillate 10% diluted: Single dose 2 drops/each eye, 3-6 times a day.

Route of administration (art. 16a(1)(c))/duration of use

Hamamelis products are mainly recommended for cutaneous application. The average duration of use is two weeks. In case of application on the eye, the duration of use should be limited to 4 days.

Non clinical safety

Limited information is available on toxicology of herbal preparations of hamamelis. Details of the preparations used in the studies reported are usually lacking. There are only few studies with Hamamelis virginiana, destillatum (Hamamelidis Aqua USP), fractions of hamamelis preparations and isolated compounds such as hamamelitannin.

Reliable data from test on genotoxicity are only available for Hamamelidis aqua preparations.

According to the experience acquired during the prolonged use of hamamelis preparations, the external application can be regarded as safe.

Clinical Safety

The external application of hamamelis preparations can be regarded as safe at the recommended doses.

Contact allergic dermatitis has been reported only in rare cases.

Conjunctivitis case has been reported for eye drops (dilution of hamamelis distillate (1.6:1)), the frequency is not known.

In view of the results of the preclinical toxicological studies, clinical trials and several decades of experience of its use in human beings, as well as the degree of satisfaction expressed by the patients, the hamamelis preparations can be classified as safe and well tolerated medicines, proved not to be harmful in the specified conditions of use. Their pharmacological effects or efficacy are plausible on basis of long-standing use and experience.

These preparations comply the criteria for traditional herbal medicinal products as established in the Art 16 c(1)(e) of the Directive 2004/24/EC.

The safe use of hamamelis distillates has been accepted by the MLWP and HMPC, taking into account the data of the AR toxicology section (II.2.3) and all available data for the therapeutic indications for cutaneous use as well as the short-term duration recommended for treatments. As the requirements have been found to be fulfilled, a positive decision has been taken for the preparation of a List entry on hamamelis leaf and bark or twigs distillate.

ANNEXES

- II.5** **COMMUNITY HERBAL MONOGRAPHS ON
HAMAMELIS VIRGINIANA L., CORTEX;
HAMAMELIS VIRGINIANA L., FOLIUM;
HAMAMELIS VIRGINIANA L., FOLIUM ET CORTEX OUT RAMUNCULUS DESTILLATUM^{4,5}**
- II.6** **COMMUNITY LIST ENTRY ON HAMAMELIS VIRGINIANA L., FOLIUM ET CORTEX OUT
RAMUNCULUS DESTILLATUM⁶**
- II.7** **LITERATURE REFERENCES**

⁴ According to the “Procedure for the preparation of Community monographs for traditional herbal medicinal products” (EMEA/HMPC/182320/2005 rev.2)

⁵ 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)

⁶ According to the “Structure of the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products” (EMEA/HMPC/100824/2005 rev.2)