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List of references supporting the assessment of *Aesculus hippocastanum* L., semen

Draft – Revision 1

The European Medicines Agency acknowledges that copies of the underlying works used to produce this monograph were provided for research only with exclusion of any commercial purpose.

First version

Bisler H, Pfeifer R, Klüken N and Pauschinger P. Wirkung von Rosskastaniensamenextrakt auf die transkapilläre Filtration bei chronischer venöser Insuffizienz. *Deutsche Medizinische Wochenschrift* 1986, 111: 1321 – 1329.

Blaschek W, Hänsel R, Keller K, Reichling J, Rimpler H, Schneider G, editors. Hagers Handbuch der Pharmazeutischen Praxis. Drogen A-D. Vol 4. 5th ed. Springer-Verlag, Berlin-Heidelberg 1992.

Bombardelli E, Morazzoni P and Griffini A. *Aesculus hippocastanum* L. *Fitoterapia* 1996, 67: 483 – 511.

Bradley P. British Herbal Compendium Vol. 2. *British Herbal Medicine Association*, 2006.

Brunner F, Hoffmann C and Schuller-Petrovic S. Responsiveness of human varicose saphenous veins to vasoactive agents. *Journal of Clinical Pharmacology* 2001, 51: 219 – 224.

Bässler D, Okpanyi S, Schrödter A, Loew D, Schürer M and Schulz H-U. Bioavailability of β -aescin from horse chestnut seed extract: comparative clinical studies of two galenic formulations. *Advances in Therapy* 2003, 20(5): 295 – 304.

Carrasco OF and Vidrio H. Endothelium protectant and contractile effects of the antivaricose principle escin in rat aorta. *Vascular Pharmacology* 2007, 47: 68 – 73.

Cloarec M. Study on the effect of a new vasoprotective Venostasin administered over a period of 2 months in chronic venous insufficiency of the lower limb (data from 1992). Data on file. Unpublished.

CosIng [The European Commission database with information on cosmetic substances and ingredients (contained in the Cosmetics Regulation EC No 1223/2009, Cosmetics Directive 76/768/EEC and Inventory of Cosmetic Ingredients)]. Available at: <http://ec.europa.eu/consumers/cosmetics/cosing/>. Accessed March 2018

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- Diehm C, Trampish HJ, Lange S and Schmidt C. Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency. *Lancet* 1996, 347: 292 – 294.
- Diehm C, Schmidt C. Venostasin retard gegen Plazebo and Kompression bei Patienten mit CVI II/III1A. Final Study Report. Klinge Pharma GmbH Munich, Germany. Reported in: Ottillinger B, Greeske K. *BMC Cardiovascular Disorders* 2001, 1-5.
- Diehm C, Vollbrecht D, Amendt K and Comberg HU. Medical edema protection – clinical benefit in patients with chronic deep vein incompetence. A placebo controlled double blind study. *VASA* 1992, 21(2): 188 – 192.
- Dittgen M, Zimmermann H, Wober W, Höflich C, Breitsbarth H und Timpe C. Untersuchung der Bioverfügbarkeit von β -aescin nach oraler Verabreichung verschiedener Darreichungsformen. *Pharmazie* 1996, 51: 608 – 610.
- Draft monograph intended for inclusion in the European Pharmacopoeia. Horse-chestnut. *Pharmeuropa* 1995, 7.
- Draft monograph intended for inclusion in the European Pharmacopoeia. Horse-chestnut dry extract, standardised. *Pharmeuropa* 1996, 8.
- Edem E, Kahyaoglu B, Çakar MA. Acute effusive pericarditis due to horse chestnut consumption. *American Journal of Case Reports* 2016, 17: 305-308.
- Ehringer H. Zum venentonisierenden Prinzip des Rosskastanienextraktes. *Die Medizinische Welt* 1968, 19: 1781 – 1785.
- Enghofer E, Seibel K und Hammersen F. Die antiexsudative Wirkung von Rosskastanienextrakt. *Die Therapiewoche* 1984, 34: 4130 – 4144.
- Erdlen F. Klinische Wirksamkeit von Venostasin retard im Doppelblindversuch. *Die Medizinische Welt* 1989, 40: 994 – 996.
- Erler M. Rosskastaniensamenextrakt bei der Therapie peripherer Odeme - ein klinischer Therapievergleich. *Die Medizinische Welt* 1991, 42: 593 – 596.
- Ernst E et al. *The Desktop Guide to Complementary and Alternative Medicine*. Mosby, 2001.
- ESCOP Monographs. ESCOP, the European Scientific Cooperative on Phytotherapy, Exeter, UK, 2003.
- European Pharmacopoeia 9th ed. Horse-chestnut – Hippocastani semen. Council of Europe 01/2017:1830.
- European Pharmacopoeia 9th ed. Horse-chestnut dry extract, standardised – Hippocastani seminis extractum siccum normatum. Council of Europe 01/2017:1829.
- Facino RF, Carini M, Stefani R, Aldini G and Saibene L. Anti-elastase and anti-hyaluronidase activities of saponins and sapogenins from *Hedera helix*, *Aesculus hippocastanum* and *Ruscus aculeatus*: factors contributing to their efficacy in the treatment of venous insufficiency. *Archiv der Pharmazie (Weinheim)* 1995, 328(10): 721 – 724.
- Friederich HC, Vogelsberg H and Neiss A. Ein Beitrag zur Bewertung von intern wirksamen Venenpharmaka. *Zeitschrift für Hautkrankheiten* 1978, 53: 369 – 374.
- Felixsson E, Persson IA, Eriksson AC, Persson K. Horse chestnut extract contracts bovine vessels and affects human platelet aggregation through 5-HT_{2A} receptors: an in vitro study. *Phytother Res* 2010, 24(9): 1297-1301.

- Guillaume M and Padioleau F. Veinotonic effect, vascular protection, antiinflammatory and free radical scavenging properties of horse chestnut extract. *Arzneimittel-Forschung/Drug Research* 1994, 44(1): 25 – 35.
- Hartleb M, Gutkowski K. Unexpected liver cirrhosis in a young patient with long-term use of the horse chestnut seed extract. *Gazz Med Ital – Arch Sci Med* 2015, 174: 141-142.
- Hitzenberger, G. Die therapeutische Wirksamkeit des Rosskastaniensamenextraktes. *Wiener Medizinische Wochenschrift* 1989, 139: 385 – 389.
- Huang Y, Zheng S-L, Zhu H-Y, Xu Z-S, Xu R-A. Effects of aescin on cytochrome P450 enzymes in rats. *Journal of Ethnopharmacology* 2014, 151 (1): 583-590.
- Iannitti T Rottigni V Palmieri B. Corticosteroid transdermal delivery to target swelling, edema and inflammation following facial rejuvenation procedures. *Drug Des Devel Ther* 2013, 7: 1035-1041.
- Jahad AR, Moore A, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996, 17(1): 1 – 12.
- Kalbfleisch W, Pfalzgraf H. Ödemprotektiva, Äquipoternite Dosierung - Rosskastaniensamenextrakt und O- β -Hydroxyethylrutoside im Vergleich. *Therapiewoche* 1989, 39: 3703 – 3707.
- Koch R. Comparative study of Venostasin and pycnogenol in chronic venous insufficiency. *Phytotherapie Research* 2002, 16(1): 1–5 .
- von Kreybig T und Prechtel K. Toxizitäts- und Fertilitätsstudien mit Aescin bei der Ratte. *Arzneimittel-Forschung/Drug Research* 1977, 27: 1465 – 1466.
- Kunz K, Schaffler K, Biber A und Wauschkuhn CH. Bioverfügbarkeit von β -aescin nach oraler Gabe zweier Aesculus Extrakt enthaltender Darreichungsformen an gesunden Probanden. *Pharmazie* 1991, 46: 145 – 146.
- Kunz K, Lorkowski G, Petersen G, Samcova E, Schaffler K and Wauschkuhn CH. Bioavailability of escin after administration of two oral formulations containing Aesculus extract. *Arzneimittel-Forschung/Drug Research* 1998, 48(8): 822 – 825.
- Lang W und Mennicke WH. Pharmakokinetische Untersuchungen mit titriertem Aescin an Maus und Ratte. *Arzneimittel-Forschung/Drug Research* 1972, 22(11): 1928 – 1932.
- Li C, Liu Z, Gao Y and Liu K. Investigation of blood toxicity in association with aescin (the horse chestnut seed extract). *Toxicology Letters* 2006, 164(1): 90.
- Liehn HD, Franco PA, Hampel H and Hofrichter G. A toxicological study of extractum hippocastani semen (EHS). *Panminerva Medica* 1972, 14(3): 84 – 91.
- Loew D, Schrödter A, Schwankl W and März RW. Measurement of the bioavailability of aescin-containing extracts. *Methods and Findings in Experimental Clinical Pharmacology* 2000, 22(7): 537 – 542.
- Lochs H, Baumgartner H, Konzett H. Zur Beeinflussung des Venentonus durch Roßkastaniensamenextrakt. *Arzneim-Forsch/Drug Res* 1974, 24: 1347-1350.
- Lohr E, Garanin G, Jesau P, Fischer H. Ödempräventive Therapie bei chronischer Veneninsuffizienz mit Ödemneigung. *Münchener Medizinische Wochenschrift* 1986, 128: 579 – 581.
- Longiave D, Omini C, Nicosia S and Berti F. The mode of action on isolated veins: relationship with PGF₂ α . *Pharmacological Research Communications* 1978, 10(2): 145 – 152.

- Lorenz D and Marek ML. Das therapeutisch wirksame Prinzip der Rosskastanie (*Aesculus hippocastanum*). *Arzneimittel-Forschung/Drug Research* 1960, 10: 263 – 272.
- Mills S and Bone K. Principles and Practice of Phytotherapy. Churchill Livingstone, 2000.
- Montopoli M, Froidi G, Comelli MC, Prosdocimi M and Caparotta L. Aescin protection of human vascular endothelial cells exposed to cobalt chloride mimicked hypoxia and inflammatory stimuli. *Planta Medica* 2007, 73: 285 – 288.
- Morales Paris CA and Barros Soares RM. Eficácia e segurança do extrato seco da semente de castanha-da Índia no tratamento da insuficiência venosa crônica de membros inferiores. *Revista Brasileira de Medicina* 1993, 50: 1563 – 1565.
- Nehring U. Zum venentonisierenden Prinzip des Rosskastanienextractes. Wirkung von Rosskastanienextrakt und von Aescin auf Venenkapazität, Venentonus und Durchblutung der Extremitäten. *Die Medizinische Welt* 1966, 17: 1662-1665.
- Neiss A and Bohm C. Zum Wirksamkeitsnachweis von Rosskastaniensamenextrakt beim varikösen Symptomenkomplex. *Münchener Medizinische Wochenschrift* 1976, 118: 213 – 216.
- Newall CA, Anderson LA and Phillipson JD. Herbal Medicines. A guide for health-care professionals. The Pharmaceutical Press, 1996.
- Oschmann R, Biber A, Lang F, Stumpf H und Kunz K. Pharmakokinetik von β -aescin nach Gabe verschiedener Aesculus-Extrakt enthaltender Formulierungen. *Pharmazie* 1996, 51: 577 – 581.
- Pauschinger P, Wörz E und Zwerger E. Die Messung des Filtrationskoeffizienten am menschlichen Unterschenkel und seine pharmakologische Beeinflussung. *Die Medizinische Welt* 1953, 32: 55 – 58.
- Pharmeuropa 26.3. Note on the monographs Horse-chestnut and Horse-chestnut dry extract, standardised. August 2014, pp. 182-194.
- Pilz E. Ödeme bei Venenerkrankungen. *Die Medizinische Welt* 1990, 41: 1143 – 1144.
- Pittler MH and Ernst E. Horse chestnut seed extract for chronic venous insufficiency. *Cochrane Database of Systematic Reviews* 2006, Issue 1, Art No.: CD003230.
- Pittler MH, Ernst E. Horse chestnut seed extract for chronic venous insufficiency. *Cochrane Database Syst Rev* 2012; 11:CD003230.
- Raffetto JD, Khalil RA. Ca²⁺-dependent contraction by the saponoside escin in rat vena cava: Implications in venotonic treatment of varicose veins. *Journal of Vascular Surgery* 2011, 54 (2): 489-496.
- Rehn D, Unkauf M, Klein P, Jost V and Lücker PW. Comparative clinical efficacy and tolerability of oxerutins and horse chestnut extract in patients with chronic venous insufficiency. *Arzneimittel-Forschung/Drug Research* 1996, 46(1): 483 – 487.
- Renaudin JM, Beaudouin E, Ponvert C, Demoly P, Moneret-Vautrin D-A. Severe drug-induced anaphylaxis: analysis of 333 cases recorded by the Allergy Vigilance Network from 2002 to 2010. *Allergy* 2013, 68: 929–937
- Reynolds JEF and Prasad AB. Martindale the Extra Pharmacopoeia. 28th Ed. The Pharmaceutical Press, 1982.
- Rote Liste® Arzneimittelverzeichnis für Deutschland. Rote Liste® Service GmbH Frankfurt/M. (Hrsg.), ECV Aulendorf 1969, 1980.

- Rudofsky G, Neiss A, Otto K and Seibel K. Ödemprotektive Wirkung and klinische Wirksamkeit von Rosskastaniensamenextrakt im Doppeltblindversuch. *Phlebologie und Proktologie* 1986, 15: 47 – 54.
- Schimmer O, Krüger A, Paulini H and Haefele F. An evaluation of 55 commercial plant extracts in the Ames mutagenicity test. *Pharmazie* 1994, 49: 448 – 451.
- Schrader E, Schwankl W, Sieder C und Christoffel V. Vergleichende Untersuchung zur Bioverfügbarkeit von β -aescin nach oraler Einmalverabreichung zweier Rosskastaniensamenextrakt enthaltender, galenisch unterschiedlicher Darreichungsformen. *Pharmazie* 1995, 50: 623 – 627.
- Schrödter A, Loew D, Schwankl W und Rietbrock N. Zur Validität radioimmunologisch bestimmter Bioverfügbarkeitsdaten von β -aescin in Rosskastaniensamenextrakten. *Arzneimittel-Forschung /Drug Research* 1998, 48: 905 – 910.
- Siebert U, Brach M, Sroczynski G and Überla K. Efficacy, routine effectiveness, and safety of horsechestnut seed extract in the treatment of chronic venous insufficiency. A meta-analysis of randomized controlled trials and large observational studies. *International Angiology* 2002, 21: 305 – 315.
- Sirtori CE. Aescin: pharmacology, pharmacokinetics and therapeutic profile. *Pharmacological Research* 2001, 44: 183 – 193.
- Snow A, Halpenny D, McNeill G, Torreggiani WC. Life-threatening rupture of a renal angiomyolipoma in a patient taking over-the-counter horse chestnut seed extract. *J Emerg Med* 2012, 43(6): 401-403.
- Steinegger E and Hänsel R. *Lehrbuch der Pharmakognosie*. Springer Verlag, 1972.
- Steinegger H and Hänsel R. *Pharmakognosie*. 5th Ed., Springer Verlag, 1992.
- Steiner M and Hillemanns HG. Untersuchung zur oedemprotektiven Wirkung eines Venentherapeutikums. *Münchener Medizinische Wochenschrift* 1986, 128: 551 – 552.
- Steiner M and Hillemanns HG. Venostasin retard in the management of venous problems during pregnancy. *Phlebology* 1990, 5: 41 – 44.
- Takegoshi K, Tohyama T, Okuda K, Suzuki K, Ohta G. A case of Venoplast-induced hepatic injury. *Gastroenterol Jpn* 1986, 21(1): 62-65.
- Zaj CM, Winiewski M, Sein AJ. [Intoxication by powdered seeds of horse chestnut (*Aesculus hippocastanum*) used nasally as snuff - a case report.] *In Polish Przegl Lek.* 2014, 71(9): 502-503.
- Wang T, Zhao S, Wang Y, Yang Y, Yao L, Chu L, Du H, Fu F. Protective effects of escin against indomethacin-induced gastric ulcer in mice. *Toxicol Mech Methods* 2014, 24(8): 560-566.
- Widmer LK and Stähelin HB. *Peripheral venous disorders Basel III*. Bern: Huber 1978.
- Wren RC. *Potter's new cyclopaedia of botanical drugs and preparations*. Saffron Walden the C.W. Daniel Company, 1988.
- Wulff G and Tschesche R. Über Triterpene – XXVI. Über die Struktur der Rosskastaniensaponine (Aescin) und die Aglykone verwandter Glykoside. *Tetrahedron* 1969, 25: 415 – 436.