EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 January 2017
EMA/HMPC/80630/2016 - *Corr*[1]
Committee on Herbal Medicinal Products (HMPC)

European Union herbal monograph on *Salix* [various species including *S. purpurea* L., *S. daphnoides* Vill., *S. fragilis* L.], cortex

Final

Initial assessment	
Discussion in Working Party on European Union monographs and European Union list (MLWP)	July 2007 September 2007
Adoption by Committee on Herbal Medicinal Products (HMPC) for release for consultation	07 September 2007
End of consultation (deadline for comments2).	15 December 2007
Re-discussion in MLWP	September 2008 January 2009
Adoption by HMPC Monograph (EMA/HMPC/295338/2007) AR (EMA/HMPC/295337/2007) List of references (EMA/HMPC/394997/2007) Overview of comments received during public consultation (EMA/HMPC/451855/2008) HMPC Opinion (EMA/HMPC/11545/2009)	14 January 2009
First systematic review	
Discussion in Working Party on European Union monographs and list (MLWP)	February 2016 April 2016 July 2016 September 2016 November 2016
Adoption by HMPC	31 January 2017

[1] Correction: minor change in section 4.2 in alignment with section 4.3 and monograph template EMA/HMPC/107436/2005
[2] No comments were received during the period of public consultation. Therefore the final monograph is published together with the final assessment report and list of references, without an 'Overview of comments received during the public consultation'.

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Keywords	Herbal medicinal products; HMPC; European Union herbal monographs; well-established medicinal use; traditional use; *Salix* [various species including *S. purpurea* L., *S. daphnoides* Vill., *S. fragilis* L.], cortex; willow bark

BG (bulgarski): Върба, кора CS (čeština): Vrbová kůra DA (dansk): Pilebark DE (Deutsch): Weidenrinde EL (elliniká): φλοιός ιτέας EN (English): Willow Bark ES (español): sauce, corteza de ET (eesti keel): pajukoor FI (suomi): paju, kuori FR (français): saule (écorce de) HR (hrvatski): vrbova kora HU (magyar): fűzfakéreg IT (italiano): salice corteccia	LT (lietuvių kalba): Gluosnių žievė LV (latviešu valoda): Vītolu miza MT (Malti): qoxra tas-safsafa NL (Nederlands): Wilgenbast PL (polski): Kora wierzby PT (português): salgueiro, casca RO (română): scoarţă de salcie SK (slovenčina): kôra vŕby SL (slovenščina): skorja vrbe SV (svenska): vide, bark IS (íslenska): NO (norsk): pilebark

European Union herbal monograph on *Salix* [various species including *S. purpurea* L., *S. daphnoides* Vill., *S. fragilis* L.], cortex

1. Name of the medicinal product

To be specified for the individual finished product.

2. Qualitative and quantitative composition[3, 4]

Well-established use	Traditional use
With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC *Salix* [various species including *S. purpurea* L., *S. daphnoides* Vill., *S. fragilis* L.], whole or fragmented dried bark i) Herbal substance Not applicable ii) Herbal preparations a) Dry extract (8-14:1) extraction solvent ethanol 70% V/V, 15% total salicin[5].	With regard to the registration application of Article 16d(1) of Directive 2001/83/EC *Salix* [various species including *S. purpurea* L., *S. daphnoides* Vill., *S. fragilis* L.], whole or fragmented dried bark i) Herbal substance Not applicable ii) Herbal preparations a) Comminuted herbal substance b) Powdered herbal substance c) Dry extract (DER 8-20:1) extraction solvent water[6] d) Dry extract (DER 16-23:1) extraction solvent water e) Liquid extract (DER 1:1), extraction solvent ethanol 25% V/V f) Tincture (1:5), extraction solvent ethanol 25% V/V

3. Pharmaceutical form

Well-established use	Traditional use
Quantified herbal preparation in solid dosage form.	Herbal preparation in solid or liquid dosage form, or as herbal tea for oral use.

[3] The declaration of the active substance(s) for an individual finished product should be in accordance with relevant herbal quality guidance.
[4] The material complies with the Ph. Eur. monograph (ref. 1583)
[5] 15% total salicin represents an average value. The exact range should be established for each finished product on the basis of the manufacturer's specifications in accordance with the relevant herbal quality guidance.
[6] The DER should be specified for the specific product by the registration holder.

Well-established use	Traditional use
The pharmaceutical form should be described by the European Pharmacopoeia full standard term.	The pharmaceutical form should be described by the European Pharmacopoeia full standard term.

4. Clinical particulars

4.1. Therapeutic indications

Well-established use	Traditional use
Herbal medicinal product used for the short-term treatment of low back pain.	Indication 1) Traditional herbal medicinal product used for the relief of minor articular pain. Indication 2) Traditional herbal medicinal product used for the relief of fever associated with common cold. Indication 3) Traditional herbal medicinal product used for headache. The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use.

4.2. Posology and method of administration[7]

Well-established use	Traditional use
Posology Adults and elderly Single dose: 393 mg to 786 mg up to 2 times daily Daily dose: 393 to 1572 mg The use in children and adolescents under 18 years of age is contraindicated (see section 4.3. 'Contraindications'). **Duration of use** If the pain or symptoms persist during the first week of use of the medicinal product, a doctor or a pharmacist should be consulted.	**Posology** Adults and elderly Indication 1), 2) and 3) a) Herbal tea: 1-3 g of the comminuted herbal substance in 150 ml of boiling water as an herbal infusion 3 times daily. Decoction: 4 g of the comminuted herbal substance pour with 1 cup (200 ml) of water and boil covered for 15 minutes. Let stand for 15 minutes, strain. Drink after meals, 3 times a day a glass of warm, freshly prepared decoction. b) Powdered herbal substance: 260-500 mg 3-8 times daily.

[7] For guidance on herbal substance/herbal preparation administered as herbal tea or as infusion/decoction/macerate preparation, please refer to the HMPC 'Glossary on herbal teas' (EMA/HMPC/5829/2010 Rev.1).

Well-established use	Traditional use
Not to be used for more than 4 weeks. **Method of administration** Oral use	To be taken after meals. It is advised to take with larger quantity of hot water. c) Dry aqueous extract (8-20:1): 600 mg twice daily d) Dry aqueous extract (16-23:1): 480 mg twice daily e) Liquid extract 1-3 ml, three times daily f) Tincture (1:5): 15-24 ml per day The use in children and adolescents under 18 years of age is contraindicated (see section 4.3 'Contraindications'). **Duration of use** Indication 1) Not to be used for more than 4 weeks. Indication 2) If the symptoms persist longer than 3 days during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. Indication 3) If the symptoms persist longer than one day during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. **Method of administration** Oral use

4.3. Contraindications

Well-established use	Traditional use
Hypersensitivity to the active substance. Hypersensitivity to salicylates or to other NSAIDs (e.g. history of angioedema, bronchial spasm, or chronic urticaria in response to salicylates or to other NSAIDs). Asthma due to sensitivity to salicylates. Active peptic ulcer disease.	Hypersensitivity to the active substance. Hypersensitivity to salicylates or to other NSAIDs (e.g. history of angioedema, bronchial spasm, or chronic urticaria in response to salicylates or to other NSAIDs). Asthma due to sensitivity to salicylates. Active peptic ulcer disease.

Well-established use	Traditional use
Third trimester of pregnancy (see section 4.6 Pregnancy and lactation). Glucose-6-phosphate dehydrogenase deficiency. Children and adolescents under 18 years of age due to the risk of Reye's syndrome. Severe liver or renal dysfunction. Coagulation disorders.	Third trimester of pregnancy (see section 4.6 Pregnancy and lactation). Glucose-6-phosphate dehydrogenase deficiency. Children and adolescents under 18 years of age due to the risk of Reye's syndrome. Severe liver or renal dysfunction, Coagulation disorders.

4.4. Special warnings and precautions for use

Well-established use	Traditional use
Concomitant use with salicylates and other NSAIDs is not recommended without medical advice. If the symptoms worsen during the use of the medicinal product, a doctor or a pharmacist should be consulted.	The product is not intended to be used in case of acute arthritis as this condition requires medical advice. If fever exceeds 39°C, persists or is associated with severe headache or if symptoms worsen during the use of the medicinal product, a doctor should be consulted. Concomitant use with salicylates and other NSAIDs is not recommended without medical advice. If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. For tinctures, extracts, containing ethanol, the appropriate labelling for ethanol, taken from the 'Guideline on excipients in the label and package leaflet of medicinal products for human use', must be included.

4.5. Interactions with other medicinal products and other forms of interaction

Well-established use	Traditional use
Willow bark may increase the effects of anticoagulants such as coumarin derivatives.	Willow bark may increase the effects of anticoagulants such as coumarin derivatives.

4.6. Fertility, pregnancy and lactation

Well-established use	Traditional use
The use during the first and second trimester of pregnancy and during lactation is not recommended. Salicylates cross the placenta and appear in breast milk. Contraindicated in the third trimester of pregnancy. No fertility data available.	The use during the first and second trimester of pregnancy and during lactation is not recommended. Salicylates cross the placenta and appear in breast milk. Contraindicated in the third trimester of pregnancy. No fertility data available.

4.7. Effects on ability to drive and use machines

Well-established use	Traditional use
No studies on the effect on the ability to drive and use machines have been performed.	No studies on the effect on the ability to drive and use machines have been performed.

4.8. Undesirable effects

Well-established use	Traditional use
Allergic reactions such as rash, pruritis, urticaria, asthma, exanthema and gastrointestinal symptoms such as, nausea, vomiting, abdominal pain, diarrhea, dyspepsia, heartburn, may occur. The frequency is not known. If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.	Allergic reactions such as rash, pruritis, urticaria, asthma, exanthema and gastrointestinal symptoms such as, nausea, vomiting, abdominal pain, diarrhea, dyspepsia, heartburn, may occur. The frequency is not known. If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.

4.9. Overdose

Well-established use	Traditional use
No case of overdose has been reported.	No case of overdose has been reported.

5. Pharmacological properties

5.1. Pharmacodynamic properties

Well-established use	Traditional use
Pharmacotherapeutic group: analgesics and antipyretics. Proposed ATC code: N02BG (other analgesics and	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC.

Well-established use	Traditional use
antipyretics). Dose-dependent analgesic effects of willow bark dry extract (8-14:1) ethanol 70% were observed in controlled clinical studies in patients with low back pain exacerbations. Antiphlogistic effects of willow bark were studied *in vitro* (hen's egg chorioallantoic membrane test, effects on COX-1, COX-2, HLE and 5-LOX, tests on antioxidant effects) and in vivo (rat paw oedema, air pouch, adjuvant-induced arthritis, rithing-test, Randall-Sellito test, brewer's yeast induced fever reaction). AA and ADP-induced platelet aggregation was decreased in patients receiving willow bark extract. Constituents other than salicin may contribute to the overall analgesic effects.	

5.2. Pharmacokinetic properties

Well-established use	Traditional use
Salicylglycosides of willow bark form salicin after hydrolysis. Salicin is degraded into saligenin (salicyl alcohol) and glucose. Saligenin is oxidized in the blood and liver to salicylic acid. Intake of quantified willow bark extract (1,360 mg, equivalent to 240 mg salicin), resulted in salicylic acid as the major metabolite of salicin detected in the serum (86% of total salicylates), besides salicyluric acid (10%) and gentisic acid (4%). Peak levels were reached within 2 hours after oral administration. Peak serum levels of salicylic acid were on average 1.2 mg/l and the AUC was equivalent to that expected from an intake of 87 mg acetylsalicylic acid. Renal elimination occurred predominantly as salicyluric acid.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC.

5.3. Preclinical safety data

Well-established use	Traditional use
Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.	Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC, unless necessary for the safe use of the product. Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

6. Pharmaceutical particulars

Well-established use	Traditional use
Not applicable	Not applicable

7. Date of compilation / last revision

31 January 2017