European Medicines Agency
Evaluation of Medicines for Human Use

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Table 1: Organisation(s) that commented on the draft 'Community herbal monograph on Salix, cortex' as released for consultation on 7 September 2007 until 15 December 2007.

	Organisation
1	Association of the European Self-Medication Industry (AESGP)
2	Kooperation Phytopharmaka, Germany.
3	Phytolab, Vestenbergsgreuth, Germany.
4	European Scientific Cooperative on Phytotherapy (ESCOP)
5	A. Nelson & Company Ltd, United Kingdom

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Table 2: Discussion of comments

GENERAL COMMENTS TO DRAFT DOCUMENT		
The monograph which may provide harmonised assessment criteria for HMPs, is welcomed. Specific comments are listed below.		
SPECIFIC COMMENTS ON TEXT		
2 QUALITATIVE AND QUANTITATIVE COMPOSITION		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
WEU	Add **Aqueous dry extract (16-23:1), quantified for total salicin,** Rationale : Clinical data also exist for this preparation (Khayyal et al, 2005). The composition of products authorised in Germany containing aqueous extract (DER 16-23:1, or not specified ratio) or other extracts (solvent not indicated) are provided for a number of single and combination products (combination with colae semen or betulae folia).	*Not accepted:* *Khayyal et al reported on the pharmacological effects of the aqueous dry extract (16-23:1) in two inflammation models in rats. There are however insufficient clinical data to substantiate a WEU for this aqueous dry extract (16-23:1).* *The TU section of the monograph covers the aqueous dry extract (16-23:1) of willow bark. The DER and/or solvent is not indicated in some of the products mentioned by the interested parties. The TU section 2 covers the various aqueous extracts (and other herbal preparations) that are on the German and other markets.* *The monograph is on willow bark only (as a single ingredient).*
WEU	The extract mentioned is characterised as a quantified one. (*dry extract (8-14:1) ethanol 70 % V/V, quantified for total salicin*). As quantified extracts have a constant inner composition and due the nature of herbal starting material a variable content of salicin, the requirement to dose dry extract equivalent to 240mg necessitates a standardized extract. Informations on herbal substance (Willow bark) and aqueous extracts are lacking. Decision is not	*Accepted*: *The substance and preparation should comply with the Ph Eur. and are quantified : the amount of native extract is fixed, while the amount of total salicin varies in a defined range. The amount of extract and the % total salicin in the extract studied is included.* *The sections 2 and 4.2 are amended accordingly.* *Not accepted:*

	comprehensible. Marketing authorizations for Willow bark products (drug or aqueous extracts) exist (AMIS 04/2007: Proaktiv/Steigerwald: dry extract, solvent water, DER 16-23:1 480 mg, corr. 120 mg Salicin / Sidroga Rheumatee). The ESCOP-Monograph (ESCOP 2003) approves in addition to hydroalcoholic extracts also aqueous extracts, tinctures or fluids, equivalent to 120 to 240 mg of total salicin.Commission E demands simply an average daily dosage of liquid and solid preparations for internal use which should correspond to 60-120 mg total salicin without mentioning the number of daily single doses. The randomized double-blind study by LARDOS et al. 2004 (Wirksamkeit und Verträglichkeit eines wässrig ausgezogenen Weidenrindenextraktes bei Patienten mit Hüft- und Kniearthrose) indicates a good tolerance of the willow bark extract and demonstrates, statistically supported, its therapeutically relevant analgesic activity as well as in regard of pain intensity an effect comparable to diclofenac sodium	*Taking into account the body of available published trials, their respective quality and outcome, the controlled clinical trials published so far provide moderate evidence for the analgesic activity of 1572mg dry extract (8-14:1) (extraction solvent ethanol 70% V:V) in the clinical setting of low back pain. The herbal substance and other herbal preparations are included in the TU section 2 (and 4). The monograph on willow bark represents the current legislative framework and available body of evidence.* *The following comments on the clinical study of Lardos et al (2004) can be made: the aqueous extract is not sufficiently described (DER); the study is considered as a pilot study (very small number of patients per arm; comparability of the 3 arms at baseline is difficult to assess. It was also noted that a double dosis of aqueous extract was not reflected in a better analgesic activity.*
TU	As extracts of Willow bark are described in the European Pharmacopeia 6.1 it should be mentioned in the monograph draft that contents of salicin in extracts are analysed by using the Ph. Eur method. The monograph for Willow bark dry extract of the European Pharmacopeia 6.1 does require a minimum level for salicin only and no maximum concentration. In contradiction the requirement to dose extracts 600 mg twice a day and the single and daily dose should not contain equivalent amount of salicin exceeding 120 mg and 240 mg, respectively, leads to extracts of 20 % salicin with	*Accepted:* *The footnote with regard to compliance with the respective Ph. Eur. monographs (willow bark and willow bark extract) is updated.* *Partly accepted:* *The substance and preparation should comply with the Ph. Eur. Willow bark herbal substance and herbal preparations are quantified for total salicin. The amount of herbal substance/ preparation is fixed, while the amount of total salicin varies in a defined range. Reference is made to the Quality guidelines on (traditional) herbal medicinal products*

	a fixed inner composition. Such extracts are simply impossible to produce. Consequently either a range for the dose of extract or salicin as to be specified. The data given in the Community Herbal Monograph on Salicis cortex are not clear and consistent. It must be clarified if a standardised or a quantified extracts are needed. It has also to be taken into account that the Ph. Eur. Monograph 6.1 requires a minimum value of 1,5% for the herbal drug and of 5% for the extract only. Neither a quantification nor a standardisation is required. Ph. Eur. Monograph and HMPC-Monograph have to be consolidated.	
TU	Although we recognise that it is not neceassrily reasonable to list all possible extraction ratios, the monograph should not suggest that other ratios are excluded and cannot be registered under TU. For instance, the British Herbal Compendium (Volume1) also list the tincture 1:5 in EtOH 25%. A more flexible wording (cfr in ESCOP monograph) would reflect better those THPs currently on the market.	*Partly accepted:* *Section 2 is amended to include the tincture 1:5 (extraction solvent EtOH 25%).*

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.1 Therapeutic indications (WEU)	Herbal medicinal product used for the ~~short symptomatic~~ treatment of low back pain, **the relief of osteoarthritic and rheumatic complaints, and the treatment of headache and fever**. Rationale: "The relief of osteoarthritic and rheumatic complaints" corresponds with the clinical studies. The use in treatment of headache and fever corresponds to the WHO monograph as clinically supported indications. Treatment of mild rheumatic conditions (EMEA HMPWP 2004) or symptomatic relief of mild osteoarthritic and rheumatic complaints (ESCOP 2003) or rheumatic ailments (COMISSION E 1984) is not mentioned Willow bark extract has been studied in clinical trials for as long as 4 weeks, which is not necessarily a short-term treatment, and there are no facts pointing to a limited efficacy if used for a treatment over a longer duration. Also safety is checked in longer "treatment by the sys tematically collected pharmacovigilance data existing at manufacturers and at regulatory agencies, as well as by the comprehensive data on the mechanisms of action which do not indicate any possible risk for a long term treatment. In a post-authorisation surveillance study on willow bark dry extract (8-14:1, EtOH 70%; daily doses equivalent to 120 or 240mg total salicin), 922 physicians observed 4731 patients with chronic back pain or arthralgia after 3-4 weeks and after 6-8 weeks. Pain intensity was assessed (scale) and was decreased (Werner, 2004, abstract). Symptomatic should be removed, as relief of symptoms is described.	*Not accepted:* *Taking into account the body of available published trials, their respective quality and outcome, the controlled clinical trials published so far provide moderate evidence for the analgesic activity of 1572mg dry extract (8-14:1) (extraction solvent ethanol 70% V:V) in the clinical setting of low back pain. Efficacy could not be demonstrated neither in OA nor RA. Results for a particular extract are not extrapolated to other extracts. It should be reminded that the salicin derivatives are considered as active markers (quantified extract).* *For the treatment of pain and fever, only general evidence and references are available supporting the TU in these conditions.* *The duration of use (see also section 4.2) corresponds with the duration studied in the clinical studies. The safety and efficacy beyond this duration is not fully established. Continuation of treatment beyond 4 weeks is at the appreciation of the medical practioner who considers the condition and the patient who is under treatment.* *Full details of the post-authorisation study of Werner are missing, only an abstract was made available.* *Accepted: "symptomatic" is deleted. The sentence is amended accordingly.*

4.1 Therapeutic indications (TU)	Traditional herbal medicinal product used for the symptomatic relief of: a) minor articular pain, **low back pain, rheumatic complaints,** b) fever associated with common cold, c) headache. The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use. Rationale: Regarding the traditional use, it is reported that the Greek physician Dioscorides, already in the first century A.D., has noted the use of Willow Bark to ease pain and reduce fevers, and that he even specifically mentioned its use for lower back pain and complaints which are today often described as rheumatic kind. Regarding the term rheumatic complaints it is important to be aware of the difference of this term with 'rheumatoid arthritis' from a physiopathological point of view. The term 'rheumatic complaints' is used commonly instead of 'articular pain' which would be the correct medical term. The terms rheumatic complaints and low back pain are also frequently found in literature referring to the traditional use of willow bark. Therefore, it is advisable to add them to the list	*Not accepted:* *The standard wording of "minor articular pain" reflects the general references, pharmacological data and clinical experience with the (traditional) uses of willow bark in these conditions.* *A moderate efficacy was demonstrated in LBP for a specific herbal preparation only which is reflected in the WEU section of 4.1.* *Note that "symptomatic" is also deleted in the TU section 4.1.*
4.2 Posology and method of administration **Posology (WEU)**	*Adults, elderly* The daily dose is dry extract **(8-14:1, solvent ethanol 70% v/v or 16-23:1, solvent water)**, equivalent to **120**-240 mg of total salicin, divided into two doses. Not recommended for use in children and adolescents under 12 ~~18~~ years of age (see section 4.4 Special warnings and precautions for use)	*Not accepted:* *Taking into account the body of available published trials, their respective trial quality and outcome, the controlled clinical trials published so far provide moderate evidence for the analgesic activity of the dry extract 8-14:1, solvent ethanol 70% v/v. There are however insufficient clinical data to substantiate a WEU of the aqueous dry extract (16-23:1).A dose-dependent analgesic activity was observed in the clinical trials. The clinial evidence was most conclusive for the highest dose (2x 786mg extract 8-14: 1, extraction solvent EtOH 70% v/v, 15% total*

	Rationale: The daily dose for the well-established used dry extract (8-14:1, extraction solvent: 70% (V/V) ethanol is missing) is mentioned "equivalent to 240 mg total salicin", divided into two doses. A **constant** amount of total salicin, however, can only be achieved by **standardisation** and not by quantification. Standardisation, however, would include that the amount of (native) extract varies in a defined range, which is not allowed for a quantified extract (see also the HMPC "Declaration" Guideline).	*salicin).* Despite the lack of understanding of the syndrome and the fact that a clear, conclusive link between the syndrome and aspirin (salicylates) is not yet established, the decision has been taken in many countries to advice against the use of salicylates in children. Because of the clinical importance of the syndrome and the avoidable risk, use of salicylates in patients below 18 years should in general be avoided. *Accepted:* *The substance and preparation should comply with the Ph Eur. and are quantified: the amount of native extract is fixed, while the amount of total salicin varies in a defined range. Reference is made to the Quality guidelines on (traditional) herbal medicinal products* *The amount of extract and the % total salicin in the extract that was administered, is included.* *The sections 2 and 4.2 are amended accordingly.*
4.2 Posology and method of administration **Posology (WEU)**	*Adults, elderly*: the daily dose is the quantity of willow bark dry extract prepared with EtOH 70% V/V (8-14:1), **or water (16-20:1, 16-21:1, 16-23:1)**, corresponding **to 120-**240mg total salicin, **in one or 2 doses**. Not recommended for use in children and adolscents under 18 years of age **(extreme rare cases of Reye's syndrome following a viral infection)** Rationale : Clinical studies for smaller dosages of willow bark preparations (corresponding to 120mg-180mg salicin are supported by the ESCOP monograph and some clinical data (Lardos et al 2004,	*Not accepted:* *Taking into account the body of available published trials, their respective quality and outcome, the controlled clinical trials published so far provide moderate evidence for the analgesic activity of the dry extract 8-14:1, solvent ethanol 70% v/v. There are however insufficient clinical data to substantiate a WEU of the aqueous dry extract (16-23:1).* *Not accepted : The pivotal studies were double-checked with regard to the administration of the dose. The daily dose was subdivided in 2.* *Not accepted: the information is included in section 4.4.*

	Chrubrasik 200 and the PMS study of Werner et al 2004). The ESCOP monograph does not specify that the daily dose must be divided in two doses as some clinical studies were performed following administration of a single dose.	
4.2 Posology and method of administration **Posology (TU)**	*Adults, elderly* Dry bark for herbal tea preparation: 1 to 3 g, three to four times daily Dry aqueous extracts **(8-16:1)** ~~(16-20:1, 16-21:1, 8-16:1)~~: **480**-600 mg twice daily Liquid extract (1:1 in 25% ethanol v/v): 1 to 3 ml, three times daily Powdered dry bark: **260-500** mg three times daily ~~The single and the daily dose should not contain equivalent amount of **total** salicin exceeding 120 mg and 240 mg, respectively.~~ Not recommended for use in children and adolescents under 12 ~~18~~ years of age (see section 4.4 Special warnings and precautions for use). <u>Rationale</u> The draft mentions various drug extract ratios for the aqueous extract. Traditionally used German medicinal products had a ratio of 8:1, whereas "modern" extracts have a range of 16-23:1. The exact ratio depends on the choice of the herbal substance. The ratio can therefore not be restricted to three different ranges, but should rather reflect the variability of preparations in the traditional sector. In addition, all German registered tablet preparations with powdered willow bark contain 500 mg of powder per unit, not 400. Additionally, a capsule containing 260 mg willow bark powder is also registered in France (Marketing authorisation from 11/1988,	*Partly accepted:* *Posology is included in section 4.2 (TU) for herbal substance and preparations where such a posology is described in literature, product labelling…* *The substance and preparation should comply with the Ph. Eur. Willow bark herbal substance and herbal preparations are quantified. Reference is made to the Quality guidelines on (traditional) herbal medicinal products* *The TU posology section with regard to the aqueous extracts and powdered willow bark is amended.* *Not accepted: see section 4.3*

	Arkogelules saule). The quantity per single dose should therefore be adapted correspondingly. Furthermore ,data given for the liquid extract 1:1 are not in accordance with the "Declaration" Guideline. It is not clear whether *"in alcohol 25 % (V/V)"* means the extraction solvent according to the HMPC "Declaration" Guideline. The dose for the traditionally used extract (in the draft: 600mg twice daily) is mentioned which should not contain "equivalent amount of total salicin *("total"* is missing!) exceeding 120mg (single dose) and 240mg (daily dose). A constant amount of extract and a constant amount of total salicin at the same time is not possible to produce and does not mean a quantified extract. This means, however, that the daily dose of 300mg extract should contain at maximum 20% total salicin. 20% total salicin e.g. can only be achieved by standardisation and not by quantification. In this case, the amount of extract (native) would vary in a defined range, which is not allowed for a quantified extract (see also the HMPC "Declaration" Guideline). It should be clarified whether a standardised or a quantified extract is needed. It also has to be taken into account that the Ph. Eur. Monograph 6.0 only requires a minimum value of 1.5 % for the herbal drug and of 5 % for the extract. Neither quantification nor standardisation is required. Thus the Ph. Eur. monograph and HMPC monograph are not in line with each other.	
4.2 Posology and method of administration **Posology (TU)**	The listed dry aqueous extracts are not documented in theliterature dealing with TU and appear to be more appropriate for a WEU application. These extracts should move under WEU with a daily dosage equivalent to 120-240mg total salicin. The sentence with regard to maximal content of total salicin should be deleted as dry bark and other preparations, with the given daily dose, contain far too little total salicin to reach 240mg salicin equivalent per day. Moreover this restriction could only be verified if quantification of salicin is required in the posology for TU, which is not.	*Not accepted: see section 4.1.* *Partly accepted: the sentence is deleted. Willow bark substance and preparation should comply with the Ph. Eur. Willow bark herbal substance and herbal preparations are quantified for total salicin. Furthermore, reference is made to the relevant Quality guidelines on (traditional) herbal medicinal products.*

4.2 Posology and method of administration **Posology (TU)**	Various dry extract ratios are listed in section 4.2 that are not listed in section 2. We would ask that there be consistency between these sections of the monograph	*Accepted: sections 2 and 4 are revised accordingly.*
4.2 Posology and method of administration **Duration of use (WEU)**	If the pain or symptoms ~~persist~~ **do not ameliorate** during the first week of the use of the medicinal product, a doctor or a pharmacist should be consulted. ~~Duration should be restricted to a maximum of 4 weeks.~~ Rationale: Regarding the duration of use, there is no clinical or pharmacological/toxicological data justifying a restriction of use to maximum four weeks. Such a limitation is also not stated in the ESCOP monograph and also not part of the SPC of currently (re)registered willow bark preparations in Germany. In fact, clinical trials have shown that the effect of willow bark is gradually building up. Clinical and pharmacovigilance data of the registered products document the safety of the drug irrespective of the duration of application. Rheumatic disorders is a chronic disease hence a prolonged treatment is necessary.	*Not accepted:* *The standard wording with regard to persistance of symptoms is maintained.* *The duration of use (see also section 4.2) corresponds with the duration studied in the clinical studies. The safety and efficacy beyond this duration is not fully established. Continuation of treatment beyond 4 weeks is at the appreciation of the medical practioner who considers the condition and the patient who is under treatment.*
4.2 Posology and method of administration **Duration of use (WEU and TU)**	The limitation in duration of use is not justified. Reference is made to the post-authorisation surveillance study of Werner et al (2004) and Zenner-Weber (2004) where patients were followed for 6-8 weeks. Despite of the longstanding use of willow bark preparations in Germany, in February only 4 suspected ADR were recorded since 1990 in the BfArM database.	*Not accepted:* *The duration of use (see also section 4.2) corresponds with the duration studied in the clinical studies. The safety and efficacy beyond this duration is not fully established. Continuation of treatment beyond 4 weeks is at the appreciation of the medical practioner who considers the condition and the patient who is under treatment.* *It should be noted that only an abstract was available for the post-authorisation surveillance study by Werner et al (2004).*
4.2 Posology and method of administration **Duration of use (TU)**	Indication a) ~~Duration should be restricted to a maximum of 4 weeks.~~	*Not accepted:* *The safety is not fully established beyond 4 weeks.*

	Indication b) A doctor should be consulted after 3 days. **Medical attention should be sought if the symptoms persist during the use of the medicinal product.** ~~If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.~~ <u>Rationale</u>: Regarding the duration of use, there is no clinical or pharmacological/toxicological data justifying a restriction of use to maximum four weeks. Such a limitation is also not stated in the ESCOP monograph and also not part of the SPC of currently (re-)registered willow bark preparations in Germany. In fact, clinical trials have shown that the effect of willow bark is gradually building up. Clinical and pharmacovigilance data of the registered products document the safety of the drug irrespective of the duration of application. Rheumatic disorders is a chronic disease hence a prolonged treatment is necessary.	*Continuation of treatment beyond 4 weeks requires advice from the medical practitioner.* *The standard wording on persistance of symptoms is maintained.*
4.2 Posology and method of administration (WEU and TU)	It is agreed that the use of salix in children is not recommended due to the lack of adequate data. However, there is also no clinical evidence available not to use salix in older children and adolescents. Thus, it is recommended to change the wording both for WEU / traditional use to: Not recommended for the use in children under 12 years of age.	*Not accepted: see sections 4.3 and 4.4.*
4.3 Contraindications WEU and TU	~~Active peptic ulcer disease.~~ <u>Rationale</u> Based on the following literature data, it does not seem justified to maintain the following contraindication "*Active peptic ulcer disease*": In randomised placebo-controlled, double blind clinical trials, willow bark dry extracts test group showed fewer cases of gastro-intestinal adverse effects than placebo group (Biegert et al, 2004;	*Not accepted:* *The available data on patients were considered. The site(s) of conversion of salicin into saligenin need(s) further confirmation.* *In view of the lack of more toxicity data on willow bark, the usual precautions associated with salicylate therapy are also applied to willow bark. Therefore, individuals with active peptic ulceration should be aware of the*

	Schmid et al, 2001, Chrubasik et al, 2000). Total for the 3 studies: willow bark: 10 cases (n=222) / placebo: 32 cases (n=150). In a post-authorisation surveillance study on 4731 patients, after 3 to 4 weeks and after 6 to 8 weeks, no gastrointestinal bleeding or ulceration were mentioned (Werner at al, 2004). Willow bark does not appear to inhibit cyclooxygenase 1 in the stomach wall, because its active metabolites are generated in the intestine after passing through the stomach as intact glycosides, thereby preventing the development of stomach lesions. The metabolic profile of willow bark salicin derivatives has been detailed. After oral administration, salicin did not induce gastric lesions in the mucosa of rat stomach at doses of 1.0, 2.5 and even 5.0 mmol/kg (i.e. 1.43 g/kg) ; sodium salicylate and saligenin induced severe gastric lesions at doses of 1.0, 2.5 and 5.0 mmol/kg (respectively : 0.80 g/kg ; 0.62 g/kg). On the other hand, Lardos et al (2004) mentioned the development of a peptic ulcer in one patient with pre-existing lesions and newly developed lesion in another patients. The authors assessed the ADR as unlikely to willow bark preparations because its constituent salicin is lacking the reactive groups.	*possible risks associated with the intake of willow bark.*
4.3 Contraindications **TU**	Children and adolescents below ~~18~~ **12** years of age because medical supervision should be sought. Rationale: Why are children and adolescents below 18 years of age excluded from the use of willow bark whereas use of acetylsalicylic acid is allowed.	*Not accepted:* *The use of willow bark in children and adolescents below 18 years requires medical advice.*
4.4 Special warnings and precautions for use **WEU**	Well-established use In children and adolescents below ~~18~~ **12** years, the product should only be used in medical advice and only in cases where other therapies failed to succeed. ~~In a child or adolescent who has~~	*Not accepted:* *The use of willow bark in children and adolescents below 18 years requires medical advice. It should also be noted that patients younger than 18 years were not included in*

	~~become very unwell with severe vomiting, drowsiness or loss of consciousness following a viral infection, a serious disease may be suspected. This **is** an extreme**ly** rare but life-threatening disease, which requires immediate medical attendance.~~ **Not recommended for use in children and adolescents under 12 years of age due to the occurrence of rare cases of Reye's syndrome following a viral infection.** Rationale The WHO monograph as well as the SPC of willow bark preparations registered, for example, in Germany do not show restrictions in children and adolescents of an age of 12 and above. This is also supported by the recommendations of Ernst et al. (2001). There are no grounds for restricting the use of willow bark extract for persons between 12 and 18 years. Articular pain and low back pain can occur also in this age group, and there is no safety concern justifying restricting the use of willow bark to the adult population (i.e. 18 years and above). Furthermore, it is clearly stated that a doctor should be consulted if pain or symptoms worsen during the first week of use. There are also no special precautions necessary in this age group with regard to the content of salicin derivatives and Reyes syndrome, as this is only an issue in children of younger age. Moreover, it is dose-dependent and unlikely to occur with the low doses and low bioavailability of the salicin derivatives in willow bark extracts. Therefore the use should be not restricted to patients at the age of 12 and above, for well-established use as well as for traditional use.	*the clinical studies.*
4.4 Special warnings and precautions for use **WEU and TU**	~~Concomitant use with salicylates and other NSAIDs is not recommended without medical advice.~~ Rationale As willow bark extract does not show gastrointestinal side effects like acetyl salicylic acid and other NSAIDs, as clinical data already mentioned and pharmacological data demonstrate,	*Not accepted:* *As a matter of precaution, concomitant use with salicylates and other NSAIDs is not recommended without medical advice.*

	undesired interactions with these preparations are not to be expected. This is also reflected in the ESCOP monograph and in the SPCs of recently re-registered willow bark preparations in Germany, which give no special restrictions for concomitant use with NSAIDs. It is worth pointing out that a significant amount of polyphenols -including the procyanidins- which are important components of willow bark extract, are known for their gastroprotective properties. From the available literature, no data on pharmacodynamic or pharmacokinetic interactions of willow bark (preparations) with salicylates and other NSAIDs is available.	
4.5 Interactions with other medicinal products and other forms of interaction	**None reported.** Willow bark may **theoretically** increase the effects of anticoagulants such as coumarin derivatives. <u>Rationale</u> Pharmacokinetic interactions with willow bark extracts have not been observed. The interaction with oral anticoagulants is hypothetical. In a clinical double-blind trial a 4-week treatment with ethanolic willow bark extract (corresponding to 240 mg of total salicin in the daily dose) the mean maximal effect for arachidonic acid-induced platelet aggregation *ex vivo* was 13% for acetylsalicylic acid, 61% for willow bark extract, and 78% with placebo (10,11). This small anticoagulant effect is probably related to the transformation of a part of salicin into salicylic acid. However, the relevance of this effect seems rather questionable and would not be of concern for potential pharmacodynamic interactions with platelet aggregation inhibitors. The salicylic derivatives in willow bark lack the acetylic residue. If used as recommended, there is no particular risk seen.	*Not accepted:* *Pharmacokinetic and pharmacodynamic interactions with anti-coagulants cannot be ruled out and may increase their effects.*
4.7 Effects on ability to drive and use machines **WEU and TU**	No studies on the effect on the ability to drive and use machines have been performed. **No negative effects on cognitive functions are known.**	*Not accepted.* *No studies on the effect on the ability to drive and use of machines have been performed.*

	Rationale According to recent monographs, the effects of Salicis cortex on the ability to drive or use machinery are not to be expected	
4.8 Undesirable effects **WEU and TU**	Allergic reactions such as rash, pruritis, urticaria, asthma, exanthema and gastrointestinal symptoms such as, nausea, vomiting, abdominal pain, diarrhea, dyspepsia, heartburn, may occur in rare frequency. ~~The frequency is not known.~~ If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted. Rationale The frequency of allergic reactions and gastrointestinal symptoms can be established as "rare" based on a post-authorisation surveillance study on 4731 patients (Werner et al, 2004). After 3 to 4 weeks and after 6 to 8 weeks, gastrointestinal side effects were notified with an incidence of 0,93 %, in most cases as abdominal pain (incidence = 0,59 %) ; no gastrointestinal bleeding or ulceration were mentioned ; skin reactions or potential allergic reactions were notified with an incidence of 0,30 %. Frequency of ADR notification was independent of daily dosage (mostly 2 or 4 sct per day) and did not increase with treatment duration	*Not accepted.* *Undesirable effects that occurred in the clinical trials with willow bark are listed.* *It should be noted that only an abstract was available for the post-authorisation surveillance study by Werner et al (2004).*
4.9 Overdose **WEU and TU**	This is in line with the literature (3). Overdose resulting from acute ingestion of ASA usually produces serum ASA levels of 300 mg/l of greater. More than 50 g per day of salicin would need to be ingested in order to achieve this blood level of salicylate (3), which is practically impossible with willow bark extract.	*Agreed.*
5.1 Pharmacodynamic properties **WEU**	Well-established use Pharmacotherapeutic group: Analgesics and antipyretics.	*Not accepted.* *Taking into account the body of available published trials,*

	ATC code: N02BG (other analgesics and antipyretics) Dose-dependent analgesic effects of willow bark dry **extracts (DER 8-14:1, ethanol 70% and DER 16-23:1, water)** were observed in recent controlled clinical studies in patients with low back pain exacerbations **and mild rheumatic disorders**. Antiphlogistic effects of willow bark extracts (aqueous and 70% ethanolic) were studied *in vitro* (hen's egg chorioallantoic membrane test, **inhibition of COX-1, COX-2, HLE and 5-LOX, tests on antioxidant effects) and in vivo (rat paw oedema, air pouch, adjuvant-induced arthritis, writhing-test, Randall-Sellito test, brewer's yeast-induced fever reaction).** AA- ~~and ADP~~ induced platelet aggregation was **only marginally** decreased in patients receiving willow bark extract. Constituents other than salicin may contribute to the overall analgesic effects. <u>Rationale</u> The therapeutic efficacy of Willow bark extract was evaluated in clinical and post-marketing studies. Two placebo-controlled double-blind studies were performed with combination products containing willow bark extracts, several placebo and/or reference-controlled studies with mono-preparations of willow bark , among them a study with positive outcome conducted with aqueous willow bark extract . In addition, open-label monitoring studies were presented , among them one with willow bark tea and one performed with aqueous willow bark extract. All but two studies (one open study with willow bark tea, one placebo-controlled trial with a combination product containing willow bark powder examined the application of willow bark extracts manufactured in agreement with the definitions of the ESCOP monograph on Salicis cortex These extracts contained 60-120 mg salicin per unit dose and were administered in a daily dose range of 60 to 240 mg of salicin equivalents.	*their respective quality and outcome, the controlled clinical trials published so far only provide moderate evidence for the analgesic activity of 1572mg dry extract (8-14:1 EtOH 70% v/v, 15 % salicin) in the clinical setting of low back pain.* *There are insufficient clinical data to substantiate a WEU of the aqueous dry extract (16-23:1) as a single active ingredient. The following comments on the clinical study of Lardos et al (2004) can be made: the aqueous extract is not sufficiently described (DER); the study is considered as a pilot study (very small number of patients per arm; comparability of the 3 arms at baseline is difficult to assess). It was also noted that doubling the dosis of aqueous extract was not reflected in a better analgesic activity* *Willow bark significantly decreased the mean percentage of maximal AA- and ADP-induced platelet aggregation (but to a significantly lesser extent than acetylsalicylate did).*

	As an overall conclusion from these trials a comparable efficacy of the 70% ethanolic and the aqueous willow bark extract against pain and rheumatic disorders can be deduced. With the existence of at least one controlled trial with aqueous willow bark extract this specific galenical form should specifically be mentioned in the well-established section. As described in the comments to section 4.5 (interactions), the inhibitory effect on arachidonic acid-induced platelet aggregation was only minor after 4 weeks of application of willow bark extract corresponding to a daily dose of 240 mg of total salicins . On induction with ADP or collagen, however, neither willow bark (69%) nor acetylsalicylic acid (77%) had a notable effect compared to placebo (88%). Arachidonic acid-induced platelet aggregation was minimally inhibited by the willow bark extract, but to a far lesser degree than by acetyl salicylic acid. Consequently, ADP-induction of platelet aggregation is unlikely to produce relevant information in the case of salicylates. Reference to ADP-induced platelet aggregation should therefore be removed. Pharmacological testing of willow bark extracts, fractions and isolated constituents involved *in vitro* testing of inhibition of enzymes of the arachidonic acid cascade (COX-1, COX-2, HLE, 5-LOX, LTB_4, PGE_2, IL-1β, IL-6, TNF-α), as well as nitrogen monoxide release and apoptosis. Willow bark extract consistently showed its action on the relevant biochemical parameters of inflammation . In addition, willow bark extract demonstrated strong antioxidative effects. The results of *in vitro* testing negate any inhibiting action of willow bark on enzymes of the arachidonic acid cascade (COX-1, COX-2 and 5-LOX). *In vitro* models were confirmed by testing in standard models *in vivo*. Dose-dependent effects of willow bark extracts and isolated constituents corresponding to those of the same dose of ASA were found in models of acute and chronic inflammation (rat paw oedema and air pouch, adjuvant-induced arthritis in rats),	*Accepted:* *A number of recent in vitro and in vivo studies were published on the investigation of anti-inflammatory effects of willow bark extracts.*

	analgesia (writhing test in mice , Randall-Sellito test in rats), and antipyretic effects (brewer's yeast-induced fever reaction in rats).	
5.1 Pharmacodynamic properties **WEU**	It is recommended to check the ATC code: N02BG-other analgesics and antipyretics- is a section for chemically defined drugs. Alternative suggestions are M09AP05-other herbal preparations for the treatment of muscular-skeletal disorders.	*The ATC code* N02BG-*other analgesics and antipyretics is maintained.*
5.1 Pharmacodynamic properties **TU**	Not required as per article 16c(1)(a)(iii) of Directive 2001/83/ES as amended. AA ~~and ADP~~-induced platelet aggregation was **slightly** decreased in patients receiving willow bark extract.	*Not accepted:* *Willow bark significantly decreased the mean percentage of maximal AA- and ADP-induced platelet aggregation (but to a significantly lesser extent than acetylsalicylate did).*
5.2 Pharmacokinetic properties **WEU**	Salicylglycosides of willow bark form salicin after hydrolysis. Salicin is absorbed from the upper intestinal tract and degraded ~~by the intestinal flora~~ into saligenin (salicylic alcohol) and glucose. Saligenin is ~~absorbed and~~ oxidised in the blood and liver to salicylic acid. Intake of quantified willow bark extract (1,360 ml, 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 <u>Rationale</u> The data on pharmacokinetics indicated in the draft monograph refer to the study of Schmid et al. (2001) . The	*Agreed.* *The section is amended accordingly.*

	hypothesis of a cleavage of salicin to saligenin by the intestinal flora must be reconsidered, as according to all available pharmacokinetic studies the tmax points to absorption from the upper intestinal tract. The site of conversion is currently unknown.	
5.3. Preclinical safety data WEU	Willow bark extract had no damaging effect on the gastric mucosa of rats up to equivalents of 100 mg/kg salicin. ~~Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.~~ <u>Rationale</u> Directive 2001/83/EC does not require pre-clinical safety data. The safety of traditionally used products is sufficiently characterised by long-standing experience. Thus, the restriction "unless necessary for the safe use of the product" is misleading in the case of *Salix*, as there is no evidence of unsafe use. According to the "Guideline on non-clinical documentation for herbal medicinal products for marketing authorisation (bibliographical and mixed applications) and in applications for simplified registration (EMEA/HMPC/32116/2005)", the testing of organ toxicity, single dose and repeated dose toxicity, immunotoxicity as well as local tolerance testing of well-established drug preparations is not necessary. Studies on carcinogenicity are not needed in cases where there is no suspicion for a carcinogenic potential. Pre-clinical safety data is available with regard to effects on the gastric mucosa . In acute toxicity studies, the LD50 of a liquid willow bark extract (extraction solvent 30% ethanol) was 28 ml/kg in mice (3,40). With an extract standardised to 12% salicin no toxic dose could be determined in rats . No toxic effects were observed in rats which were administered	*Not accepted:* *Very limited data on acute toxcity of willow bark are available and only indirect data on chronic toxicity, reproductive toxicity, genoxicity and carcinogenicity of willow bark are available. The standard wording is maintained.*

	per os a combination of willow bark and Primula root extracts for 13 weeks. The preparation contained 35 mg/100 mg of a willow bark extract prepared with 30% ethanol. It corresponded to approximately 1.6 mg/kg.	
5.3. Preclinical safety data **TU**	Not required as per article 16c(1)(a)(iii) of Directive 2001/83/ES as amended~~, unless necessary for the safe use of the product~~. ~~Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.~~ <u>Rationale</u> Directive 2001/83/EC does not require pre-clinical safety data. The safety of traditionally used products is sufficiently characterised by long-standing experience. Thus, the restriction "unless necessary for the safe use of the product" is misleading in the case of *Salix*, as there is no evidence of unsafe use	*Not accepted.* *The standard wording is maintained. The tests have not been performed.*