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**ASSESSMENT REPORT ON
SALICIS CORTEX (WILLOW BARK)
AND HERBAL PREPARATION(S) THEREOF WITH WELL-ESTABLISHED USE AND
TRADITIONAL USE**

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TABLE OF CONTENTS

I.	REGULATORY STATUS OVERVIEW	3
II.	ASSESSMENT REPORT ON WILLOW BARK AND HERBAL PREPARATION(S) THEREOF WITH WELL-ESTABLISHED USE (WEU) AND/OR TRADITIONAL USE (TU)	5
II.1	INTRODUCTION.....	6
II.1.1	<i>Description of the herbal substance(s), herbal preparation(s) or combinations thereof</i>	6
II.1.2	<i>Information on period of medicinal use in the Community regarding the specified indication</i>	8
II.2	NON-CLINICAL DATA	9
II.2.1	<i>Pharmacology</i>	9
II.2.1.1	Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof.....	9
II.2.1.2	Assessor's overall conclusions on pharmacology	10
II.2.2	<i>Pharmacokinetics</i>	11
II.2.2.1	Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof.....	11
II.2.2.2	Assessor's overall conclusions on pharmacokinetics	11
II.2.3	<i>Toxicology</i>	12
II.2.3.1	Overview of available data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof.....	12
II.2.3.2	Assessor's overall conclusions on toxicology.....	12
II.3	CLINICAL DATA	12
II.3.1	<i>Clinical Pharmacology</i>	12
II.3.1.1	Pharmacodynamics.....	12
II.3.1.2	Pharmacokinetics.....	13
II.3.2	<i>Clinical Efficacy</i>	14
II.3.2.1	Dose response studies.....	14
II.3.2.2	Clinical studies (case studies and clinical trials)	15
II.3.2.3	Clinical studies in special populations (e.g. elderly and children).....	22
II.3.2.4	Assessor's overall conclusions on clinical efficacy	22
II.3.3	<i>Clinical Safety/Pharmacovigilance</i>	23
II.3.3.1	Patient exposure	23
II.3.3.2	Adverse events	23
II.3.3.3	Serious adverse events and deaths.....	24
II.3.3.4	Laboratory findings	24
II.3.3.5	Safety in special populations and situations	24
II.3.3.6	Assessor's overall conclusions on clinical safety.....	27
II.4	ASSESSOR'S OVERALL CONCLUSIONS	27
III.	ANNEXES	27
III.1	COMMUNITY HERBAL MONOGRAPH ON SALIX, CORTEX	27
III.2	LITERATURE REFERENCES	27

I. REGULATORY STATUS OVERVIEW¹

MA: Marketing Authorization;

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 ²
Austria	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	combinations
Belgium	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" 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 checked="" type="checkbox"/> Other Specify:	combinations
Denmark	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
France	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Germany	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	combinations
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Hungary	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	combinations
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	combinations
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 checked="" type="checkbox"/> Other Specify:	combinations
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 type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Romania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
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Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Spain	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Sweden	<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.

² Not mandatory field

Member State	Regulatory Status				Comments ²
United Kingdom	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	combinations

Superseded

**II. ASSESSMENT REPORT ON
WILLOW BARK AND HERBAL PREPARATION(S) THEREOF WITH WELL-
ESTABLISHED USE (WEU) AND/OR TRADITIONAL USE (TU)**

BASED ON ARTICLE 10A OF DIRECTIVE 2001/83/EC AS AMENDED

(WELL-ESTABLISHED USE)

**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)	Whole or fragmented dried bark of young branches or whole dried pieces of current year twigs of various species of genus <i>Salix</i> including <i>S. purpurea</i> L., <i>S. daphnoides</i> Vill. and <i>S. fragilis</i> L.
Herbal preparation(s)	Quantified herbal preparations thereof
Pharmaceutical forms	Herbal substance or preparation for oral use
Rapporteur	Dr. Heidi Neef

II.1 INTRODUCTION

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

- Herbal substance(s):

There are about 500 species of *Salix* species called willow, mainly found in Europe and North America. The species of medical interest include *Salix alba*, *S. nigra* and *S. purpurea*, but *S. daphnoides* and *S. fragilis* along with *S. purpurea* contain the greatest yield of salicylate precursors.

According to the Ph. Eur. (01/2005:1583), the herbal substance is the whole or fragmented dried bark of young branches or whole dried pieces of current year twigs of various species of genus *Salix* including *S. purpurea* L., *S. daphnoides* Vill. and *S. fragilis* L. The drug contains not less than 1.5 per cent of total salicylic derivatives, expressed as salicin (C₁₃H₁₈O₇; Mr 286.3), calculated with reference to the dried drug.

The characteristic constituents are derivatives of salicin, mainly salicortin, 2'-*O*-acetylsalicortin and/or tremulacin. Other constituents are flavonoids, condensed tannins (8-20%) and catechins.

Salicylates, calculated as total salicin (and determined after hydrolysis) vary between species: 0.5% in *Salix alba*, 1-10% in *Salix fragilis*. The concentration and availability of salicylates also vary within species according to growing conditions, processing and preparation (Steele et al 1969, Meier et al 1985a, Meier et al 1985b, Julkunen-Tiitto et al 1992a, 1992b and 2001, Blashek et al 1998). It should be noted that tannins may interfere with the absorption of salicylic acid.

The bark of *Salix purpurea* L. contains 4-8% of total salicin (after hydrolysis). Phenol glucosides include salicortin (up to 9%), tremulacin (rarely more than 1%) and salireposide (0.1-1.2%) with small amounts of syringin and purpurein (up to 0.4%). Other constituents include the yellow chalcone isosalipurperoside (0.15-2.2%), the flavanones eriodictyol-7-glucoside (0.18-0.4%) and (+) and (-)-naringenin-5-glucoside (0.4-1.5% each), approximately 0.5% of (+)-catechin and 5% of polyphenols. Young twigs (bark and wood) contain the same constituents in lower concentrations than bark alone.

The bark of *Salix daphnoides* Vill. contains more than 4% of total salicin. Phenol glucosides include salicortin (3-11%), tremulacin (up to 1.5%) and salicin (up to 1%) with small amounts of syringin (up to 0.2%). Other constituents include the yellow chalcone isosalipurperoside (0.2-1.5%), the flavanones (+) and (-)-naringenin-5-glucoside (0.3-1% each) and naringenin-7-glucoside (0.3-1.5%), approximately 0.5% of (+)-catechin and 5% of polyphenols. Young twigs (bark and wood) contain the same constituents in lower concentrations than bark alone.

Willow monographs are included in general reference books on herbal substances such as the American Herbal Pharmacopoeia (1999), British Herbal Compendium (1983), British Herbal Compendium (1992), Commission E monographs (1984) and ESCOP (2002).

DAB 10 (and DAB 10 Kommentar) and Bisset (1994) recommend 2-3 g herbal substance (finely chopped or coarsely powdered) 3 to 4 times per day, with mean daily doses of 60-120 mg salicin.

Barnes et al (2002) recommended 1-3 g dry bark for decoction, three times daily, corresponding to 60-120 mg total salicin daily.

The concentration of salicin in the herbal substance varies (see above). The Ph. Eur. stipulates a minimum content of 1.5% total salicin in the herbal substance. It is clear that 6-12 g powdered bark (as a decoction) will usually not deliver amounts of salicin that are comparable to the doses of salicin administered in the preparations studied in the clinical trial settings.

The herbal substance as such is however not used; only the bark reduced in size to comminuted or powdered is used (herbal preparations).

- Herbal preparation(s):

According to the Ph. Eur. (04/2008: 2312), willow bark dry extract contains minimum 5.0 per cent of total salicylic derivatives, expressed as salicin (C₁₃H₁₈O₇; Mr 286.3) (dried extract). The extract is produced from the herbal drug by a suitable procedure using either water or a hydro-alcoholic solvent equivalent in strength to a maximum of 80 per cent V/V ethanol.

The Ph. Eur. monograph only stipulates a minimum content of total salicylic derivatives, expressed as salicin. Each manufacturer needs to provide a range for the quantified extract used in his finished product. The 15% total salicin, as contained in the extract for which moderate clinical efficacy was demonstrated, represents an average value. The exact range needs to be established for each finished product on the basis of the manufacturer's specifications.

The MLWP discussed in September 2008 whether preparations in the TU part of the monograph should be quantified or not. Some members were in favour of such quantification because 1) salicin is a source of salicylates and in view of interactions and safety profile, the amount of salicin is an important piece of information to have, 2) for eligibility to TU registration, the pharmacological effect of the preparations should be plausible and the plausibility is linked to the amount of salicin, 3) at the time of assessment of the quality dossier, if the quantification for salicin is not provided, which criteria should be applied to accept or refuse 4) quantification is justified given that it concerns an active substance. On the contrary some members were against the quantification for salicin. The HMPC Chair in particular pointed out that the quantification is irrelevant given the very low posology of the preparations. Whether a product is quantified to 15 mg or to 50 mg has no relevance to the activity and both products should be granted a TU registration. The quantification is relevant if a minimum amount of salicin is established that guarantees the plausibility of the effect. A choice is to be made between relying purely on the traditional use of the preparations or requiring some scientific evidence in which case quantification must be associated with the requirement for a minimum of salicin. The MLWP decided to delete the term "quantified" in the TU part of the monograph.

ESCOP: Dried hydro-alcoholic or aqueous extracts, tinctures or liquid extracts, equivalent to 120-240mg of total salicin per day.

The Commission E monograph (1984) on willow bark recommends liquid and solid preparations; daily dose corresponding to 60-120 mg total salicin, as antipyretic, antiphlogistic and analgesic.

The British Herbal Pharmacopoeia (1983) and British Herbal Compendium volume 1 (1992): liquid extract (1:1 in 25% alcohol): 1-3 ml three times daily and tincture (1:5) (extraction solvent ethanol 25%): 15-24 ml per day.

In Germany, a Marketing Authorisation (MA) was granted for the following hydro-alcoholic and aqueous extracts: dry extract ethanol 70% 8-14:1 (dosage: 1-2 times 393.34 mg extract / day) and dry aqueous extracts with ratio's 16-20:1; 8-16:1 (dosage: 2 x 600 mg extract/day) and dry aqueous extract (16-23:1). The maximal daily doses range from 120 mg salicin to 240 mg salicin (Wagner et al 2003b, information from the Rote Liste 2002).

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

This AR assesses willow bark as a sole active substance in (traditional) herbal medicinal products (HMPs).

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

Willow bark has had a long tradition as febrifuge dating back to the 18th century. Following the identification of salicin and the subsequent synthesis of salicylic acid and more importantly acetyl salicylic acid (end of 19th century), the interest in willow bark had decreased substantially. However, the demand for phytoanalgetica with better tolerability versus anti-inflammatory drugs has increased scientific interest in willow bark (Kaul et al 1999).

Willow bark has traditionally been used for muscular and arthroidal rheumatism with inflammation and pain, influenza, respiratory catarrh, gouty arthritis, ankylosing spondylitis, and specifically for rheumatoid arthritis (RA) and other systemic connective tissue disorders characterised by inflammatory changes (Barnes et al 2002).

Wichtl (2002) / Hänsel (1991) / Hagers Handbuch (Blaschek et al 1998) and ESCOP (2002) state the use as a relief of low back pain; symptomatic relief of mild osteoarthritic and rheumatic complaints.

HagerROM (2001) mentions the traditional use of powdered drug and herbal teas in case of flu-like conditions and treatment of minor pain (daily dose equivalent to 60-120 mg salicin).

The German Commission E monograph (1992) approved internal use for diseases accompanied by fever, rheumatic complaints and headaches.

In Germany, MAs were granted for HMPs containing:

- Dry extract ethanol 70% 8-14:1 with indications: headache, fever, minor articular pain. Dosage: 1-2 x 393, 34 mg extract / day (MA dated 1997)
- Dry aqueous extracts 16-20:1 and 8-16:1 with indications: headache, fever, rheumatic complaints. Dosage: 2 x 600 mg extract/day (MAs date from 1997 & 2003)
- Dry aqueous extract 16-23:1 with indication of fever. Dosage: 2 x 480 mg extract / day (MA 2003)
- Powdered willow bark: 500 mg per coated tablet or capsule (MAs since 1991 and 1992 respectively).
- Cut herb: 1.995 g/teabag, 3-6 cups/day (MA dated 1999).

All preparations for which MA for "TU" had been granted (according to former national regulations) were included in the overview by Germany (some of them not in accordance with the actual provisions of Directive 2004/24/EC). Traditional preparations were authorised in 10-50% of WEU doses when in parallel the same preparations were authorised under WEU. The MLWP concluded in September 2008 that it is not appropriate that the dry extract ethanol 70% 8-14:1 should appear in the TU section of the monograph (as well as in the WEU section, with different posology)

Willow bark is also ingredient in combination products (3 WEU products and 2 TU products) and a standard MA for combination products with willow bark as a herbal tea exists.

In Spain, 400 mg powdered willow bark is administered every 8 hours.

In France, capsules containing 260 mg willow bark powder are authorised since 1988.

No single ingredient products are authorised / registered in the other Member States: willow bark is included in combination HMPs in Belgium, Malta, Czech Republic, UK, Austria, Latvia and Italy.

In Austria, a MA exists for a combination willow-bark containing HMP (120 mg aqueous extract 20-1, 15% salicin; in combination with Tilia flos and vitamin C). In addition, a combination herbal tea is on the market.

No willow bark containing products are authorised in Norway, Finland and Portugal.

For information, in Italy food supplements with the following preparations were notified:

- Capsules with a combination of 400 mg dry extract of *Salix alba* (15% salicin) and 460 mg powdered bark (notified in 2004) : claim that it may favour osteo-articular well-being
- Oral solution (drops) containing extract ethanol 60%

In central Italy dried willow bark is applied topically to treat warts (Leporatti 1990).

Hagers Handbuch includes external use to help healing of wounds (50 g herbal substance per 0.5L water).

In the MLWP September 2007 the conditions associated with “fever” and “pain” in which HMPs containing willow bark are traditionally used were specified as “a) the symptomatic relief of minor articular pain” with a duration restriction to a maximum of 4 weeks, “b) the symptomatic relief of fever associated with common cold” for no longer than 3 days (in common cold, fever is experienced for 3 days), and “c) the symptomatic relief of headache”. If fever exceeds 39°C, persists or is associated with severe headache (meningitis) or if symptoms worsen during the use of the medicinal product, a doctor should be consulted. If headache persists for more than one day or is recurrent, medical advice is sought.

These TU uses are contra-indicated in children and adolescents under 18 years of age. It was specified that THMPs containing willow bark are not intended to be used in case of osteoarthritis (OA) as this condition requires medical advice.

The posology section covers only the preparations for which posology is documented. A posology for dry bark for herbal tea preparation, dry aqueous extracts, liquid extract and powdered dry bark were specified

II.2 NON-CLINICAL DATA

II.2.1 Pharmacology

II.2.1.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Pharmacological actions normally associated with salicylates are also applicable to willow which support most of the herbal uses, although no studies are available for willow covering most uses.

Salicin is probably the most active anti-inflammatory compound in willow; it is metabolised to salicylic acid.

The hen’s egg choriollantoic membrane test system has been used to study the anti-inflammatory effect of the willow bark constituents salicin and tremulacin (isolated from *Populus spp*). Onset of this anti-inflammatory effect is delayed in comparison with saligenin (salicyl alcohol), sodium salicylate and acetylsalicylic acid, indicating that the active principles may be metabolites of salicin and tremulacin (Albrecht et al 1990).

Isolated tremulacin, sc injected at 100mg/kg bwt significantly inhibited carrageenan-induced paw oedema and peritoneal leucocyte migration in rats, and croton oil induced ear oedema and acetic acid induced writhing in mice. Inhibition of leukotriene B4 biosynthesis in pleural leucocytes also supported its anti-inflammatory activity in acute inflammatory animal models (Cheng et al 1994).

A water extract of *Salix caprea* bark showed moderate inhibition of prostaglandin synthesis and PAF-induced exocytosis in vitro (Tunón et al 1995).

A water extract of willow bark strongly inhibited oxidation of LDL by copper ions in a number of vitro tests. Copper chelation seemed to be only partially involved in inhibition of copper-dependent oxidations and only at a certain concentration of extract (Rohnert et al 1998).

Willow bark extract ethanol 70% (total salicin 15%) demonstrated a dose-dependent inhibition of COX-1 and COX-2 in vitro on whole-blood samples of 3 healthy volunteers, but inhibited less efficiently TNF- α and IL-1 β release. The concentration of extract tested did not affect cell viability (Wagner et al 2003a). It should be noted that after oral ingestion of the extract, these inhibitory effects were no longer demonstrated. In another in vitro study with primary human monocytes, the extract 70% 8-14:1 inhibited LPS-induced release of PGE2 reflecting COX-2-mediated PGE2 release. Salicin and salicylate had no effect on the parameters, while rofecoxib was included as the active control. The extract inhibited the LPS-induced release of TNF- α , IL-1 β and IL-6 (Chrubasik et al 2003; Fiebich et al 2004, Wagner et al 2003). A third study examined a water extract 33:1 in two inflammation models in rats, the 6day air pouch model and the adjuvant-induced arthritis. The extract was at least as active as acetylsalicylic acid (ASA) on a mg/kg basis in reducing inflammatory exudates and in inhibiting leukocytic infiltration as well as in preventing the rise in cytokines, was more effective than ASA in suppressing leukotrienes, but equally effective in suppressing PGs. Again, other constituents than salicin are thought to contribute to the overall activity as the extract contains considerably lower amounts of salicylates (Khayyal et al 2005).

A pharmacological in vivo and in vitro study on an aqueous willow bark extract (16-23:1, 23-26% total salicin) pointed to contributions of the fraction of polyphenols and flavonoids to the overall effect of willow bark on the inhibition of enzymes of arachidonic acid (AA) metabolism (COX-1, COX-2, HLE isolated enzymes, 5-LOX), inhibition of gene expression of mediators of inflammation, anti-oxidative effects whereas the contribution of salicin derivatives was found to be minor (note that no metabolic activation of the salicins took place). Dose-dependent effects of the extract (50-150mg/kg) were found in the carrageenan-induced rat paw oedema test and the Randall-Sellitto-test (anti-nociceptive effect), comparable to 150 mg/kg ASA. The results and the mg-mg comparison with regard to salicylic derivatives again suggest that other fractions than salicins distinctly contribute to the effects of the extract (Nahrstedt et al 2007).

Wuthold et al (2004) published an analysis of 22 various extracts (aqueous and hydro-ethanolic) with HPTLC and 2 in vitro tests (anti-oxidative effects). The models were used to predict activity of willow bark extracts.

Salicin administered orally to rats at 5 mmol/kg bwt significantly reduced yeast-induced fever, producing a normal temperature, and completely prevented fever when administered simultaneously with yeast. However, salicin at this dose level did not affect the renal body temperature of afebrile rats. On the other hand, both sodium salicylate and saligenin at 5 mmol/kg lowered body temperature significantly in afebrile rats (Akao et al 2002).

Other ingredients of the extract may contribute to the overall analgesic effects. These constituents may include naringenin, catechins and eriodictyol, that inhibit lipoxygenase (Wurm 1982), hyaluronidase (Kuppsamy et al 1990) and scavenge free radical (Rice-Evans et al 1995).

Tannins are known to have astringent properties.

II.2.1.2 Assessor's overall conclusions on pharmacology

The relatively low number of studies published may be due to the fact that pharmacological actions normally associated with salicylates are also estimated to be applicable to willow bark and salicin.

A number of recent in vitro and in vivo studies were published on the anti-inflammatory effects of willow bark. Different study designs are however used, and the results are not in line with the results found after oral administration of the extract to healthy volunteers.

Recent understandings concur that other ingredients of the extract (such as naringenin, catechins and eriodictyol) may contribute to the overall effects of willow bark.

II.2.2 Pharmacokinetics

II.2.2.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

In vitro

Salicortin was unchanged after 1 hour of incubation in artificial gastric juice (pH 1.0). After 6 hours of incubation with artificial intestinal juice (pH 7.4-7.6), salicortin was degraded to salicin with $t_{1/2} = 4.02$ h (Meier et al 1990).

Salicin is stable under acidic conditions (0.5% hydrochloric acid with or without pepsin) and produces no saligenin, even after incubation with human saliva at pH 7.2) (Steinegger et al 1972, Fötsch et al 1989 a and b).

β -glucosidase extracted from almonds and β -glucosidase from guinea pig liver converted salicin and salicortin to saligenin. However, salicin derivatives acetylated on the sugar moiety and tremulacin were not decomposed (Julkunen-Tiito et al 1992a, Gopalan et al 1992). Non-specific esterases from rabbit and pig liver transformed salicortin to salicin (98.1%), acetylsalicortin to acetylsalicin (75.5%) and tremulacin to tremuloidin (63.9%). Pancreatic proteases degraded salicortin to salicin and tremulacin to tremuloidin (Wutzke 1991).

Transport of salicin and saligenin into erythrocytes was rapid for saligenin (1 minute to saturation) and delayed for salicin (4 hours to saturation). The process was reversible exhibiting rapid release for saligenin and slower release for salicin. Saligenin and salicin both bind to human serum albumin but saligenin has a significantly higher affinity (Matsumoto et al 1993).

Saligenin was transformed to salicylic acid by homogenised liver, lung and kidney. Salicylic acid was quantitatively detectable in homogenised liver after incubation with saligenin (Fötsch et al 1989 a and b). Salicin was partially metabolised to saligenin and salicylic acid after incubation with homogenised kidney from rats (Adamkiewicz et al 1961).

Salicin injected into an isolated closed-off section of the male rat intestine, appendix and colon, was hydrolysed by intestinal bacteria to its main metabolite saligenin (Fötsch et al 1989). Transport of salicin and saligenin through the isolated intestinal wall was confirmed using the closed-off posterior section of the male rat intestine. When salicin and saligenin were injected into the closed intestine both passed the ileal wall unchanged. Saligenin appeared to penetrate the intestinal wall faster than salicin (Adamkiewicz et al 1961).

In vivo

After oral administration of salicin (400 mg/kg bwt) or sodium salicylate (29 mg/kg bwt) to rats, salicylic acid appeared slowly (salicin, C_{max} of 82.4 μ g/ml after 5 h) or rapidly (sodium salicylate, C_{max} of 104.2 μ g/ml after 1.5 h). Elimination was slower with sodium salicylate. The relative bio-availability of salicylic acid from salicin was only 3.25% of that from sodium salicylate (Fötsch et al 1990), which was much lower than postulated after administration of 1mmol salicin / kg bwt = 268mg/kg bwt (Fötsch et al 1989). Salicin appears to be a pro-drug, which is gradually transported to the lower part of the intestine, hydrolysed by intestinal bacteria to saligenin, and converted to salicylic acid after absorption. Absorption of salicin is slow compared to that of saligenin or salicylic acid (Akao et al 2002).

II.2.2.2 Assessor's overall conclusions on pharmacokinetics

The *in vitro* and *in vivo* pharmacokinetics of salicin and its precursors are well documented in literature. The data should be read in conjunction with the clinical pharmacology data (pharmacokinetic data).

II.2.3 Toxicology

II.2.3.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

Salicin did not induce gastric lesions in rats even at a dose of 5 mmol/kg bwt. Saligenin and sodium salicylate induced severe gastric lesions in a dose-dependent manner in the range of 1-5 mmol/kg (Akao et al 2002). It may be that willow bark is less prone to induce adverse reactions in the stomach than acetylsalicylic acid is. This may be due to the generation of active metabolites in the intestine after passing through the stomach as intact glycosides that do not inhibit cyclo-oxygenase in the stomach wall.

An LD50 of 28 ml/kg is described for an hydro-alcoholic extract of willow bark (Leslie et al 1978).

Only indirect data on chronic toxicity, reproductive toxicity and theratogenicity are available for willow bark. No data on willow bark as a single ingredient were found. Teratogenicity of salicylates in animal models is described.

II.2.3.2 Assessor's overall conclusions on toxicology

Very limited data on willow bark are available.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

II.3 CLINICAL DATA

II.3.1 Clinical Pharmacology

II.3.1.1 Pharmacodynamics

II.3.1.1.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

It is mainly salicin and the salicyl glycosides which form salicin after hydrolysis that represents a salicylic-acid pro-drug. Salicin and salicyl glycosides have antipyretic, analgesic, anti-rheumatic and anti-phlogistic actions.

In view of the considerable variation in salicylate concentrations between different *Salix* species, the salicin content of the products should be quantified and declared.

The analgesic activity of willow bark was studied in double-blind study and open controlled studies on patients with low back pain exacerbations. Dose-dependent analgesic effects were observed. In addition, willow bark showed a moderate but significant analgesic effect in one double-blind placebo-controlled study in patients with osteoarthritis but the effect was not confirmed in a later clinical study in OA patients (Biegert et al 2004).

Influence on cyclooxygenase activity and TNF α and IL-1 β was studied on whole blood samples of healthy volunteers. Oral intake of a willow bark extract ethanol 70% (total salicin 15%, equivalent to 240 mg salicin) by 3 healthy volunteers did not show significant inhibitory effects in the 4 test systems. Diclofenac was included as an active control (Wagner et al 2003a).

In contrast to acetylsalicylic acid, aggregation of thrombocytes is affected to a far lesser extent by willow bark. Platelet aggregation was followed in patients receiving willow bark extract (corresponding to 240 mg salicin per day), 100 mg acetylsalicylic acid per day or placebo. Willow bark decreased AA- and ADP-induced aggregation but to a significantly lower extent than acetylsalicylic acid. Collagen-induced aggregation was not influenced by willow bark (Krivoy et al 2001). Clinical relevance in patients with impaired thrombocyte function has to be further studied.

Serum salicylate concentrations during treatment suggest that a daily consumption of 240 mg of salicin as extract is bio-equivalent to 50-87 mg acetylsalicylic acid (Schmid 1998 + 2001a). Other ingredients of the extract may contribute to the overall analgesic effects. These constituents may include naringenin, catechins and eriodictyol, that inhibit lipoxygenase (Wurm 1982), hyaluronidase (Kuppusamy et al 1990) and scavenge free radical (Rice-Evans et al 1995).

II.3.1.1.2 Assessor's overall conclusions on pharmacodynamics

Willow bark is the phyto-therapeutic precursor of acetylsalicylic acid. The pharmacological actions of salicylates in humans are well-documented, and are considered to be applicable to willow. However, the serum salicylate levels that are produced by the recommended doses of willow bark are too low to explain the analgesic activity, and it has been suggested that other constituents such as flavonoids or salicin esters may contribute to the overall effect.

Dose-dependent analgesic effects of willow bark dry extract (8-14:1) ethanol 70% were observed in recent controlled clinical studies in patients with low back pain exacerbations. In OA patients, the (borderline) significant effect could not be confirmed in a later clinical study.

Orally administered willow bark dry extract (8-14:1) ethanol 70% did not significantly inhibit COX-1, COX-2 or inhibit the release of TNF alpha and IL-1beta in a small study in 3 healthy volunteers.

AA and adenosine diphosphate (ADP)-induced platelet aggregation was decreased in patients receiving willow bark extract. This information should be included in both WEU and TU sections of the monograph for safety reasons.

II.3.1.2 Pharmacokinetics

II.3.1.2.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

In a recent 24 hours pharmacokinetic study in 10 healthy volunteers (Schmid et al 2001a), intake of standardized willow bark extract (1360 mg, equivalent to 240 mg salicin, dose divided into 2 tablets at T0h and another 2 tablets at T3h), 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. Considerably higher peak levels of salicylic acid are observed after analgesic doses of acetylsalicylic acid.

Renal elimination occurred predominantly in the form of salicyluric acid (71% of total salicylates), followed by salicylic acid (15%) and gentisic acid (14%). No saligenin or salicin could be detected in serum or urine. After 24 hours, on average 15.8% of the orally ingested dose of salicin was detected in the urine as salicylates. Since approximately 5% of the salicylates had not yet been excreted by the kidneys after 24 hours, it could be estimated that at least 16.6% of the ingested salicin had been absorbed and metabolized to salicylates.

Based on the in vivo findings in rats, it was repeatedly suggested that in humans salicin is also hydrolysed by the flora of the lower intestine prior to absorption of the aglycone (salicyl alcohol). This is contradicted by the studies of Schmid et al (2001a), Steinegger et al (1972, 4 g pure salicin) and Pentz et al (1989) (combination product of caffeine and willow bark) that found salicylic acid in the serum as early as 1 hour after ingestion, and peak levels recorded after 1-3 hours. This suggests that absorption takes place in the upper intestine, and possibly in the stomach. After oral administration, salicin is obviously hydrolysed before or during absorption. The resulting salicyl alcohol is oxidized to salicylic acid, which is the first detectable metabolite in the serum. After parenteral or rectal administration in humans, salicin is excreted unchanged in the urine (Steinegger et al 1972)

II.3.1.2.2 Assessor's overall conclusions on pharmacokinetics

The pharmacokinetics of willow bark extract are well described (Schmid et al 2001a).

II.3.2 Clinical Efficacy

In spite of its long (traditional) use, only a few controlled trials have been conducted with willow bark to support its analgesic and/or antipyretic action.

The clinical studies (all located in the therapeutic area of (minor) articular disorders) are summarized below (cut-off August 2008).

Acute Low Back Pain (LBP) is a symptom, heterogeneous and non-specific, and its aetiology often remains elusive. Studies should be designed on the basis of the claimed indications. Duration varies from 1 week (no radiation) to 1 month (radiating). Studies can be against placebo or active but should always be double-blind. The primary endpoint should be based on a validated pain assessment tool (generic or oriented); secondary endpoints could include the assessment of functional performance (Devogelaer et al 2003). A minimal level of pain, as well as a homogeneous distribution between groups is mandatory. Any concomitant therapy should be well documented and comparable between groups. A dose-range study should be performed.

CPMP (1998 and 2003) issued Points to consider papers on clinical investigation of medicinal products for treatment of OA and RA, respectively.

II.3.2.1 Dose response studies

Low back pain (LBP)

Chrubasik S, Eisenberg E et al (2000). Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study. Am J Med 109:9-14

Methods:

Randomized double blind clinical trial, 3 arms, no report of randomization method, 4 weeks

Participants:

210 patients, N=70 in each group, 191 completed the trial. Inclusion criteria: >18 years, at least 6 months of intermittent low back pain that could not be attributed to identifiable causes, a current exacerbation of their pain at rest and with movement that caused pain of at least 5 of 10 on a VAS and that was expected to require at least 4 weeks of treatment. The characteristics of the participants were similar in the 3 groups (e.g. radiation into leg(s), neurological signs), except that the high-dose salicin group had a greater invalidity, physical impairment index and overall Arhus LBP score and Beck depression inventory. Exclusion criteria are presented.

Intervention:

placebo versus daily dose ~ 120 mg salicin (786 mg dry extract) versus daily dose ~ 240 mg salicin (1572 mg dry standardized willow bark extract, 15 % salicin, Plantina manufacturer, Assalix, 70% ethanol, DER 8-14:1); daily dose divided into 2. Tramadol was the sole rescue medication

Primary outcome parameter:

% of patients pain-free without tramadol for at least 5 days during the final week of the study

Secondary outcome:

Change from baseline in modified Arhus score; % of patients requiring tramadol

Results: dose-dependent analgesic effects were observed:

- Primary outcome: 6% responders in the placebo group, 21% in the low dose group and 39% in the high dose group ($P < 0.001$). Similar results were obtained when drop-outs were excluded.
 - A significant increase in proportion of patients without rescue medication in the high dose group was apparent after 1 week of treatment and became progressively greater during the 4 weeks of treatment. The smaller effect seen in the 120 mg group was significantly different from placebo by the second week of treatment.
 - significantly more patients in the placebo group required tramadol during each week of the study
 - declines in the modified Arhus score (overall and its individual components) were significant. Change in overall Arhus score and its pain component was significantly greater in the 240 mg than in the 120 mg group.
- adverse effects*
- Willow bark groups: N=140 patients): 1 patient suffered a severe allergic reaction (exanthema, pruritis, swollen eyes; 120 mg group, could be attributed); other adverse effects (N=2) attributed to tramadol).
 - Placebo group : N=70 : 3 cases of mild abdominal pain in placebo group (with or without diarrhoea)

Assessor's comment: The study is of good quality. The results indicate a dose-dependent analgesic effect of willow bark dry extract.

II.3.2.2 Clinical studies (case studies and clinical trials)

Low Back Pain

Chrubasik S, Eisenberg E et al (2000). Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study. Am J Med 109:9-14

Details see II.3.2.2

Chrubasik S, Kunzel O et al (2001a). Treatment of low back pain with a herbal or synthetic anti-rheumatic: a randomized controlled study. Willow bark extract for low back pain. Rheumatology 40:1388-93.

Methods:

Open randomized active-controlled clinical trial, 2 arms, 4 weeks

Participants:

228 patients, N=114 with per group. 183 patients completed the trial. Inclusion criteria: >18 years, at least 6 months of non-specific LBP that could not be attributed to identifiable causes. Pain was recorded on VAS, the modified Arhus index and its pain component, and the Total Pain Index. Groups at baseline differed slightly in duration of LBP, and the NSAID group included more patients with pain radiating into legs and was in slightly more pain. Exclusion criteria are presented.

Intervention:

Daily dose ~ 240 mg salicin (1572 mg standardized willow bark extract, 4 capsules of Assalix, ethanol 70%, 8-14:1 DER, 15% salicin) versus 12.5 mg rofecoxib (1 single tablet). Patients had free access to conventional treatments (including whatever medication they usually used in the event of severe pain, but also NSAIDs, acupuncture, physical therapy...).

Outcome parameters:

pain on a VAS, modified Arhus index, its pain component and the total pain index (TPI), physician and patient-rated success and the acceptability of the treatment on a verbal scale.

Results:

- After 4 weeks of treatment, the Arhus index had improved by 20% (both groups) and its pain component by 30%, and the TPI by 35%.
- Number of pain-free patients (VAS <2) was about 20 in both groups
- Patients that resorted to NSAIDs and/or tramadol: 9 in willow bark group (average of 120 mg diclofenac equivalents and 5 mg tramadol) versus 12 in rofecoxib group (average of 42 mg diclofenac equivalents and 17 mg tramadol).
- Patients that resorted to other treatments: 13 in willow bark group versus 17 in rofecoxib group.
- Patients' and physicians' judgments of effectiveness were largely concordant.
- The multivariate analyses of changes in Arhus score and TPI did not identify significant differences related to willow bark versus rofecoxib

Adverse effects

- Willow bark group, N=114:
 - allergy: 1 possible, 3 likely, 1 clear connection
 - GI (dyspepsia, vomiting, heartburn, diarrhoea): 7 possible, 3 likely, 1 clear connection
 - Dizziness: 1 possible
 - Headache: 1 possible
 - blood pressure instability: 1 possible
- Rofecoxib: 27 adverse effects in total: asthma, dyspepsia, nausea, diarrhoea, heartburn, ulcer, GI bleeding, dizziness, headache, oedema

Assessor's comment: the open study design may induce bias and jeopardizes results/conclusions regarding equivalence or non-equivalence of both interventions. Furthermore, (slight) differences in baseline characteristics of the groups are noted (willow bark group slightly favoured). It is also noted that patients with lower disease activity were enrolled in this study (compared with Chrubasik et al 2000). Free access to other treatments, even though resorted to by a fairly small and comparable number of patients in both groups, does not facilitate conclusions on the efficacy of willow bark versus rofecoxib.

Chrubasik S., Kunzel O et al (2001b). Potential economic impact using a proprietary willow bark extract in outpatient treatment of low back pain: an open non-randomized study. Phytomedicine 8(4):24 1-251

Methods:

Open, non-randomised study (post-marketing surveillance) with 3 arms; 4 weeks

Patients:

451 patients > 18 years (N=115 in 120 mg salicin group, N=112 in 240 mg salicin group, N=224 in "placebo" group) with acute exacerbations of chronic (at least 6 months) nonspecific LBP. The baseline characteristics of the 3 groups were slightly different: the "placebo" group had a shorter duration of exacerbation but their pain tended to be more severe as judged by the Arhus index and TPI.

Interventions

Daily dose of 120 mg salicin + conventional treatment, versus 240 mg salicin + conventional treatment versus conventional treatment alone. Salicin groups received standardized willow bark extract, (Assalix, ethanol 70%; 8-14:1), respectively 2 capsules/day (120 mg salicin) or 4 capsules/day (240 mg salicin). Conventional treatment, prescribed by GPs or orthopaedists, included analgesics, NSAIDs, acupuncture.

Objective:

Study of safety and economic impact of including a regular intake of willow bark extract in the conventional treatment scheme. Outcome parameters: pain-free patients with or without additional treatment, modified Arhus index and total pain index

Results:

- The study design does not allow conclusions on efficacy of willow bark because conventional treatment that was resorted to was variable between groups.
- When limiting to the patients included in this study that only used willow bark (no conventional treatment), pain relief of 240 mg dose seems to be superior to 120 mg and control group: 41% pain-free after 4 weeks in 240 mg group versus 8% pain-free in the 120 mg group (results for the 240 mg group are fairly consistent with Chrubasik, et al (2000)).
- 18% of the “placebo” group (with conventional treatment) were pain-free after 4 weeks versus 5.7% in the placebo group of Chrubasik et al 2000.

Adverse effects

- Willow bark groups, N=112+115 patients: GI (6), allergic skin reaction (3)

Assessor’s comment: Important flaws in the study design make conclusions on the efficacy of willow bark based on the results impossible. The open study design may induce bias and jeopardizes results/conclusions regarding equivalence or non-equivalence of interventions. Furthermore, (slight) differences in baseline characteristics of both groups are noted (willow bark group slightly favoured). Patients had access to other conventional treatments (via GP/orthopaedist), and these treatments were not comparable between the groups.

The adverse effects are taken into account for evaluation of clinical safety.

Gagnier et al (2007) published a systematic Cochrane review of the randomized clinical trials to determine the effectiveness of herbal medicine compared with placebo, no intervention or standard/accepted/conventional treatments for nonspecific LBP. A total of 10 studies met the criteria, among those the above-discussed studies of Chrubasik (2000), Chrubasik (2001a) plus Krivoy et al (2001, on effects on human platelet aggregation). Methodological quality of the trials was assessed. A trial was considered high quality if more than 50% of internal validity items scored positively (quality criteria and definitions are given; Chrubasik (2000), Chrubasik (2001a) are classified as “high”). The clinical relevance of each study was assessed independently by 2 reviewers (all criteria fulfilled by Chrubasik et al 2001a). Because of insufficient data and clinical heterogeneity, a qualitative analysis was conducted using a rating system (Strong/moderate/limited/conflicting/no evidence). The trial of Chrubasik et al 2000 suggests there is moderate evidence that 240 mg salicin dose of a willow bark extract reduces pain more than placebo and 120 mg of salicin. The trial of Chrubasik et al 2001 suggests that there is moderate evidence that there are no differences in effectiveness between a 240 mg salicin dose of a willow bark extract and 12.5 mg rofecoxib per day in treatment of acute episodes of chronic nonspecific LBP in the short term. As conclusion it is given that a daily 240 mg salicin dosage of willow bark has strong evidence for the short-term treatment of acute episodes of chronic non-specific LBP. Additional trials testing against standard treatments are needed to confirm efficacy/equivalency/the relative safety of these herbals to standard medications such as NSAIDs, paracetamol. The quality of reporting in the trials should in general improve (CONSORT statement: Gagnier et al 2006).

Schnitzer et al (2004) reviewed clinical trials (1980-2002) on the efficacy and safety of drugs for the treatment of LBP. Trials with willow bark were not included. The authors concluded that limited evidence was found regarding the effectiveness of drug treatments for LBP and current studies focused on the short-term usage of the therapies. Available evidence supported the effectiveness of NSAIDs in acute and

chronic LBP, of muscle relaxants in acute LBP and of antidepressants in chronic LBP. Data on the other therapeutic approaches were considered inadequate to allow conclusions. Standardized approaches to evaluate therapies in LBP are needed, as well as rigorous clinical trial methodology, standardized outcome measures to evaluate many current and future therapeutic interventions.

Osteoarthritis and Rheumatoid Arthritis

Schmid, Ludtke et al (2001b). Efficacy and tolerability of a standardized willow bark extract in patients with osteoarthritis: randomized placebo-controlled db clinical trial. Phytother Res 15:344-50.

Methods

Randomized, placebo-controlled double-blind clinical trial with 2 arms; 4-6 days wash-out, then 2 weeks trial.

Patients

78 patients, N=39 per group. Inclusion criteria: >18 years, OA of hip or knee, verified according to the clinical, laboratory and radiographic criteria of the American College of Rheumatology (ACR). Baseline characteristics are similar between both groups except that the baseline WOMAC pain score was lower for the willow bark group. Exclusion criteria are described. 5 patients withdrew during the study and 10 were excluded from the per-protocol analysis.

Intervention

placebo versus daily dose ~ 240 mg salicin (340 mg standardized willow bark extract *Salix daphnoides* and *S. purpurea*, 17.6% total salicin, ~ 60 mg salicin per coated tablet). Daily dose was divided into 2 tablets twice daily. No additional analgesics, NSAIDs or systemic corticoids were allowed during wash-out and study phases.

Primary endpoint:

Difference in pain dimension WOMAC OA Index between day 0 and day 14.

Secondary endpoints:

Differences in the stiffness and physical function dimensions of the WOMAC, daily VAS on pain and physical function and final overall assessments by patients and investigators.

Results

- A (borderline) significant superiority of willow bark over placebo with regard to WOMAC pain dimension after 2 weeks (intent-to-treat : $p=0.047$; per-protocol analysis: $p=0.0196$)
- No significant differences between the 2 groups with regard to the secondary parameters, except for patients' and investigators' assessment (willow bark significantly superior).

Adverse effects

- Willow bark group, N=38 patients: allergic skin reactions (6), GI (3). No evaluation presented on causality.
- 1 patient in the willow bark group withdrew due to allergic symptoms.

Assessor's conclusion: A moderate analgesic effect was observed in the willow bark group; a difference in pain dimension in the treated group compared to the placebo group just reached statistical significance. There are deficiencies in the quality of the methodology of the study that may affect the outcome/conclusions: namely the relatively low number of patients, the shortness of the duration (the maximum treatment effect was probably not yet reached after 2 weeks) and the differences in baseline WOMAC pain dimension scores between the 2 groups. The extraction solvent and DER of the used willow bark extract is not given. Additional studies, with NSAID (diclofenac) control group were stated to be in preparation.

Biegert C et al. (2004). Efficacy and safety of willow bark extract in the treatment of OA and RA: results of 2 randomised db controlled trials. *J Rheumatol* 31, 2121-30.

Methods

Randomised, double-blind controlled clinical trial; 3 arms (2 groups in RA trial); 7 days wash-out, then 6 weeks trial

Patients

OA trial: 127 patients; N=43 in willow bark group, N=43 in control group, N=41 in placebo group. Inclusion criteria: > 18 years, OA of hip or knee, verified according to the clinical, laboratory and radiographic criteria of the American College of Rheumatology (ACR) with WOMAC pain score of at least 30mm. Baseline characteristics are similar between the groups. Exclusion criteria are described. 106 patients completed the study and were included in the efficacy and safety analysis. The willow bark group received significantly less physical therapy.

RA trial: 26 patients, N=13 in each group. Inclusion criteria: diagnosis of RA according to ACR: RA functional class I, II or III, evidence of at least moderate disease activity (criteria given). The willow bark group showed a more active disease in all baseline arthritis assessments. Exclusion criteria are described.

Intervention

OA trial: Placebo versus salicin 240 mg/day (393 mg extract *Salix daphnoides* ethanol 70% 8-14:1 ~ 60 mg salicin per coated tablet) versus diclofenac 100 mg/day. Daily dose was divided into two tablets twice daily. No additional analgesics/NSAIDs/systemic or intra-articular corticoids were allowed. Aspirin was allowed up to 100 mg daily. Physical therapy could be continued but had to remain unchanged.

RA trial: Placebo versus salicin 240 mg/day (393 mg extract 8-14:1 ~ 60 mg salicin per coated tablet). Daily dose was divided into two tablets twice daily. Disease modifying anti-rheumatic drugs (except TNF-inhibitors) were allowed as concomitant therapy if taken since at least 6 months before (and dosage stable). NSAIDs and analgesics had to be discontinued; up to 100 mg aspirin/day was allowed.

Primary endpoint:

OA trial: pain sub-score of the WOMAC OA index

RA trial: patient's assessment of pain rated on a 100mm VAS.

Secondary endpoints:

OA trial: WOMAC stiffness and function sub-scores and WOMAC total index, and patients' and investigators' assessment of overall efficacy.

RA trial: included number of tender/swollen joints, physical function (HAQ), disability index, patients' assessment of severity of morning stiffness (100 mm VAS), patients' and assessors' assessment of overall efficacy, Quality of life (SF-36), ESR, CRP, number of patients who met the ACR criteria for improvement.

Results:

OA trial

- Primary: WOMAC scores decreased for willow bark (but not significantly) and diclofenac (P=0.0002)
- Secondary: willow bark only significantly improved the physical function sub-score of the SF-36, while diclofenac was (highly) significantly superior over placebo with regard to all endpoints except the mental component of Quality of life and the investigators' assessment of overall efficacy (P=0.05).

RA trial:

- Primary: RA trial: pain on the VAS decreased for willow bark but not significantly. A power estimate of the study showed that that a true difference in pain reduction between willow bark and placebo of 15 mm (suggested as the minimum clinically relevant difference) or more can be excluded with a probability of 93%.

- Secondary: no significant changes between willow bark and placebo.

Adverse events

- Willow bark group in OA trial (N=43): GI (7), plus allergy (exanthema, 1). Significantly lower adverse events in willow bark versus diclofenac
- Willow bark group in RA trial (N=13): allergy (mild itching, 1)

Assessors comment: The studies are in general of high quality but numbers of patients are small.

With regard to the OA trial, the study did not confirm efficacy of willow bark in OA as willow bark only significantly improved the physical function sub-score of the SF-36 while the WOMAC OA index (primary endpoint) was not significantly decreased. OA is the most common form of degenerative joint disease. The sensitivity of the study was demonstrated by the (highly) significant superiority of the control-group (diclofenac) over placebo.

With regard to the RA trial, again no efficacy was demonstrated for willow bark in RA, the most common inflammatory rheumatic disease. The number of patients included in the RA trial is very small and is therefore considered as a pilot study.

Lardos et al (2004) carried out a randomised double blind clinical trial with 60 patients (intention to treat) with hip or knee arthrosis. The study included 3 arms (N=17 diclofenac 150 mg/day; N=22 aqueous extract equivalent to 90 mg salicin/day; N=21 aqueous extract equivalent to 180 mg salicin/day). Inclusion and exclusion criteria are described. A 3 week wash-out period was followed by 3 weeks study period. No additional analgesics/NSAIDs were allowed during the study. Primary endpoint: pain on a 100 mm VAS and evaluation of physical function according to Steinbrocker. All 3 interventions statistically improved both endpoints after 3 weeks' treatment (diclofenac > salicin 90 mg ~ salicin 180 mg). Dose-dependency in analgesic activity (willow bark arms) was not observed.

Assessor's comment: The study indicates analgesic effects of an aqueous extract of willow bark in patients with arthrosis. The sample size is however small; the study is considered as a pilot study. The herbal preparation is not fully characterised (DER). Comparability of the 3 arms at baseline is difficult to interpret. No dose-dependency in effect could be observed.

An unpublished trial was provided by Poland. Samochowiec (2001) studied the efficacy of willow bark extract (Salix ®) in patients with arthrosis (knee or hip) in a double-blind, randomized controlled clinical trial during 3 weeks. Stage II and III (according to Kellgren) patients received either sodium diclofenac (3 x 50 mg daily, N= 17), Salix tablet (quantity extract, and equivalent salicin not known) + 2 placebo tablets / day (N=22), or 2 Salix tablets + 2 placebo tablets / day (N=20). The exact administration scheme is unclear. Analgesics and anti-inflammatory drugs were not allowed during the study. Baseline characteristics of the 3 groups (functional capacity according to Steinbrocker, subjective pain evaluation on VAS, stiffness etc were fairly comparable. Primary and secondary endpoints are not clearly defined. All treatments significantly improved pain on VAS, pain during walking and walking downstairs on even surface, pain during passive and active motion, functional capacity and decreased impairment of daily activity. No significant differences between the 3 groups were observed. 1 patient withdrew (Salix) due to malaise. Gastroscopy and laboratory findings were not affected by any of the treatments.

Assessor's comment: The willow bark preparation is insufficiently characterized. It is not possible to situate the results in relation to the other clinical trials with willow bark. Patient numbers are rather small, and end points should be more clearly defined.

In a post-authorisation surveillance study on willow bark dry extract (8-14:1, ethanol 70%; daily doses equivalent to 120 or 240 mg 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).

Assessor's comment: Full details of the post-authorisation study of Werner are missing, only an abstract was available.

In an observational study with duration 6-8 weeks (Saller et al 2008), 204 physicians treated 877 patients with different types of rheumatic pain (OA, RA, LBP, soft tissue disorders) with willow bark dry extract (8-14:1, ethanol 70%, 15% total salicin). The scope is to get a better estimate of the frequency of ADR and a broader picture of efficacy. Additional anti-inflammatory drugs were co-prescribed in 39.3% of the cases. Pain intensity was assessed (scale). Final data were compared with the corresponding values at baseline. No blood chemistry, coagulation nor haematology data were recorded. Pain scores tended to decrease. 38 patients (4.3%) reported a total of 46 ADRs relating predominantly to GI (3.1%) and skin (1.6). There were no serious ADRs.

Assessor's comment: This concerns an observational study, no control group is included. Records of dose administered (1572 mg or 786 mg dry extract) are not presented. Baseline characteristics are not given (per grouped diagnosis). No conclusions can be drawn with regard to efficacy.

A 2-month randomized non-cross over study in 82 patients with chronic arthritis pain showed a small but statistically significant improvement in symptoms with a low dosage combination willow bark formulation (containing 100 mg *Salix alba* extract, guaiacum, black cohosh, sarsaparilla and poplar bark) compared to placebo (Mills et al 1996).

Migraine prophylaxis

Tanacetum parthenium and *Salix alba* either alone or in combination were shown to strongly inhibit binding to 5-HT_{2A/2C} receptors (targets of prophylacting agents such as methysergide, pizotifen, oxetorone, cyproheptadine) while only *Salix alba* (and the combination) recognized 5-HT_{1D} receptors (targets of triptans), leading to the hypothesis that the combination would provide superior migraine prophylactic activity compared with Tanacetum alone (randomized double-blind placebo-controlled clinical trials with Tanacetum alone show mixed results).

Shrivastava et al (2006) performed a prospective open-label study in 12 patients diagnosed migraine without aura (IHS criteria), aged > 18 years. After a 6 weeks' baseline-period (3-15 attacks / 6 weeks observed), twelve weeks' treatment with a combination product of Tanacetum parthenium 300 mg and *Salix alba* 300 mg (salicin content \geq 1.5%) twice daily was administered to determine the effects on migraine attack frequency (primary outcome parameter), intensity and duration (secondary outcome parameters). Attack frequency was reduced by 57.2% after 6 weeks (P=0.029) and 62.6% at 12 weeks (P=0.025) in 9 out of 10 patients (no significant improvement between 6 and 12 weeks) with 70% of patients having a reduction of at least 50%. Attack intensity was reduced by 38.7% after 6 weeks and 62.6% after 12 weeks in 10 out of 10 patients (both significant), with 70% having a reduction of at least 50%. Attack duration decreased by 67.2% after 6 weeks and 76.2% after 12 weeks in 10 out of 10 patients (both significant). Two patients were excluded for reasons unrelated to treatment. No adverse events occurred. In patients with more than 2 migraine attacks per month, current prophylaxis reduces the number of attacks by up to 50% but in only half the patients. A placebo-effect of approximately 30% is generally observed in migraine prophylaxis studies. The results of this open pilot trial demand a randomized double-blind placebo-controlled trial with a larger patient population (including those with aura).

An overview of 15 systematic reviews of herbal medicines used in the treatment of osteoarthritic complaints and chronic low back pain was recently published by Chrubasik et al (2007). The evidence was found as conflicting for willow bark due to the confirmatory study of Biegert et al (2004) in OA and RA with negative result (no statistically significant results).

Setty et al (2005) reviewed herbal preparations commonly used in the treatment of rheumatic indications. The resurgent interest in willow bark as a treatment for chronic pain syndromes was illustrated by a

summary of the clinical trials. The authors concluded that trials longer than 4 weeks must be performed before declaring salicin's safety and efficacy as the conditions are chronic (OA).

Willow bark is safer than aspirin, but effective dosing may be difficult to obtain. Several controlled trials have demonstrated benefits for extract products in the treatment of rheumatic and musculoskeletal pain. A pure historic interest may be a premature judgement (Rottblatt 2002).

The clinical studies are re-iterated by a number of articles, including März et al (2002), Chrubasik et al (2002), Wagner et al (2003b and c), Kaul et al (1999), Bruneton (2002), Bogduk (2004).

II.3.2.3 Clinical studies in special populations (e.g. elderly and children)

No clinical studies were performed in patients below 18 years..

II.3.2.4 Assessor's overall conclusions on clinical efficacy

Under WEU: General conclusion on the clinical studies on analgesic effects of willow bark:

The disease studied, the design and quality of the published trials was variable (see assessors comments per study, see also Garnier et al 2007). Shortcomings in some of the controlled clinical trials are: small numbers of patients and/or short duration of the study, slightly different baseline characteristics which hamper conclusions on changes towards baseline, open study design, and access to rescue analgesics/NSAIDs/corticoids again hampering conclusions on efficacy of willow bark. The willow bark preparations are not always carefully characterized and described (extraction solvent, DER). The quantity of salicin should be stated although other constituents may contribute to the activity. The composition with regard to salicylates and other constituents varies among extracts (Kammerer et al 2005). Results for a particular extract cannot be extrapolated to other extracts.

Taking into account the body of available published trials and their respective trial quality and outcomes, the controlled clinical trials published so far provide moderate evidence for the analgesic activity of a daily dose of willow bark extract ethanol 70% 8-14:1 corresponding to 240 mg salicin (single ingredient preparation). Based on the double-blind, placebo/active-controlled randomized clinical trials (Chrubasik et al 2000, Schmid et al 2001b, Biegert et al 2004), it can be concluded that willow bark is superior over placebo in a dose-dependent manner in the clinical setting of low back pain. An additional 3-arm trial including placebo and active comparator is recommended. With regard to the analgesic effects in OA and RA, willow bark exerts none to a moderate analgesic activity. It should be taken into account that responders in the placebo group are in general relatively high in pain trials. Additional studies should have sufficient power.

Based on the available clinical studies, daily intake of willow bark dry extract ethanol 70% (total salicin content 15%), equivalent to 240 mg total salicin is advised. The daily dose should be divided into 2 doses. The patient is referred to the physician in case of worsening or no improvement after the first week of use. This limitation of duration of use is based/in accordance with the clinical studies, where improvement is observed after 1 week of treatment with willow bark (Chrubasik et al 2000). The use is not recommended under 18 years of age.

During discussion in the MLWP in September 2007 some members indicated that they would not support a "WEU" indication of "symptomatic treatment of minor articular pain" as they considered that the efficacy of willow bark in treating this condition as not proven. Some clinical studies are indeed of pilot-scale size. However, the human pharmacological data would be sufficient to support an indication in "articular pain" and the body of clinical evidence is more expanded than for e.g. nettle herb. Some members advised caution in defining the indications for willow bark in the knowledge that effective pain relief medicinal products are available. As the evidence for low back pain was stronger than the evidence available for OA, the WEU indication was consequently revised to "HMP used for the short-term treatment of low back pain" in adults and elderly with a duration of use restricted to a maximum of 4 weeks.

II.3.3 Clinical Safety/Pharmacovigilance

II.3.3.1 Patient exposure

Minor adverse effects have been reported in a relatively small number of patients. Based on the published clinical data, from a total of 620 patients and healthy volunteers treated with various single-ingredient preparations containing willow bark, adverse events, predominantly mild, were reported in 45 cases (7.3%), predominantly GI (N=27, 4.4%) and allergic reactions (N=17, 2.7%, including 2 severe). Data obtained with combination products are not included in this overview of adverse events.

In a post-authorisation surveillance study on willow bark dry extract (8-14:1, ethanol 70%; daily doses equivalent to 120 or 240 mg total salicin), 922 physicians observed 4731 patients with chronic back pain or arthralgia after 3-4 weeks and after 6-8 weeks. "63 patients reported ADR, no serious ADR occurred. GI side effects were notified with an incidence of 0.93%, in most cases as abdominal pain (incidence = 0.59%). No GI 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 dosage and did not increase with treatment duration" (Werner 2004, abstract).

Assessor's comment: Full details of the post-authorisation study of Werner are missing, only an abstract was made available which makes assessment of the study impossible.

II.3.3.2 Adverse events

- Chrubasik et al (2000): Willow bark groups : N= 70+70 patients:
 - 1 patient suffered a severe allergic reaction (exanthema, pruritis, swollen eyes; 120mg group, could be attributed);
 - note that the other adverse effects (N=2) were attributed to tramadol (rescue medication).
- Chrubasik et al (2001): Willow bark group, N= 114 patients:
 - allergy : (1 possible, 3 likely, 1 clear connection)
 - GI (dyspepsia, vomiting, heartburn, diarrhoea) (7 possible, 3 likely, 1 clear connection)
 - Dizziness: (1 possible)
 - Headache: (1 possible)
 - blood pressure instability (1 possible)
- Chrubasik et al (2001b) Willow bark groups, N=112+115 patients:
 - GI (6),
 - allergic skin reaction (3)
 - no evaluation of causality presented
- Schmid et al (2001b) Willow bark group, N=38 patients:
 - allergic skin reactions (6)
 - GI (3)
 - No evaluation of causality presented.
 - Note that 1 patient in the willow bark group withdrew due to allergic symptoms.
- Biegert et al (2004): Willow bark group in OA trial (N=43) and in RA trial (N=13) :
 - GI (7)
 - allergy (exanthema, 1) (mild itching, 1)
 - no evaluation of causality presented.
- Schmid et al (2001a): willow bark group N=10 volunteers
 - adverse events not recorded / reported
- Krivoy et al (2001): willow bark group N=35 patients
 - adverse events not recorded / reported

Plants that contain more than 10% tannins (willow bark: 8-20%) have potential adverse effects including stomach upset, nausea, vomiting (Rotblatt 2002).

The undesirable effects are reflected in section 4.8 of the monograph.

II.3.3.3 Serious adverse events and deaths

One patient suffered a severe allergic reaction (exanthema, pruritis, swollen eyes; 120 mg group, could be attributed (Chrubasik et al 2000).

Literature reports a case of anaphylaxis resulting from the use of a willow-bark containing dietary supplement in a patient with a history of aspirin allergy (Boullata et al 2003).

II.3.3.4 Laboratory findings

II.3.3.5 Safety in special populations and situations

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

Adverse effects and signs of toxicity normally associated with salicylates (such as gastric and renal irritation, hypersensitivity, blood in stools, tinnitus, nausea and vomiting) may occur. Salicin is documented to cause skin rashes.

In view of the lack of more toxicity data on willow bark, the usual precautions associated with salicylate therapy are also applicable to willow bark. Therefore, in individuals with known hypersensitivity to aspirin, asthma, active peptic ulceration, haemophilia and other bleeding disorders, gout should be aware of the possible risks associated with the intake of willow bark (Clauson et al 2005; Aronson).

Concurrent administration of willow bark with other salicylate-containing products should be avoided as such combination may increase the risk of gastric irritation.

Hypersensitivity to salicylates or other NSAIDS

There is a considerable cross-reactivity of acetylsalicylic acid with other NSAIDS and the now widely banned tartrazine. For willow bark preparations, the risk for an idiosyncratic response (skin reactions, bronchospasm) in sensitive individuals cannot be excluded; the use of willow bark is therefore contra-indicated. Mechanism of (aspirin) hypersensitivity: the current theory relates to inhibition of COXs and interference with PEG2 synthesis allowing PGF2 to predominate in susceptible individuals. Avoidance of aspirin and substances to which there is a cross-sensitivity is the only satisfactory solution (Meylers).

Asthma

Patients with existing asthma and nasal polyps or chronic urticaria have a greater frequency of hypersensitivity. Because of the relatively high incidence of aspirin-induced broncho-constriction, urticaria or anaphylaxis, aspirin should not be used in patients with asthma or those already believed to be hypersensitive to salicylates, NSAIDS or tartrazine (Meylers, Rotblatt 2002). The use of willow bark in asthma patients is contra-indicated as severe reactions could be induced.

Children

Reye's syndrome was previously regarded as a side-effect of aspirin, but it has become clear that the syndrome cannot be assigned to a specific cause. Reye's syndrome presents itself a few days after the prodrome of a viral illness, including influenza A and B, adenovirus, varicella virus and rheovirus. Various other factors have been incriminated such as pesticides. Only in case of aspirin, some epidemiological studies have been performed but the clarity of the link between Reye's syndrome and aspirin has been questioned.

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 (Meylers, Rotblatt 2002). Because of the clinical importance of the syndrome and the avoidable risk, use of salicylates in patients below 16 years should in

general be avoided. Therapeutic alternatives are available (paracetamol, ibuprofen) except for juvenile arthritis.

Examples of regulatory action are:

- The UK authorities position paper (2002): not to be used below 16 years as from October 2003.
- PhVWP did not issue a contra-indication for children below 12 years / 16 years
- The Belgian authorities issued an advice against use in children below 12 years in case of suspicion of viral infection. A class labelling in the section 4.4 (not 4.3) was imposed for acetylsalicylic acid containing medicinal products : only to be used for these patients in case other products lack efficacy; information on symptoms of Reye's syndrome is given; a statement is included that relationship between syndrome and acetylsalicylic acid is not yet established with certainty.

A special warning on Reye's syndrome for patients under 18 is included in the monograph: "In children and adolescents under 18 [product name] should only be used on medical advice and only in cases when other therapies failed to succeed. In a child or adolescent who has become very unwell with severe vomiting, drowsiness or loss of consciousness following a viral infection, a serious disease may be suspected. Reye's syndrome is an extremely rare but life threatening condition which requires immediate medical attention". Taking into account the age limit for OTC products, willow bark should only be used in children and adolescents below 18 years under medical supervision. Traditional HMPs containing willow bark are therefore contra-indicated in children and adolescents below 18 years of age (in the monograph, under TU: in section 4.3; under WEU: in section 4.4)

Other precautions with regard to intake of salicylates

When willow bark preparations are taken according to the normal dosage recommendations, they will produce relatively low salicylate serum levels. Still, reactions in sensitive individuals cannot be ruled out.

Precautions associated with salicylate therapy are also applicable to willow bark. In case of severe liver or renal dysfunction, coagulation disorders (risk of hemorrhagia), gastric/duodenal ulcer, willow bark should be used with caution and under medical supervision. Traditional HMPs containing willow bark are therefore contra-indicated in these patients (in the monograph, under TU: in section 4.3; under WEU: in section 4.4)

In patients with glucose-6-phosphate dehydrogenase deficiency, the use of willow bark is contra-indicated (risk of haemolysis). There is a case report of a woman with G6PD who developed massive haemolysis after taking an herbal preparation containing salicin (Baker et al 1987). In Sardinia there is a high incidence of G6PDH deficiency. Salicylates have been contraindicated by all the experts for these patients. Therefore, the use of willow bark in case of G6PD deficiency is contra-indicated.

The use of willow bark in patients with active peptic ulcer disease is contra-indicated.

II.3.3.5.2 Drug interactions

Only the interactions documented with willow bark are included. A number of theoretical interactions listed for acetylsalicylic acid (anti-hypertensive agents, uricosurics and others) were not included.

Interaction (pharmacokinetic and pharmacodynamic) with oral anticoagulants (heparin, coumarine derivatives) is plausible and of therapeutic importance and therefore included: Krivoy et al (2001) investigated whether treatment with willow bark during treatment of LBP affected platelet aggregation. 35 patients having acute exacerbations of LBP were enrolled in a double-blind placebo-controlled study to receive for 28 days *Salix daphnoides* and *Salix purpurea* extract with 240 mg salicin per day, "Assalix"(N=19) versus placebo (coated tablets, N=16). A further 16 patients with stable chronic ischemic heart disease were given 100 mg acetylsalicylate per day during the study period. After 28 days of treatment, platelet aggregation was measured. Willow bark significantly decreased AA- and ADP-induced

aggregation but to a significantly lesser extent than acetylsalicylate did. The mean percentages of maximal AA-induced platelet aggregation were 61% (willow bark), 78% (blank) and 13% (acetylsalicylate). Collagen-induced aggregation was not influenced by willow bark (or acetylsalicylate). Further investigation is needed to clarify the clinical relevance of these findings in patients with impaired thrombocyte function or with vitamin K antagonistic treatment (structural similarity of salicylate and warfarin).

Salicylates are extensively bound to plasma proteins. A recent study on the pharmacokinetics of salicin after oral administration of a standardized willow bark extract (Schmid et al 2001a) demonstrates that the AUC of salicylate after ingestion of a dose corresponding to 240 mg salicin was equivalent to that expected from an intake of 87 mg acetylsalicylic acid; bio-availability was 43.3%; peak serum levels were 1.2 mg/L and were reached within 2 hours after ingestion. Pharmacokinetic interactions due to plasma protein binding cannot be ruled out. Salicylic acid does not irreversibly acetylate COX-1. Taking into account the study of Krivoy and the fact that salicylates are highly bound to plasma proteins, the potential for interaction cannot be ruled out.

Shalansky et al (2007) carried out a prospective longitudinal study (171 adults) to determine the risk of bleeding and supratherapeutic international normalised ratios (INR) associated with use of complementary and alternative medicine (CAM) in patients receiving warfarin. Statistically significant associations between the use of willow bark and bleeding events were identified. The risk of a supratherapeutic INR was not increased. After adjustment for the identified non-CAM risk factors, association was not statistically significant.

The combined use of willow bark with acetylsalicylic acid/other NSAIDs is not recommended even though an increased risk of gastric irritation has never been described (Rotblatt 2002). The MLWP decided in September 2007 to add a warning that concomitant use with salicylates and other NSAIDs is not recommended without medical advice.

The very high concentration of tannins present may interfere with absorption of other products.

II.3.3.5.3 Use in pregnancy and lactation

Salicylates cross the placenta. Acetylsalicylic acid is teratogenic in rodents, but till now there is no clear evidence of teratogenesis when used in human pregnancy. Increased PG production during pregnancy and/or placental metabolism may have protective roles.

Due to increased bleeding risk, delay of parturition and induction of early closure of the ductus arteriosus, use of acetylsalicylic acid/NSAIDs is contra-indicated in the third trimester of pregnancy (Aronson; Barnes et al 1992).

Conflicting reports have been documented concerning the safety of acetylsalicylic acid taken during the first and second trimester of pregnancy. The safety of willow bark has not been established. Occasional ingestion of salicylates does not seem to be a problem (no contra-indication in Belgium for first and second trimester), but due to lack of conclusive data on the use during the first and second trimester of the pregnancy are not available, the use is not recommended as a general precaution

Salicylates appear in breast milk and have been reported to cause macular rashes in babies. The two major pathways of salicylate degradation (formation of salicylic acid and salicyl phenol glucuronide) become saturated at relatively low body levels of the drug. The drug is slowly eliminated by the newborn infant.

Because data on the use during lactation are not available, the use is not recommended as a general precaution.

II.3.3.5.4 Overdose

No toxic effects reported.

Taking into account the relatively low serum levels after oral intake of willow bark and the high content of tannins in willow bark (GI disturbances) which makes intake of large amounts less likely, the MLWP agreed in September 2007 not to include the symptoms of overdose with acetylsalicylic acid.

II.3.3.5.5 Drug abuse

No data available.

II.3.3.5.6 Withdrawal and rebound

No data available.

II.3.3.5.7 Effects on ability to drive or operate machinery or impairment of mental ability

None known.

The MLWP decided in September 2007 to mention that no studies on the effect on the ability to drive and use machinery had been performed.

II.3.3.6 Assessor's overall conclusions on clinical safety

Minor adverse effects have been reported in a relatively small number of patients. Based on the published clinical data, from a total of 620 patients and healthy volunteers treated with various single-ingredient preparations containing willow bark, adverse events were predominantly mild.

Adverse effects and signs of toxicity normally associated with salicylates may occur. In view of the lack of more toxicity data on willow, the usual precautions associated with salicylate therapy are also applicable to willow. Therefore individuals with known hypersensitivity to aspirin, asthma, active peptic ulceration, haemophilia and other bleeding disorders, gout should be aware of the possible risks associated with the intake of willow bark. Appropriate contra-indications and special warnings and precautions for use are introduced in the monograph (WEU and TU).

II.4 ASSESSOR'S OVERALL CONCLUSIONS

In spite of its long (traditional) use, only a few controlled trials have been conducted with willow bark to support its analgesic and/or antipyretic action. Recent renewed interest in willow bark resulted in a number of clinical trials studying the efficacy in acute exacerbations of LBP, in OA and RA. The design and quality of the published trials was variable.

- Taking into account the body of available published trials and their respective trial quality and outcomes, the controlled clinical trials published so far provide moderate evidence for the analgesic activity of a daily dose of willow bark extract 8-14:1 corresponding to 240 mg salicin (single ingredient preparation) in low back pain (WEU).
- For the symptomatic treatment of fever and pain, only general evidence is available (TU).

In view of the lack of more toxicity data on willow, the usual precautions for use associated with salicylate therapy are also applicable to willow. Appropriate contra-indications and special warnings and precautions for use are introduced in the monograph (WEU and TU).

III. ANNEXES

III.1 COMMUNITY HERBAL MONOGRAPH ON SALIX, CORTEX

III.2 LITERATURE REFERENCES