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FINAL

**COMMUNITY HERBAL MONOGRAPH ON *ALOE BARBADENSIS* MILLER
AND ON *ALOE* (VARIOUS SPECIES, MAINLY *ALOE FEROX* MILLER AND ITS
HYBRIDS)**

DISCUSSION IN THE SAFETY AND EFFICACY DRAFTING GROUP / WORKING PARTY ON COMMUNITY MONOGRAPHS AND COMMUNITY LIST	January 2006 March 2006
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¹ Changes introduced in sections 4.9 and 5.1

**COMMUNITY HERBAL MONOGRAPH
ON *ALOE BARBADENSIS* MILLER**

AND ON *ALOE* (VARIOUS SPECIES, MAINLY *ALOE FEROX* MILLER AND ITS HYBRIDS)

1. NAME OF THE MEDICINAL PRODUCT

To be specified for the individual finished product.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION^{2, 3}

<u>Well-established use</u>	<u>Traditional use</u>
<p>With regard to the marketing authorisation application of Article 10a of Directive 2001/83/EC, as amended</p> <p><i>Aloe barbadensis</i> Miller (barbados aloes) <i>Aloe</i> [various species, mainly <i>Aloe ferox</i> Miller and its hybrids (cape aloes)]</p> <ul style="list-style-type: none">• Herbal substance concentrated and dried juice of the leaves, standardised• Herbal preparation standardised herbal preparations thereof	<p>With regard to the registration application of Article 16d(1) of Directive 2001/83/EC, as amended</p>

3. PHARMACEUTICAL FORM

<u>Well-established use</u>	<u>Traditional use</u>
<p>Standardised herbal substance or herbal preparation for oral use in solid or liquid dosage forms. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.</p>	

² The material complies with the Ph. Eur. monographs.

³ The declaration of the active substance(s) should be in accordance with relevant herbal quality guidance.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

<u>Well-established use</u>	<u>Traditional use</u>
Herbal medicinal product for short-term use in cases of occasional constipation.	None

4.2. Posology and method of administration

<u>Well-established use</u>	<u>Traditional use</u>
<p>Posology</p> <p>The maximum daily dose of hydroxyanthracene glycosides is 30 mg. This is equivalent to(dose of the preparation).</p> <p>The correct individual dose is the smallest required to produce a comfortable soft-formed motion.</p> <p><i>Adolescents over 12 years of age, adults, elderly</i></p> <p>Herbal substance/preparation equivalent to 10 – 30 mg hydroxyanthracene derivatives, calculated as barbaloin (= aloin), to be taken once daily at night. Normally it is sufficient to take this medicinal product up to two to three times a week.</p> <p>Not recommended for use in children under 12 years of age (see section 4.3 Contraindications).</p> <p>The pharmaceutical form must allow lower dosages.</p> <p>Method of administration</p> <p>As described in the package leaflet corresponding to the pharmaceutical form.</p> <p>Duration of use</p> <p>Use for more than 1 - 2 weeks requires medical supervision.</p> <p>If the symptoms persist during the use of the medicinal product, a doctor or a pharmacist should be consulted.</p> <p>See also section 4.4 Special warnings and precautions for use.</p>	

4.3. Contraindications

<u>Well-established use</u>	<u>Traditional use</u>
<p>Known hypersensitivity to the active substance.</p> <p>Cases of intestinal obstructions and stenosis, atony, appendicitis, inflammatory colon diseases (e.g. Crohn's disease, ulcerative colitis), abdominal pain of unknown origin, severe dehydration state with water and electrolyte depletion.</p> <p>Children under 12 years of age.</p>	

4.4. Special warnings and precautions for use

<u>Well-established use</u>	<u>Traditional use</u>
<p>Patients taking cardiac glycosides, antiarrhythmic medicinal products, medicinal products inducing QT-prolongation, diuretics, adrenocorticosteroids or liquorice root, have to consult a doctor before taking aloe concomitantly.</p> <p>Like all laxatives, aloe should not be taken by patients suffering from faecal impaction and undiagnosed, acute or persistent gastro-intestinal complaints, e.g. abdominal pain, nausea and vomiting unless advised by a doctor because these symptoms can be signs of potential or existing intestinal blockage (ileus).</p> <p>If laxatives are needed every day the cause of the constipation should be investigated. Long-term use of laxatives should be avoided.</p> <p>If stimulant laxatives are taken for longer than a brief period of treatment, this may lead to impaired function of the intestine and dependence on laxatives. Aloe preparations should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents.</p> <p>When aloe preparations are administered to incontinent adults, pads should be changed more frequently to prevent extended skin contact with faeces.</p> <p>Patients with kidney disorders should be aware of possible electrolyte imbalance.</p>	

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

<u>Well-established use</u>	<u>Traditional use</u>
<p>Hypokalaemia (resulting from long-term laxative abuse) potentiates the action of cardiac glycosides and interacts with antiarrhythmic medicinal products, with medicinal products, which induce reversion to sinus rhythm (e.g. quinidine) and with medicinal products inducing QT-prolongation. Concomitant use with other medicinal products inducing hypokalaemia (e.g. diuretics, adrenocorticosteroids and liquorice root) may enhance electrolyte imbalance.</p>	

4.6. Pregnancy and lactation

<u>Well-established use</u>	<u>Traditional use</u>
<p>Pregnancy There are no reports of undesirable or damaging effects during pregnancy and on the foetus when used at the recommended dosage. However, as a consequence of experimental data concerning a genotoxic risk of several anthranoids, e.g. emodin and aloe-emodin, use is not recommended during pregnancy.</p> <p>Lactation Use during breastfeeding is not recommended as there are insufficient data on the excretion of metabolites in breast milk. After administration of other anthranoids, active metabolites, such as rhein, are excreted in breast milk in small amounts. A laxative effect in breast fed babies has not been reported.</p>	

4.7. Effects on ability to drive and use machines

<u>Well-established use</u>	<u>Traditional use</u>
<p>Not relevant.</p>	

4.8. Undesirable effects

<u>Well-established use</u>	<u>Traditional use</u>
<p>Hypersensitivity reactions may occur.</p> <p>Aloes may produce abdominal pain and spasm and passage of liquid stools, in particular in patients with irritable colon. However, these symptoms may also occur generally as a consequence of individual overdosage. In such cases dose reduction is necessary.</p> <p>Chronic use may lead to disorders in water equilibrium and electrolyte metabolism and may result in albuminuria and haematuria.</p> <p>Furthermore, chronic use may cause pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when the patient stops taking the preparation.</p> <p>Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment.</p> <p>If other adverse reactions not mentioned above occur, a doctor or a pharmacist should be consulted.</p>	

4.9. Overdose

<u>Well-established use</u>	<u>Traditional use</u>
<p>The major symptoms of overdose/abuse are griping pain and severe diarrhoea with consequent losses of fluid and electrolytes, which should be replaced. Diarrhoea may cause potassium depletion, in particular. Potassium depletion may lead to cardiac disorders and muscular asthenia, particularly where cardiac glycosides, diuretics, adrenocorticosteroids or liquorice root are being taken at the same time.</p> <p>Treatment should be supportive with generous amounts of fluid. Electrolytes, especially potassium, should be monitored. This is especially important in the elderly.</p> <p>Chronic ingested overdoses of anthranoid containing medicinal products may lead to toxic hepatitis.</p>	

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

<u>Well-established use</u>	<u>Traditional use</u>
<p>Pharmaco-therapeutic group: contact laxatives ATC-code: A 06 AB</p> <p>1,8-dihydroxyanthracene derivatives possess a laxative effect.</p> <p>Aloinosides and aloins are respectively C,0-diglycosides and C-glycosides, which are not absorbed in the upper gut, but are converted by bacteria of the large intestine into the active metabolite (aloe-emodin-9-anthrone).</p> <p>There are two different mechanisms of action:</p> <ol style="list-style-type: none">1. stimulation of the motility of the large intestine resulting in accelerated colonic transit.2. influence on secretion processes by two concomitant mechanisms <i>viz.</i> inhibition of absorption of water and electrolytes (Na⁺, Cl⁻) into the colonic epithelial cells (antiabsorptive effect) and increase of the leakiness of the tight junctions and stimulation of secretion of water and electrolytes into the lumen of the colon (secretagogue effect) resulting in enhanced concentrations of fluid and electrolytes in the lumen of the colon. Defaecation takes place after a delay of 6 - 12 hours due to the time taken for transport to the colon and metabolisation into the active compound.	<p>Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.</p>

5.2. Pharmacokinetic properties

<u>Well-established use</u>	<u>Traditional use</u>
<p>Aloinosides, aloins and hydroxyaloins pass directly into the large intestine where they are metabolised by bacterial enzymes (viz. Eubacterium sp. strain BAR) into the active anthrone compounds mainly aloe-emodin-9-anthrone. It is not known to what extent aloe-emodin-9-anthrone is absorbed. However, in the case of senna, animal experiments with radio-labeled rhein-anthrone administered directly into the caecum show that only a very small proportion (less than 10%) of rhein-anthrone is absorbed. Systemic metabolism of free anthranoids depends on their ring constituents. In the case of aloe-emodin, it has been shown in animal experiments that at least 20-25% of an oral dose is absorbed. The bioavailability of aloe-emodin is much lower than the absorption, because it is quickly oxidised to rhein and unknown metabolite, or conjugated.</p> <p>After administration of other anthranoids, active metabolites, such as rhein, pass in small amounts into breast milk. Animal experiments demonstrated that placental-passage of rhein is low.</p>	<p>Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.</p>

5.3. Preclinical safety data

<u>Well-established use</u>	<u>Traditional use</u>
<p>There are no new, systematic preclinical tests for aloes or preparations thereof.</p> <p>No teratogenic or foetotoxic effects were seen in rats after oral treatment with aloes extract (up to 1,000 mg/kg) or aloin A (up to 200 mg/kg).</p> <p>Some <i>in vitro</i> assays show genotoxicity of aloemodin. Positive results were obtained in the Ames test with <i>Salmonella typhimurium</i> strains TA1537, TA1538, TA98 and TA1978. In the HPRT test, no reproducible induction of mutations was obtained, while unscheduled DNA synthesis (UDS) and cell transformation was induced.</p> <p>In <i>in vivo</i> studies (micronucleus assay in bone marrow cells of NMRI mice; chromosome aberration assay in bone marrow cells of Wistar rats; mouse spot test [DBA/2J x NMRI]) no indication of a mutagenic activity of aloemodin was found.</p> <p>No specific toxicity was observed in mice when aloes extract was orally administered up to 50 mg/kg daily for 12 weeks and aloin was orally administered up to 60 mg/kg daily for 20 weeks.</p> <p>Further 2-year studies on male and female rats and mice with emodin gave no evidence of carcinogenic activity for male rats and female mice, and equivocal evidence for female rats and male mice.</p> <p>Laxative use as a risk factor in colorectal cancer (CRC) was investigated in some clinical trials. Some studies revealed a risk for CRC associated with the use of anthraquinone-containing laxatives, some studies did not. However, a risk was also revealed for constipation itself and underlying dietary habits. Further investigations are needed to assess the carcinogenic risk definitely.</p>	<p>Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended, unless necessary for the safe use of the product.</p>

6. PHARMACEUTICAL PARTICULARS

<u>Well-established use</u>	<u>Traditional use</u>
Not applicable.	

7. DATE OF COMPILATION/LAST REVISION

26 October 2006