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COMMITTEE FOR HERBAL MEDICINAL PRODUCTS (HMPC)

DRAFT

COMMUNITY HERBAL MONOGRAPH ON BARBADOS ALOES (ALOE BARBADENSIS) AND CAPE ALOES (ALOE CAPENSIS)

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Community herbal monograph on Barbados aloes (aloe barbadensis) and Cape aloes (aloe capensis)

1. NAME OF THE MEDICINAL PRODUCT

To be specified for the individual finished products.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Well-established use	Traditional use
With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC, as amended **Active ingredients** Barbados aloes and Cape aloes in the crude or processed state in appropriate dosage units **Definition** Barbados aloes (Aloe barbadensis) consists of the concentrated and dried juice of the leaves of *Aloe barbadensis* Miller. It contains not less than 28 % hydroxyanthracene derivatives, expressed as barbaloin ($C_{21}H_{22}O_9$; M_r 418.4) and calculated with reference to the dried herbal substance.[1] Cape aloes (Aloe capensis) consists of the concentrated and dried juice of the leaves of various species of Aloe, mainly *Aloe ferox* Miller and its hybrids. It contains not less than 18 % hydroxyanthracene derivatives, expressed as barbaloin ($C_{21}H_{22}O_9$; M_r 418.4) and calculated with reference to the dried herbal substance.[1] **Constituents** The constituents with known therapeutic activity of *Barbados aloes* are anthrone-10-C-glycosides *viz*. a mixture of aloin A (10S,1'S) and aloin B (10R,1'S), named barbaloin and their 6'-0-p-coumaroylesters, a mixture of 7-hydroxyaloins A (10S) and B (10R) (characteristic of Barbados aloes) and their 6'-0-p-coumaroylesters and a mixture of 8-0-methyl-7-hydroxyaloins A (10S) and B (10R) and their 6'-0-cinnamoylesters. The constituents with known therapeutic activity of *Cape aloes* are anthrone-10-C-glycosides *viz*. a	With regard to the registration application of Article 16d(1) of Directive 2001/83/EC, as amended

[1] The herbal substance complies with the European Pharmacopoiea.

mixture of aloins A (10S) and B (10R), named barbaloin, and 5-hydroxyaloin A (10S) (characteristic of Cape aloes) besides 10-C-11-0-diglycosides *viz*. aloinosides A and B (11-0-α-L-rhamnosides of aloins A an B). There are also small quantities in both aloes of the aglycones, aloe-emodin and chrysophanol, and 2-alkylchromones named aloeresins.	

3. PHARMACEUTICAL FORM

Well-established use	Traditional use
Standardised crude or processed herbal substance for oral preparation in solid or liquid dosage forms (to be specified for the individual finished product). The pharmaceutical form should be described according to the standard terms by the European Pharmacopoeia.	

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Well-established use	Traditional use
For short term use in cases of occasional constipation.	None

4.2. Posology and method of administration

Well-established use	Traditional use
Dosage The maximum daily dose of hydroxyanthracene glycosides is 30 mg. This is equivalent to ....(dose of the preparation). The correct individual dose is the smallest required to produce a comfortable soft-formed motion. *Adolescents over 12 years of age, adults, elderly* Herbal substance / preparation equivalent to 10 – 30 mg hydroxyanthracene derivatives, calculated as Barbaloin (= aloin), to be taken at night. The dosage refers to one administration. The pharmaceutical form must allow lower dosages. **Method of administration** For oral administration	

4.3. Contraindications

Well-established use	Traditional use
Patients with known hypersensitivity to aloes should not use aloes preparations. Not to be used in 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 states with water and electrolyte depletion. Children under 12 years.	

4.4. Special warnings and precautions for use

Well-established use	Traditional use
Patients taking cardiac glycosides, antiarrhythmic medicinal products, medicinal products inducing QT-prolongation, diuretics, adrenocorticosteroids or liquorice root, have to consult a doctor before taking aloes concomitantly. Like all laxatives, aloes 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 a potential or existing intestinal blockage (ileus). If laxatives are needed every day the cause of the constipation should be investigated. Long-term use of laxatives should be avoided. Use for more than 1 - 2 weeks requires medical supervision. If stimulating laxatives are taken for longer than a brief period of treatment, this may lead to dependence requiring increasing quantities of the medicinal product, an atonic colon with impaired function and aggravation of the constipation. Aloes preparation should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents. When aloes preparations are administered to incontinent adults, pads should be changed more frequently to prevent extended skin contact with faeces.	

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

Well-established use	Traditional use
The absorption of orally administered medicinal products may be reduced. 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.	

4.6. Pregnancy and lactation

Well-established use	Traditional use
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. **Lactation** Breastfeeding is not recommended as there are insufficient data on the excretion of metabolites in breast milk. Small amounts of active metabolites (rhein) are excreted in breast milk. A laxative effect in breast fed babies has not been reported.	

4.7. Effects on ability to drive and use machines

Well-established use	Traditional use
Not known	

4.8. Undesirable effects

Well-established use	Traditional use
Hypersensitive reactions may occur very rarely. Very rarely 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. Chronic use/abuse may lead to disorders in water equilibrium and electrolyte metabolism. 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. Chronic use may result in albuminuria and haematuria. Furthermore, chronic use may cause pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when the patient stops taking the preparation. Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment.	

4.9. Overdose

Well-established use	Traditional use
The major symptoms are griping pain and severe diarrhoea with consequent losses of fluid and electrolytes, which should be replaced. Treatment should be supportive with generous amounts of fluid. Electrolytes, especially potassium, should be monitored. This is especially important in the elderly and the young.	

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Well-established use	Traditional use
Pharmaco-therapeutic group: contact laxatives ATC-code: A 06 AB 1,8-dihydroxyanthracene derivatives possess a laxative effect. 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). There are two mechanisms of action: 1. an influence on the motility of the large intestine (inhibition of the Na^+/K^+pump and of the Cl^- channels at the colonic membrane) resulting in accelerated colonic transit.	Not applicable as per Article 16 c(1)(a)(iii) of Directive 2001/83/EC as amended

2. an influence on secretion processes (stimulation of mucus and chloride secretion) resulting in enhanced fluid secretion. The motility effects are mediated by direct stimulation of colonic neurons and possibly by prostaglandins. 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.	

5.2. Pharmacokinetic properties

Well-established use	Traditional use
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. Active metabolites, e.g. rhein, pass in small amounts into breast milk. Animal experiments demonstrated that placental-passage of rhein is small.	Not applicable as per Article 16 c(1)(a)(iii) of Directive 2001/83/EC as amended

5.3. Preclinical safety data

Well-established use	Traditional use
There are no new, systematic preclinical tests for aloes or preparations thereof. No teratogenic or foetotoxic effects were seen in rats after oral treatment with aloes extract (up to 1000 mg/kg) or aloin A (up to 200 mg/kg). Some *in vitro* assays show genotoxicity of aloe-emodin. Positive results were obtained in the Ames test with Salmonella typhimurium 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.	Not applicable as per Article 16 c(1)(a)(iii) of Directive 2001/83/EC as amended

In *in vivo* 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 aloe-emodin was found. 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. Commercial laxative use as a risk factor in colorectal cancer was investigated in some clinical trials. The results of the more recent studies are inconsistent and the possibility of a carcinogenic risk of long-term use of anthranoid-containing laxatives cannot be assessed definitely.	

6. DATE OF COMPILATION

9 March 2006