European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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Table 1: Organisations that commented on the draft 'Community herbal monograph on Frangula bark (Frangulae cortex)' as released for consultation in March 2006 until 30 June 2006

	Organisation
1.	Association of the European Self-Medication Industry (AESGP)
2.	The Herbal Forum
3.	Krakowskie Zakłady Zielarskie "Herbapol" w Krakowie S.A., Poland

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Table 2: Discussion of comments

General comment	Comment and rationale	Outcome
Title	We note the restriction of single ingredient Frangula products to well-established use market authorisation. We do not understand why this should be the case, as products containing this herb have many years of traditional use for the treatment of constipation and should, therefore, be registerable as a traditional herbal medicinal product, with the appropriate therapeutic indication. We are also concerned about the position of those traditionally used combination herb products, which include Frangula amongst their ingredients. In our view it should be possible to register such traditionally used products, which are unlikely to hold the level of evidence required for a well-established use market authorisation, under the traditional herbal medicinal products Directive.	According to Article 16(3) of Directive 2001/83/EC as amended, the provision of chapter 2a shall not apply in cases where the competent authorities judge that a traditional herbal medicinal product fulfils the criteria for authorisation in accordance with Article 6 or registration pursuant to Article 14. Frangula bark fulfil these criteria like other anthranoid-containing laxatives. On the other hand possible risks have to be taken into account. This was discussed in the HMPC with the result that a traditional use cannot be supported.

Line no or section and paragraph no	Comment and rationale	Outcome
4.1. Therapeutic indications	With regard to the *"short term use"* we would like to mention that, according to newer expert opinions, the use of stimulant laxatives (anthranoids, bisacodyl, sodium picosulphate) taken in correct dosages is permissible up to two to three times weekly, the indicator for correct use (this includes long-term/chronic use) being the absence of laxative-induced diarrhoea. A consensus conference held in 1999 came to the conclusion that in most cases of obstipation, giving a laxative is the best solution. The choice depends on the severity of obstipation, possible side effects, and patient compliance. Generally, starting with the intake of high fiber-containing products is justified. Should this not achieve the desired results, a treatment with a stimulant laxative and fibre or an osmotic laxative is required.	Frangula bark preparations are not medicinal products on prescription. Without medical supervision a short-term use can only be recommended. The diagnosis "constipation" has to be established before taking laxatives for a long time. Therefore we recommend a special warning in section 4.4: "Use for more than 1 – 2 weeks requires medical supervision. …". We agree to modify the wording in section 4.4 Posology and method of administration: *Adolescents over 12 years of age, adults, elderly* Herbal substance / preparation equivalent to 10 – 30 mg hydroxyanthracene derivatives, calculated as glucofrangulin A, to be taken at night. The dosage refers to one administration. Normally it is sufficient to take this medicinal product up to two to three times **a week**.
4.2. Posology and method of administration	The sentence *"The dosage refers to one administration"* is contradictory and should be deleted, because in the same section, information is given that *"the pharmaceutical form must allow lower dosages"* with respect to the maximum daily dosage of hydroxyanthracene glycosides (30 mg). Furthermore it is mentioned in the same chapter that the dose has to be taken at one time of the day, i.e. "to be taken at night". Therefore an individual dosage is required and advised. The necessary dosage should not only be administered at once but also taken in combination with bulk-forming laxatives, each administration being followed by drinking plenty of liquid, and at least two or more doses should be taken at one time of the day, i.e. "to be taken at night".	In our opinion this sentence is not contradictory. The information that the pharmaceutical form must allow lower dosages with respect to the maximum daily dosage of hydroxyanthracene glycosides (30mg) does not mean that the maximum daily dosage can be distributed to more than one single dose. It means that the patient must have the ability to take less than the maximum daily dosage because the correct individual dose is the smallest required producing a comfortable soft-formed motion. One single dose daily takes into account the fact that in general defaecation takes place after a delay of 8 – 12 hours and the patient is not disturbed in his sleep. Alternatively we propose the wording: "Herbal substance/preparation equivalent to 10 – 30 mg hydroxyanthracene derivatives, calculated as glucofrangulin A, to be taken once daily at night.

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4.2. Posology and method of administration Continuation	The use of fresh bark could cause nausea and vomiting, because of the high content of reduced forms of anthraquinones (anthrones). The information about raw material preparation could be useful, e.g. such as in Polish Pharmacopoeia (Farmakopea Polska VI, Warsaw 2002): "Bark... dried in dark place and heated 2 h in temperature 100?C or stored not less than 1 year from harvesting".	The herbal substance has to comply with the European Pharmacopoiea which requires the identification of anthrones as part of the purity testing. Therefore no further information is necessary.
4.3. Contra-indications	The use of Frangulae cortex should be contraindicated in menstruation period due to menorrhoea.	The causality is not plausible.
4.4. Special warnings and precautions for use	The content of the first sentence: "*Patients taking cardiac glycosides, antiarrhythmic medicinal products, medicinal products inducing QT-prolongation, diuretics, adrenocorticosteroids or liquorice root, have to consult a doctor before taking frangula bark concomitantly"* is redundant and should only be mentioned in Chapter 4.5 "Interactions with other medicinal products" since this is a description of interactions.	According to the 'Guideline on Summary of Product Characteristics' of October 2005 cross-references are possible and sometimes recommended. The wording in this chapter describes the precaution which should be taken (consult a doctor when taking these medicinal products) and in chapter 4.5 the interaction is described.
	To our knowledge there are no scientific evidence and no data available concerning interactions of medicinal products inducing QT-prolongation and hydroxyanthracene glycosides. Furthermore the concentrations of hydroxyanthracene glycosides systemically available are too low to make an interaction plausible.	Chronic use or abuse of anthranoid-containing laxatives may lead to hypokalaemia. This hypokalaemia and the increased loss of potassium may interfere with the action of medicinal products inducing QT-prolongation. Including this interaction was a decision of the HMPC (Haverkamp W et al. Medikamentenbedingte QT-Verlängerung und Torsade de pointes. Drug-induced QT Prolongation and Torsade de Pointes. Deutsches Ärzteblatt 2002; 99: A 1972-9 [Heft 28-29].

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4.4. Special warnings and precautions for use Continuation	With regard to addiction, dosage increase, dysfunction through nerve damage and worsening of obstipation, there is no evidence from literature on the development of tolerance. Müller-Lissner (2005) states that tolerance to laxatives has not been systematically studied in humans, and the fact that in many clinical studies a proportion of patients with chronic laxative intake could be switched to dietary fibre or prokinetics or to behavioural treatment, is a strong argument against the development of tolerance. The author concludes that the development of tolerance to stimulant laxatives occurs in the most severe patient group with slow colonic transit in whom other types of laxatives are ineffective. Tolerance thus seems to be uncommon in the majority of users.	Recent studies are not available. Also Müller-Lissner states that it is only **unlikely** (not safe) that stimulated laxatives at recommended doses are harmful to the colon. The references (Smith B 1968; Riemann JF et al. 1980 and 1982; Berkelhammer C et al. 2002; Meisel JL et al. 1977; Pockros PJ et al. 1985) show abnormalities observed in humans (damage to enteric nerves, smooth muscle atrophy; distension or ballooning of axons, reduction of nerve-specific cell structures and increase in lysosomes, and sometimes a total degeneration of whole nerve fibers; short-lived superficial damage to the mucosa). They are uncontrolled observations and therefore the author concludes that the cause of these damages can also be the constipation itself or pre-existing changes of unknown aetiology. The only study comparing the morphology of the autonomous nervous system of constipated patients taking anthraquinones (aloe) to that of an appropriate control group of constipated patients without laxative intake (Riecken EO et al. 1990) does not support the hypothesis that anthraquinone containing laxatives are able to provoke relevant degenerative changes in the colonic nerve tissue.
	From his point of view, the belief that chronic use of stimulant laxatives damages the colonic myenteric system is largely derived from uncontrolled observations in humans and from conflicting data obtained in prospective studies of animals, and the arguments in favour of laxative-induced damage to the autonomous nervous system of the colon have been advocated on the basis of poorly documented experiments. In contrast, investigations that do not support such damage are well done and performed by using a variety of techniques. It is therefore unlikely that stimulant laxatives at recommended doses are harmful to the colon.	Müller-Lissner concludes that the arguments in favour of laxative-induced damage to the autonomous nervous system of the colon are based on poorly documented experiments and that the investigations that do not support such damage are well done. But he ignores that the investigations by Riecken EO 1990 were conducted in 11 matched pairs only. A definite assessment is not possible. Therefore we do not agree to delete information concerning this but we reword this advice as follows "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."

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4.4. Special warnings and precautions for use Continuation	It is suggested to give in every monograph a special information for people with kidney and/ or liver disorders- even if there is no precautions for them.	In our opinion this is not necessary. Information will be given, only if special concerns exist for these patients. It has to be discussed if, in the monographs of anthranoid-containing laxatives, a precaution should be given for patients with kidney disorders because the possibility of electrolyte imbalance might be greater: "Patients with kidney disorders should be aware of possible electrolyte imbalance."
4.5. Interactions with other medicinal products and other forms of interaction	The sentence "*The absorption of orally administered medicinal products may be reduced"* should be deleted. This effect is not documented and described for hydroxyanthracene glycosides in the dosage range of 15-30 mg daily.	We agree to delete this sentence. Most medicinal products are absorbed in the stomach or small intestine. The anthranoid-containing laxatives develop their effect in the colon. Only some medicinal products to treat inflammatory colon diseases are expected to dissolve in the colon. These diseases are listed as contraindications and therefore such medicinal products must not be considered.
	Furthermore, the interaction regarding medicinal products inducing QT-prolongation should be deleted (see comment on section 4.4.).	QT-prolongation see above
	Concomitant use of laxatives with medicinal products against diarrhoea should be avoided.	We take this for granted.
	It could be useful to give brief information that product/ preparation is intended to use in monotherapy and should not be administer with other laxatives.	We do not think that the concomitant use of other laxative (e.g. bulk producers) is contra-indicated e.g. reducing the amount of ingested hydroyanthracene-derivatives.

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4.8. Undesirable effects	From our point of view, equating the terms "chronic use" and "abuse" is not correct. The above-mentioned consensus conference stated that in the discussion of the risks associated with laxatives, laxative abuse plays a large role. It is very often equated with chronic laxative use which is in no way justified. Contrary to many other drugs, though, the abuse can be determined very easily through the resulting diarrhoea. Compared to the large number of "normal" laxative users in the population, the "abusers" are rare and extreme exceptions that have nothing to do with the therapeutic use of laxatives.	We agree to reword this chapter and the chapter 'overdose' as follows (frequencies see below): Hypersensitive reactions may occur. Frangula bark 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 may lead to disorders in water equilibrium and electrolyte metabolism and 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. Overdose The major symptoms of overdose / abuse are griping pain and severe diarrhoea with consequent losses of fluid and electrolyte, which should be replaced. Diarrhoea may especially cause potassium depletion, which may lead to cardiac disorders and muscular asthenia, particularly where cardiac glycosides, diuretics, adrenocorticosteroids or liquorice root are being taken at the same time. Treatment should be supportive with generous amounts of fluid. Electrolytes, especially potassium, should be monitored. This is especially important in the elderly. Chronic ingested overdoses of anthranoid containing medicinal products may lead to toxic hepatitis." According to the 'Guideline on Summary of Product Characteristics' of October 2005 choice of frequency category is based on studies. The frequencies based on reporting rates from a spontaneous reporting system should not be used for choosing a frequency category in any situation. Because there are no studies available, we omit the frequency categories.

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4.8. Undesirable effects Continuation	Several reported ADRs	No further information (mono- or combination preparation, dosis, medicinal products concomitantly used etc.) is given and the causality cannot be assessed.
5.3. Preclinical safety data	Results from *in vivo* studies The results from the NTP study on emodin should be included as follows: *"In further 2-year studies on male and female rats and mice, emodin did not significantly increase the spontaneous tumor ratio in comparison to controls."* This corresponds to reference no. 46 of the ESCOP monograph "Frangulae cortex".	We propose to include the results as follows: "Further 2-year studies on male and female rats and mice with emodin give no evidence of carcinogenic activity for male rats and female mice, and equivocal evidence for female rats and male mice."
	No risk of colorectal cancer In terms of a potential risk of colorectal cancer we strongly disagree with the closing statement on the risk of colorectal cancer (CRC). Amongst others, a recent study of Müller-Lissner (2005) concludes that "all subsequent studies failed to find an association between anthranoid laxative intake and CRC." For this reason, it is incomprehensible why a statement which implies potential risk and spurs unfounded fear should be part of a new monograph.	We cannot ignore the former findings. Up to now some questions remain. Müller-Lissner cites 2 recent case-control investigations: Jacobs EJ et White E (Constipation, laxative use, and colon cancer among middle-aged adults. Epidemiology 1998; 9: 385-91) did not include subjects which took anthraquinone-containing laxatives. Roberts MC et al. (Constipation, laxative use, and colon cancer in a North Carolina population. Am J Gastroenterol 2003; 98: 857-64) did not mention anthraquinone-containing laxatives. They mentioned the group "stimulants, fibers, natural remedies, stool softeners, oils, osmotic agents, enemas, suppositories, and unknown". In table 4 of the publication, they only listed 'phenolphthalein', 'fiber', 'magnesium', 'other commercial', 'non-commercial or unknown'. Conclusions cannot be drawn from these publications about the carcinogenic risk of anthraquinone-containing laxatives. Therefore we propose the following rewording: "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."

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5.3. Preclinical safety data Continuation	The authors came to the conclusion that neither anthranoid laxative use, even in the long term, nor macroscopic or marked microscopic melanosis coli were associated with any significant risk for the development of colorectal adenoma or carcinoma. Müller-Lissner [1] states that care should be taken when extrapolating the findings of animal studies to humans since the results have been obtained using very high doses of anthranoids for a relatively long period compared to the lifespan of animals. A large number of clinical studies failed to find an association between anthranoid laxative intake and CRC. In conclusion, although chronic constipation appears to be associated with an increased risk of CRC, there are no data to support that stimulant laxatives are an independent risk factor for CRC. Furthermore, in a case control study performed by Loew et al [5,6] with retrospective and prospective evaluation, no causal relationship between anthranoid laxative use and colorectal cancer could be detected. For these reasons, the last section *"Commercial laxative use … cannot be definitely assessed"* should be replaced by the following sentence: *"Despite a lack of formal preclinical data on frangula, epidemiological studies suggest that there is no carcinogenic risk in humans from the use of anthranoid laxatives."*	See above. Epidemiological studies with limited population and inconsistent results cannot compensate lack of formal preclinical studies.