EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 March 2013
EMA/HMPC/48932/2012 *Corr.*[1]
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on Community herbal monograph on *Glycyrrhiza glabra* L. and/or *Glycyrrhiza inflata* Bat. and/or *Glycyrrhiza uralensis* Fisch., radix (EMA/HMPC/571119/2010)

Table 1: Organisations and/or individuals that commented on the draft Community herbal monograph on *Glycyrrhiza glabra* L. and/or *Glycyrrhiza inflata* Bat. and/or *Glycyrrhiza uralensis* Fisch., radix as released for public consultation on 15 August 2011 until 15 November 2011

	Organisations and/or individuals
1	Diapharm Regulatory Services GmbH, Germany
2	AESGP
3.	KOOP PHYTO
4.	EBF

[1] Completed with comments from AESGP, KOOP PHYTO, EBF as received during public consultation.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 718 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.eurpa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
Diapharm	Diapharm welcomes the preparation of this Community herbal monograph which may provide harmonised assessment criteria for Glycyrrhiza products and thus facilitate mutual recognition in Europe. We thank for the opportunity to provide our input, which you will find as follows:	
AESGP	AESGP in principle welcomes the development of the above-mentioned Community herbal monograph which, by providing harmonised assessment criteria for Liquiritiae radix-containing products, should facilitate mutual recognition in Europe. We have the following specific comments.	
EBF	No comments	
KOOP PHYTO	Kooperation Phytopharmaka, a German scientific organisation, would like to comment on this HMPC draft monograph, because an important preparation is missing which is marketed in Germany. In the following, detailed remarks are given.	

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
2.Qualitative and quantitative composition	Diapharm	Under ii) Herbal preparations we suggest to add: “Dry extract (DER 4 - 6 : 1), extraction solvent water” and “Dry extract (DER 3 - 4 : 1), extraction solvent water”	Partially endorsed. The specific dry extracts mentioned are in combination products having a different posology.

		On the one hand a dry extract is in principle already covered by the present wording of the draft HMPC monograph, because a dry extract is nothing but the native dry residue of the liquid extract But, just to make it more clear and precise, we suggest mentioning the dry extracts explicitly in section 2. Proof of traditional use of the liquid extract also covers proof of traditional use for the corresponding dry extract, as the native extract (which is regarded as the active principle according to current EU quality guidelines for Herbal medicinal products) is identical in both dry and liquid extract. On the other hand different Traditional Herbal Registrations granted in Germany with glycyrrhiza dry extract substantiate to include the dry extracts in the HMPC monograph. Please see the corresponding SmPCs in Annex 1 for the following THMPs:	However, taking into consideration that the dry extract is the native dry residue of the liquid/soft extract, the dry extracts corresponding to the soft extracts already in the monograph are accepted.

Tradename	**Reg. No.**	**Glycyrrhiza Extract, DER**
HEUMANN Bronchialtee SOLUBIFIX® T	6777533.00.00	Dry extract (DER 3 – 4 : 1), extraction solvent water
Mixtura solvens Lichtenstein N	6867265.00.00	Dry extract (DER 3 – 4 : 1), extraction solvent water
Liquirit®	6854682.00.00	Dry extract (DER

<table>
<tr><td></td><td></td><td><table><tr><td></td><td></td><td>4 – 6 : 1), extraction solvent water</td></tr></table></td><td></td></tr>
<tr><td>2. Qualitative and quantitative composition</td><td>AESGP</td><td>We propose to add to the mentioned extracts
• Soft extract (1:0,4 – 0,5:1) extraction solvent water
• Soft extract (3:1) extraction solvent water
the following one
• Dry extract (3 - 6 :1) extraction solvent water
Reasons:
The dry extract (3 – 6:1), extraction solvent water, containing 5 – 7% glycyrrhizic acid according to DAC, is part of the following preparations in the German market:
<table><tr><th>Eingangsnr.</th><th>AM-Name</th><th>Dar.-Form</th><th>Wirkstoff (Art und Menge)</th><th>Register-Nr.</th><th>Anmelder</th></tr><tr><td>0206842</td><td>Bongast N</td><td>Kapsel</td><td>Süßholzwurzel, TE o.w.A. 280. - 350. mg</td><td>n.a.</td><td>Dr.med.Mainz Arzneimittel GmbH</td></tr><tr><td>0266092</td><td>Lakriment Neu Bronchial-Pastillen</td><td>Pastille</td><td>Süßholzwurzel, TE o.w.A. 187. mg</td><td>L793</td><td>Dolorgiet GmbH & Co.KG</td></tr><tr><td>0401058</td><td>Liquiritia P Kapsel</td><td>Kapsel</td><td>Süßholzwurzel, TE mit Wasser 250. mg</td><td>n.a.</td><td>Leopold-Arzneimittel Apotheker Dr.Walter Probst</td></tr><tr><td>0006824</td><td>Suczulen mono</td><td>Kapsel</td><td>Süßholzwurzel, TE o.w.A. 280.-350. mg</td><td>47555</td><td>Abbott GmbH & Co. KG</td></tr><tr><td>0266198</td><td>Ulgastrin Neu</td><td>Tablette</td><td>Süßholzwurzel, TE mit Wasser 200. - 280. mg</td><td>U87</td><td>Dolorgiet GmbH & Co.KG</td></tr></table>
Furthermore, a dry extract (4 - 6:1), extraction solvent water, is marketed as Liquirit® in Germany, Reg.no. 6854682.00.00, a dry extract (3 - 4:1), extraction solvent water, as HEUMANN Bronchialtee SOLUBIFIX® T, Reg.no. 6777533.00.00 and Mixtura solvens Lichtenstein N, Reg.no. 6867265.00.00. The</td><td>Partially endorsed.
Insufficient information about the preparations in the German market containing the dry extract (3 – 6:1), extraction solvent water (5-7% glycyrrhizic acid according to DAC) is provided to substantiate the 30 years of long standing use.
The medicinal products reported in the table are not on the German market anymore and the elapsed time of marketing does not fulfil the 30 years criterion: even supposing that the dry extract is the same in all different products, it was introduced in the formulation in 1989 at the earliest (only Lakriment Neu Bronchial-Pastillen for indication 2, while in the other products the dry extract dates back to 1993 for both indications) and the medicinal products were marketed until 2010 at the latest (Bongast N).
The specific dry extracts (4 - 6:1), extraction solvent water, and dry extract (3 - 4:1), extraction solvent water are in combination products having a different posology.
However, taking into consideration that the dry extract is the native dry residue of the liquid/soft extract, the dry extracts corresponding to the soft extracts already in the monograph are accepted.</td></tr>
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		corresponding expert information texts are attached	
3. Pharma-ceutical form	AESGP Diapharm	With reference to above mentioned Traditional Herbal Registrations granted in Germany we suggest to add solid dosage forms as additional pharmaceutical form: "Herbal preparation in solid or liquid dosage forms for oral use."	Endorsed.
4. Clinical particulars	EBF	Indication Indication 1 Traditional herbal medicinal product for the relief of digestive symptoms including burning sensation and dyspepsia. is proposed to be amended as follows: „Adjuvant therapy of gastric and duodenal ulcers and gastritis" *Rationale in the ESCOP Monographs, 2nd Edition, Thieme 2003, p.297*	Not endorsed. Duodenal ulcers and gastritis are indication not appropriate for traditional use because requiring medical supervision for diagnosis and control
4.1 Therapeutic indications	KOOP PHYTO	Comment and Rationale: For indication 1, there has recently been published a clinical study of good quality (Raveendra et al. 2012, Epub 2011) in the indication of functional dyspepsia. The indication was functional dyspepsia. Patients were included according to the most modern diagnostic scheme for functional dyspepsia, the Rome-III criteria. The study was conducted in a double-blind, placebo-controlled manner. The test preparation was a soft extract, analytically characterised by glabridin (≥3.5% w/w), glabrol (≥0.5% w/w), eicosanyl caffeate (≥0.1% w/w), docosyl caffeate (≥0.1% w/w), glycyrrhizin (≤0.5% w/w), and total flavonoids (≥10% w/w), in a dose of 75 mg twice daily, for a duration of 30 days. There was a clearly significant improve of the dyspeptic symptom score and the Nepean Dyspepsia score.	As also reported in the introduction of the article of Raveendra et al. 2012 mentioned by KOOP PHYTO, functional dyspepsia is known as dyspepsia in the absence of clinically identifiable, structural gastrointestinal lesions, i.e. in absence of pathology. IC-10 classification reports the word dyspepsia but not functional dyspepsia. This interesting article shows the results of a clinical study on functional dyspepsia, but the greatest limit is represented by the number of recruited patients. For the study 50 subjects were recruited and only 25 of them were treated with the product studied. Although the sample size was statistically calculated total number of patients remains low to justify definite therapeutic conclusion and it

		The study indicates, despite its relatively small size, a clear clinical efficacy in functional dyspepsia. Relevant adverse events were not reported. Therefore, for soft extracts (2., preparation b) and c) respectively 4.2., Posology b), the use is not longer exclusively based upon long-standing use, but on a well established use supported by modern clinical data. Therefore, these extracts should be moved from the right to the left column. Literature cited: Raveendra KR, Jayachandra, Srinivasa V, Sushma KR, Allan JJ, Shankargo K, Shivaprasad HN, Venkateshwarlu K, Geetharani P, Sushma G, Agarwal A: An extract of Glycyrrhiza glabra (GutGard) alleviates symptoms of functional dyspepsia: a randomized, double-blind, placebo controlled study. Evid. Based Complement. Alternat. Med. 2012; 2012: 216970. Epub 2011 June 16 The well-established use of Glycyrrhiza glabra extracts in functional dyspepsia is supported by a large number of data on related mechanisms of action. To these belongs data on the affinity to gastrointestinal 5-HT3 receptors (Simmen et al. 2006), mechanisms inhibiting the subclinical inflammatory changes, which are often involved in the aetiology of functional dyspepsia (Schempp et al. 2006) and which have also been confirmed in models of inflammation induced gastric ulceration (Alkofahi et al. 1999, Dehpour et al. 1995, 1996, Khayyal et al. 2006), and data on the action on gastrointestinal motility changes involved with functional dyspepsia (Wrociński et al. 1960, Shihata et al. 1963, Schemann et al. 2006).	cannot support the well established use. Nonetheless, the beneficial effects shown in this study are useful to corroborate the traditional indication 1. The remaining scientific articles referred to by Koop Phyto do not support clinical use but confirm preclinical activities already cited in the assessment report.

		References: Alkofahi A, Atta AH: Pharmacological screening of the antiulcerogenic effects of some Jordanian medicinal plants inrats. J. Ethnopharmacol. 1999; 67: 341-345 Dehpour AR, Zolfaghari ME, Samadian T, Kobarfard F, Faizi M, Assari M: Antiulcer activities of liquorice and its derivatives in experimental gastric lesion induced by ibuprofen in rats. Int. J. Pharm. 1995; 119: 133-138 Dehpour AR, Zolfaghari ME, Samadian T, Vahedi Y: The protective effect of liquorice components and their derivatives against gastric ulcer induced by aspirin in rats. J. Pharm. Pharmacol. 1994; 46: 148-149 Khayyal MT, Seif-El-Nasr M, El-Ghazaly MA, Okpanyi SN, Kelber O, Weiser D: Mechanisms involved in the gastroprotective effect of STW 5 and its components against ulcers and rebound acidity. Phytomedicine 2006; 13: SV 56-66 Schemann M, Michel K, Zeller F, Hohenester B, Ruhl A: Region-specific effects of STW 5 and its components in gastric fundus, corpus and antrum. Phytomedicine 2006; 13:SV 90-99 Schempp H, Weiser D, Kelber O, Elstner EF: Radical scavenging and anti-inflammatory properties of STW 5 and its components. Phytomedicine 2006; 13: SV 36-44 Shihata IM, Elghamry M I: Experimental studies on the effect of Glycyrrhiza glabra. Planta Medica 1963; 1: 37-43 Simmen U, Kelber O, Okpanyi SN, Jaeggi R, Bueter B, Weiser D: Binding of STW 5 and its components to intestinal 5-HT, muscarinic M3, and opioid receptors. Phytomedicine 2006; 13:	

		SV 51-55 Wrociński T: Determination of efficacy of spasmolytic drugs using the papaverine standard. Biuletyn Instytutu Roslin Leczniczych 1960: 236-254	
4.1 Therapeutic indications	AESGP	Both mentioned traditional indications are applicable to this extract as well.	The traditional indication 1 for the soft extract (DER 1:0.4-0.5, extraction solvent water) and the corresponding dry extract is substantiated by the long standing use in Germany, at least since 1976, only to support gastric function. The traditional indication 2 for the soft extract (DER 3:1, extraction solvent water) and the corresponding dry extract is substantiated by the long standing use in Denmark since more than 70 years only as an expectorant.
4.2 Posology and method of administration		Under “Indication 1” we suggest to add “b) Dry extract (DER 4 – 6 : 1) Up to 270 mg 2-3 times daily for oral use. Not more than 810 mg daily.” Under “Indication 2” we suggest to add “d) Dry extract (DER 3 – 4 : 1) 120 mg up to 6 times daily for oral use. Not more than 720 mg daily.” The dosage should be adjusted to the dosage of the registered THMPs in Germany.	Not endorsed. The posology for the dry extracts must correspond to the posology of the soft extracts. The monograph is amended accordingly.
4.2 Posology and method of administration	AESGP	Posology The dosage recommendations should be adjusted to the	Partially endorsed. Posology is given for soft extracts and their corresponding dry extracts for their accepted indication.

		posology of the registered products in Germany. The following examples are given for the posology of these products: Dry extract (3 – 6 :1), extraction solvent water used in both indications of the draft monograph: 350 mg extract containing 6% glycyrrhizic acid (according to DAC), 3- 4 times daily. Daily dose = 1050 – 1400 mg extract corresponding to 63 – 84 mg glycyrrhizic acid or 4.7 – 6.3g herbal drug, respectively. Dry extract (4 – 6 : 1) used in "Indication 1": Up to 270 mg 2-3 times daily for oral use. Not more than 810 mg daily." Dry extract (3 – 4 : 1) used in "Indication 2": 120 mg up to 6 times daily for oral use. Not more than 720 mg daily." Furthermore, we are of the opinion that exclusion of persons below 18 years of age is not justified. Liquorice preparations are widely consumed as food by the population including children and even smaller children.	Not endorsed. Despite the use in food and candies, there is insufficient data to support the safety of Liquorice root as a medicinal product in children and adolescents under 18 years
4.2 Posology and method of administration	KOOP PHYTO	Comment and Rationale: With regard to the fact, that the use in children and adolescents below 18 years is not recommended, it is appreciated, that reference is given to section 4.4 and the lack of adequate data. This reference clarifies, that there are no fundamental mechanistic reasons not to use liquorice in this age group. It is well known, that sweets prepared from liquorice are	Endorsed.

		marketed as food products and are widely used in this age group, without age specific safety problems.	
4.4 Special warnings and precautions for use	AESGP	From our point of view, the exclusion of persons below 18 years of age is not justified. The reasons are given under 4.2. Posology.	Not endorsed Despite the use in food and candies, there is insufficient data to support the safety of Liquorice root as a medicinal product in children and adolescents under 18 years
4.4-4.8. Special warnings and precautions for use etc.	KOOP PHYTO	Comment and Rationale: It is important to mention, that the warnings given, do not apply to preparations containing liquorice in general, independent from its dose, but to preparations dosed according to this monograph. It is well established, that the adverse events mentioned in the warnings, as are hypokalemia, hypertension, cardiac rhythm disorders, are clearly dose dependent, so that low doses do not have these effects. Van Gelderen et al. (2000) have determined the ADI of glycyrrhicinic acid from human data and came to an acceptable daily intake of 0.2 mg/kg b.w. An other determination was conducted on the basis of animal data by Isbrucker and Burdock 2006 and gave a range of 0.015-0.22 mg/kg, so supporting the ADI of 0.2 mg/kg of van Gelderen. For a person with a body weight of 60 kg this is 12 mg/d. Assuming that liquorice root drug contains 3-5 % glycyrrhicine, 0.24-0.40 g of the drug would correspond to this ADI. While this dose is significantly below the doses recommended in this monograph draft, there is a significant number of preparations, mostly fixed combination preparations (including teas), which	Comments on dosages are noted. Community monographs are referred to the specific preparations.

		are dosed below the ADI. It is important to take into account that the warnings and precautions given here do not apply to these low dosed preparations. The same is the case for points 4.5, 4.6 and 4.8, as also the information on potential side effects and the restrictions of the use in pregnancy and lactation have to be seen in the context of the dose, as mentioned above, and therefore do not apply automatically to all other preparations with e.g. lower daily doses or to combination preparations. References: Isbrucker R.A., Burdock G.A.: Risk and Safety Assessment on the Consumption of Licorice Root (Glycyrrhiza sp.), its Extract and Powder as a Food Ingredient, with Emphasis on Pharmacology and Toxicology of Glycyrrhizin. Reg Toxicol Pharmacol 2006; 46: 167-192 (available at HMPC). van Gelderen C. E., Bijlsma J. A., van Dokkum W., Savelkoul T. J.: Glycyrrhizic acid: the assessment of a no effect level. Hum Exp Toxicol 2000; 19:434-439.	

AESGP

References:

Monographs German DAC:
Eingestellter Süßholztrockenextrakt DAC 1986
Standardisierter Süßholztrockenextrakt DAC2006

Further monographs:
BP 1973 Liquorice Liquid extract
Potter´s New cyclopaedia of Botanical Drugs and Preparations Liquorice
Plantes Medicinales Glycyrrhizia glabra
Pharm Franc Reglisse 1986
Ph.Helv VII 1989 Liquiritiae Radix
Kommission E: Liquiritiae radix
ESCOP: Liquiritiae Radix
WHO: Radix Glycyrrhizae

Excerpts from DIMDI database:
Bongast N
Lakriment Pastillen
Liquiritia P Kapsel
Suczulen mono
Ulgastrin Neu

Product-related documents:
Expert Information Solubifix, Mixtura solvens, Liquirit,
Package leaflet Suczulen mono
Expert information Suczulen mono