5 April 2016
EMA/HMPC/150876/2015
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph (EMA/HMPC/159075/2014) and European Union list entry (EMA/HMPC/685372/2014) on *Crataegus spp*., folium cum flore

Final

Table 1: Organisations and/or individuals that commented on:

draft European Union herbal monograph on *Crataegus* spp., folium cum flore as released for public consultation on 14 October 2014 until 15 January 2015.

draft European Union European Union list entry on *Crataegus* spp., folium cum flore as released for public consultation on 9 January 2015 until 15 May 2015.

	Organisations and/or individuals
1	Association of the European Self-Medication Industry (AESGP)
2	European Scientific Cooperative on Phytotherapy (ESCOP))
3	Dr. Willmar Schwabe GmbH & Co. KG , Germany

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	AESGP welcomes the development of the above-mentioned Community herbal monograph which, by providing harmonised assessment criteria for Crataegus-containing products, should facilitate mutual recognition in Europe.	
ESCOP	ESCOP welcomes the draft Community herbal monograph on Crataegus spp., folium cum flore, accompanied with companion documents (draft assessment report and draft reference list), prepared by the Committee on Herbal Medicinal Products (HMPC).	

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
2. Qualitative and quantitative composition	AESGP	We suggest to include the herbal preparation 2d) dry extract (4-7.1:1, ethanol 45-70% V/V) and 2c) (4-7:1, methanol 70% V/V) under "well-established use". The reasons are given under "indications". **Indications** According to the monographs on Crataegus published by ESCOP as well as by Kommission E (1984 and 1994, quoted in the HMPC reference list), a medicinal use of hawthorn can be proven in general. It includes extracts of leaves and flowers which have been used for relief of symptoms of congestive heart failure (CHF) in case of severity level I or II as per NYHA classification. This indication differs from the suggested traditional indication (1) of the HMPC draft monograph.	Not endorsed.

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		1. **Well-established medicinal use** The dry extract d) (4-7.1:1, ethanol 45-70% V/V) and c) (4-7:1, methanol 70% V/V) have well-established indications and should be moved to the "well-established use" column. Efficacy of these extracts in treatment of CHF has been proven in many clinical trials listed in the HMPC assessment report (AR). In accordance with the EMA HMPC 'Guideline on the Assessment of clinical safety and efficacy in the preparation of Community herbal monographs for well-established and of Community herbal monographs / Entries to the Community list for traditional herbal medicinal products / substances / preparations', these extracts fulfil the requirements for "well-established use". A Cochrane review from 2009, quoted in the AR, confirms this. Pittler (2008) demonstrates a statistically significant increase in workload and exercise tolerance compared to placebo. Furthermore, the SPICE trial (Holubarsch 2008) demonstrates that the use of a specific Crataegus extract (daily dose 900 mg) is safe and well-tolerated. No indication for therapy-related risk has become apparent as an add-on treatment in adults suffering from congestive heart failure (NYHA II or III) with impaired left ventricular ejection fraction (LVEF ≤35%). With regard to the primary endpoint (time to the first cardiac event) there was a clear but non-significant tendency in favour of Crataegus, particularly after one year. Cardiac mortality as second endpoint was significantly reduced after 6 and 18 months. Additionally in the subgroup with LVEF between 25% and 35%, the extract significantly reduced sudden cardiac death (39.7% at month 24, p=0.025). This study demonstrates that prescribing hawthorn products within a guideline-conform therapy concept is not associated with an increased mortality. In contrast, it is shown to be efficacious in	In the older studies mentioned in the AR of the HMPC only surrogate parameter (ergometer capacity, pressure-rate product etc.) were investigated. These are no longer sufficient to current knowledge and to corresponding guidelines (European Society of Cardiology (ESC) 2012, CPMP/EWP/235/95 Rev. 1)to prove efficacy in indication such as "Symptoms such as slight limitation of physical activity, shortness of breath and fatigue due to decreased cardiac performance" as suggested (see below). Within the "Guideline for the diagnosis and treatment of acute and chronic heart failure 2012) of the European Society of Cardiology the definition of heart failure is given as follows: "Heart failure is defined, clinically, as a syndrome in which patients have typical symptoms (e.g. **breathlessness**, ankle swelling, and **fatigue**) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an **abnormality of cardiac** structure or **function**". Therefore such symptoms as described are clearly belonging to a medical condition, in which treatment according to the general treatment recommendations should be performed. For the proof of efficacy for such conditions the

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		targeted patient populations. Moreover, for this reason the assessment of the benefit-risk ratio in the drafted HMPC assessment report (EMA/HMPC/159076/2014) is therefore not justified and ought to be removed.	relief of symptoms and signs, the prevention of hospital admission and/or improvement in survival has to be shown. That was not shown with the older studies. Within the SPICE-trial the patients were on optimal pharmacological treatment (almost 90% had at least three concomitant cardioactive drugs as baseline). For the composite primary endpoint that included cardiac death, non-fatal myocardial infarction and hospitalization due to progressive heart failure, confirmatory proof of efficacy of the *Crataegus*-preparation was not achieved. Secondary efficacy outcome measures included each individual endpoint contributing to a cardiac event, workload during exercise testing, echocardiographic measures, as well as quality of life and pharmacoeconomic assessments. Among the events contributing to the composite endpoint, patients treated with the *Crataegus*-preparation showed a **tendency** towards lower 24-month event rates than the placebo group for death of any cause, death of cardiac cause, sudden cardiac death, death due to progressive heart failure and non-fatal myocardial infarction, **but none of the differences reached the level of statistical significance.** In a pre-specified sub-group (initial left

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			ventricular ejection fraction (LVEF) between 25% and 35% cardiac mortality in the *Crataegus*-group as compared to placebo, was reduced, with a significant reduction in sudden cardiac deaths. These represent an exploratory analysis, and therefore should be treated with caution. The authors described the effects as "tendency". A further study, aiming on such a subgroup as primary endpoint is not available. Furthermore a marketing authorisation (with an indication such as concomitant use in patient with optimal standard pharmacological therapy and LVEF between 25-35%) does not exist, which prerequisite (together with a positive study) for a well-established use.
		2. **Traditional use** We suggest adding another therapeutic indication within the cardiovascular area of application. This should be added as "Indication 1b" complementing the existing indication 1 (new 1a): Indication 1: changed to 1a New Indication 1b to be added: "Traditional herbal medicinal product used to support cardiovascular function. If symptoms are of unclear origin, persist for longer than two weeks, or worsen, a medical doctor	Not endorsed. A traditional indication "to support cardiovascular function" was not acceptable by the HMPC. The majority was of the opinion that for such an indication the requirement laid down in Article 16a(1)(a) of Directive 2001/83/EC that the indications are "exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the

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		should be consulted. The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use." This is justified by the longstanding therapeutic use of Crataegus in the support of cardiac and circulatory functions (BfArM § 109a list, WHO, ESCOP). Pharmacological effects, which were demonstrated in nonclinical and human studies (increase of myocardial contractility, vasorelaxation, increased left ventricular ejection fraction and decreased afterload), further support the plausibility of this use. Safe use is ensured by adding the wording "*If symptoms are of unclear origin, persist for longer than two weeks, or worsen, a medical doctor should be consulted*". This guarantees that patients consult a doctor for any new, persisting or worsening symptoms.	supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment" is not fulfilled.
2. Qualitative and quantitative composition	ESCOP	We suggest to move preparations c) and d) into the left column "well-established medicinal use". Rationale: We do not agree with the statement "the reported well-established use for hawthorn extract cannot be regarded as proven by the available data." (AR) for the preparations c) and d). Pittler et al. analysed several studies and concluded "that hawthorn extract has significant benefits". [Pittler *et al.* 2008]. The ESCOP monograph states a well-established use for "Declining cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA". Herbal teas and other preparations are listed under "traditional use" [ESCOP].	Not endorsed. In Pittler *et al.* (2008) it is explained, that a beneficial effect could be seen for the physiological outcome of the maximal workload and that exercise tolerance was significantly increased. Goals of treatment of patients with heart failure are relief of symptoms and signs, prevention of hospital admission and/or improvement in survival. Reductions in mortality and hospital admission rates, which reflects both the ability of effective treatments to slow or prevent progressive worsening of heart failure was not assessed by Pittler *et al*. (2008).

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2. Qualitative and quantitative composition	Schwabe	*Summary and Overall Conclusions on Benefit-Risk-Ratio* From the efficacy and safety results of the studies with Crataegus extract WS1442 illustrated below, we conclude that patients with heart failure (HF) with any type of left ventricular ejection fraction (LVEF), with symptoms of mild to moderate severity should not be deprived of the treatment with hawthorn extract preparations. Based on the large evidence regarding the beneficial treatment effects and the safety of Crataegus extract WS1442 it is deduced that the benefit-to-risk-ratio is positive. *1. Heart Failure: Symptoms and Definitions* Heart failure is a clinical syndrome characterized by clinical signs and symptoms, such as dyspnea at exercise or at rest, peripheral edema and/ or lung congestion, reduced exercise capacity, and overall fatigue. There must be evidence of left ventricular dysfunction [1]. Patients presenting with symptoms suggestive of heart failure have to undergo cardiological examination. Echocardiography reveal an impaired (HF-REF, heart failure with reduced ejection fraction [EF]) or preserved left ventricular ejection fraction (HF-PEF, heart failure with preserved EF), although there is no consensus concerning the cut-off for preserved ejection fraction. In this regard, it is worthy to point out that there is a poor correlation between symptom severity (NYHA classification of functional capacity) and left ventricular ejection fraction (LVEF) [2]. While HF with reduced ejection fraction (HF-REF) is the best understood type of HF in terms of pathophysiology and treatment options and represents the focus of the ESC guide-lines, HF with preserved ejection fraction (HF-PEF) seems to have different epidemiological and etiological profiles [2].	Not endorsed. See above.

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		However, patients of both types of heart failure suffer from similar clinical symptoms, which subsequently are staged in their severity according to the NYHA classification on the basis of their influence on functional capacity. Symptoms may worsen over time, leading to declining functional capacity and diminished quality of life, suggesting that adequate and clinically proven symptom-related treatment is warranted. The ESC guidelines for diagnosis and treatment of acute and chronic heart failure 2012 underline that the relief of symptoms, improvement in quality of life, and increase in functional capacity are of the utmost importance to patients [2]. As shown below, Crataegus WS1442 has beneficial effects on symptoms, can improve quality of life as well as increase functional capacity. *2. Treatment recommendations of HF* *2.1 Treatment recommendations of HF-REF (systolic heart failure)* There is a great body of evidence that - in HF-REF - the application of ACE-inhibitors (or ARBS), of beta-receptor-blockers and aldosterone-antagonists prevents hospital admission and improves survival. In patients with HF-REF, it would be therefore unethical to withhold any of the above mentioned medical treatment. Crataegus extract WS1442 can therefore be only applied in addition to the standard treatment (see SPICE-trial below). However, HF-REF patients enrolled in randomized controlled trials had an LVEF ≤35% or ≤40% and it is only in these patients that efficacious therapies have been demonstrated to date [3]. However, since EF in HF-PEF is generally considered to be ≥50% [2,3], the efficacy of the recommended pharmacological treatment in the ESC guidelines for diagnosis and treatment of acute and chronic heart failure 2012 [2] for a considerable proportion of HF	

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		patients with an EF between 40% and 50% is not proven and thus, not evidence-based. Crataegus extract WS1442 may close this gap in the treatment of HF patients with reduced ejection fraction, especially in this EF range. *2.2. Treatment recommendations of HF-PEF (diastolic heart failure)* Actually, not any pharmacological therapy has been proven for treatment efficacy of HF-PEF on the basis of evidence-based medicine [4-8]. Especially in these patients, Crataegus extract WS1442 may be a treatment option (even as monotherapy) for improving symptoms. *3. Mechanism of action of Crataegus extract WS1442* In various in-vivo nonclinical investigations, Crataegus extract WS1442 has shown an in-crease in coronary blood flow and myocardial circulatory perfusion, an anti-arrhythmic effect, a protective effect on reperfusion-induced reduction of blood pressure, a protective effect on the myocardium from damage due to ischaemia, an inhibition of endothelin (ET-1)-mediated myocardial ischemia, an anti-proliferative effect on neointimal formation, a decrease of pe-ripheral vascular resistance and a reduction of cardiac hypertrophy due to primary or secondary hypertension [9-17]. *4. Effect of Crataegus extract WS1442 on symptoms, exercise capacity, quality of life, and LV EF in patients with heart failure* The efficacy and safety of WS1442 in the treatment of mild to moderate heart failure (HF) symptoms (NYHA class I and II) have been shown in several randomised, double-blind clinical trials [18-22]. The most recent Cochrane review on the use of hawthorn extracts	

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		concludes that the results of 14 randomized, double-blind, and placebo controlled trials suggest that there is a significant benefit in symptom control and physiologic outcomes from hawthorn extract as an adjunctive treatment for chronic heart failure. Exercise tolerance, shortness of breath and fatigue are significantly improved with hawthorn as compared with placebo [23]. In a multi-center post-marketing surveillance study, 1011 patients with NYHA II heart failure were treated with 2 x 1 capsule WS1442 (900 mg extract/day) for 24 weeks. During and at the end of the observation period a significant improvement of performance in the bicycle exercise testing, fatigue and palpitation was seen. The improvement and economization of cardiac performance were additionally shown by a reduction of blood pressure and increased maximum exercise tolerance. The positive effects of WS1442 were further demonstrated by an improved ejection fraction. Almost 2/3 of the patients felt "better" or "much better" following the 24 weeks of treatment. More than 3/4 of the participating physicians noted a "good" or a "very good" efficacy, and 98.7% noted a "good" or a "very good" tolerance [24]. In a prospective, open, two armed, multi-center cohort study, the influence of the treatment with WS1442 (cohort 1) on quality of life (using the Quality of Life Profile for the Chronically Ill [PLC] questionnaire, disease-related symptoms (i.e. limitation of physical capacity, fatigue, exertional dyspnea, heart palpitation) in comparison to conventional treatment with chemical substances (cohort 2) was investigated in patients suffering from heart failure (NYHA II) due to coronary heart disease. The individual study duration was 6 months and data of 711 patients were recorded. The results show that the	

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		treatment with WS1442 in cohort 1 significantly improved the quality of life and decreased the severity of disease-related symptoms in comparison to the corresponding data obtained from cohort 2 [25]. In a group of 209 patients with NYHA III class HF, Tauchert [18] found that there may be a dose-dependent effect of WS1442 on exercise capacity. The results of an analysis of individual data of 687 patients pooled from 10 studies [26] indicate that the improvement in both objectively measured exercise tolerance and HF symptoms may be more pronounced in patients more severely symptomatic at baseline. The study by Haertel et al. [27] specifically addressed the use of Crataegus extract WS1442 on top of endurance exercise training in patients with HF-PEF. In this study WS1442 tended to increase exercise capacity and improve symptoms as compared to exercise program alone. As opposed to other studies with WS1442, the HERB CHF study [28] including 120 patients with NYHA class II HF did not find an improvement in 6 minute walk test, quality of life, peak oxygen consumption, neuro-hormones or oxidative stress. There was, however, a modest but significant difference in LV EF in favour of WS1442. More extensive summaries on clinical effects of WS1442 have been previously published [29-30]. Overall, we are convinced that these study results provide evidence for the therapeutic efficacy of WS1442 in the symptomatic treatment of HF patients. The patients in these studies had an established diagnosis	

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		of HF made by cardiologists. The diagnosis was based on the clinical HF symptoms, confirmed by echocardiography as objective parameter. Furthermore, the patients had either a reduced (≤40%) or a preserved left ventricular ejection fraction. *5. Effect of WS 1442 on mortality and morbidity in patients with heart failure* A large randomized, double-blind, placebo-controlled Survival and Prognosis: Investigation of Crataegus Extract WS1442 in CHF (SPICE) outcome trial with Crateagus extract WS1442 has been conducted [31-32]. In the SPICE study [31], the efficacy and safety of WS1442 as an add-on treatment were investigated in adults suffering from congestive HF (NYHA II-III) with impaired left ventricular ejection fraction (LVEF ≤35%). In this study, 2681 patients were randomised to an additional treatment with WS1442 (one film-coated tablet containing 450 mg WS1442 twice daily; total daily dose 900 mg WS1442) or placebo for 24 months. The primary endpoint was the number of days between baseline and the first cardiac event, defined as a composite of car-diac death, non-fatal myocardial infarction, or hospitalization due to progressive heart failure. The patients in SPICE study were receiving adequate background treatment: 85% were on diuretics, 83% on ACE inhibitors, 64% on beta-blockers and 35% on spironolactone. There was no effect of WS1442 on the primary outcome. Although the study was neutral, it is of note that the absolute numbers of patients with death from any cause, cardiac death and non-fatal myocardial infarction was consistently lower in the WS1442 group as compared to placebo. There was a non-significant trend for decreased all-cause	

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		mortality, and a significant decrease in sudden cardiac death (Tab. 1). Table 1: Cardiac mortality and sudden cardiac death in total population and subgroup with LVEF ≥ 25% (*p*-values are explorative, two-sided log rank test) In the overall analysis in all patients there was a clear but non-significant tendency in favour of WS1442 regarding the composite endpoint (especially after one year). Cardiac mortality as second endpoint was significantly reduced after 6 and 18 months by WS1442.	

	Event rate in %		*p*-value
	WS®1442	Placebo	
All patients:			
Cardiac mortality			
6 months	2.9	4.9	0.009
12 months	7.1	8.6	0.142
18 months	9.5	11.9	0.046
24 months	13.5	14.9	0.269
Sudden cardiac death			
6 months	1.9	2.8	0.103
12 months	4.2	5.1	0.238
18 months	5.8	7.4	0.091
24 months	7.6	9.0	0.184
Subgroup LVEF ≥ 25%			
Cardiac mortality			
6 months	2.3	3.8	0.154
12 months	5.2	7.3	0.153
18 months	7.0	10.4	0.044
24 months	10.4	13.0	0.158
Sudden cardiac death			
6 months	1.3	2.2	0.204
12 months	2.1	4.5	0.029
18 months	3.8	6.7	0.024
24 months	5.0	8.3	0.025

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		Additionally in the subgroup with LVEF between 25% and 35%, WS1442 significantly reduced sudden cardiac death (39.7% at month 24, p=0.025). *6. Safety profile of Crataegus extract WS1442* Crataegus extract WS1442 has an excellent tolerability, as shown in a large number of studies [18-22]. In the systematic review on the safety profile of hawthorn extract in the treatment of HF patients it is concluded that the extract is safe and rarely associated with serious adverse events [33]. It must be noted that, based on the analysis of HERB CHF data, Zick et al. [28] suggest that WS1442 may be associated with an increased risk of HF progression. Their findings must be treated with caution, since they come from a post-hoc analysis of a relatively small study (120 patients), which was not powered for clinical outcomes. Importantly, in the SPICE-trial [31] that included 2681 patients followed-up for 2 years, reported adverse events were similar in both groups concerning their number as well as the nature. There was no difference between the groups in the incidence of heart failure hospitalizations due to HF progression (p=0.78). *7. Overall Conclusions on Risk-Benefit-Ratio* Taking into consideration the entire body of evidence on the efficacy and safety of Crataegus extract WS1442 administration, it may be concluded that the drug: 1. has several proven mechanisms of action, 2. exerts a beneficial effect on heart failure symptoms, most importantly exercise toler-ance, both in patients with reduced and preserved LV EF,	

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		3. has been extensively tested as monotherapy and on top of guidelines-related medications, showing a favorable safety profile. There is a signal that it might reduce sudden cardiac death. These data give a strong support for the statement that the benefit-to-risk ratio of Crataegus extract WS1442 should be assessed as positive.	
4.1. Therapeutic indications	AESGP	We suggest adding the following indication under the well-established use column: *"Symptoms such as slight limitation of physical activity, shortness of breath and fatigue due to decreased cardiac performance."*	Not endorsed, since well-established use is not endorsed (see above). This wording is only a circumscription of heart failure, which requires a treatment according to current Guidelines (see above).
4.1. Therapeutic indications	ESCOP	**Well-established use** We propose the following wording: "Symptoms such as shortness of breath and fatigue due to declining cardiac performance." **Traditional use** We suggest adding a further indication in accordance with the ESCOP monograph: "Traditional herbal medicinal product used to support cardiovascular function. If symptoms are of unclear origin, persist for longer than two weeks, or worsen, a medical doctor should be consulted. The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use."	Not endorsed, since well-established use is not endorsed (see above). Not endorsed (see above).
4.2. Posology and method of administration	AESGP	The "duration of use" for indication 1a is given as "If the symptoms persist for more than 4 weeks, a doctor or a qualified health care practitioner should be consulted."	Not endorsed. In some MS a duration of use of 6 weeks without consulting a doctor exist (see

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		The AR does not explain why a time period of 4 weeks was chosen. In contrast all previous monographs on Crataegus recommend a duration of treatment of 6 weeks. <u>Commission E monograph (Germany), ESCOP monograph</u> “A physician must be consulted in cases where symptoms continue unchanged for longer than 6 weeks…” <u>WHO monograph</u> “Consult a physician if symptoms worsen, remain unchanged for longer than 6 weeks…”. For this reason, package leaflets of products on the market recommend patients use the Crataegus-preparations for 6 weeks. It is not clear why this common practice should be changed. Moreover, indication 1a itself requires a consultation of a doctor already at the start of the medication: “… after serious conditions have been excluded by a medical doctor”, which has not been the case of the former indication given by Commission E monograph, WHO monograph and ESCOP monograph. If serious conditions have already been excluded it is not obvious why the duration of treatment should be reduced. Thirdly, the onset of therapeutic effect may require at least 6 weeks which is recommended by Commission E monograph and WHO monograph. Consultation of a doctor a second time if the symptoms persist after 4 weeks is therefore inefficient, as the full therapeutic effect is not expected before 6 weeks of intake.	information on products on the market within the AR). However, the topic was discussed extensively during the establishment of the monograph. For safety reasons – for the traditional use supervision by a medical doctor is not foreseen – the duration of use was shortened to 2 weeks. No studies exist which support this point.

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		Finally, all studies listed in the Assessment report, with two exceptions, show study durations of at least 6 weeks, up to 2 years. No undesirable effects are listed in the HMPC monograph, so that no adverse effects of the medication are to be expected. We therefore suggest changing the "Duration of use" for indication 1 into "If the symptoms persist for more than 6 weeks, a doctor or a qualified health care practitioner should be consulted."	
4.2. Posology and method of administration	ESCOP	We do not agree with the statement "If the symptoms persist for more than 4 weeks, a doctor or a qualified health care practitioner should be consulted." The ESCOP monograph [ESCOP] suggests consultation of a physician if the symptoms continue unchanged for more than 6 weeks. Therefore the statement should be changed to "If the symptoms persist for more than 6 weeks, a doctor or a qualified health care practitioner should be consulted."	Not endorsed (see above).
5.1. Pharmacodynamic properties	AESGP	In section 5.1 it is proposed "Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended." However, according to the report of the AESGP/MLWP hearing on 6 May 2014 (EMA/HMPC/540095/2014), pharmacological data can be considered to be included in section 5.1. of a traditional use monograph on a case-by-case basis. This is especially the case if the pharmacological properties support the plausibility of the long-standing therapeutic use. In fact, some Crataegus extracts belong to the best-documented herbal preparations. Animal and human pharmacological data	Not endorsed. According to the SmPC-Guideline the description of the mechanism of action and pharmacological effects could be included if there is relevance to the approved indication. In the case of *Crataegus* there exist no data supporting the indications mentioned in the monograph.

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		demonstrate clearly the plausibility of the traditional use of Crataegus for the support of the cardiovascular system (EMEA/HMPC/104613/2005). Therefore section 5.1 should read as follows: Human pharmacological data show increase of myocardial contractility (positive inotropic action), vasorelaxation and increased left ventricular ejection fraction. From pharmacological studies, positive inotropic effects, peripheral vasodilation, increase myocardial perfusion as well as stroke volume and decreased afterload were reported.	
List entry	AESGP	In the comments AESGP submitted on the draft European Union monograph on Crataegus spp., folium cum flore in January 2015, we proposed to move dry extract d) (4-7.1:1, ethanol 45-70% V/V) to the "well-established use" column as, from our point of view, its efficacy is proven in many clinical trials. Consequently, in our opinion, establishing a European Union list entry is not possible since according to Directive 2001/83/EC, a European Union list entry can only cover herbal substances, preparations or combinations thereof for use in traditional herbal medicinal products. In case a list entry is nonetheless established, we propose to include all extracts covered by the definition "4-7.1:1, ethanol 45%" into the list entry. Although according to the HMPC draft assessment report, genotoxicity studies have been performed with a specific extract (4-6.6:1, ethanol 45% m/m), we are of the opinion that other extracts can also make reference to the mentioned genotoxicity data. This can be deduced from the HMPC Guideline on the selection of test materials for genotoxicity testing (EMEA/HMPC/67644/2009).	Not endorsed. See above. There are no (phytochemical) data on comparability available to extend the genotoxicity data to other extracts (as demanded by the "Guideline on the selection of test materials for genotoxicity testing" (EMEA/HMPC/67644/2009).

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List entry	ESCOP	ESCOP has submitted comments on the European Union monograph on Crataegus spp., folium cum flore on 14 January 2015 and suggested a well-established medicinal use for preparations c) and d) of the HMPC draft monograph, because the ESCOP monograph decribes a well-established medicinal use of the respective preparations [1]. These preparations include the dry extract (DER 4-6.6:1; ethanol 45% m/m). As a consequence of our comments submitted earlier, we do not support establishment of a European Union list entry. [1] ESCOP Monographs 2nd ed. Crataegi folium cum flore. ESCOP 2003, 98-106.	Not endorsed. See above.
		References – see below	The references mentioned have been assessed and only additional references which were considered relevant were added into the AR.
References	AESGP	[1] Commission E (Germany) monograph. Crataegus. Bundesanzeiger Nr. 1, 03 January 1984. [2] Commission E (Germany) monograph. Crataegi folium cum flore. Bundesanzeiger Nr. 133, 19 July 1994. [3] Pittler MH, Guo R, Ernst E. Hawthorn extract for treating chronic heart failure (Review), 2009. The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. [4] Holubarsch CJ1, Colucci WS, Meinertz T, Gaus W, Tendera M. The efficacy and safety of Crataegus extract WS 1442 in patients with heart failure: the SPICE trial. Eur J Heart Fail. 2008 Dec;10(12):1255-63. [5] ESCOP Monographs 2nd ed. Crataegi folium cum flore. ESCOP 2003, 98-106. [6] WHO Monographs on selected medicinal plants. Vol. 2. WHO. 2002, 66-82. [7] BfArM. List according to section 109a of the German Medicines Law. http://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Zulassung/zulassungsarten/besTherap/amTrad/indikatlistepara109-040824.pdf?__blob=publicationFile&v=2	

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		References – see below	The references mentioned have been assessed and only additional references which were considered relevant were added into the AR.
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