EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Crataegus monogyna* Jacq. (Lindm.), *C. laevigata* (Poir.) DC. or their hybrids; *C. pentagyna* Waldst. et Kit. ex Willd.; *C. azarolus* L.

Draft – Revision 1

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC (traditional use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Crataegus* spp., folium cum flore
Herbal preparation(s)	a) Comminuted herbal substance b) Powdered herbal substance c) Dry extract (DER 4-7:1), extraction solvent: methanol 70% (V/V) d) Dry extract (DER 4-7.1:1), extraction solvent: ethanol 45-70% (V/V) e) Liquid extract (DER 1:0.9-1.1), extraction solvent: ethanol 45% (V/V) f) Liquid extract (DER 1:2), extraction solvent: ethanol 45% (V/V) g) Liquid extract (DER 1:19.2-20), extraction solvent: sweet wine h) Expressed juice from the fresh leaves and flowers (DER 1:0.63-0.9) i) Expressed juice from the fresh leaves and flowers (DER 1:0.9-1.1) j) Tincture (DER 1:3.5-4.5), extraction solvent: ethanol 35% (V/V)

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	k) Dry extract (DER 4-5:1), extraction solvent: water l) Soft extract (DER 2.8-5.3:1), extraction solvent: ethanol 45% (m/m) m) Liquid extract of fresh leaves and flowers (1:1); ethanol 95% (V/V) n) Tincture (ratio herbal substance: extraction solvent 1:5); ethanol 60% (V/V)
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use. Powdered herbal substance in solid dosage forms for oral use. Herbal preparations in solid or liquid dosage forms for oral use.
Rapporteur(s)	J. Wiesner
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Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Crataegus* spp., folium cum flore. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

Whole or fragmented, dried flower-bearing branches of *Crataegus monogyna* Jacq. (Lindm.), *C. laevigata* (Poir.) DC. or their hybrids or, more rarely, *C. pentagyna* Waldst. et Kit. ex Willd. or *C. azarolus* L. These species may be mixed.
Content: minimum 0.2 per cent of total vitexin-2-o-rhamnosidede derivations, expressed as vitexin-2-O-rhamnoside ($C_{27}H_{30}O_{14}$; M_r 578.5) (dried drug) (European Pharmacopoeia 01/2021:1432).

- Herbal preparation(s)

European Pharmacopoeia "Hawthorn leaf and flower liquid extract": liquid extract produced from Hawthorn leaf and flower: minimum 0.4 per cent of total vitexin-2″-O-rhamnoside derivatives, expressed as vitexin-2″-O-rhamnoside. The extract is produced from the herbal drug by a suitable procedure using ethanol (30-70 per cent V/V) (European Pharmacopoeia 01/2021:1864).

European Pharmacopoeia "Hawthorn leaf and flower dry extract": dry extract produced from Hawthorn leaf and flower

- aqueous extracts: minimum 1.0 per cent of total vitexin-2″-O-rhamnoside derivatives, expressed as vitexin-2″-O-rhamnoside (dried extract)
- hydroalcoholic extracts: minimum 2.0 per cent of total vitexin-2″-O-rhamnoside derivatives, expressed as vitexin-2″-O-rhamnoside (dried extract).

The extract is produced from the herbal drug by a suitable procedure using either water or a hydroalcoholic solvent at least equivalent in strength to ethanol (45 per cent V/V) (European Pharmacopoeia 01/2021:1865).

- Constituents of the plant

Constituents of the leaves and flowers are: flavonoids (flavones and flavonoles) mainly in form of glycosides (e.g. vitexin, vitexin-2''-rhamnoside, isovitexin, hyperoside, quercetin), flavan compounds (e.g. (+)-catechin, (-)-epicatechin, oligo- and polymeric procyanidins), triterpenic acids (e.g. crataegolic acid, urolic acid, oleanic acid), amines (e.g. phenethylamine, acetylcoline, ethylamine), organic acids (e.g. caffeic acid, chlorogenic acid) and other constituents (e.g. purine derivatives, minerals) (Blaschek et al., 2011; Edwards et al., 2012; Chang et al., 2002; WHO, 2002).

1.2. Search and assessment methodology

For 1st revision

Scientific databases
Scientific data (e.g. non-clinical and clinical safety data, clinical efficacy data)

Scientific/Medical/Toxicological databases

Medline Complete; Base; Embase; Pubmed; Biomedical Reference Collection; DynaMed (May 2014-July 2023); key words "Crataegus ssp.", "Crataegus folium cum flore" and "hawthorn leaves and flowers"

Pharmacovigilance databases

data from EudraVigilance (01.01.2014-24.07.2023); key words were "Spontaneous, Other, Not available to sender (unknown), Report from studies, suspect interacting, from the European economic area (EEA)"

Regulatory practice

Old market overview in AR (i.e. check products fulfilling 30/15 years of TU or 10 years of WEU on the market)

New market overview (including pharmacovigilance actions taken in member states)

PSUSA

Feedback from experiences with the monograph during MRP/DCP procedures

Ph. Eur. monograph

Consistency (e.g. scientific decisions taken by HMPC)

Public statements or other decisions taken by HMPC

Consistency with other monographs within the therapeutic area

A call for data was performed by the EMA. The company Dr W. Schwabe, Karlsruhe, performed a literature search from 01.04.2014 – 03.03.2022. 427 references were found and checked for relevance and 28 references were provided to the BfArM.

1.3 Main changes introduced in the 1st revision

In 2016, when the HMPC monograph was established, the European Pharmacopoeia 2014 (European Pharmacopoeia 01/2010:1432) defined the herbal substance as "whole or cut, dried flower-bearing branches of *Crataegus monogyna* Jacq. (Lindm.), *Crataegus laevigata* (Poir.) DC. (syn. *Crataegus oxyacanthoides* Thuill.; *Crataegus oxyacantha* auct.) or their hybrids or, more rarely, other European *Crataegus* species including *Crataegus pentagyna* Waldst. et Kit. ex Willd., *Crataegus nigra* Waldst. et Kit. and *Crataegus azarolus* L. It contains minimum 1.5% of total flavonoids, expressed as hyperoside (dried drug)".

The European Pharmacopoeia was comprehensively updated. In the European Pharmacopoeia 11.0 (01/2021:1432) *Crataegus nigra* as parent plant was deleted, the content requirement was specified and an HPLC method was introduced for the content determination. The identity test B was reformulated and provided with an illustration.

Furthermore, the liquid extract described in the Ph. Eur. was changed from former "quantified extract" (European Pharmacopoeia 01/2008:1864) to "other extracts" (European Pharmacopoeia 01/2021:1864). The actual pharmacopoeia requires a minimal content of ingredients for quality reasons.

From the updated market overview and literature and EudaraVigilance research in review-1 procedure, the following changes result for the monograph:

(1) The posology is changed for the herbal preparations a), b), e).
(2) Indication 1 is added for preparation k).
(3) Three new herbal preparations are added to the monograph (preparations l, m, n).
(4) The undesirable effects gastrointestinal disorders (abdominal pain and nausea) and skin and subcutaneous tissue disorders (rash and pruritus) are added. The frequency is not known.
(5) The warning is added that the use of hawthorn extract may increase the risk of bleeding after surgery. The cause is unknown.

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	**Indication**	**Pharmaceutical form** Strength (where relevant) Posology Duration of use	**Regulatory Status** (date, Member State)
Comminuted herbal substance for tea preparation			
Comminuted herbal substance	THMP for support of the cardiovascular system in case of beginning of age related reduction of performance of the heart with symptoms of exhaustion during exercise	1 filter bag contains 1.7 g Crataegi folium cum flore adults: 3-4 x daily 1 cup of tea [max. DD dose 6.8 g]	1993; AT; TU
Comminuted herbal substance	THMP for support of the cardiovascular system in case of beginning of age related reduction of performance of the heart with symptoms of exhaustion during exercise	1 filter bag contains 1.5 g Crataegi folium cum flore adults: 3-4 x daily 1 cup of tea	1997; AT; TU
Comminuted herbal substance	Traditionally used to support cardiovascular function at first signs of reduced cardiac performance with symptoms such as exhaustion and fatigue during exercise.	Herbal tea, 1 tea bag contains 1.7 g hawthorn leaves and flowers adults: 3-4 times daily 1 cup of tea (1 tea bag)	2011; AT; TU
Comminuted herbal substance	Traditionally used to support cardiovascular function at first signs of reduced cardiac performance with symptoms such as exhaustion and fatigue during exercise.	Herbal tea, 1 tea bag contains 1.5 g hawthorn leaves and flowers adults: 3-4 times daily 1 cup of tea (1 tea bag)	2013; AT; TU
Comminuted herbal substance	An adjuvant in mild forms of hypertension, for heart blood flow improvement, for support of heart function, consultation with a doctor is needed before the first use.	Herbal tea for oral use 1 tea bag (1.5 g)/250 ml of boiling water 3 times daily	1996; CZ; TU
Comminuted herbal substance	Declining cardiac performance; sensation of pressure and anxiety in the region of the heart.	Herbal tea SD: 1.5 g DD: 4.5-6 g	1986, DE, Standard Marketing Authorisation
Comminuted herbal substance	Traditionally used in support of cardiovascular function.	Herbal tea, 1 tea bag contains 2 g hawthorn leaves and flowers	1976; DE; TU

Active substance	**Indication**	**Pharmaceutical form** Strength (where relevant) Posology Duration of use	**Regulatory Status** (date, Member State)
		adults: 2-3 times daily 1 cup of freshly brewed tea Duration of use is not limited.	
Comminuted herbal substance	Traditionally used in support of cardiovascular function	Herbal tea, 1 tea bag contains 1.44 g hawthorn leaves and flowers adults: 3-4 times daily one cup of freshly brewed herbal tea Duration of use is not limited.	1976; DE; TU
Comminuted herbal substance	Traditional herbal medicinal product used to relieve cardiovascular symptoms of nervous tension. The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.	Herbal tea, 1 g tea contains 1 g of hawthorn leaves and flowers (SD and DD unclear)	1995; LT; TU
Comminuted herbal substance	Traditional herbal medicinal products used in mild neurotic heart ailments such as the feeling of heart palpitations if any serious forms of heart disease have been ruled out and as a support of the work of the heart and circulatory system.	Comminuted herbal substance in sachets 2 g for herbal tea, infusion. Infuse one sachet 10-15 min. Drink 2-3 times daily ½ glass of the infusion	1990; PL; TU
Comminuted herbal substance	Supportive in the initial period of impaired heart efficiency, not requiring the use of other medications.	Comminuted herbal substance for herbal tea, decoction. 2 g of the herbal substance pour with 200 ml of boiling water, heat to boiling and boil 2 min., and strain. Drink fresh prepared decoction 2 times daily	2002; PL; TU
Comminuted herbal substance	Supportive in the initial period of impaired heart efficiency, not requiring the use of other medications	Comminuted herbal substance for herbal tea, decoction. 2 g of the herbal substance pour with a glass (200 ml) of cool water, heat to boiling and boil 2 min., and strain. Drink fresh prepared decoction 3 times daily.	2002; PL; TU
Comminuted herbal substance	Used in mild coronary insufficiency with symptoms of easy fatigue that does not	1 sachet [1.5 g] pour with 200 ml of water, heat nearly to boil but not to boil. Stay	2007; PL; TU

Active substance	**Indication**	**Pharmaceutical form** Strength (where relevant) Posology Duration of use	**Regulatory Status** (date, Member State)
	require the use of stronger drugs and a slight weakening of the heart muscle	under cover 10-15 min. Drink still warm infusion 3-4 times daily.	
Comminuted herbal substance	Traditional herbal medicinal product used to relieve symptoms of temporary nervous cardiac complaints (e.g. palpitations, perceived extra heart beat due to mild anxiety) after serious conditions have been excluded by a medical doctor.	Herbal tea 1.5 g adults: 1 bag (1.5 g) of the comminuted herbal substance in 150 ml of boiling water as a herbal infusion 3- 4 times daily Duration of use: 2 weeks	1998; SK; TU
Powdered herbal substance			
Crataegus spp., folium cum flore, powder	Declining cardiac performance corresponding to Functional Capacity Class I to II as defined by the New York Heart Association (NYHA). Sensation of pressure and anxiety in the region of the heart.	Capsule, hard, containing 270 mg hawthorn leaves and flowers adults: 3 times daily 1-2 capsules	1994; AT; TU
Crataegus monogyna Jacq. folium cum flore, powder	To reduce the nervousness of adults and adolescents, particularly in case of extra perception of heart beats, after any serious pathology has been excluded.	Hard capsule, 270 mg adults and adolescents: 2-6 capsule a day Maximum 8 capsules a day single dose: 270 mg daily dose: 540-1620 mg	1997; BE; WEU
Crataegus monogyna Jacq. and/or *Crataegus laevigata* D.C., folium cum flore, powder	For relief of mild symptoms of mental stress and to aid sleep	Hard capsule, 350 mg adults: 1 capsule 3 times daily (up to 5 capsules, if necessary) adolescents (12 years and older): 1 capsule at the evening meal and 1 capsule at bedtime	2019; BE; TU
Crataegus spp., folium cum flore powder	Traditionally used in support of cardiovascular function.	Coated tablet, containing 190 mg powder adults: 3 times daily 1 coated tablet In the case of complaints of unclear origin self-medication should be stopped after 2 weeks.	1976; DE; TU
Crataegus monogyna, C. laevigata, C. oxyacanthoides, powder	Traditional herbal medicinal product for relief of mild symptoms of nervous tension such as nervous palpitations, and to aid sleep, based exclusively on its traditional use.	Hard capsules, 350 mg adults: mild symptoms of nervous tension 1 capsule 3 times daily to aid sleep: 2 capsules 2 times daily	2010; EE; TU

Active substance	**Indication**	**Pharmaceutical form** Strength (where relevant) Posology Duration of use	**Regulatory Status** (date, Member State)
		Duration of use: 4 weeks	
Crataegus oxyacanthoides Thuill, powder [Assessor´s comment: *Crataegus* laevigata (Poir.) DC. = syn. *Crataegus* oxyacanthoides Thuill.; *Crataegus* oxyacantha auct.]	Traditional herbal medicinal product for relief of mild symptoms of nervous tension such as nervous palpitations, and to aid sleep, based exclusively on its traditional use	Hard capsules, 400 mg adults: 2 capsules 3 times daily Duration of use: 4 weeks	2013; EE; TU
Crataegus spp., folium cum flore, powder	Traditionally used in disorders of cardiac erethism in adults (healthy heart). Traditionally used in the symptomatic treatment of neurotonic conditions of adults and children, notably in cases of mild disorders of sleep.	Hard capsule, containing 350 mg powder 1 capsule 3 times daily (up to 5 capsules, if necessary)	1981; FR; TU
Crataegus spp., folium cum flore comminuted	Traditional herbal medicinal product for relief of mild symptoms of nervous tension such as nervous palpitations, after serious conditions have been excluded by a medical doctor. Traditional herbal medicinal product to aid sleep.	Hard capsule 2.4 g per day	1990; ES; TU
Dry extract (DER 4-7:1), extraction solvent: methanol 70% (V/V)			
Dry extract (4-7:1); extraction solvent: methanol 70% (V/V)	Declining cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA.	solid dosage forms for oral use adults and adolescents: SD: 80-300 mg DD: 240-900 mg	1976; DE; WEU
Dry extract (4.3-7.7:1); extraction solvent: methanol 70% (V/V)	Declining cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA.	Oral liquid, 100 ml containing 0.9 g extract adults and adolescents: 2 times daily 15 ml SD: 135 mg DD: 270 mg	1996; DE; WEU
Dry extract (DER 4-7.1:1), extraction solvent: ethanol 45-70% (V/V)			
Dry extract (4-7:1); extraction solvent: ethanol 45% (V/V)	THMP for support of the cardiovascular system in case of beginning of age related reduction of performance of the heart with symptoms of exhaustion during exercise	1 film-coated tablet contains 450 mg dry extract adults: 2 tablets per day. After 2 weeks, a doctor should be consulted.	2015; AT; TU
Dry extract (4-7:1); extraction	THMP for support of the cardiovascular system in case	1 Film-coated tablet contains 450 mg dry extract	2018; AT; TU

Active substance	**Indication**	**Pharmaceutical form** Strength (where relevant) Posology Duration of use	**Regulatory Status** (date, Member State)
solvent: ethanol 45% (V/V)	of beginning of age related reduction of performance of the heart with symptoms of exhaustion during exercise; in case of temporary nervous cardiac complaints such as palpitations	adults: 1-2 tablets per day. No limitation of the duration of use	
Dry extract (4-7:1); extraction solvent: ethanol 45% (V/V)	An adjuvant in mild forms of hypertension, for heart blood flow improvement, for support of heart function, consultation with a doctor is needed before the first use.	Coated tablet, containing 80 mg extract oral use, 1 tablet 3 times daily, if necessary 2 tablets 3 times daily	2001; EE; WEU
Dry extract (4-7:1); extraction solvent: ethanol 45% (V/V)	Declining cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA.	Oral liquid, 100 ml contain 20.2 g extract 2 times daily 1 ml (=2 x 202 mg extract)	1976; DE; WEU
Dry extract (4-7:1); extraction solvent: ethanol 45% (V/)V	Declining cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA. The medicinal product should only be used in elderly.	Oral liquid, 10 g liquid contain 2.5 g extract 3 times daily 30 drops (300 mg extract)	1976; DE; WEU
Dry extract (4-7:1); extraction solvent: ethanol 45% (V/V)	Declining cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA.	solid dosage forms for oral use adults and adolescents: SD: 80-350 mg, 2-3 times daily DD: 240-900 mg	1976; DE; WEU
Dry extract (4-7:1); extraction solvent: ethanol 45% (V/V)	Declining cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA.	Film-coated tablets adults and adolescents: SD: 450 mg DD: 900 mg	1976; DE; WEU
Dry extract (4-6.6:1); extraction solvent: ethanol 45% (m/m)	Declining cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA.	Film-coated tablets SD: 450 mg DD: 900 mg	1976; DE; WEU
Dry extract (4-6.6:1); extraction solvent: ethanol 45% (m/m)	Declining cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA.	Film-coated tablets SD: 80-160 mg DD: 240-480 mg	1976; DE; WEU
Dry extract (4-6.6:1); extraction solvent ethanol 45% (m/m)	Declining cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA.	film-coated tablet adults and adolescents: SD: 300 mg DD: 600-900 mg	1998; DE; WEU

Active substance	**Indication**	**Pharmaceutical form** Strength (where relevant) Posology Duration of use	**Regulatory Status** (date, Member State)
Dry extract (4-6.6:1), extraction solvent: ethanol 45% (m/m)	Traditionally used in support of cardiovascular function.	Solid dosage form for oral use adults: SD: 160-450 mg DD: 480-900 mg	2018; DE; TU
Dry extract (4-7.1:1); extraction solvent: ethanol 70% (V/V)	Traditionally used in support of cardiovascular function.	soft capsule adults: SD: 112.5-225 mg DD: 337.5-675 mg In the case of complaints of unclear origin self-medication should be stopped after 2 weeks.	1976; DE; TU
Dry extract (4-7:1); extraction solvent: ethanol 60%	Traditionally used in disorders of cardiac erethism in adults (healthy heart). Traditionally used in the symptomatic treatment of neurotonic conditions of adults and children, notably in cases of mild disorders of sleep.	Coated tablet, containing 100 mg extract cardiac erethism: 1-2 tablets 3 times daily sleep disorders: 2-3 tablets daily	2001; FR; TU
Dry extract (4-7:1); extraction solvent: ethanol 45% (V/V)	Treatment of heart failure of I-II functional class according NYHA classification.	Coated tablet, containing 80 mg extract adults: 1-2 coated tablets 3 times daily	2007; LT; WEU
Dry extract, (4-6.6:1); extraction solvent: ethanol 45% (V/V); corresponding to 13.88-16.13 mg OPC, estimated as epicatechin	Treatment of slight heart failure (II functional class according NYHA).	Film-coated tablet, containing 80 mg extract adults: 1-2 film-coated tablets 3 times daily. The use in children under 12 years of age is not recommended.	2008; LT; WEU
Dry extract (DER 4-5:1), extraction solvent: water			
Dry extract (4-5:1); extraction solvent: water	Traditionally used in disorders of cardiac erythrism in adults (healthy heart). Traditionally used in the symptomatic treatment of neurotonic conditions of adults and children, notably in cases of mild disorders of sleep.	Hard capsule, containing 250 mg extract 3-4 capsules daily	1986; FR; TU
Liquid extract (DER 1:0.9-1.1), extraction solvent: ethanol 45% (V/V)			
Liquid extract (1:1); extraction solvent: ethanol 45% (V/V)	THMP for support of the cardiovascular system in case of beginning of age related reduction of performance of	100 g (=100.2 ml) containing 24 g liquid extract adults: 2-3 x daily 0.75-1 ml of the drug product	2013; AT; TU

Active substance	**Indication**	**Pharmaceutical form** Strength (where relevant) Posology Duration of use	**Regulatory Status** (date, Member State)
	the heart with symptoms of exhaustion during exercise	[SD: 2-3x daily 0.18-0.24 g DD: 0.36-0.75 g liquid extract]	
Quantified liquid extract (1:1); extraction solvent: ethanol 45% (V/V)	Traditionally used to support cardiovascular function at first signs of reduced cardiac performance with symptoms such as exhaustion and fatigue during exercise.	Oral liquid, 100 g containing 24 g extract (1 ml=0.99 g; 1 ml corresponds to approximately 20 drops) adults: 2-3 times daily 15-20 drops	2013; AT; TU
Quantified liquid extract (1:0.9-1.1); extraction solvent: ethanol 45% (V/V)	Declining cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA.	Oral liquid, 10 g liquid (9.75 ml) contain 10 g extract adults and adolescents: 3 times daily 40 drops (1.25 g liquid)	1976; DE; WEU
Quantified liquid extract (1:1); extraction solvent ethanol 45% (V/V)	Traditionally used in support of cardiovascular function.	Oral liquid adults: SD: 0.5606 g DD: 1.6818-2.2424 g	1976; DE; TU
Quantified liquid extract (1:1); extraction solvent: ethanol 45% (V/V)	Traditionally used in support of cardiovascular function.	Oral liquid, 100 ml contain 59.8 g extract adults: 3-4 times daily 30 drops (1 ml=32 drops)	1976; DE; TU
Liquid extract (DER 1:2), extraction solvent: ethanol 45% (V/V)			
Quantified liquid extract (1:2); extraction solvent: ethanol 45% (V/V)	Declining cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA.	Oral liquid, 10 ml containing 10 ml (9.74 g) extract adults and adolescents: 3 times daily 40 drops (3 x 1.89 ml)	1976; DE; WEU
Liquid extract (DER 1:19.2-20), extraction solvent: sweet wine			
Liquid extract (1:19.2-20); extraction solvent: sweet wine [finished product contains 0.049% absinthe herba as flavouring]	Traditionally used for strengthening cardiovascular function.	Oral liquid, 20 ml contain 8.24 g extract adults: up to 2 times daily 20 ml In the case of complaints of unclear origin, self-medication should be stopped after 2 weeks.	1976-2021; DE; TU
Liquid extract from fresh leaves and flowers (DER 1:1), extraction solvent: ethanol 95% (V/V)			
Liquid extract of fresh leaves and flowers (1:1); ethanol 95% (V/V)	Traditional herbal medicinal product supporting the work of the heart and cardiovascular system, used for age-related ailments, after	Oral liquid 2.5 ml of product, dissolved in small amount of water, 4 times a day. Period of use 3 weeks.	1988; PL; national registration

Active substance	**Indication**	**Pharmaceutical form** Strength (where relevant) Posology Duration of use	**Regulatory Status** (date, Member State)
	the exclusion of serious heart diseases by the doctor.	Not advised for children and adolescents. Warnings: in the case of aggravation of symptoms in the period of 6 weeks of use of product, swealling of foods, weakness, shortness of breath or pain in the heart area, immediately consult the doctor.	
Expressed juice from the fresh leaves and flowers (DER 1:0.63-0.9)			
Pressed fresh juice (1:0.63-0.9)	Traditionally used in support of cardiovascular function.	Oral liquid, 100 ml contain 70 ml pressed juice adults: 3 times daily 10 ml liquid (corresponds to 7 ml pressed fresh juice) Duration of use is not limited.	1976; DE; TU
Expressed juice from the fresh leaves and flowers (DER 1:0.9-1.1)			
Pressed fresh juice (1:0.9-1.1)	Traditionally used in support of cardiovascular function	Oral liquid, 100 ml contain 82.7 g adults: 3 times daily 50 drops (3 ml) In the case of complaints of unclear origin self-medication should be stopped after 2 weeks.	1976; DE; TU
Pressed juice from fresh Crataegi folium cum flore (1:0.9-1.1)	Traditionally used in support of cardiovascular function	Liquid dosage form for oral use adults: SD: 2.5 ml DD: 7.5 ml	1976-2017; DE; TU
Tincture (DER 1:3.5-4.5), extraction solvent: ethanol 35% (V/V)			
Tincture (1:3.5-4.5); extraction solvent: ethanol 35% (V/V)	Traditionally used in support of cardiovascular function.	Tincture, 100 ml contain 100 ml tincture adults: 3 times daily 59 drops (1 g= 35 drops) In the case of complaints of unclear origin self-medication should be stopped after 2 weeks.	1976; DE; TU
Tincture (ratio herbal substance: extraction solvent 1:5), extraction solvent: ethanol 68% (V/V)			
Crataegi folium cum flore tinctura (1:5);	Neurogenic disturbances of heart activity after mental and physical exertion in healthy	200 mg/g oral drops, solution adolescents and adults:	2003; BG; WEU

Active substance	**Indication**	**Pharmaceutical form** Strength (where relevant) Posology Duration of use	**Regulatory Status** (date, Member State)
extraction solvent: ethanol 68% (V/V)	heart.	15-20 drops orally 3 times daily Maximum application duration 6 weeks.	
Tincture (ratio herbal substance: extraction solvent 1:5); ethanol 60% (V/V)			
Tincture (1:5); ethanol 60% (V/V)	Product traditionally used in states of easy fatigue, in the initial period of impaired heart efficiency, not requiring the use of other drugs, as a support for the work of the heart and circulatory system.	in adults: 1 teaspoon (5 ml) dissolve in a glass (200 ml) of water and drink during a day in 4-5 doses.	1990; PL; national registration
Spissum extract (5-6.5:1), extraction solvent: ethanol 70% (V/V)			
Crataegus folium cum flore extr. spissum (5-6.5:1); extraction solvent: ethanol 70% (V/V)	Supportive treatment of the initial period of impaired cardiac efficiency, corresponding to the I–II NYHA stages, not requiring the use of other drugs, without symptoms of circulatory stasis and weakening of the heart muscle in the elderly.	Coated tablets containing 124.8 mg of the extract adults: one tablet, 2-3 daily Not advised in adolescents.	2002; PL; TU
Soft extract (2.8-5.3:1), extraction solvent: ethanol 45% (m/m)			
Crataegi folium cum flore soft extract (2.8-5.3:1); extraction solvent: ethanol 45% (m/m)	Traditionally used in support of cardiovascular function.	Liquid dosage form for oral use adults: SD: 188-250 mg DD: 564-750 mg	1990; DE; TU

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

Information on relevant combination medicinal products marketed in the EU/EEA

Combination products containing the herbal substance are on the market in some EU Member States. The main combination substances are *Valeriana officinalis*, radix; *Passiflora incarnata*, herba; *Viscum album*, herba; *Mentha* x *piperita*, folium; *Melissa officinalis*, folium; *Hypericum perforatum*, herba; *Convallaria majalis*, herba; *Matricaria recutita*, flos; *Salix* spp., cortex, minerals and/or vitamin E.

This monograph refers only to monopreparations.

Information on other products marketed in the EU/EEA (where relevant)

According Blaschek et al. (2021), different species and parts of the hawthorn plant and different combinations thereof are medicinally used worldwide and are included in pharmacopoeias. Behind Crataegi folium cum flore, two further categories of drugs of the plant are considered relevant:

Crateagi flos and Crataegi fructus. Medicinal products on the market containing such preparations or combinations thereof have not been included in table 1.

2.1.2. Information on products on the market outside the EU/EEA

Not applicable.

2.2. Information on documented medicinal use and historical data from literature

Crataegus is mentioned in phytotherapeutic literature since ancient times. In the European cultural area it was mentioned for the first time in the 1st century AD by Pedacios Dioscorides.

Since that time, hawthorn seems to have been an integral part of European folk medicine. However, it is not always clearly described which parts of the plant were used. In the Middle Ages and modern times, it appears again and again in various herbal books, but only unspecific beneficial effects were attributed to it. The areas of application described include the treatment of colic, kidney stones, cough, nervous complaints such as anxiety, insomnia and dizziness that are not due to heart disease, as well as use for increased blood pressure or as a heart-strengthening agent. In the second half of the 19th century, the Irish physician Green introduced hawthorn extract into homeopathy and used it to treat various heart diseases. In later publications on homeopathic use, it was stated that hawthorn is ineffective in advanced heart disease and should be used in cases of incipient myocardial weakness and current infectious diseases, while in non-homeopathic pharmacopoeias and herbal textbooks of the 19th and early 20th centuries Hawthorn is often not mentioned. It seems that hawthorn was only included in the official European pharmaceutical catalogue in the middle of the last century, then with reference to its effect on the heart (Schulz, 1919; Ripperger, 1937; Madaus, 1938; Kaul, 1998; Czygan, 2005).

Crataegi folium cum flore is included in many monographs and publications related to efficacy and safety, such as Wichtl (1984, 2009), Kommission E (1994); WHO (2002), ESCOP (2003), Grünwald et al. (2007), Blaschek et al. (2021).

Table 2: Overview of historical data

Herbal preparation	**Documented use / Traditional use**	**Strength (where relevant) Posology Duration of use**	**Reference**
Native, hydroalcoholic extract (ethanol 45% (V/V) or methanol 70% (V/V) (DER 4-7:1) with defined flavonoid or procyanidin content	Declining cardiac performance corresponding to functional capacity class II as defined by the NYHA	Daily dose: 160-900 mg in 2 or 3 single doses The route of administration is for oral use in solid or liquid forms. The duration of use: 6 weeks minimum.	Kommission E (1994)
Crataegus leaves and flowers	a) beginning of congestive heart failure, particularly coronary insufficiency b) mild forms of myocardial insufficiency (stage I-II of NYHA) c) age-related heart failure,	Herbal tea: 1-1.5 g fine cut herbal substance with boiling water, strain after 15 minutes, apply 3-4 times daily, for several weeks	Wichtl (1984)

Herbal preparation	Documented use / Traditional use	Strength (where relevant) Posology Duration of use	Reference
	that do not yet need cardiac glycoside treatment d) sensation of pressure and anxiety in the region of the heart e) mild forms of bradycardiac arrhythmias Before use, it should be ensured that the symptoms do not have an organic cause (in which case other medication is required), which is why hawthorn should not be recommended uncritically for self-medication.		
a) hydroalcoholic preparations b) herbal substance	For a): declining cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA For b): declining cardiac performance and sensation of pressure and anxiety in the region of the heart	For a): see Kommission E monograph b) Herbal tea: see standard Marketing Authorisation DE	Blaschek et al. (2011) [quoting Kommission E and Standard Marketing Authorisation DE]
a) Powdered whole drug b) Herbal tea c) Aqueous extract and aqueous alcoholic extracts prepared with ethyl alcohol of a low strength (ethanol <30% (V/V)) d) Aqueous alcoholic extracts prepared with ethyl alcohol of a strength (ethanol >30% (V/V)) e) Tincture	a) Traditionally used in disorders of cardiac erythrism in adults (healthy heart). b) Traditionally used for the symptomatic treatment of neurotonic conditions of adults and children, notably in cases of mild disorders of sleep.	Duration of use: 1 month for adults and children over 6 years of age (for indication b)	Les Cahier de l'Agence N°3 (1998)
Crataegus folium cum flore a) Preparations based on hydroalcoholic extracts (DER 4-7:1), with defined content of oligometric	a) declined cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA b) Nervous heart complaints. Support of cardiac and circulatory functions	a) 160-900 mg daily b) 1-1.5 g comminuted drug as an infusion, 3-4 times daily. Powdered drug: 2-5 g daily Tincture (Codex Fr. IX): 20 drops 2-3x daily;	ESCOP (2003) [quoting: Loew, 1994; Eichstädt et al., 1989; Weikl & Noh, 1992; Weikl et al., 1996; Leuchtgens, 1993; Schmidt et al., 1994; Förster et al., 1994; Tauchert et al.,

Herbal preparation	Documented use / Traditional use	Strength (where relevant) Posology Duration of use	Reference
procyanidins or flavonoids b) Herbal teas and other preparations		Fluid extract (Codex Fr IX): 0.5-2 g daily, 60-120 drops 3x daily; Dry extract (Belg Farm V): 50-300 mg 3x daily; Glycerol macerate: 50 drops 3x daily	1994; Schmidt et al., 1998; Tauchert et al., 1999; Wichtl, 1997; van Hellemont, 1988; Pfister-Hotz, 1997]
Crataegus folium cum flore a) Dried extract, extraction solvent ethanol 45% (V/V) or methanol 70% (V/V) (DER 4-7:1) with defined flavonoid or procyanidin content b) Comminuted herbal substance	treatment of chronic congestive heart failure stage II, as defined by the NYHA support of cardiac and circulatory functions	a): Daily dose: 160-900 mg dried extract in 2 or 3 single doses b) Herbal tea: 1.0-1.5 g comminuted crude drug as an infusion 3-4 times daily Therapeutic effects may require 4-6 weeks of continuous therapy.	WHO (2002) [quoting: Eichstädt et al., 1989; Förster et al., 1994; Leuchtgens, 1993; Loew, 1994; Schmidt et al., 1994; Tauchert et al., 1994; Weikl & Noh, 1992; Weikl et al., 1996; Wichtl, 1997; Blumenthal et al., 1998]
a) Crataegus folium cum flore Preparations based on hydroalcoholic extracts (DER 4-7:1), with defined content of oligometric procyanidins or flavonoids b) Other preparations	To support cardiovascular function at first signs of reduced cardiac performance with symptoms such as exhaustion and fatigue during exercise. The therapy should be overviewed by a physician and incorporated in a therapy-concept Indication acc. Kommission E	DD: 360 mg of ethanolic or water extract (DEV 4-7:1) The dose can be extended to 720 mg It is recommended to use the quantified extracts of the marked	Schilcher et al. (2007)
Crataegus folium cum flore extracts ethanol 45% (V/V) or methanol 70% (V/V) standardized on procyanidin or flavonoids	Indication according Commission E: decrease in cardiac output (stage II NYHA)	Single dose: 1 g of drug Daily Dosage: The average daily dose is 5 g of drug or 160 to 900 mg extract administered in divided doses, 3 times daily The duration of treatment is minimum 6 weeks	Grünwald et al. (2007)

2.3. Overall conclusions on medicinal use

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology/Strength	Period of medicinal use
a) Comminuted herbal substance	Indication 1: Traditional herbal medicinal product used to relieve symptoms of temporary nervous cardiac complaints (e.g. palpitations, perceived extra heart beat due to mild anxiety) after serious conditions have been excluded by a medical doctor.	Herbal tea: 1-2 g of the comminuted herbal substance in 150-250 ml of boiling water as a herbal infusion up to 4 times daily (max. 6.8 g)	since 1976
b) Powdered herbal substance	Indication 1: see a) Indication 2: Traditional herbal medicinal product for relief of mild symptoms of mental stress and to aid sleep	SD: 190-800 mg, 3 times daily DD: 570-2400 mg	since 1976
c) Dry extract (4-7:1); extraction solvent: methanol 70% (V/V)	Indication 1: see a)	SD: 80-300 mg, 3 times daily DD: 240-900 mg	since 1976
d) Dry extract (4-7.1:1); extraction solvent: ethanol 45-70% (V/V)	Indication 1: see a)	SD: 80-450 mg, 2-3 times daily DD: 240-900 mg	since 1976
e) Liquid extract (1:0.9-1.1), extraction solvent: ethanol 45% (V/V)	Indication 1: see a)	SD: 0.18-1.25 g, 2-3 times daily DD: 0.36-3.75 g	since 1976
f) Liquid extract (1:2), extraction solvent: ethanol 45% (V/V)	Indication 1: see a)	SD: 1.84 g, 3 times daily DD: 5.52 g	since 1976
g) Liquid extract (1:19.2-20); extraction solvent: sweet wine	Indication 1: see a)	SD: 8.24 g, 2 times daily DD: 16.5 g	since 1976
h) Expressed juice from the fresh leaves and flowers (1:0.63-0.9)	Indication 1: see a)	SD: 7 ml, 3 times daily DD: 21 ml	since 1976
i) Expressed juice from the fresh leaves and flowers (1:0.9-1.1)	Indication 1: see a)	SD: 2.5 ml, 3 times daily DD: 7.5 ml	since 1976
j) Tincture (1:3.5-4.5); extraction	Indication 1: see a)	SD: 1.68 g, 3 times daily DD: 5.1 g	since 1976

Herbal preparation Pharmaceutical form	Indication	Posology/Strength	Period of medicinal use
solvent: ethanol 35% (V/V)			
k) Dry extract (4-5:1); extraction solvent: water	Indication 1: see a) Indication 2: see b)	SD: 250 mg, 3-4 times daily DD: 750–1000 mg	since 1986
l) Soft extract (2.8-5.3:1); extraction solvent: ethanol 45% (m/m)	Indication 1: see a)	SD: 188-250 mg, 3 times daily DD: 564-750 mg	since 1976
m) Liquid extract of fresh leaves and flowers (1:1); ethanol 95% (V/V)	Indication 1: see a)	SD: 2.5 ml, 4 times daily DD: 10 ml	since 1988
n) Tincture (ratio herbal substance: extraction solvent 1:5); ethanol 60% (V/V)	Indication 1: see a)	SD: 1-1.25 ml, 3-4 times daily DD: 5 ml	since 1990

The majority of licenced WEU-marketed products in Europa are used over 30 years in the context of treatment of chronic congestive heart failure stage II, as defined by the NYHA/ for treatment of declining cardiac performance the support of cardiovascular function, by incorporating the therapy in a treating concept by a physician.
The clinical evidence about the effects of hawthorn in people with heart failure, does not fulfil the criteria for well-established-use set down by the EMA, in the procedure for establishing HMPC monographs.

Registered TU-preparations are used 30 years in self-medication in context to support cardiovascular function (at first signs of reduced cardiac performance with symptoms such as exhaustion and fatigue during exercise), after serious conditions have been excluded by a medical doctor or after excluding the need of other cardiac medication or in addition to the recommended conventional treatments for heart failure.

In 2016, an indication in the context of heart failure was considered not appropriate for self-medication. Therefore, the acceptable indication based on traditional usage was formulated with: Traditional herbal medicinal product used to relieve symptoms of temporary nervous cardiac complaints (e.g. palpitations, perceived extra heart beat due to mild anxiety), after serious conditions have been excluded by a medical doctor.

3. Non-Clinical Data

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

The pharmacology of *Crataegus* spp. was analysed intensive *in vivo* and *in vitro* from different extracts of one *Crataegus* plant part (only flowers, leaves or fruits), extracts of different mixtures thereof (flowers with leaves; flowers with leaves and fruits) and for substances thereof (flavonoids, procyanidins) since the 1940s.

The overview of pharmacology given below is not exhaustive. It provides information on pharmacology of different *Crataegus* extracts or substances thereof, focussed on *in vivo* studies and oral administration.

The review report of Martinelli *et al*. (2021) deals with the pharmaceutical, functional and therapeutic properties of *C. monogyna*. They listed preclinical in vitro and in vivo studies of different plant extracts, mixtures thereof or compounds thereof and the type of action. The review includes studies with preparations of different plant parts.

There are a many reviews and books available discussing older studies (e.g. Kaul, 1998; Chang *et al.*, 2005b; Koch & Malek, 2011; Pittler et al., 2008; Vogel et al., 2005; Frishman et al., 2005; Momekov & Benbassat, 2013; Garcia-Oliveira *et al*., 2020; Cui *et al*., 2024).
Zorniak et al. (2017) published an up-to date review of experimental and clinical experiences with a distinct extract (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)).

3.1.1. Primary pharmacodynamics

In the review articles, several effects are discussed: inotropic effects; vasodilator, vasoprotective, antihypertensive and antiischemic effects; antihyperlipidemic effects and anti-arrhythmic effects. This is based on *in vitro* and *in vivo* results with defined as well as not further defined preparations and various concentrations and posologies.

It is not clear if theses described effects can be seen as supportive for the traditional use to relieve symptoms of temporary nervous cardiac complaints (e.g. palpitations, perceived extra heart beat due to mild anxiety).

Effect on cardiac frequency/Negative bathmotropic action

Older studies (Occhiuto *et al*., 1986; Krzeminski & Chatterjee, 1993; Al Makdessi *et al*., 1999) reported that after oral administration of Crataegus preparations (not further specified) a reduced heart rate in normotensive rats was seen, as well as protective effects on induced arrhythmia as well as hypotensive crises and ventricular tachycardia.

Zorniak et al. (2019) reported a dose- and time-dependent cardioprotective effect of an extract (dry extract from hawthorn leaves and flowers (DER 4-6.6:1); ethanol 45% (m/m)). Analyzed data coming from a model of reperfusion-induced arrhythmias in rats. The mortality rate was significantly lower in experimental groups where WS-1442 was administered once in dose 100 mg/kg (p.o.). as well as in twice scheme (100 mg/kg + 50 mg/kg, 100 mg/kg + 100 mg/kg) in comparison to control group and 25 mg/kg group. The dose-dependent cardioprotective effect was also observed regarding severe ventricular arrhythmias. The VF occurrence and duration were significantly lower in groups treated with higher doses of WS-1442 (50 mg/kg, 100 mg/kg, 100 + 50 mg/kg 100 + 100 mg/kg) compared to control group and the group treated with the lowest dose of extract (25 mg/kg).

Effects on blood pressure

Older studies (Occhiuto et al., 1986; Fehri et al., 1991) showed that preparations of *Crataegus* leaves and flowers (not further specified) reduced blood pressure in normo- and hypertensive rats.

Veveris et al. (2004) reported oral administration of an extract from hawthorn leaves and flowers (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) for 7 days before ligation of the left coronary artery dose-dependently suppressed the decrease of the pressure rate product (100 mg/kg/day). Treatment also attenuated the elevation of the ST-segment in the ECG, diminished the incidence of ventricular fibrillations (control: 67%; 100 mg/kg: 27%) and reduced the mortality rate (control: 47%; 100 mg/kg: 9%). Furthermore, the area of myocardial infarction within the ischemic zone was

significantly smaller in treated rats (10 mg/kg: 64.3±5.1%; 100 mg/kg: 42.8±4.1%) when compared with controls (78.4±2.6%). Protective effects within rat models of ischemic reperfusion after myocardial infarction have been described, which lead to a reduced spreading of the infarction area.

Koch & Spörl-Aich (2006) investigated the effect of Crataegus dry extract (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) on the development of cardiac hypertrophy (CH) in rat models of hypertension. Hypertension and subsequent CH was induced in rats by aortic bending (AB) or administration of deoxycorticosterone (DOCA) in combination with NaCl/KCl-substituted drinking water, respectively. Animals were treated orally for a period of 14 (AB) or 28 days (DOCA-salt) with vehicle (0.2% agar suspension) or the dry extract from hawthorn leaves and flowers (DER 4-6.6:1); ethanol 45% (m/m), 100 and 300 mg/kg/day. On the final day, animals were anaesthetised and blood pressure (BP) and heart rate were measured following cannulation of the left carotic artery. Treatment with ethanolic Crataegus dry extract dose-dependently lowered the pathologically increased BP but had no effect on the BP in normal control animals. In parallel with the reduction of the BP development of cardiac hypertrophy was inhibited.

Table 4: Overview of the main non-clinical data/conclusions

Herbal preparation tested	**Posology** Strength; Dosage; Route of administration	**Experimental model** in vivo/in vitro	**Reference** Year of publication	**Main non-clinical conclusions**
Extract from hawthorn leaves and flowers (DER 4-6.6:1) ethanol 45% (m/m)	100 mg/kg bw (p.o.)	in vivo rat	Zorniak et al. (2019)	reduction of the average prevalence of malignant arrhythmias
Extract from hawthorn leaves and flowers (DER 4-6.6:1) ethanol 45% (m/m)	10 + 100 mg/kg bw/day (p.o.)	in vivo rat	Veveris et al. (2004)	decrease in blood pressure and incidence of ventricular fibrillations and reduction of mortality rate
Extract from hawthorn leaves and flowers (DER 4-6.6:1) ethanol 45% (m/m)	100 and 300 mg/kg bw/day (p.o.)	in vivo rat	Koch & Spörl-Aich (2006)	decrease in blood pressure

3.1.2. Secondary pharmacodynamics

Antiplatelet activity

Shatoor et al. (2012) investigated the possible antiplatelet effect of aqueous *Crataegus aronia* (syn. *Crataegus azarolus*) extract (not further specified). In an animal experiment over 7 days with 42 male albino wistar rats it was claimed that the extract had effective antiplatelet activity at doses of 100, 200, and 500 mg/kg as indicated by the increase in bleeding time, decrease in platelet aggregation and reduction in serum levels of thromboxane B2 (also with 1000 mg/kg). There was no change in the bleeding time at doses of 1000 and 2000 mg/kg and thromboxane B2-levels were increased with 2000 mg/kg.

Oedema preventing effect/Endothelial activity

Idris-Khodja et al. (2012) investigated whether a hawthorn extract (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) prevents the development of aging-related endothelial dysfunction in rats, and, if so, to determine the underlying mechanisms. Wistar rats received a control diet or a diet containing 100 or 300 mg extract/kg/day from week 25 until week 65. Vascular reactivity was assessed in mesenteric artery rings using organ chambers, oxidative stress by dihydroethidine staining and cyclooxygenase-1 (COX-1) and -2 (COX-2) expression by immunohistochemistry. Acetylcholine-induced endothelium-dependent relaxations in mesenteric artery rings were blunted in 65-week-old rats compared to 16-week-old rats. This effect was associated with a marked reduction of the endothelium-derived hyperpolarising factor (EDHF) component whereas the nitric oxide (NO) component was not affected. Aging was also associated with the induction of endothelium-dependent contractile responses to acetylcholine. Both aging-related impairment of endothelium-dependent relaxations and the induction of endothelium-dependent contractile responses were improved by the hawthorn treatment and by COX inhibitors. An excessive vascular oxidative stress and an upregulation of COX-1 and COX-2 were observed in the mesenteric artery of old rats compared to young rats, and these effects were improved by the hawthorn treatment.

Effects on blood lipids

Kanyonga et al. (2011) investigated the effects of the extract of *Crataegus oxyacantha* (DER 3:1; methanol) in rats by monitoring blood homeostasis and body weight. Animals were treated daily with an oral dose of 100 mg/kg for 12 weeks. Changes in hepatic enzymes levels were not observed in treated rats. The serum cholesterol, triglycerides and glucose levels and the count of leukocytes and platelets decreased significantly by 15.5, 22, 16.5, 35 and 32%, compared to control values, respectively; while haematocrit and haemoglobin levels increased significantly by 6.4 and 17.4%, respectively. In parallel, significant slowdown of the body weight evolution was observed in treated animals comparatively to the animal control group.

Preparations of the monograph: dry extract from hawthorn leaves and flowers (DER 4-6.6:1) ethanol 45% (m/m)

Xia et al. (2017) analysed the effect on restoration of perivascular adipose tissue function in diet-induced obese mice. Male C57BL/6J mice were fed a high-fat diet (HFD) for 22 weeks to induce obesity. During the last 4 weeks, animals in the HFD +extract group were treated with dry extract from hawthorn leaves and flowers (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) in a dose of 150 mg/kg/day, suspended in 0.2% agar) via gavage. The daily dose of the extract for mice was extrapolated from the standard human dose (900 mg/day) (Holubarsch et al., 2008) using the body surface area normalization method of dose conversion (Reagan-Shaw et al., 2008). *In vivo* treatment of obese mice with the extract had no effect on body weight or epididymal fat mass, but completely restored the vascular function of PVAT-containing aorta. Feeding a HFD led to a reduced phosphorylation and an enhanced acetylation of PVAT eNOS, both effects were reversed by extract treatment.

3.1.3. Safety pharmacology

Several review articles discussed older studies with effects on cardiovascular system. This is based on *in vitro* and *in vivo* results with defined or something not further defined preparations and various concentrations and posologies.

Bleske et al. (2007) determined the influence of hawthorn extract (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) on rats with aortic constriction after 6 months of treatment (0.13, 13 and 130 mg/kg). The mortality rate following 6 months of aortic constriction was comparable in the treatment and control group (40% in the control group compared to 41%, 60%, and 53% for the low

dose, medium dose, and high dose groups, respectively). Aortic constriction produced a similar increase in the left ventricle/body weight ratio for all groups. Furthermore, hawthorn extract had no effect on the immunomodulatory markers measured in this study (IL-1, IL-2, IL-6, IL-10 and leptin).

Hwang *et al.* (2009) determined the effects of dry hawthorn extract (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) 1.3, 13, or 130 mg/kg bw on left ventricular remodelling and function in pressure overload-induced heart failure model. Rats and their hearts were weighed, and echocardiographic measurements were performed at baseline and at 2, 3, 4, and 5 months after aortic constriction. Protein expression for markers of fibrosis and for atrial natriuretic factor was also measured. Aortic constriction increased the left ventricular body weight ratio by 53% in vehicle-treated rats; hawthorn treatment did not significantly affected the aortic constriction-induced increase in this ratio. Left ventricular volumes and dimensions at systole and diastole significantly increased 5 months after aortic constriction compared with baseline in rats given vehicle (>20% increase) but not in those given hawthorn 130 mg/kg (<10% increase).

Fürst et al. (2010) aimed to assess the potential of a hawthorn dry extract (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) to prevent balloon catheter-induced intimal hyperplasia and to elucidate the underlying mechanisms. Rats received the extract (300 mg/kg) 2 days prior and 14 days after catherisation. The extract significantly reduced neointima formation after balloon catheter dilatation of the carotid artery.

Jayachandran et al. (2010) evaluated the efficacy and mechanism of a dry extract of *Crataegus oxyacantha* (not further specified) in preventing ischemia-reperfusion injury in an in vivo rat model of acute myocardial infarction. It was induced by a 30 minutes regional ischemia followed by 72 hours of reperfusion. The sample (100 mg/kg) was administered 12 hours after the surgical procedure and then at 24 hours intervals for 3 days. Animals treated with the sample showed a significant decrease in creatine kinase activity and infarct size. The authors suggested that the reduced apoptotic incidence is mediated by the regulation of signalling pathways comprising the serine-threonine kinase and hypoxia-inducible factor 1 (HIF-1).

Halver et al. (2019) reported that a quantified Crataegus dry extract (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) stimulated cardiomyogenesis from murine and human embryonic stem cells (0.25 mg/ml). Mechanistically, this effect was found to be induced by promoting differentiation of cardiovascular progenitor cell populations but not by proliferation. The authors concluded, however, the in vivo relevance of this pharmacological activity of Crataegus spp. remains to be investigated.

A 60% methanol extract of the flowers (not further specified) at a dose of 800 mg/kg has been found to increase hexobarbital-induced sleeping times, and to decrease the spontaneous motility and exploratory behavior in female mice (Momekov & Benbassat, 2013).

The effects of a leaves and flowers extract from *Crataegus monogyna* (DER 4–7:1; extraction solvent ethanol 45% (V/V)) on cardiac and haematological parameters were evaluated in Sprague Dawley rats. Male rats were randomly assigned into four groups. Group 1 served as control while groups 2-4 served as the experimental groups and were administered the extract at doses of 100, 200, and 500 mg/kg. All the doses were given orally once/day and the treatment was continued for three weeks. Hawthorn treatment resulted in a significant increase in the cardiac antithrombin III among hawthorn treated group compared to the control (4.18 (3, 24); P<0.0001). On the other hand, hawthorn treatment decreased significantly the liver factor-X level (0.1341 (3, 22); P<0.0001), while no significant changes were seen in soluble-platelet endothelial cell adhesion molecule-1 (P=0.0599). The authors concluded that the hawthorn extract possesses blood-thinning properties (Rababa'h et al., 2020).

3.1.4. Pharmacodynamic interactions

Dasgupta et al. (2010) investigated potential interference of hawthorn in serum digoxin measurements using immunoassays as well as pharmacodynamic interaction between hawthorn and digoxin. The effects of hawthorn extract (not further specified) on serum digoxin measurements were investigated using Digoxin III (a polyclonal-based digoxin assay) and the Tina-Quant digoxin assay (a monoclonal antibody-based assay), using 2 different brands of Crataegus liquid extract. One extract contained a mixture of leaves, flowers and berries (brand 1) and the other was made from the berries only (brand 2). Both extracts contained 12% ethanol and were used in final volumes of 5, 10, 20, or 50 µl/ml of serum. The used serum-digoxin was prepared from serum specimens from patients receiving digoxin (no further details). Hawthorn preparations interfered only with the less specific polyclonal-based Digoxin III immunoassay but had no effect on the monoclonal antibody-based Tina-Quant assay.
In a second set of experiment the pharmacodynamic interaction between hawthorn and digoxin on isolated adult rat cardiomyocyte system was studied, measuring calcium transients by real-time fluorescence spectrophotometry. The final digoxin concentration used was 1 ng/ml (within the therapeutic range) and that of hawthorn was 0.06 µl/ml. Both hawthorn extracts increased intracellular calcium levels, but the lack of additive response with digoxin suggests both may bind to the same site of Na^+/K^+-ATPase.

3.1.5. Conclusions

Results from relevant experimental studies are limited and not required.
Effects on reducing the heart frequency and blood pressure have been reported by several *in vivo* studies, while studies on sedative effects are missing.

Further effects on parameters of the cardio-vascular system were reported, but results were sometimes contradictory. Furthermore, they were not regarded as connected to the indication "relieve temporary nervous cardiac complaints" and "mild symptoms of mental stress and to aid sleep".

Data on safety pharmacology might point to influences on coagulation parameters and should be discussed together with clinical studies/reports.

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Apart from the initial animal studies with radiolabelled procyanidins only few pharmacokinetic studies have been carried out and therefore, the metabolism and elimination of the hawthorn-derived ingredients remain largely unknown.

Ammon & Händel (1981) reported of experiments from Laparra *et al.* (1977) with ^{14}C-labelled oligomeric proanthocyanidins (OPC). After oral administration of these substances, they were resorbed and the maximum radioactivity was measured after 45 minutes in the blood of the mouse. Half-life was 5 hours.

Hecker-Niediek (1983) determined the absorption and distribution of the radioactivity of ^{14}C-labelled catechins, a trimeric procyanidine, an OPC total fraction, and higher OPC after intravenous and oral administration in mice. Total radioactivity was measured in blood and different organs without determination of individual metabolites. Already one hour after oral administration absorption of radioactivity could be detected for all labelled substances. Within 1-7 hours after administration, the absorption rate for the OPC total fraction was about 31% in the organs, and those for trimetric procyanidins ranged from 16 to 40%.

Liang et al. (2007) assessed the oral bioavailability of vitexin rhamnoside using a combination of chromatographic and mass spectroscopic techniques. Bioavailability was only 3.57% indicating either poor absorption or extensive first-pass metabolism.

Ma et al. (2010) observed a low oral bioavailability for vitexin-4''-O-glucoside (VOG) and vitexin-2''-O-rhamnoside (VOR). The levels of VOG and VOR in plasma, tissues (heart, liver, spleen, lung, kidney and brain), bile, urine and faeces were measured by HPLC-UV. The results showed that VOG and VOR have the similar pharmacokinetics. Both of them were absorbed quickly into plasma with maximal plasma concentrations of VOG and VOR being reached within 0.75 h. The mean elimination half-life of VOG and VOR were 2.53 hours and 2.32 hours, respectively. High levels of tissue distribution of VOG and VOR were observed in liver and kidney. No VOG and VOR were detected in brain tissue. There was no long-term accumulation of VOG and VOR in rat tissues examined. The total recovery of the dose in 24 hours was 64.91% (0.70% in urine; 64.21% in faeces) for VOG and 89.01% (0.72% in urine; 88.29% in faeces) for VOR. The cumulative VOG and VOR excreted in bile represented 0.58% and 13.38% of the doses, respectively. VOG and VOR in hawthorn leaf flavonoids were not efficiently absorbed in the rodent gastrointestinal tract.

Chang et al. (2005a) investigated the pharmacokinetics of (-)-epicatechin, chlorogenic acid, hyperoside, and isoquercitrin following administration of an extract formulation (ethanolic extract of *Crataegus pinnatifida* fruits was extracted with ether, extracted with ethylacetate, concentrated and filtered), which contained the active compounds or equivalent doses of individual pure compound in male Sprague-Dawley rats. The hawthorn extract or pure compounds were administered both orally and intravenously. After the i.v. injection of hawthorn extract, higher plasma drug concentration, larger $AUC_{0-\infty}$, longer terminal elimination half-life, smaller Vd, lower Cl_{tot}, and higher urinary excretion of each compound were obtained when compared to that after the pure compound.
Following the oral administration of either hawthorn extract or pure compound, only epicatechin was absorbed, and their pharmacokinetics were generally not significantly different between extract and pure substance. The authors discussed that the differences in the pharmacokinetics following i.v. but not oral administration may be attributable to the existence of other co-occurring components in the hawthorn extract (which may be present in the body after i.v. but not after oral administration).

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

3.3.1. Single dose toxicity

Schlegelmilch & Heywood (1994) demonstrated in a single dose toxicity study, in a "limit-test" dosing of 3000 mg/kg dry extract from hawthorn leaves and flowers (DER 4-6.6:1, extraction solvent ethanol 45% (m/m)) in 1% carboxymethylcellulose by gavage in five male and five female rats (Sprague-Dawley, CD strain) and five male and five female mice (NMRI). The oral administration of 3 g/kg were tolerated without causing clinical signs or death. By the intraperitoneal route, sedation, piloerection, dyspnea, and tremor were recorded in both the mouse and the rat; here an LD_{50} value of 1.17 g/kg bw was calculated in the rat and 750 mg/kg in the mice.

For a alcoholic extract (not further specified) of *Crataegus* flowers, leaves and fruits, the LD_{50} p.o. is 18.5 ml /kg bw in mice and 33.8 ml/kg bw in rat (Ammon & Händel, 1981).

3.3.2. Repeat dose toxicity

Schlegelmilch & Heywood (1994) conducted the following study using the rat as a rodent species and the beagle as a non-rodent species with a dry extract from hawthorn leaves and flowers (DER 4-6.6:1, extraction solvent ethanol 45% (m/m)).
Rats: The extract was given to groups of 20 male and 20 female Sprague-Dawley rats (CD strain) at doses of 30, 90, or 300 mg/kg/day, respectively in 1% methylcellulose daily. A fourth group receiving the vehicle only served as controls. The compound was given by gavage for 26 weeks.
Dogs: Thirty-two beagles, equally divided with respect to sex, were assigned to four groups, three of which received dry extract at doses of 30, 90, or 300 mg/kg/day, respectively. Crataegus dry extract was administered orally in gelatine capsules. A fourth group received empty gelatine capsules and acted as controls. Clinical signs and food consumption were monitored daily throughout the study. Body weight was determined at weekly intervals. Ophthalmoscopy was performed before dosing and during week 26. Haematological and biochemical examinations before dosing, as well as after 13 and 26 weeks of dosing.
After administration of *Crataegus* dry extract to rats and beagles for 26 weeks, no abnormalities in clinical, chemical, haematological, gross morphological, and histological findings were observed.

3.3.3. Genotoxicity

Ames test
Schlegelmilch & Heywood (1994) conducted a study with *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100. The dry extract from leaves and flowers (DER 4-6.6:1;exraction solvent ethanol 45% (m/m)) was tested at up to 1500 µg/plate, this having been chosen after a preliminary toxicity test, limited by solubility in dimethyl sulfoxide (DMSO). Each study was conducted with and without metabolic activation (S9 - liver homogenate from Aroclor-1254 pre-treated male rats) and the experiment was performed twice on separate dates. The results showed that the Ames test was negative.

Mouse lymphoma assay
In the mouse lymphoma TK locus assay four independent tests were carried out, two in the presence and two in the absence of exogenous metabolic activation (S9). The dry extract from leaves and flowers (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) was tested up to a concentration of 525 µg/ml without S9 and 625 µg/ml with S9. The results led to the conclusion, that the dry extract has no mutagenic potential in this mammalian gene mutation assay in vitro (Schlegelmilch & Heywood, 1994).

Chromosomes aberration test
In a cytogenetic analysis in cultured human lymphocytes the dry extract from leaves and flowers (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) was tested up to a concentration of 150 µg/ml in the absence and presence of S9 mix. The extract showed no evidence of clastogenic activity in this cytogenetic test system in vitro (Schlegelmilch & Heywood, 1994).

Micronucleus assay
In the mouse micronucleus assay CD-1 mice received a high single oral dose of 5000 mg/kg by intra-gastric gavage of the dry extract from leaves and flowers (DER 4-6.6:1, extraction solvent ethanol 45% (m/m)). Bone marrow smears were obtained at three sampling times, 24, 48, and 72 hours after dosing. At each sampling time, five males and five females per dose were killed. There was no evidence of mutagenic potential or bone marrow toxicity (Schlegelmilch & Heywood, 1994).

3.3.4. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

Yao et al. (2008) determined the safety of a non-further specified preparation of leaves of *Crataegus monogyna*. The extract was constituted in 45% ethanol, which contained 500 mg/ml hawthorn, standardized to 12.9 mg/ml of oligomeric proanthocyanidins) to the developing foetus (in vivo) and to whole embryo cultures (ex vivo).
For the in vivo study the preparation was given to pregnant rats daily by gavage using 2.8 g hawthorn extract/kg (standardised to 51.6 mg OPC). Administration was carried out on either gestation days (GD) 1-8 or GD 8-15. On GD 20, foetuses were weighed and examined for signs of external, internal or skeletal malformations.
In the second experiment rat foetuses were explanted on GD 10.5 and cultured (1 embryo/ml culture medium) with hawthorn extract for 26 hours (3 mg/ml medium).
Maternal weight at GD 8 of hawthorn and ethanol dams treated from GD 1 to 8 was significantly less than historical ethanol control groups. However by GD 20, there was no significant difference, nor was there a difference in maternal weight gain or maternal weight gain corrected for the weight of the conceptuses. No further influence on dams could be observed. While, the mean weight of the foetuses treated with hawthorn GD 8–15 was larger than that of ethanol-treated foetuses from the same dosing period the effect was not statistically significant. The only effect seen in foetal observation was a significant effect of treatment on mean foetal weight (reduced) on dams exposed from GD 8 to 15 after controlling for litter size.
The embryos of the ex vivo experiment were morphologically normal after 26 hours treatment. The mean crown-rump length of embryos grown in the presence of hawthorn was significantly larger than that of the ethanol control group embryos.

3.3.6. Local tolerance

No data available.

3.3.7. Other studies

No data available.

3.3.8. Conclusions

Adequate toxicological data regarding the herbal substances/herbal preparations of the monograph are not available.

Crataegus dry extract (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) produced no lethality up to 3 g *Crataegus* extract per kg body weight after oral administration in rats and mice.
The oral administration of this ethanolic dry extract up to 300 mg/kg body weight per day for 26 weeks induced no toxic symptoms in rats and dogs.

Tests on genotoxicity are only available for one dry extract (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)). It was negative in the AMES assay (TA 1535, TA 1537, TA 1538, TA 98, and TA 100), the mouse lymphoma assay and the cytogenetic analysis assay and also turned out to be negative in the in vivo micronucleus test (*in vivo*).

Adequate tests on reproductive toxicity have not been performed. Tests on carcinogenicity have not

been performed.

3.4. Overall conclusions on non-clinical data

Results from relevant experimental studies to support the proposed indications are very limited. The reported pharmacological effects are not considered contradictory to the traditional uses.

Specific data on pharmacokinetics and interactions are not available.

Non-clinical information on the safety of *Crataegus* folium cum flore regarding all the preparations is scarce. Available studies for one *Crataegus* dry extract (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) produced no toxic symptoms in rats and mice after oral administration in doses up to 300 mg/kg body weight per day for 26 weeks.
The full testing on genotoxicity according to ICH guideline S2 (R1) (EMA/CHMP/ICH/126642/2008) have been performed with this extract. It was negative in the in vitro and in vivo test in the concentrations and doses tested.

As there is no information on reproductive and developmental toxicity for all preparations, the use during pregnancy and lactation cannot be recommended.

4. Clinical Data

4.1. Clinical pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Increase of myocardial contractility (positive inotropic action)

Ex vivo

Brixius et al. (1998) investigated the effect of Crataegus dry extract (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) on force of contraction in human failing myocardium. To study the inotropic effect of the extract independently of heart frequency, vegetative nervous system, pre-load and afterload, the concentration dependent effect of the extract was investigated on isometric force of contraction in isolated, electrically stimulated (1 Hz) left ventricular muscle strips of human failing myocardium. The human myocardium was obtained from eight patients, aged 51.7±4.3 years, who had to undergo heart transplantation due to terminal heart failure (congestive cardiomyopathy, NYHA IV).
The extract significantly increased force of contraction [basal: 1.8±0.2 mN, extract (50 µg/ml): 2.4±0.1 mN (130%)].
Furthermore, the effect of the extract on frequency-dependent force-generation in human failing myocardium was investigated. To this end, changes of the force of contraction were measured by increasing the stimulation frequency from 0.5 Hz (30 beats/minute) to 3.0 Hz (180 beats/minute) step by step in the presence of the extract or solvent. In the presence of the extract, the force of contraction was enhanced compared to the control (0.5 vs. 2.5 Hz: delta mN: control +0.1±0.1 mN, extract (50 µg/ml) +0.9±0.3 mN).

Schmidt-Schweda et al. (2000) analysed the effect of a Crataegus dry extract (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) and different sub-extracts for the relative shortening of enzymatically isolated human myocytes. They were isolated from the right atrium (21 patients, 30 cells, EF 52±3%, aortocoronary bypass operation) and left ventricular myocardium from terminally insufficient, explanted hearts (5 patients, 6 cells, EF 21±2%). The hearts were electrically stimulated (0.2 Hz; 32°C; 1.25 mM extracellular calcium).

The extract enhanced dose-dependently the relative shortening of myocytes in the atrium myocardium (from 4.4±0.7% to 10.2±1.5% at 10^{-7} mg/ml, $p<0.05$ from 10^{-9} on) as well as in the ventricular myocardium (from 3.7±1% to 7.7±2.2% at 10^{-7} mg/ml, $p<0.05$ from 10^{-8} on).
At a dose of 10^{-8} mg/ml the sub-extract crsblr80242C (content OPC 57.8%, flavonoids <0.04%) enhanced the shortening about 100±29% ($p<0.05$), crsblr80242A (OPC 12.5%, flavonoids 14.9%) about 83±24% ($p<0.05$) and crsblr80242B (OPC 10.5%, flavonoids 4.1%) about 16±12% (n.s.). For comparison, on the ventricular myocardium the effect of isoprenaline (from 3.2±0.3% to 7.9±1.4% at 10^{-7} M) and increasing extracellular calcium concentration up to 15 mM (from 3.7±0.4% to 13.5±1.3%) was investigated. The authors concluded the analysed substance has a positive inotrope effect and flavonoids may enhance the effect.

Schwinger et al. (2000) examined the mode of inotropic action of a *Crataegus* dry extract (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) in human myocardium from patients with congestive heart failure (left ventricular myocardium from explanted heart; NYHA IV, n=8) as well as in non-failing controls (right auricular trabeculae from patients with coronary heart disease, n=8). The extract effectively displaced specifically bound 3H-ouabain but did not influence the activity of adenylate cyclase [control, + Gpp(NH)p (10-4 µM) 3500 pmol cyclic adenosine monophosphate (cAMP)/20 minutes). In isolated left ventricular papillary muscle strips, the extract significantly increased the force of contraction [basal, 1.8±0.2 mN; Crataegus extract (50 µg/ml), 2.4±0.1 mN (130%)] and improved the frequency-dependent force generation (0.5 vs. 2.5 Hz: control, +0.1±0.01 mN; extract, +0.9±0.3 mN) even in failing human myocardium. In fura-2-loaded muscle strips (right atrial trabeculae), the extract increased both the Ca^{2+}-transient and force generation. These effects also were observed in the lipophilic ethyl acetate-soluble fraction, an enriched in flavone derivatives.

Vasorelaxation

Ex vivo

Brixius et al. (2006) investigated the influence of a Crataegus dry extract (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) on the relaxation of human mammalian artery (coronary bypass patients). Experiments were performed in the presence and absence (mechanical disruption) of endothelium. In addition, three fractions of the extract were investigated: fraction A: lipophilic, containing flavonoids and oligomeric procyanidins (OPC), fraction B: hydrophilic, containing flavonoids and low molecular weight OPC, fraction C: hydrophilic, essentially flavonoid-free and rich in high molecular weight OPC. The extract induced a concentration-dependent vasodilation in isolated vessel rings that had been precontracted by 10 µM phenylephrine (concentration for half-maximal relaxation (IC_{50}: 19.3±3.4 µg/ml (n=6)). The maximal vasorelaxation induced after application of 100 mg extract was 79.2±5.8% of the papaverine (0.1 mM)-induced vasodilation. If the experiments were performed in the presence of L-nitroarginine methylester (10 µM, eNOS-inhibition) or after mechanical disruption of the endothelium, no vasorelaxation was observed in the presence of the extract. The vasorelaxant properties of the extract were mediated by fraction C. The extract induced an NO-liberation from human coronary artery endothelial cells as measured by diaminofluorescein and induced eNOS-activation due to a phosphorylation at serine 1177. No eNOS-translocation or phosphorylation at serine 114 or threonine 495 was observed after application of the extract.

Change in artery flow mediated dilatation, brachial artery diameter and blood pressure

Asher et al. (2012) investigated brachial artery flow mediated dilatation (FMD) in response to placebo or hawthorn extract (DER appr. 4:1, extraction solvent ethanol / water, standardised to 50 mg oligomeric procyanidin per 250 mg extract; not further specified) in a four-period cross-over design in 21 prehypertensive or mildly hypertensive adults. Randomly sequenced doses of hawthorn extract

(1000 mg, 1500 mg, and 2500 mg) and placebo were assigned to each participant. Doses were taken twice daily for 3.5 days followed by FMD and a 4-day washout before proceeding to the next dosing period. There was no evidence of a dose-response effect for the main outcome (FMD percent) or any of the secondary outcomes (absolute change in brachial artery diameter and blood pressure).

QT Interval

Trexler et al. (2018) evaluated the electrocardiographic effects of hawthorn in healthy adult volunteers. In this double-blind cross-over trial randomized 20 healthy adult volunteers received either a single oral 160 mg dose of hawthorn (reported to be standardized to 18.75% oligomeric procyanidins, not further specified) or matching placebo. Triplicate 12-lead electrocardiograms were taken before treatment and at 1-, 2-, 4-, and 6-hr post-dose. Following at least a 7-day washout period, participants were crossed over to the opposing treatment arm and had the measurements repeated. The primary endpoint was the change in corrected (Fridericia) QT intervals (QTcI) at 4 and 6 hr. Maximum post-dose QTcI and changes in PR and QRS intervals were measured. No significant differences in 4- or 6-hr QTcI were seen between hawthorn and placebo. Maximum post-dose QTcI in the hawthorn and placebo groups were similar (346±35 vs 346±40 ms). A single dose of oral 160 mg hawthorn had no effect on electrocardiographic parameters in healthy volunteers.

Assessor's comment:
This study had limitations that should be considered. Effects of potassium channel blockade would manifest as prolongation of the QTc-I on a surface electrocardiogram. In healthy subjects, a single dose of oral hawthorn had no effect on QT intervals. It is not clear if the single dose of hawthorn would have achieved the peak plasma levels necessary to exert a pharmacologic effect.

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Data on resorption and distribution, metabolism and elimination of substances of are not available.

4.2. Clinical efficacy

Definition of heart failure

Diagnosis and treatment of acute and chronic heart failure (ESC, 2021) is defined for each phenotype of heart failure (HF) stand-alone in term of its diagnosis and management. Heart failure is not a single pathological diagnosis, but a clinical syndrome consisting of cardinal symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise.

Main types are heart failure with preserved, mildly reduced, and reduced ejection fraction (HFpEF; HFmrEF; HFrEF) and right ventricular (RV) dysfunction. Other common terminology used in heart failure are chronic heart failure (CHF) and acute heart failure (AHF). CHF describes those who have had an established diagnosis of HF or who have a more gradual onset of symptoms. Terminology related to the symptomatic severity of heart failure is the New York Heart Association (NYHA) functional classification (Class I-IV).

There are three major goals of treatment for patients with HFrEF: (i) reduction in mortality, (ii) prevention of recurrent hospitalizations due to worsening HF, and (iii) improvement in clinical status, functional capacity, and QOL (ESC, 2021). The therapy depends on the indication type of HF and is categorized according evidence-based classes. Examples of used medication are ACE-I, ARNI,

Betablocker, MRA, Dapaglifozin/Empagliflozin, Loop diuretics for fluid retention, Valsartan, etc. *Crataegus* preparations are not listed in the guideline.

The guideline CPMP/EWP/235/95 Rev. 1 (2016) summarises the recommendation to clinical investigation of medicinal products for the treatment of cardiac failure (e.g.). The preferred primary endpoints in such studies are clinical symptoms, cardiovascular morbidity and all-cause-mortality. Secondary endpoints might be quality of life, exercise capacity, physical signs, haemodynamic changes, renal function and neurohumoral variables. To evaluate the effect on mortality at least one long-term controlled study of a minimum duration of 12 months will be required, while to demonstrate efficacy in relation to symptomatic benefit or cardiovascular morbidity a minimum duration of 6 month is required.

No studies are available with validated questionnaire as the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ; scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations).

4.2.1. Dose response studies

Tauchert (2002) investigated whether long-term therapy with Crataegus dry extract is efficient as add-on therapy to pre-existing diuretic treatment in patients with heart failure with a more advanced stage of the disease (NYHA class III), whether effects are dose dependent, and whether the treatment is safe and well tolerated. 209 patients were randomised to treatment with 1800 mg of Crataegus extract, 900 mg Crataegus extract, or with placebo for 16 weeks. The used extract was a dry extract with a DER of 4-6.6:1 (extraction solvent: ethanol 45% (m/m)) standardised to 18.75% OPC. In the 1800 mg extract group maximal tolerated workload during bicycle exercise showed a statistically significant increase in comparison with the other groups, placebo and 900 mg Crataegus extract. Typical heart failure symptoms as rated by the patients were reduced to a greater extent by the extract than by placebo. This difference was significant for both doses of Crataegus extract. Both efficacy and tolerability were rated best for the 1800 mg extract group by patients and investigators alike. The incidence of adverse events was lowest in the 1800 mg extract group, particularly with respect to dizziness and vertigo.

Assessor´s comment:
This clinical study is performed in another user group as the licenced preparations, which are used only in patients with congestive heart failure (NYHA I-II) not in severe cases of congestive heart failure (NYHA II-III). The clinical study is performed as ad-on therapy, another therapy schema as the licenced preparations.
The tested primary endpoint was the maximal tolerated workload during bicycle exercise doesn't meet the criteria for a primary endpoint. In the tested objective, the high dose of 1800 mg had a better effect compared to 900 mg. For the purpose of regulatory approval of the therapeutic use of drugs in chronic CF, primary endpoints should be clinical symptoms, cardiovascular morbidity and all-cause mortality.
The most important objectives in the treatment of heart failure are improvement in symptoms, cardiovascular morbidity and mortality. Typical heart failure symptoms were significantly reduced to a greater extent by both doses of the extract than by placebo. Nevertheless, the duration of the study of 16 weeks is too short. Cardiovascular morbidity and mortality was not analysed.

4.2.2. Clinical studies (case studies and clinical trials)

4.2.2.1. Placebo controlled studies

Placebo controlled clinical studies are available for two extracts: dry extract (DER 4-6.6:1) extraction solvent ethanol 45% (m/m)) and dry extract (DER 4-7:1, extraction solvent methanol 70% (V/V)).

I. Ethanolic dry extract from hawthorn leaves and flowers (DER 4-6.6:1, extraction solvent ethanol 45% (m/m))

Holubarsch et al. (2008) investigated the efficacy and safety of the *Crataegus* dry extract in a randomised, double-blind placebo-controlled and multicentre clinical study (SPICE trial) as an add-on treatment in adults suffering from congestive heart failure (NYHA II-III) with impaired left ventricular ejection fraction (LVEF ≤ 35%). In this study 2681 patients were included and randomised to additional treatment with *Crataegus* dry extract (daily dose 900 mg) or placebo for 24 months.
The primary endpoint was the number of days between baseline and the first cardiac event (death of cardiac cause such as sudden cardiac death, death due to progressive heart failure, fatal myocardial infarction as well as non-fatal myocardial infarction, hospitalisation due to progression of heart failure). In the subgroup with LVEF ≥ 25%, the extract significantly reduced sudden cardiac death (39.7% at month 24, p=0.025), whereas the trend for the combined endpoint did not reach statistical significance.
Most patients in this study were already treated with three or more concomitant drugs according to current treatment guidelines (especially ACE-inhibitors, AT-II-antagonists, beta-blockers, diuretics, spironolactone, and digitalis) and may not have gained an additional benefit from Crataegus extract taken on top of optimal pharmacological therapy due to a severely reduced overall health status.
The extract was safe to use in patients receiving optimal medication for heart failure. Adverse events were comparable in both groups concerning the number as well as the kind of events. There was no hint for an interaction between *Crataegus* extract and the given cardiac concomitant medication.

Cicero et al. (2020) commented the study Holubarsch et al. (2008). While it was shown that there was an insignificant trend towards cardiac mortality reduction with the extract (11% at month 24), in the subgroup with LVEF ≥25%, the extract reduced sudden cardiac death by 41% at month 24. The authors concluded that current data suggest that the extract can potentially reduce the incidence of sudden cardiac death, at least in patients with less compromised LV function.

Assessor´s comment:
This clinical study Holubarsch et al. (2008) is performed in another user group as the licenced preparations. Licenced preparations are used only in patients with congestive heart failure (NYHA I-II) not in severe cases of congestive heart failure (NYHA II-III) with impaired left ventricular ejection fraction (LVEF ≤ 35%). The clinical study is performed as ad-on therapy, another therapy schema as the licenced preparations.
For the purpose of regulatory approval of the therapeutic use of drugs in chronic CF, primary endpoints should be clinical symptoms, cardiovascular morbidity and all-cause mortality. The tested primary endpoint was the number of days between baseline and the first cardiac event, what doesn't meet the criteria. The results showed no significant differences between the groups, what means that the guideline conform treatment cannot be exceeded by the herbal.
The information on mortality is of the greatest interest in studies with CF. Cardiac mortality was significantly reduced after 6 (p=0.009) and 18 months (p=0.046).
The results showed that hawthorn had no adverse effects on the prognosis of patients with chronic heart failure as ad on therapy.

Zick *et al*. (2009) performed a randomised, double-blind, placebo-controlled trial (HERB CHF trial) in 120 ambulatory patients aged ≥18 years with NYHA class II-III chronic heart failure. All patients received standard medical therapy, defined as ACE-inhibitors or AT-receptor antagonists, beta-blockers and diuretics, as tolerated, and were randomised to receive additionally either the *Crataegus* dry extract 450 mg twice daily or placebo for 6 months. The primary outcome was change in 6 minutes' walk distance at 6 months. There were no significant differences between groups in the change in 6 minutes' walk distance (p=0.61), or on secondary outcomes like quality of life measures, functional capacity, neurohormones, oxidative stress, or inflammation. For the LVEF a significant difference (p=0.04) in favour of *Crataegus* extract was observed. There were significantly more adverse events reported in the hawthorn group (p=0.02), although most were non-cardiac. This trial had not been powered to investigate an effect on hospitalisation or mortality.

Assessor´s comment:
This clinical study is performed in another user group as the licenced preparations. Licenced preparations are used only in patients with congestive heart failure (NYHA I-II) not in severe cases of congestive heart failure (NYHA II-III). The clinical study is performed as ad-on therapy, another therapy schema as the licenced preparations.
For the purpose of regulatory approval of the therapeutic use of drugs in chronic CF, primary endpoints should be clinical symptoms, cardiovascular morbidity and all-cause mortality. The tested primary endpoint was the change in 6 minutes' walk distance at 6 months, which does not meet the criteria. The results showed no significant differences between the groups, what means that the guideline conform treatment cannot be exceeded by the herbal.
The most important objectives in the treatment of chronic heart failure are improvement in symptoms, cardiovascular morbidity and mortality, objectives not analysed in this study. The duration of only 6 month was too short.

Zapfe jun (2001) investigated the clinical efficacy and safety of *Crataegus* dry extract in a randomised, placebo-controlled, double-blind study in 40 female and male outpatients suffering from congestive heart failure NYHA II. Following a wash-out period of up to seven days, the patients were randomised to be treated for 12 weeks with either the extract (3 x 80 mg per day) or placebo. The primary outcome variable was exercise tolerance determined by bicycle exercise testing. As a secondary outcome variable, the difference of the double product was calculated. On average, the exercise tolerance increased by 66.3 watt x minute (10.8%) in the *Crataegus* extract group while in the placebo group a reduction of 105.3 watt x minute (−16.9%) was measured. This difference between the groups was borderline statistically significant (p=0.06). During the three months therapy the difference of the double product decreased by 14.4 mmHg/s (−26.8%) in the extract group and by 1.3 mmHg/s (−2.7%) in the placebo group, respectively. Recording of laboratory parameters and adverse events showed that *Crataegus* extract was safe and well tolerated.

Assessor's comment:
The most important objectives in the treatment of chronic heart failure are improvement in symptoms, cardiovascular morbidity and mortality, objectives not analysed in this experimental study. The duration of only 3 month was too short and he number of patients is too small for efficacy and safety conclusions.

Weikl *et al.* (1996) treated 136 patients with NYHA II heart failure in a multicentre, randomised, placebo-controlled, and double-blind study with Crataegus dry extract versus placebo for 8 weeks. The daily dose was 2 x 80 mg of *Crataegus* extract. The treatment phase was preceded by a 2-week placebo run-in phase. The primary target parameter was the change in the difference of the pressure-heart rate product (systolic blood pressure x heart rate/100) (50 watt load versus rest) at the end of the study. The data of 129 patients (63 patients of the active treatment group, 66 patients of the

placebo treated group) were used for biometric evaluation of the primary outcome variable. The group treated with *Crataegus* extract showed a decrease (−5.6 = mean difference between end and start of therapy) of the pressure-heart rate product (systolic blood pressure x heart rate/100), whereas the placebo treated group showed an increase (+4.2). The difference between the two therapy groups was statistically significant ($p<0.05$).
The positive result for the objective efficacy parameter was confirmed by a statistically obvious superiority of Crataegus in the patient´s own assessment of improvement in the main symptoms (reduced performance, shortness of breath, ankle oedema etc.). In addition, active treatment led, in comparison with placebo, to a considerably better quality of life for the patient, in particular with respect to mental wellbeing.

Assessor´s comment:
The tested primary endpoint the change in the difference of the pressure-heart rate product at the end of the study, doesn't meet the criteria for a primary endpoint. Typical heart failure symptoms were significantly reduced to a greater extent by the extract than by placebo. The duration of the study of 8 weeks is to short. Cardiovascular morbidity and mortality was not analysed.

Leuchtgens (1993) investigated in a randomised, placebo-controlled and double-blind study *Crataegus* dry extract in patients with heart failure according to NYHA II. Thirty patients were treated with hawthorn extract (2 x 80 mg per day) or placebo for 8 weeks. Target parameters were the changes of the pressure-heart rate product under standardised exercise on a bicycle ergometer and improvement of subjective complaints (B-L-scores) obtained with the subjective complaints list according to von Zerssen, which records the extent in subjective restriction of wellbeing using 48 items. After 8 weeks of treatment the hawthorn group showed a statistically significant improvement over placebo in terms of changes in pressure-heart rate product (systolic blood pressure x heart rate/100; at a load of 50 W) and the symptom score. The pressure-heart rate product decreased by about 23% in patients treated with hawthorn extract compared to a small decrease of about 8% in patients treated with placebo ($p<0.05$). In the hawthorn group the symptom score decreased significantly by 16.5 points (from 38 to 21.5) compared with a decrease of 4 points (from 31 to 27) in the placebo group ($p<0.05$).

Assessor's comment:
The tested primary endpoint the change in the difference of the pressure-heart rate product doesn't meet the criteria for a primary endpoint. Typical heart failure symptoms were significantly reduced largely by the extract than by placebo. The duration of the study of 8 weeks is too short for a chronic disease. Cardiovascular morbidity and mortality was not analysed.

II. Methanolic dry extract from hawthorn leaves and flowers (DER 4-7:1, methanol 70% (V/V))

Schmidt et al. (1994) investigated the efficacy of the dry extract at a dosage of 3 x 200 mg per day in a randomised, placebo-controlled and double-blind clinical trial. Seventy-eight male and female patients aged from 45-73 with NYHA stage II heart failure received hawthorn extract or placebo for 8 weeks. The confirmatory parameter for assessing efficacy was bicycle ergometry exercise tolerance. While tolerance under the hawthorn preparation improved by a mean of +28 watts at the end of treatment, it remained virtually unchanged under placebo (+5 watts). This difference was statistically significant ($p<0.001$). The score for clinical symptoms also improved significantly.

Assessor´s comment:
The tested primary endpoint doesn't meet the criteria for a primary endpoint. Typical heart failure symptoms were significantly reduced largely by the extract than by placebo. The duration of the study of 8 weeks is too short for a chronic disease. Cardiovascular morbidity and mortality was not analysed.

Förster *et al.* (1994) analysed in a placebo-controlled, randomised and double-blind study with 72 patients aged from 31-79 the efficacy of *Crataegus* for moderately reduced left ventricular ejection fraction. Patients were treated either with *Crataegus* dry extract at a dosage of 3 x 300 mg per day or placebo. The patients had clinical and ergospirometric examinations at study start and after 8 weeks of oral therapy. The confirmatory parameters were defined as the oxygen uptake as well as the tolerance period until the patients reached the anaerobic threshold and when exercise was discontinued. In the verum group the mean time until the anaerobic threshold was reached was 30 seconds; that in the placebo group only 2 seconds. A significant improvement of the oxygen uptake was observed by 75% of patients in the verum group and 42% of patients in the placebo group.

Assessor´s comment:
The tested primary endpoint doesn't meet the criteria for a primary endpoint. Typical heart failure symptoms were significantly reduced largely by the extract than by placebo. The duration of the study of 8 weeks is too short for a chronic disease. Cardiovascular morbidity and mortality was not analysed.

Bödigheimer & Chase (1994) examined the effectiveness of a dry extract at a dosage of 3 x 100 mg per day over a 4-week period. In a randomised, double-blind, placebo-controlled, multicentre trial 85 patients with heart failure (NYHA II) were enrolled. The confirmatory parameter was bicycle ergometry exercise tolerance. In addition, the typical symptoms as well as tolerability and final global assessment by the investigators and patients were evaluated. Exercise tolerance, pressure-heart rate product and clinical symptomatology all showed a trend toward, but no statistically significant, superiority of verum over placebo. Exercise tolerance increased by 13 W in the verum group compared with an increase of 3 W in the placebo group (p=0.143).

Assessor´s comment:
The tested primary endpoint doesn't meet the criteria for a primary endpoint. Typical heart failure symptoms were significantly reduced largely by the extract than by placebo. The duration of the study of 4 weeks is too short for a chronic disease. Cardiovascular morbidity and mortality was not analysed.

III. Combination products

O'Conolly et al. (1986) tested in a placebo-controlled, double-blind, randomised and cross-over study the efficacy of a product containing 60 mg of a combination of 54 mg dry extract of Crataegus fruits and 6 mg dry extract Crataegus flowers and leaves dry extract (DER 4-6.6:1, extraction solvent ethanol 45% (m/m)) versus placebo. Thirty-six multimorbid patients (62-84 years) suffering from chronic congestive heart failure according to NYHA I-II received 3 x 60 mg/day treatment or placebo for 6 weeks. Primary efficacy parameter was the pressure-heart rate product. Secondary efficacy parameters were heart rate, systolic and diastolic arterial blood pressures and psychological assessment ratings (BPRS and NOISE). The pressure-heart rate product (systolic blood pressure x heart rate/100) significantly decreased under the treatment at resting conditions ($p<0.05$), after exercise conditions at 25 W ($p<0.00001$) and 50 W x 2 minutes ($p<0.00001$) and after 2 minutes of recovery ($p<0.00001$), blood pressure values decreased as a sign of decreased afterload and the heart rate slowing. A significant decrease in the number of prematurely terminated exercise sessions in the hawthorn group was attributed to an increased tolerance to loading. This improvement of the hemodynamic parameters in the active substance group was associated with an improvement in the patients' wellbeing, including psychological parameters (BPRS and NOISE).

O'Conolly *et al.* (1987) examined in a placebo-controlled, double-blind, randomised, cross-over study with 36 multimorbid patients (61-82 years) with heart failure (NYHA I-II) the effectiveness of a product containing 60 mg of a combination of 54 mg dry extract of Crataegus fruits and 6 mg dry extract Crataegus flowers and leaves dry extract (DER 4-6.6:1, extraction solvent ethanol 45%

(m/m)). Hawthorn was administered 3 x 60 mg per day over a period of 6 weeks. Primary target parameter was the pressure-heart rate product. Secondary target parameters were heart rate, systolic and diastolic arterial blood pressures and psychological assessment ratings (Brief Psychiatric Rating Scale [BPRS] and Nurses Observation Scale for Inpatient Evaluation [NOSIE]). Under administration of the active substance, pressure-heart rate product (systolic blood pressure x heart rate/100) decreased on average significantly below that obtained with placebo under resting conditions (−2% vs. +3%) and after exercise at 25 W (−11% vs. +3%) and 50 W x 2 minutes (−11% vs. ±0%). In the active treatment group the mean values for heart rate, systolic and diastolic arterial blood pressures were significantly below those obtained with placebo. This improvement of the hemodynamic parameters after administration of the active substance could also be objectivised after the 2-minute recovery phase. In addition to this, the results from the test series involving the psychological assessment ratings BPRS and NOSIE, a significantly superior mental stabilisation of the patients after administration of the active substance was confirmed. Improvement of the NOSIE was shown in 93% of patients treated with hawthorn extract. In the following placebo period the NOSIE worsened in 68% of patients. The BPRS improved in 93% of patients in the active treatment group. In the following placebo period the BPRS worsened in 73% of patients.

4.2.2.2 Reference-controlled studies

Tauchert et al. (1994) compared the effectiveness of a dry extract (DER 4-7:1; extraction solvent methanol 70% (V/V)) with the ACE inhibitor captopril in a multicentre, double-blind study with 132 NYHA stage II heart failure patients. Patients were treated with 3 x 300 mg of the hawthorn extract or 3 x 12.5 mg captopril for 8 weeks. Primary target parameter was exercise tolerance at sitting bicycle ergometry on the days −7, 28 and 56. Secondary target parameters were the pressure-heart rate product and a score for 5 typical symptoms. Exercise tolerance increased statistically significantly during the treatment period in both treatment groups from 83 to 97 watts (verum) and from 83 to 99 watts (captopril), respectively. The pressure-heart rate product was reduced in both groups. The incidence and severity of the symptoms also decreased in both groups by around 50%. None of the target parameters showed any significant difference between the *Crataegus* preparation and the reference drug.

Assessor´s comment:
The tested primary endpoint, exercise tolerance at sitting bicycle ergometer, doesn't meet the criteria for a primary endpoint. Typical heart failure symptoms were reduced comparable to captopril in the test-period of 8 weeks. The duration of the study of 8 weeks is too short for a chronic disease. Cardiovascular morbidity and mortality was not analysed.

4.2.2.3 Open, controlled studies

Härtel et al. (2014) assessed effects of exercise training and the hawthorn extract in heart failure with preserved ejection fraction and aimed to identify mechanisms of action in an exploratory trial. One hundred forty NYHA II patients (on standard treatment) received eight weeks of aerobic endurance training and half were randomised to 2 x 450 mg extract from hawthorn leaves and flowers (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) per day. Symptoms, 2 km walking time, parameters of exercise tolerance, cardiac and vascular function, muscular efficiency and skeletal muscular haemoglobin oxygen saturation (SO_2) measured during a treadmill protocol were captured at baseline and after eight weeks. Adverse events were recorded during the trial. Mechanisms of action were explored by correlation and path analyses of changes. Symptoms and exercise capacity improved with training, but correlations between improvements were low and path models were rejected. SO_2 increased, decreased or undulated with increasing exercise intensity in individual patients and was not

altered by training. The extract improved 2 km walking time (-12.7% vs. -8.4%, p=0.019), tended to improve symptoms and to pronounce SO_2-decrease with increasing exercise, an indicator of oxygen utilisation. Endurance training and intake of extract were safe and well tolerated in combination with standard drug treatment.

Assessor´s comment:
Generally, open controlled studies cannot proof efficacy.

Effects on lipid profile

Niederseer et al. (2019) investigated whether a dry extract from hawthorn leaves and flowers (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)) and Nordic walking (NW) had comparable effects on endothelial function and lipid profile in 60 overweight subjects. In this partially blinded pilot study, overweight (BMI 25.0-29.9 kg/m^2), otherwise healthy volunteers aged 45-75 years were randomized into four groups as follows: hawthorn extract 2 x 450 mg/day (standard), hawthorn extract 2 x 900 mg/day (double), exercise 2 x 30 minutes/week (NW-low), and exercise 4 x 45 minutes/week (NW-high) for 12 weeks. Safety was assessed based on adverse events. Endothelial function testing (EndoPAT), assessment of endothelial progenitor cells, lipid profiles, and treadmill testing were performed.
At baseline, subjects in hawthorn extract standard/double groups had higher lipid levels and greater impairment of endothelial function.
Subjects with impaired endothelial function showed improvement regardless of the type of intervention. Subjects in hawthorn extract standard/double groups showed a trend towards modest decrease in triglycerides and modest increase in HDL-cholesterol; most changes were within the normal limits. In NW-low/-high groups, values also remained within the normal range. Exercise capacity improved in both NW groups. Hawthorn extract double showed no additional benefits over standard.
All adverse events were unrelated or improbably related to treatment. The authors concluded, hawthorn extract and exercise training were safe and showed beneficial effects on endothelial function and lipid profile in overweight but otherwise healthy volunteers; exercise capacity improved only by Nordic walking.

Assessor´s comment:
There are several limitations in the study presented as no placebo group, small sample size and the probably, biased comparison between extract and NW groups by coincidental baseline imbalance. No products are in the EU on the marked with this indication.
The changes of the lipid profile was in a modest decrease, within the normal range.

4.2.2.4 Non-controlled studies

Eichstädt et al. (1989) investigated in an open label trial, the hemodynamics of 20 patients with NYHA II heart failure and an angiographically confirmed left ventricular ejection fraction (LVEF) <55% via radionuclide ventriculography at rest and under exercise. The tests were performed before and after 4 weeks of treatment with 3 x 160 mg of an dry extract of hawthorn leaves and flowers (DER 4-6.6:1, extraction solvent ethanol 45% (m/m)) per day. The treatment was preceded by a one-week washout phase with 3 x 2 placebo capsules per day. After 4 weeks of treatment with *Crataegus* extract, the patients showed a significant increase in LVEF at rest from 40.18 to 43.50% (+3.32%), and also a significant increase in LVEF during exercise from 41.51 to 46.56% (+5.05%). The exercise tolerance increased significantly from 703.75 to 772.11 watt x minute. The heart rate at rest decreased from 68.6 to 66.2 per minute, while the heart rate during exercise did not change under verum. The blood pressure at rest decreased significantly from 136.5/87.5 to 134.0/83.5 mmHg, and the blood pressure

during exercise decreased also significantly from 188.42/98.16 to 176.84/95.53 mmHg (whereas significant evidence is referred to the systolic values). The clear improvement of hemodynamic parameters was accompanied by an improvement of subjective conditions in 65% (according to the patient's assessment) and 75% of the patients (according to the investigator's assessment).

Tauchert *et al*. (1999) monitored in a multicentre utilisation observational study 1011 patients with NYHA II heart failure. Patients were treated with 2 x 450 mg of a dry extract of hawthorn leaves and flowers (DER 4-6.6:1, extraction solvent ethanol 45% (m/m)) per day for 24 weeks. Efficacy parameters evaluated were the clinical symptoms: decline in physical performance, fatigue, exercise-induced dyspnoea, palpitation, which were measured by using a 5-step score. In addition, the following symptoms were determined: ankle oedema, nycturia and absolute arrhythmias. The maximal exercise tolerance, the pressure-heart rate product, blood pressure, heart rate, ejection fraction and arrhythmias were also evaluated. During and at the end of the observation period a significant improvement in clinical symptoms was observed. During the 24-weeks treatment period the score for the decline in physical performance decreased from 2.12 before treatment to 0.97 points at the end of treatment, the score for fatigue from 1.86 to 1.14, the score for exercise-induced dyspnoea from 2.05 to 0.84 and the score for palpitation from 1.22 to 0.35. Ankle oedema, nycturia and arrhythmias disappeared by 46%, 83% and 24% of patients, respectively, manifesting these symptoms before treatment. The mean maximal exercise tolerance improved from initial 88.75 W (for 7.1 minute) to 102.5 W (for 8.2 minute). The pressure-heart rate product at resting condition and at 50 W decreased from 11.2 to 10.2 mmHg/minute and from 18.3 to 16.1 mmHg/minute, respectively. The mean systolic and diastolic blood pressure decreased by 5.9 mmHg (from 142.9 to 137) and by 2.2 mmHg (from 84.5 to 82.3), respectively. Mean heart rate decreased by 3.4 beats/minute (from 76.7 to 73.3). The positive effects of the hawthorn extract were further demonstrated by an improved ejection fraction (+6.7%) and increased percentile shortening fraction (+7.9%) measured using M-mode echocardiography. More than ¾ (76.6%) of the physicians noted a "good" or a "very good" efficacy, and 98.7% noted a "good" or a "very good" tolerance.

Weikl & Noh (1992) examined the influence of treatment with a dry extract of hawthorn leaves and flowers (DER 4-6.6:1, extraction solvent ethanol 45% (m/m)) on the left ventricular function by nuclear resonance tomography. In an open study, 7 patients with NYHA II - III heart failure and angiographically determined left ventricular ejection fraction of less than 55% were treated for 4 weeks with 3 x 80 mg of *Crataegus* extract per day. Comedication of β-blockers, ACE inhibitors, calcium antagonists, cardiac glycosides or alphamimetics was not allowed during the study period. Primary target parameters were the ventricular ejection fraction and the symptomatic complaints (complaint list as defined by von Zerssen, 48 items). This treatment resulted in an increase of the LVEF from an arithmetic mean of 29.80% to 40.45% as measured by angiography. The heart rate and blood pressure remained essentially unchanged. The symptomatic complaints also showed improvement. The von Zerssen sum score decreased from 18.8 to 12.9 points.

Koller *et al*. (2005) investigated the influence of treatment with a dry extract of hawthorn leaves and flowers (DER 4-6.6:1, extraction solvent ethanol 45% (m/m)) on quality of life and disease specific symptoms (performance impairment, fatigue, exertion dyspnoea and palpitations) of NYHA II cardiac insufficiency and concomitant chronic heart disease. In a prospective, open, not randomised, two-armed, health economical study, 711 patients with NYHA II heart failure and coronary heart disease were treated for 4 weeks with 2 x 450 mg of *Crataegus* extract per day. Comedication with standard therapy was possible as well as mono-therapy. This treatment resulted in an increase of the LVEF from an arithmetic mean of 29.80% to 40.45% as the quality of life of the patients and the cardinal symptoms of chronic heart disease improved in the *Crataegus* cohort to a significantly greater extent than in the comparison cohorts. Furthermore, the direct costs in the *Crataegus* cohort were appreciably lower due to less frequent hospitalisation.

Assessor's comments:
Generally, non-controlled studies cannot proof efficacy.

4.2.2.5 Pooled studies and meta-analyses

Effect on parameters: maximal workload (MWL), left ventricular ejection fraction (LVEF), and pressure-heart rate product

Eggeling et al. (2011) evaluated in a pooled analysis the impact of baseline severity and gender on objective and patient-reported endpoints and associations between both types of outcomes in patients with early chronic heart failure. Clinical data from 10 trials conducted with of a dry extract of hawthorn leaves and flowers (DER 4-6.6:1, extraction solvent ethanol 45% (m/m)) or placebo in 687 patients were analysed. The results show that the physiologic outcome parameters maximal workload (MWL), left ventricular ejection fraction (LVEF), and pressure-heart rate product at 50 watt ergometric exercise improved more in active treatment than in placebo patients. Magnitude of improvement was independent from baseline for LVEF but increased for MWL and pressure-heart rate product with baseline severity. Improvement of typical symptoms like reduced exercise tolerance, exertional dyspnoea, weakness, fatigue, and palpitations improved more with active treatment and in patients with more severe symptoms.
A weak association between improvements in MWL, pressure-heart rate product, and symptoms could be demonstrated. Gender differences in treatment effects could be explained.

Assessor´s comment:
Main conclusions were effects on physiologic outcomes and typical symptoms are modulated by baseline severity, as the strongest effects were described in patients with more impaired baseline conditions. No differences in gender could be seen. Benefits were comparable in male and female patients.
The well-established use criteria are not fulfilled for proofing efficacy for chronical heart failure.

Effect on blood pressure

Hawthorn (not further specified)
Cloud *et al*. (2020) evaluated the clinical efficacy, dosage forms, and side effects of hawthorn mono-preparations versus placebo for their effects on blood pressure (BP) a systematic review was performed to identify randomised controlled trials (RCTs) that assessed such effect. Data on patients, interventions, methods, outcome measures, results and adverse events were extracted and assessed. The risk of bias (RoB) was assessed using the Cochrane RoB tool. Any queries in study evaluation were resolved through discussion between the authors.
The search identified 263 citations. Four trials (254 participants) met the inclusion criteria. Studies administered hawthorn (not further specified) as tablets or liquid drops and reported a reduced BP in patients with pre-hypertension or stage 1 hypertension.
No serious adverse side effects were reported. Pooled analysis of the results was not possible because of the heterogeneity of study design, participants and interventions. Hawthorn significantly reduced BP was shown in three trials of 12- and 16-week duration.
In this systematic review it was concluded by the authors that hawthorn can significantly lower BP in people with mild hypertension if applied for at least 12 weeks although further studies were suggested.

Assessor's comment:
Medicinal products corresponding to the indications (lowering blood pressure) described in the clinical studies of this review report are not reported from the EU market. Therefore, the well-established use criteria are not fulfilled.

Holubarsch *et al*. (2018) assessed the benefit-risk of a Crataegus extract (DER 4-6.6:1; extraction solvent: ethanol 45% (m/m)) in a review of published clinical studies. One of the merits of the review is, that comprehensive overview of the available information on symptoms at the time of its publication is summarized. Changes in heart failure-associated symptoms and health-related QoL during treatment with the extract were assessed in five trials.
In two trials, the von Zerssen Complaints List, a validated self-rating questionnaire assessing 24 general symptoms, some of which (e.g., shortness of breath, fatigue) are particularly important in heart failure, was used. In the study reported by Leuchtgens (1993) significantly more pronounced decrease of the total score of the scale in the verum group than those in the placebo group (mean value difference 7.3 points, 95% CI 0.9–13.7 was seen. In the study of Tauchert (2002), both extract dosages showed a significantly more pronounced total score decrease compared to placebo. He also used an ad hoc score assessing the four ''typical'' heart failure symptoms, i.e., general capability, lassitude, early fatigability, and effort dyspnoea. At the end of the 16-week treatment phase, the treatment group differences to placebo for score change versus baseline were significant for the 900 mg/day (p=0.04) and 1800 mg/day (p=0.004).

Weikl *et al.* (1996) used a health-related QoL inventory developed by Siegrist and Junge for chronically ill patients and including items focusing on functional capacity (symptom burden, ability to enjoy and relax, positive and negative mood, sociableness, and allegiance). The authors report on a trend towards more pronounced improvement of all symptoms assessed in patients treated with verum as compared to placebo.

The EuroQol-5D questionnaire was used in the study of Zick et al. (2009) for assessing health-related QoL after 6 months' treatment with a Crataegus extract (DER 4-6.6:1; extraction solvent: ethanol 45% (m/m)) or placebo in 120 patients. No significant differences were found.

In an open-label, exploratory study, Härtel et al. (2014) used the Kansas City Cardiomyopathy Questionnaire (KCCQ), specifically developed for assessing QoL in patients with chronic heart failure, to investigate 140 patients with HFpEF undergoing 8 weeks' endurance exercise training with or without co-administration of a Crataegus extract (DER 4-6.6:1; extraction solvent: ethanol 45% (m/m)). In the Symptoms scale of the KCCQ the summary score improved by 10±17 points (mean ± standard deviation) in the extract group compared to 5 ± 14 points in the control group. The validity of the QoL results is limited by potential bias attributable to the open-label design of the study.

Assessor´s comment:
All together a comparison of results is limited as different questionnaires were used. The results are inconsistent. While Zick et al. (2009) found no differences in health-related QoL, in two studies with the Zerssen Complaints List more pronounced total score decrease compared to placebo was seen. In a study with the QoL inventory developed by Siegrist and Junge, a positive trend was seen. The Kansas City Cardiomyopathy Questionnaire (KCCQ), specifically developed for assessing QoL in patients with chronic heart failure was used only in one open-label study and showed positive results, but is limited because of the design of the study.

Table 5: Controlled clinical studies on humans in chronic congestive heart failure (NYHA II-III)

Type	Study	Test product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
dry extract (4-6.6:1), extraction solvent: ethanol 45% (m/m)							
Leuchtgens (1993)	placebo-controlled, double-blind, rando-mised duration: 8 weeks	extract adjusted to 18.75% OPC 2 x 80 mg/day or placebo	verum: 7 females 8 males placebo: 5 females 10 males age: verum 66.0±8.3 females 67.9±6.1 males placebo 61.6±5.9 females 66.8±6.6 males drop outs: not specified	Chronic congestive heart failure (NYHA II).	decrease in pressure-heart rate product: verum: 24% placebo: 7% improvement of symptoms (von Zerssen symptom score): verum: 16.5 points (from 38 to 21.5) placebo: 4 points (from 31 to 27)	adaptive rank tests according to Hogg-Büning	None, only secondary endpoints according to ESC (2021) were examined.
Weikl et al. (1996)	placebo-controlled, double-blind, rando-mised, multi-center duration: 8 weeks	extract adjusted to 18.75% OPC 2 x 80 mg/day or placebo	verum: 49 females 18 males placebo: 49 females 20 males age: 40-80 years 65.5 verum 65.3 placebo drop outs: 4 verum 3 placebo	Chronic congestive heart failure (NYHA II).	change in the pressure-heart rate: verum: improvement (mean decrease 5.6 mmHg/min/100 [from 67.0 to 61.4 mmHg/min/100]) placebo: worsening (mean increase 4.2 mmHg/min/100 [from 63.8 to 68 mmHg/min/100])	ITT principle; rank-sum test according to Wilcoxon-Mann-Whitney	None, only secondary endpoints according to ESC (2021) were examined.

Type	Study	Test product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Zapfe jun (2001)	placebo-controlled, double-blind, rando-mised, parallel-group, multi-centre duration: 12 weeks	extract adjusted to 18.75% OPC 3 x 80 mg/day or placebo	verum: 15 females 5 males placebo: 14 females 6 males age: 58.2±10.6 verum 66.5±11.0 placebo drop outs: 1 placebo	Chronic congestive heart failure (NYHA II).	change of exercise tolerance (determined with bicycle exercise testing): verum: increase by 10.8% (from 616.3 to 682.5 W x min) placebo: decrease by 16.9% (from 623.8 to 527.6 W x min)	ITT principle; confirmatory analysis	None, only secondary endpoints according to ESC (2021) were examined.
Holubarsch et al. (2008)	placebo-controlled, double-blind, rando-mised, multi-centre duration: 2 years	extract adjusted to 17.3-20.1% OPC 2 x 450 mg/day or placebo	verum: 222 females 1116 males placebo: 213 females 1130 males age: 59.8±10.6 verum 60.4±10.7 placebo drop outs: 378 verum 397 placebo	Chronic congestive heart failure (NYHA II-III).	average time to first cardiac event: verum: 620 days placebo: 606 days event rates (p=0.476): verum: 27.9% placebo: 28.9%	ITT analysis time until first cardiac event: Kaplan-Meier survival analysis Treatment group comparison: log-rank test stratified for countries	No significant effect on the primary endpoint.
Zick et al. (2009)	placebo-controlled, double-blind, rando-mised duration:	2 x 450 mg/day or placebo	verum: 14 females 46 males placebo: 16 females 44 males age:	Chronic congestive heart failure (NYHA II-III).	primary outcome: change in 6 min walk distance secondary outcomes: quality of life (QOL) measures, peak oxygen consumption, anaerobic threshold during maximal	ITT principle, when possible (i.e. for deaths, hospitalisations and AEs); no imputation performed for missing values at 6 months	None, only secondary endpoints according to ESC (2021) were examined and no

Type	Study	Test product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
	6 months		54.4±12.6 verum 57.8±9.0 placebo drop outs: 6 verum 3 placebo		treadmill exercise testing, NYHA classification, left ventricular ejection fraction, neurohormones, measures of oxidative stress and inflammation No significant differences between groups in the primary (p=0.61) or secondary (p=0.04) outcome.	primary outcome: independent samples t-tests secondary outcomes: Wilcoxon rank-sum test; Fisher exact test; Cochran-Mantel-Haenzel tests	significant effect on the primary endpoint was seen.
dry extract (4-7:1), extraction solvent: methanol 70% (V/V)							
Bödigheimer & Chase (1994)	placebo-controlled, double-blind, rando-mised, multi-centre duration: 4 weeks	3 x 100 mg/day or placebo	verum: 26 females 10 males placebo: 25 females 12 males age: 61.1±10.8 verum 62.1±9.6 placebo drop outs: 6 verum 6 placebo	Chronic congestive heart failure (NYHA II).	bicycle ergometry exercise tolerance; typical symptoms; tolerability; final global assessment by the investigators and patients. trend toward superiority of verum over placebo (not statistically significant): exercise tolerance, pressure-rate product and clinical symptomatology	Mann-Whitney-U-test	None, only secondary endpoints according to ESC (2021) were examined.
Förster et al. (1994)	placebo-controlled, double-blind, rando-mised duration: 8 weeks	3 x 300 mg/day or placebo	verum: 19 females 16 males placebo: 20 females 14 males age: 49.8±9.1 verum	Moderately reduced left ventricular ejection fraction (NYHA II).	Oxygen uptake; tolerance period until the patients reached the anaerobic threshold and when exercise was discontinued. increase in exercise time taken to reach the anaerobic threshold:	t-test according to student and chi-squared test (paired comparison)	None, only secondary endpoints according to ESC (2021) were examined.

Type	Study	Test product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
			52.0±10.7 placebo drop outs: 1 verum 2 placebo		verum: 30 s (from 280 to 310 s) placebo: 2 s (from 275 to 277 s) improvement of oxygen uptake: verum: 75% of patients placebo: 42% of patients		
Schmidt et al. (1994)	placebo-controlled, double-blind, rando-mised, multi-centre duration: 8 weeks	3 x 200 mg/day or placebo	verum: 26 females 14 males placebo: 22 females 16 males age: 60.4±6.5 verum 60.3±7.7 placebo	Chronic congestive heart failure (NYHA II).	increase in exercise tolerance (determined with bicycle exercise testing): verum: 28 W (from 79 to 107 W) placebo: 5 W (from 71 to 76 W)	Wilcoxon test, Mann-Whitney-Uttest	None, only secondary endpoints according to ESC (2021) were examined.
Tauchert et al. (1994)	reference-controlled, double-blind, rando-mised, multi-centre duration: 8 weeks	3 x 300 mg/day or 3 x 12.5 mg/day captopril	verum: 36 females 32 males reference: 43 females 21 males age: 62±6 verum 63±5 reference drop outs: 3 verum 5 reference	Chronic congestive heart failure (NYHA II).	increase of workload: verum: 14 W (from 83 to 97 W; p<0.001) reference: 16 W (from 83 to 99 W; p<0.001)	Wilcoxon test, Mann-Whitney-U-test; McNemar test, chi-squared test	None, only secondary endpoints according to ESC (2021) were examined.

4.3. Clinical studies in special populations (e.g. elderly and children)

Not available.

4.4. Overall conclusions on clinical pharmacology and efficacy

Clinical pharmacology

Adequate clinical pharmacological studies are not available. The pharmacological profile of hawthorn is primary that of a cardiac drug, as reflected by the marked situation and literature.

Crataegus folium cum flore extracts show in clinical *ex-vivo* tests a positive inotropic effect (an increase in force contraction, an increase in force of contraction, an improvement of the frequency-dependent force generation, enhancement of dose-dependent relative shortening of myocytes in the atrium myocardium and in the ventricular myocardium).

In humans, a study found positive hypotensive effects in patients with type 2 diabetes but in contrast, in another study no effect was found (Walker, 2006, 2002). Clinical experimental studies found no relevant change in artery flow mediated dilatation, brachial artery diameter and blood pressure and blood pressure lowering effect remains controversial. In another study it could be shown that Crataegus preparation lead to changes of the lipid profile in a modest decrease, within the normal range.

Efficacy: Well-established use

There are old WEU preparations in the EU market for the use for declining cardiac performance corresponding to Functional Capacity Class I to II as defined by the New York Heart Association (NYHA). The use was intended for the user group with mild cases, not needed other cardiac medication.

i) There are a first kind of published clinical studies available, performed in this user group. Analysed were the mainly parameters and improvements of symptoms connected to exercise tolerance determined by bicycle (ergometer) exercise testing.
These older clinical studies show benefits and significant better result compared to placebo for the tested *Crataegus* preparations in exercise tolerance and clinical symptoms. According the ESC (2012; 2021) guideline, for the purpose of regulatory approval of the therapeutic use of drugs in chronic CF, primary endpoints should be clinical symptoms, cardiovascular morbidity and all-cause mortality.
In some of the studies, diuretics and ACE inhibitors were allowed, so there is uncertainty weather the benefit can be ascribed to hawthorn preparations alone.
Length of the treatment range from 3 to 16 weeks. None of the studies reached a duration of one year. No information on mortality is available. The actual WEU used criteria for the HMPC monograph are not fulfilled.

ii) A second kind of clinical studies are performed in patients with severe cases of congestive heart failure (NYHA II-III). An advantage of active therapy was found in the changes in the score sums according to Zerssen´s list of complain. As the duration of the study was only 16 weeks no mortality was examined. Ad-on therapy to concomitant drugs was analysed in two further studies. These clinical studies could not proof efficacy for the herbal in the tested parameters. The results showed, the guideline conform treatment cannot be exceeded by the herbal, when compared the number of days between baseline and the first cardiac event or in change in 6 min walk distance. The results of the study Holubarsch et al. (2018) reported that hawthorn had no adverse effects on the prognosis of patients with chronic heart failure as ad on therapy. The results did not demonstrate an additional beneficial effect of co-administered hawthorn on mortality in addition to

an existing anti-heart failure treatment regimen individually prescribed in accordance with applicable guidelines, but there was shown it may reduce the risk of cardiac mortality and sudden cardiac death at least in a subgroup of patients with baseline LVEF between 25 and 35% (upper limit for inclusion).

All together, the WEU is not accepted for the HMPC monograph.

In 2016 the HMPC decided, indications on context of heart failure, should generally not be implemented in the HMPC-monograph. Therefore, the traditional use was accepted for short-term use in acute situations:

Indication 1: Traditional herbal medicinal product used to relieve symptoms of temporary nervous cardiac complaints (e.g. palpitations, perceived extra heart beat due to mild anxiety), after serious conditions have been excluded by a medical doctor.
From the updated review of clinical studies in 2023 no changes ore new indications can be concluded for the HMPC-monograph.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

Table 6: Clinical safety data from clinical trials

Type	Study	Test product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
comminuted herbal substance						
Dalli et al. (2011a)	placebo-controlled, double-blind, randomised duration: 6 months	3 x 400 mg/day or placebo added to conventional treatment	verum: 24 placebo: 21 drop outs: 1 verum 3 placebo	diabetic patients with chronic coronary heart disease (NYHA I)	no AEs	-
Dalli et al. (2011b)	reference-controlled, cross-over duration: 15 days each with 2 weeks between treatments	3 x 800 mg/day or 1 x 100 mg aspirin	verum/reference: 16 drop outs: no drop outs	healthy subjects	no AEs	-
dry extract (4-6.6:1), extraction solvent: ethanol 45% (m/m)						
Eichstädt et al. (1989)	open label trial duration: 4 weeks each with 1 week between treatments	3 x 160 mg/day or placebo	verum/placebo: 20	patients with chronic congestive heart failure (NYHA II); left ventricular ejection fraction (LVEF) <55%	no AEs	-
Weikl & Noh (1992)	open study duration: 4 weeks	3 x 80 mg/day	verum: 7	patients with chronic congestive heart failure (NYHA II – III); left ventricular ejection fraction (LVEF) <55%	no AEs	-
Leuchtgens (1993)	placebo-controlled, double-blind, randomised	extract adjusted to 18.75% OPC 2 x 80 mg/day	verum: 15 placebo: 15 drop outs:	patients with chronic congestive	no AEs	-

Type	Study	Test product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
	duration: 8 weeks	or placebo	not specified	heart failure (NYHA II)		
Weikl et al. (1996)	placebo-controlled, double-blind, randomised, multicentre duration: 8 weeks	extract adjusted to 18.75% OPC 2 x 80 mg/day or placebo	verum: 67 placebo: 69 drop outs: 4 verum 3 placebo	patients with chronic congestive heart failure (NYHA II)	AEs: mild to moderate verum: 3 placebo: 6 patients verum: swelling of the lower ankle, exertional dyspnoea, inner agitation; temporary tachycardia with dizziness, dyspnoea and hot flush placebo: dizziness, concentration disorders; inner agitation, anxiety; stomach pain, nausea; peeling of the skin on the hands; pressure pain in thighs; burning left-thoracic without radiation	no significant differences in any specific category of AEs that differed in frequency between placebo and hawthorn groups; GI complaints mentioned in monograph
Tauchert et al. (1999)	prospective, multicentre observational study duration: 24 weeks	2 x 450 mg/day	verum: 1011 drop outs: 41	patients with chronic congestive heart failure (NYHA II)	AEs: 14, such as a feeling of fullness in the upper abdomen; facial pain accompanied by tachycardia and vomiting (right) none of them judged as connected to verum	GI complaints mentioned in monograph
Zapfe jun (2001)	placebo-controlled, double-blind, randomised,	extract adjusted to 18.75% OPC 3 x 80 mg/day or	verum: 20 placebo: 20 drop outs: 1 placebo	patients with chronic congestive heart failure (NYHA II)	verum: no AE placebo: 1 drop out because of an allergic skin reaction	-

Type	Study	Test product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
	parallel-group, multicentre duration: 12 weeks	placebo				
Tauchert (2002)	placebo-controlled, double-blind, randomised, multicentre duration: 16 weeks	extract adjusted to 18.75% OPC verum 1: 2 x 900 mg/day or verum 2: 2 x 450 mg/day or placebo	verum 1: 69 verum 2: 70 placebo: 70 drop outs: 1 verum 1 7 verum 2 4 placebo	patients with chronic congestive heart failure (NYHA III)	incidence of AEs (patients with at least 1 AE): verum 1: 18 verum2: 20 placebo: 36 most marked difference: dizziness and vertigo verum 1: 1.4% verum 2: 4.3% placebo: 10% difference in the number of AEs reported statistically significant for both of the verum groups versus the placebo group verum 1: 23 verum 2: 30 placebo: 50 bronchitis, flu-like symptoms, back-pain, arthritis were not seen treatment related; gastroenteritis and flatulence in all 3 groups, highest in placebo	GI complaints mentioned in monograph
Koller et al. (2005)	open, observational, multicentre duration:	2 x 450 mg/day and/or several commonly used therapy options such as	verum: 351 references: 360 158 patient pairs after matching	patients with NYHA II cardiac insufficiency and concomitant	no information about AE	-

Type	Study	Test product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
	6 months	diuretics, acetyl salicylic acid, heart glycosides, clopidrogel etc.		chronic heart disease angina pectoris according to Canadian Cardiovascular Society (CCS): 54 patients stage I 103 patients stage II 1 patient stage III in each group		
Holubarsch et al. (2008)	placebo-controlled, double-blind, randomised, multicentre duration: 2 years	extract adjusted to 17.3-20.1% OPC 2 x 450 mg/day or placebo	verum: 1338 placebo: 1343 drop outs: 378 verum 397 placebo	patients with chronic congestive heart failure (NYHA II-III)	verum: 2196 AEs in 897 patients (67%) placebo: 2279 AEs in 917 patients (68.3%) verum: 873 serious AEs in 524 patients (39.2%) placebo: 923 serious AEs in 552 patients (41.1%) most frequently reported AEs in both groups: • cardiac disorders (verum 30.3%, placebo 30.7%) • metabolic and nutritional disorders (16.5% and 17.2%, e.g., hyper-cholesterolaemia, hyperlipidaemia) • infections (13% and 16.2%, e.g., influenza, bronchitis)	no significant differences in any specific category of AEs that differed in frequency between placebo and hawthorn groups

Type	Study	Test product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
					• general disorders (10.2% and 11.9%, e.g., chest pain, pyrexia)	
Zick et al. (2009)	placebo-controlled, double-blind, randomised duration: 6 months	2 x 450 mg/day or placebo	verum: 60 placebo: 60 drop outs: 6 verum 3 placebo	patienst with chronic congestive heart failure (NYHA II-III)	significantly (p=0.02) more total AEs in the hawthorn group: verum: 36 placebo: 23 no significant difference in total cardiac events or any category of cardiac events (hawthorn/placebo): • worsening chronic heart failure: 5/5 • angina/cest pain: 2/3 • syncopal event: 3/2 • atrial fibrillation: 2/2 • infections: 7/12 • headache: 1/1 • rash: 2/1 • GI symptoms (constipation, diarrhoea, loose stool, nausea, vomiting): 5/2 • musculoskeletal: 2/1 • other (e.g. hypotension, diabetes, renal insufficiency, hyperthyroidism, phlebitis): 18/10	no significant differences in any specific category of AEs that differed in frequency between placebo and hawthorn groups; GI complaints mentioned in monograph
Härtel et al. (2014)	open, controlled duration: 8 weeks	extract adjusted to 17.3-20.1% OPC 2 x 450 mg/day	add-on treatment: 70 standard treatment: 70 drop outs:	patients with chronic congestive heart failure (NYHA II)	frequency of AEs: add-on treatment: 13% standard treatment: 17% 1 serious AE (bacterial urogenital infection) not	no significant differences in any specific category of AEs

Type	Study	Test product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
			5 add-on 8 standard		considered as related to hawthorn; other events probably or possibly related to hawthorn or drug interactions were not reported throughout the trial	
Niederseer et al. (2019)	single-centre, randomized, partially blinded duration: 12 weeks	2 x 450 mg/day (standard) (LD) or 2 x 900 mg/day (HD) or Nordic walking 2 x 30 min/week (LE) or Nordic walking 4 x 45 minutes/week (ME)	15 volunteers/ group drop outs: verum: 3 Nordic walking: 2	overweight (BMI 25.0-29.9 kg/m^2), but otherwise healthy volunteers	number of subjects with any AEs: LD: 11 (78.6%) HD: 12 (80.0%) LE: 11 (73.3%) ME: 8 (53.3%) total numbers of AEs: LD: 16 HD: 24 LE: 14 ME: 17 most AEs = symptoms of the musculoskeletal system (e.g., arthralgia, back pain) or trivial infections; 4 subjects exposed extract had a total of seven events (arthralgia, chest discomfort, diarrhoea, forehead headache, abdominal fullness, charley horse and tinnitus), in which a causal relationship with the investigational treatment was considered unlikely; in all other cases,	no serious AEs; GI complaints mentioned in monograph

Type	Study	Test product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
					causal relationship was excluded	
dry extract (4-7:1), extraction solvent: methanol 70% (V/V)						
Bödigheimer & Chase (1994)	placebo-controlled, double-blind, randomised, multicenter duration: 4 weeks	3 x 100 mg/day or placebo	verum: 36 placebo: 37 drop outs: 6 verum 6 placebo	patients with chronic congestive heart failure (NYHA II)	in 4 patients mostly unspecific AEs verum: increased migraine, nausea, flatulence; palpitations placebo: stomach pain or pressure, abdominal fullness, nausea	no serious AEs; GI complaints mentioned in monograph
Fischer et al. (1994)	reference- and placebo controlled, cross-over duration: single dosage	1 x 900 mg/day or 0.3 mg medigoxin/day or pacebo	verum/reference: 12 drop outs: no drop outs	healthy subjects	no AEs	-
Förster et al. (1994)	placebo-controlled, double-blind, randomised duration: 8 weeks	3 x 300 mg/day or placebo	verum: 35 placebo: 34 drop outs: 1 verum 2 placebo	patients with moderately reduced left ventricular ejection fraction (NYHA II)	no relevant AEs in both groups	-
Schmidt et al. (1994)	placebo-controlled, double-blind, randomised, multicentre duration: 8 weeks	3 x 200 mg/day or placebo	verum: 40 placebo: 38 drop outs: 4 verum 4 placebo	patients with chronic congestive heart failure (NYHA II)	2 AEs in both groups verum: nausea, once-only heart complaints placebo: dryness of the mouth, agitation	no significant differences in any specific category of AEs that differed in frequency between placebo and hawthorn groups; GI complaints

Type	Study	Test product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
						mentioned in monograph
Tauchert et al. (1994)	reference-controlled, double-blind, randomised, multicentre duration: 8 weeks	3 x 300 mg/day or 3 x 12.5 mg captopril/day	verum: 68 reference: 64 drop outs: 3 verum 5 reference	patients with chronic congestive heart failure (NYHA II)	AEs in 3 patients in both groups verum: gastrointestinal complaints (2 x) and cardiac pain reference: irritative cough (2 x), headache, dizziness	no serious AEs

5.2. Patient exposure

Daniele et al. (2006) assessed systematically safety data from 24 clinical studies on hawthorn mono-preparations. Data from 5577 patients were available for analysis, later several further studies with more than 1800 patients were conducted. Aside from market presence and data from studies, there are no concrete data concerning patient exposure.

5.3. Adverse events, serious adverse events and deaths

Information from the labelling of marketed preparations:
Gastrointestinal complaints, feeling of weakness, skin rash, hypersensitivity are already listed ADRs for Crataegus medicinal products in Member States.

Information from monographs and literature

Kommission E (1994)	None reported
ESCOP (2003)	None reported
Blaschek et al. (2021)	Not known (as Kommission E; Tauchert, 2002)
Grünwald et al. (2007)	Infrequent adverse events included palpitations, tachycardia, dizziness, headache, vertigo, hot flashes, gastrointestinal complaints, gastroenteritis, flatulence, and dyspnea

Safety information from review reports
Daniele et al. (2006) assessed systematically safety data from 24 clinical studies on hawthorn mono-preparations. Data from 5577 patients were available for analysis. The daily dose ranged from 160 to 1800 mg of hawthorn mono-preparations, the duration of the studies was 3 to 24 weeks. The extracts most used in the clinical trials were Crataegus dry extract from leaves and flowers (DER 4-6.6:1; extraction solvent: ethanol 45% (m/m)) and Crataegus dry extract from hawthorn leaves and flowers (DER 4-7:1; extraction solvent: methanol 70% (V/V)). 166 adverse events were reported. Most of these adverse events were, in general, mild to moderate. The most frequent adverse event were dizziness/vertigo (n=15), gastrointestinal complaints (n=24), headache (n=9), migraine (n=8) and palpitation (n=11). It remains unclear if these palpitations are symptoms of the underlying disease that seems to be likely, or if these palpitations are drug related adverse events.

The WHO spontaneous reporting scheme received 18 case reports. In the identified trials, the most frequent adverse events were dizziness (n=6), nausea (n=5), fall (n=2), gastrointestinal haemorrhage (n=2), circulatory failure (n=2) and erythematous rash (n=2). None of the AEs that could definitely be related to the use of hawthorn were considered serious and their incidence did not correlated with the dosage.

Pittler et al. (2008) assessed systematically safety data from 14 clinical studies in Cochrane review on hawthorn mono-preparations. Mostly they were used as adjuvant therapy. Ten trials including 855 patients with chronic heart failure (New York Heart Association classes I to III) provided data that were suitable for meta-analysis. No data on relevant mortality and morbidity such as cardiac events were reported, apart from one trial, which reported deaths (three in active, one in control) without providing further details. Reported adverse events were infrequent, mild, and transient; they included nausea, dizziness, and cardiac and gastrointestinal complaints.

Information from *Eudravigilance*
A search was performed in the Eudravigilance database for the period of 01.01.2014-21.07.2023. The report type was »spontaneous, other, not available to sender, report from studies«. The medical product

characterisation was »suspect, interacting«. 224 cases were reported. Case reports with a relevant time to onset and positive de-challenge have been found in EudraVigilance for gastrointestinal disorders such as abdominal pain and nausea and skin and subcutaneous tissue disorders such as rash and pruritus. Gastrointestinal complaints are also one of the most frequently reported ADRs in the literature.

Assessor's comment:
Section 4.8 is given with:
Gastrointestinal disorders: Abdominal pain and nausea. The frequency is not known.
Skin and subcutaneous tissue disorders: Rash and pruritus. The frequency is not known.

5.4. Laboratory findings

Daniele *et al*. (2006) assessed systematically safety data from 24 clinical studies on hawthorn mono-preparations. Data from 5577 patients were available for analysis. No relevant changes were documented for laboratory findings.

Fischer *et al*. (1994) assessed the effects of a hawthorn extract (900 mg; DER 4-7:1, extraction solvent: methanol 70% (V/V)) on rheology and microcirculation of 12 healthy volunteers. The preparation was taken as a single dose. Immediately before, as well as 1, 3 and 6 hours after taking the dose, the subjects haematocrit, erythrocyte aggregability, plasma viscosity, erythrocyte pre- and post-ischaemic flow rate in the nail bed capillaries as well as heart rate and blood pressure were measured. Six hours after taking hawthorn the haematocrit had dropped by a mean of 3.2%. No significant changes were observed for the remaining target parameters.

Dalli *et al.* (2011a) assessed beneficial effects of *Crataegus laevigata* on biomarkers of coronary heart disease (CHD). The study included 45 diabetic subjects with chronic CHD treated for 6 months with either a micronised flower and leaf preparation of *C. laevigata* (400 mg three times a day) or a matching placebo. Blood cell count, lipid profile, C-reactive protein, neutrophil elastase (NE) and malondialdehyde were analysed in plasma at baseline, at one month and six months. The main results were that NE decreased in the *C. laevigata* group compared to the placebo group. In the *C. laevigata* group, baseline figures (median and interquartile range) were 35.8 (4.5) and in the placebo group 31 (5.9) ng/ml. At the end of the study, values were 33.2 (4.7) ng/ml and 36.7 (2.2) ng/ml, respectively ($p<0.0001$). *C. laevigata*, added to statins, decreased LDL cholesterol (LDL-C) (mean±SD) from 105±28.5 mg/dl at baseline to 92.7±25.1 mg/dl at 6 months ($p=0.03$), and non-HDL cholesterol from 131±37.5 mg/dl to 119.6±33 mg/dl ($p<0.001$). Differences between groups did not reach statistical significance at 6 months. No significant changes were observed in the rest of parameters (blood cell count, levels of triglycerides, C-reactive protein, malondialdehyde, glucose). The authors concluded that *C. laevigata* decreased NE and showed a trend to lower LDL-C compared to placebo as add-on-treatment for diabetic subjects with chronic CHD.

Dalli *et al.* (2011b) assessed the effects of a comminuted hawthorn leafs and flowers (3 times 800 mg/day) on platelet aggregation in 16 healthy volunteers. The daily dose meant an intake of approximately 50 mg flavonoids and 134 mg proanthocyanidins (within the Spice-trial intake of approximately 70 mg flavonoids and 153 mg proanthocyanidins as measured by the authors). No effects on blood cell count, biochemistry or platelet aggregation (using inducers of aggregation, occlusion of pores on collagen-epinephrine or collagen-ADP coated membranes) or on synthesis of TXA_2 were seen.

5.5. Safety in special populations and situations

Eggeling *et al*. (2011) evaluated in a pooled analysis of 10 clinical trials the impact of baseline severity and gender on objective and patient-reported endpoints and associations between both types of

outcomes in patients with early chronic heart failure for Crataegus dry extract (DER 4-6.6:1; extraction solvent ethanol 45% (m/m)). Main conclusions were that effects on physiologic outcomes and typical symptoms are modulated by baseline severity, as the strongest effects were described in patients with more impaired baseline conditions. No differences in gender could be seen.

5.5.1. Use in children and adolescents

No safety information on the use in children and adolescents is available from clinical studies, as hawthorn is used only in adults in context of heart complaints (indication 1).

The traditional use for relief of mild symptoms of mental stress and to aid sleep (indication 2) is documented for adults and adolescents.

5.5.2. Contraindications

The HMPC monograph includes the contraindication for patients with hypersensitivity to the active substance.

5.5.3. Special warnings and precautions for use

Special warnings and precautions for use received by market overview request result in the following monograph relevant remarks:

- For indication 1:

The use in children and adolescents under 18 years of age is not recommended because of concerns requiring medical advice.

If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

If the ankles or legs become swollen, when pain occurs in the region of the heart, which may spread out to the arms, upper abdomen or the area around the neck, or in case of respiratory distress (dyspnoea), a doctor or a qualified health care practitioner should be consulted immediately.

For tinctures and extracts containing ethanol, the appropriate labelling for ethanol, taken from the 'Guideline on excipients in the label and package leaflet of medicinal products for human use', must be included.

- For indication 2:

The use in children under 12 years of age has not been established due to lack of adequate data.

If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

5.5.4. Drug interactions and other forms of interaction

Information from clinical trials

Crataegus dry extract from leaves and flowers (DER 4-6.6:1;extraction solvent: ethanol 45% (m/m)) versus digoxin

Tankanow *et al*. (2003) evaluated in a randomised, cross-over clinical trial the effects of digoxin (D) alone (0.25 mg/day) for 10 days and digoxin (0.25 mg/day) with Crataegus dry extract (DH) 450 mg twice a day for three weeks on PR-intervals and heart rate (HR) in 8 healthy volunteers.

Electrocardiograms were performed at baseline and at digoxin steady state trough concentrations. The baseline PR-interval for D and DH phase was 149±20 msec and 150±16 msec (p>0.05). Following each phase, the PR interval increased to 156±24 msec and 152±14 msec for D and DH, respectively. The mean change in PR-interval for D and DH was 6.5 ± 11 msec vs. 1.0±13 msec (p>0.05). Baseline HR during D and DH phase was 65±6 beats/minutes and 64±6 beats/minutes (p>0.05). Following each phase, the HR was 62±4 and 65±7 beats/minutes for D and DH, respectively. The mean change in HR for D and DH was –2.5±8 beats/minutes and 1.0±6 beats/minutes (p>0.05). There was no difference in digoxin trough concentrations between the two phases. Furthermore, pharmacokinetic studies were performed for 72 hours. There were no statistically significant differences in any measured pharmacokinetic parameters. The $AUC_{0\text{-infinity}}$, C_{max} – C_{min}, C_{min}, and renal clearance for the D group were 79±26 µg.h/l, 1.4±0.7 µg/l, 0.84±0.2 µg/l, and 74±10 ml/minutes versus 73±20 µg.h/l, 1.1±0.1 µg/l, 0.65±0.2 µg/l, and 81±22 ml/minutes for the DH group, respectively (p>0.05). Following 3 weeks of concomitant therapy, hawthorn did not significantly alter the electrophysiological or pharmacokinetic parameters for digoxin.

Ethanolic hawthorn extract as ad on therapy on cardioactive medication

Holubarsch *et al.* (2008) documented that all but 6 patients received concomitant cardioactive medication, and about 90% took at least 3 concomitant cardioactive drugs. In each treatment group, about 85% of the patients took diuretics (about 39% spironolactone), 83% received ACE inhibitors, 64% were treated with β-blockers (almost one half with carvedilol and almost one third with metoprolol), and 56% with digitalis and nitrates. Concomitant antiarrhythmics (mostly amiodarone) were used by about 22% of the study participants. No drug interactions have been reported.

Potential influence on bleeding rate after surgery (pharmacodynamic interaction)

Rababa'h *et al.* (2016) performed a small prospective observational study on 116 patients who underwent cardiac surgery in the period between June 2014 and May 2015 in Jordan. Patients were divided into two groups: Group I (patients recently consumed hawthorn extract, not further specified) and Group II (patients never consumed hawthorn extract). Endpoint measures included the rates of reopening to control bleeding, early mortality, duration of intensive care unit stay, total in-hospital stay period, and duration and amount of chest tube drainage. Condition of the patients before and during surgery (NYHA class, some pre-operative laboratory parameters, number of diseased coronary arteries, type of surgery) were listed in the publication. For instance, most patients had symptoms according to NYHA class I-II, while only in the intervention group also four patients had symptoms according to NYHA class III-IV.

Hawthorn patients had a significantly higher rate of postoperative bleeding necessitating take back to the operating room compared to the control group (10% versus 1%) respectively. The overall mortality rate for group I and II was 4% and 0% respectively. Chest tubes were kept in for longer times in group I compared to group II (54±14.6 versus 49±14.7 hours respectively. Group I stayed longer in the intensive care unit compared to group II (24 versus 22 hours respectively. The total in-hospital stay period was comparable between the two groups.

The authors concluded that hawthorn extract consumption increases the potential for bleeding and the amount of chest tube output after cardiac surgery.

Assessor's comment:

In this experimental retrospective study, patients reported that they had boiled the hawthorn leaves and drunk the extracted preparation daily. Quality of the herbal material, posology etc. are not described. Therefore and because of the small group size and the prospective design, the clinical relevance is not clear. However, together with pre-clinical data on influence on coagulation parameter for safety reasons a warning is included in the monograph.

Information from review reports:

Daniele *et al*. (2006) assessed systematically safety data from 24 clinical studies on hawthorn mono preparations. Data from 5577 patients were available for analysis. Three randomised clinical trials and one observational study involved concomitant use of cardioactive glycoside medications. None of these studies raised any issues regarding herb/drug interactions.

In a Cochrane review (Pittler *et al*., 2008), ten trials provided data for a meta-analysis. In most of the studies, hawthorn was used as an adjunct to conventional treatment for chronic heart failure. Reported comorbidities included previous myocardial infarction, hypertension, hyperlipidaemia, coronary heart disease, myocarditis and diabetes mellitus. Ten trials reported the use of concomitant drugs. Diuretics were allowed in four trials and ACE inhibitors were allowed in three trials. Length of the treatment range from 3 to 16 weeks and the longest follow up was 26 weeks. No interactions were reported. It was concluded, although the data suggest that hawthorn extract is relatively safe, self-medication is inappropriate among patients with heart failure, who should be treated by a licensed clinician.

Other information from literature

The NCCIH (2020) assumed, in most studies of hawthorn for heart failure, no serious safety problems have been reported. However, in one study, patients taking hawthorn were more likely than those taking a placebo (an inactive substance) to have their heart failure get worse soon after the study started. The reason for this is not clear, but one possibility is that hawthorn might have interacted with drugs the patients were taking.

Williamson *et al*. (2013) suggests in a guide to the interactions of herbal medicines, that despite theoretical concerns that hawthorn may affect treatment with digoxin, in practice, there appears to be no clinically relevant alteration in digoxin levels or effects. It was stated, it is unlikely that clinically relevant changes in hypotension would occur if hawthorn is added to existing antihypertensive treatment.

Tassell *et al*. (2010) mentioned that vasodilatory effects of hawthorn have been cited as theoretically causing complications when used with other vasodilatory agents and that no reports of adverse effects relating to this issue have been reported.

Kraft & Hobbs (2004) mentioned under "advantages of hawthorn" that since flavonoids do not reduce the afterload, hawthorn can also be used by patients with low blood pressure. Further, it is mentioned that hawthorn can be recommended for long-term use, and it combines well with cardiac glycosides, but may have a synergistic effect.

Ernst (2000a) described in a review that *Crataegus laevigata* can increase hypotensive effects of nitrates and antihypotensives and cardiac glycosides and CNS depressants. It was discussed, that the evidence is based on pharmacological effects rather on direct investigations.

Ernst (2000b) lists a number of potential interactions associated with hawthorn. References are mainly books or articles about potential interactions. Some of these references cannot be found anymore (internet pages) or if traceable they mention only purported intercations, for which no clinical studies exist. In other, more recent versions it is remarked that there are no known interactions with prescription cardiac medications or other drugs.

Gruenwald *et al*. (2007) discussed drug interactions for hawthorn with antiplatelet agents, cardiac glycosides, antiarrhytmics and cisapride. It was resumed that there is a moderate risk of a possible interaction with antiplatelet agents: Concurrent use may result in increased risk of bleeding. Clinical management: Caution is advised and m monitor for signs and symptoms of excessive bleeding.

Assessor´s comment:

No case reports are available from the Eudravigilance database. Although in some references interactions with e.g. cardiac glycosides, antiarrhytmics and cisapride are mentioned there is no clinical evidence for this. In addition, the rational for such interactions with antiplatelet agents is weak and often quoted as "may result" or "the cause is not known". Therefore, they are not mentioned in the monograph.

5.5.5. Fertility, pregnancy and lactation

A group of 5 nursing mothers were given no herb for 5 days, 15 mL of a 10% infusion of *Crataegi oxyacanthi* flowers orally 3 times daily for 10 days, followed by another 5-day control period from days 15 to 20. Their diet and environment were kept constant during the study period. Milk volume was measured daily and milk fat percentage was measured on days 5, 10, 15 and 20. The hawthorn flower infusion increased daily milk quantity in most nursing mothers and increased its fat content. The increase occurred towards the end of the experimental period and continued during the control period. Because of the lack of randomization, blinding and controls, and small number of participants, no valid conclusion can be made from this study on the galactogogue effects of hawthorn (Drugs and Lactation database, 2021).

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended. No fertility data available.

5.5.6. Overdose

No case reports on overdose of Crataegus leaves and flowers preparations are available.

5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability

No data available.

5.5.8. Safety in other special situations

No data available.

5.6. Overall conclusions on clinical safety

Safety data from clinical studies on hawthorn mono-preparations are available for patients with chronic heart failure (New York Heart Association classes I to III). No data on relevant mortality and morbidity such as cardiac events were reported. One study analysed the mortality and results showed that hawthorn had no adverse effects on the prognosis of patients with chronic heart failure as ad on therapy). Reported adverse events were infrequent, mild, and transient; they included nausea, dizziness, and cardiac and gastrointestinal complaints.

Based on information from the pharmacovigilance database and from Member States it is concluded in section 4.8 of the monograph "gastrointestinal disorders: Abdominal pain and nausea. The frequency is not known and skin and subcutaneous tissue disorders: rash and pruritus. The frequency is not known".
No relevant changes were documented for laboratory findings in clinical studies.

No safety information on the use in children and adolescents is available from clinical studies, as hawthorn is used only in adults in context of heart complaints. The use in children and adolescents under 18 years of age is not recommended to relieve symptoms of temporary nervous cardiac

complaints because of concerns requiring medical advice.
The traditional use for relief of mild symptoms of mental stress and to aid sleep is documented for adults and adolescents. The use in children under 12 years of age has not been established due to lack of adequate data.

The use is contraindicated for patients with hypersensitivity to the active substance. If the ankles or legs become swollen, when pain occurs in the region of the heart, which may spread out to the arms, upper abdomen or the area around the neck, or in case of respiratory distress (dyspnoea), a doctor or a qualified health care practitioner should be consulted immediately.

There are only rare hints from available clinical studies raised regarding herb/drug interactions and no interactions are documented in the EudraVigilance database. Since some preclinical and clinical studies suggest interactions with antiplatelet medications, such warnings have been also found in older literature. Therefore, it is be mentioned in chapter 4.5 as precautionary measure.

Safety data in special populations and situations are not available. No data exist for patients with impaired renal or liver function. Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy is not recommended.

6. Overall conclusions

The majority of licenced WEU-marketed products in Europa are used over 30 years in context of treatment of chronic congestive heart failure stage II, as defined by the NYHA/ for treatment of declining cardiac performance the support of cardiovascular function, by incorporating the therapy in a treating concept by a physician. According the ESC (2012; 2021) guideline, for the purpose of regulatory approval of the therapeutic use of drugs in chronic CF, primary endpoints should be clinical symptoms, cardiovascular morbidity and all-cause mortality.

Well established use monograph
The requirements for well-established use according to Article 10a of Directive 2001/83/EC are considered not fulfilled.
From the updated review of clinical Data in 2023, no changes can be concluded for the HMPC-monograph regarded the WEU, TU and indications thereof.
Although safety data suggest that hawthorn extract is relatively safe, self-medication is inappropriate among patients with heart failure, who should be treated by a physician.

Traditional use monograph
The requirements for traditional medicinal use according to Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC are considered fulfilled.

It has been demonstrated that Crataegus folium cum flore has been in traditional medicinal use throughout a period of at least 30 years, including at least 15 years within the EU/EEA, with an acceptable level of safety for:

Indication 1: Traditional herbal medicinal product used to relieve symptoms of temporary nervous cardiac complaints (e.g. palpitations, perceived extra heart beat due to mild anxiety), after serious conditions have been excluded by a medical doctor;

Indication 2: Traditional herbal medicinal product for relief of mild symptoms of mental stress and to aid sleep.

for the following preparations:

a) Comminuted herbal substance (indication 1)

b) Powdered herbal substance (indication 1, 2)
c) Dry extract (DER 4-7:1), extraction solvent: methanol 70% (V/V) (indication 1)
d) Dry extract (DER 4-7.1:1), extraction solvent: ethanol 45-70% (V/V) (indication 1)
e) Liquid extract (DER 1:0.9-1.1), extraction solvent: ethanol 45% (V/V) (indication 1)
f) Liquid extract (DER 1:2), extraction solvent: ethanol 45% (V/V) (indication 1)
g) Liquid extract (DER 1:19.2-20), extraction solvent: sweet wine (indication 1)
h) Expressed juice from the fresh leaves and flowers (DER 1:0.63-0.9) (indication 1)
i) Expressed juice from the fresh leaves and flowers (DER 1:0.9-1.1) (indication 1)
j) Tincture (DER 1:3.5-4.5), extraction solvent: ethanol 35% (V/V) (indication 1)
k) Dry extract (DER 4-5:1), extraction solvent: water (indication 1, 2)
l) Soft extract (DER 2.8-5.3:1), extraction solvent: ethanol 45% (m/m) (indication 1)
m) Liquid extract of fresh leaves and flowers (1:1); ethanol 95% (V/V) (indication 1)
n) Tincture (ratio herbal substance: extraction solvent 1:5); ethanol 60% (V/V) (indication 1).

Non-clinical information on the safety of Crataegus folium cum flore regarding all the preparations is scarce. Available acute and sub-chronic toxicity studies with single extracts in different animal species did not show effects in the doses tested. As there is no information on reproductive and developmental toxicity for all preparations, the use during pregnancy and lactation cannot be recommended.
Tests on genotoxicity have been performed with preparation d) only.

For Indication 1)

- The use in children and adolescents under 18 years of age is not recommended to relieve symptoms of temporary nervous cardiac complaints because of concerns requiring medical advice. The traditional use for relief of mild symptoms of mental stress and to aid sleep is documented for adults and adolescents.
- Beside a contraindication for patients with hypersensitivity to the active substance a warning is given that, if the ankles or legs become swollen, when pain occurs in the region of the heart, which may spread out to the arms, upper abdomen or the area around the neck, or in case of respiratory distress (dyspnoea), a doctor or a qualified health care practitioner should be consulted immediately.

For Indication 2)

- The use in children under 12 years of age has not been established due to lack of adequate data.

Safety data in special populations and situations are not available. No data exist for patients with impaired renal or liver function. Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy is not recommended.

It is reported that there is a moderate risk of a bleeding after surgery following intake of hawthorn preparations. A warning is given.

Undesirable effects are reported with gastrointestinal disorders (abdominal pain and nausea) and skin and subcutaneous tissue disorders (rash and pruritus). The frequencies are not known.

The pharmacological effects of the phytotherapeutic drugs cannot be attributed in generally to a specific constituent, but to the plant extract at whole.

List entry
A complete set of tests on genotoxicity has been performed with preparation d) only; these data cannot be extrapolated to the other preparations.

The genotoxicity testing for preparation d) revealed no concern, however, differences in medical approach, health care customers and patient self-management in the EU were noted with regard to indication 1 ("… relieve symptoms of temporary nervous cardiac complaints after serious conditions have been excluded by a medical doctor."). A European Union list entry is not supported due to that safety concerns, which don't refer to the herbal substance as such but the indication and use in general.

Annex

List of references