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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Crataegus* spp., folium cum flore

Final

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (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 k) Dry extract (DER 4-5:1), extraction solvent: water

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Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Crataegus* spp., folium cum flore
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use. Powdered herbal substance in solid dosage forms for oral use. Herbal preparations e) to j) in liquid dosage forms for oral use. Herbal preparations c), d) and k) in solid or liquid dosage forms for oral use.
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1. Introduction

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

- Herbal substance(s)

A monograph of hawthorn leaf and flower is published in the European Pharmacopoeia (2014a):

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 stems are dark brown, woody, 1-2.5 mm in diameter, bearing alternate, petiolate leaves with small, often deciduous stipules and corymbs of numerous small white flowers. The leaves are more or less deeply lobed with slightly serrate or almost entire margins; those of *Crataegus laevigata* are pinnately lobed or pinnatifid with 3, 5 or 7 obtuse lobes, those of *Crataegus monogyna* pinnatisect with 3 or 5 acute lobes; the adaxial surface is dark green or brownish-green, the abaxial surface is lighter greyish-green and shows a prominent, dense, reticulate venation. The leaves of *Crataegus laevigata*, *Crataegus monogyna* and *Crataegus pentagyna* are glabrous or bear only isolated trichomes, those of *Crataegus azarolus* and *Crataegus nigra* are densely pubescent. The flowers have a brownish-green tubular calyx composed of 5 free, reflexed sepals, a corolla composed of 5 free, yellowish-white or brownish, rounded or broadly ovate and shortly unguiculate petals and numerous stamens. The ovary is fused to the calyx and consists of 1-5 carpels, each with a long style and containing a single ovule; in *Crataegus monogyna* there is 1 carpel, in *Crataegus laevigata* 2 or 3, in *Crataegus azarolus* 2 or 3, or sometimes only 1, in *Crataegus pentagyna* 5 or, rarely, 4 (Ph. Eur, 2014a).

Main 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)
- other constituents (e.g. purine derivatives, minerals)

(Blaschek *et al*., 2013, Edwards *et al*., 2012; Bradley 2006; Chang *et al*., 2002; WHO, 2002).

- Herbal preparation(s)

"Hawthorn leaf and flower liquid extract, quantified" is a component part of the European Pharmacopoeia (2014b). Definition:

- Quantified liquid extract produced from hawthorn leaf with flower. It contains 0.8-3% of flavonoids, expressed as hyperoside. The extract is produced from the herbal drug and ethanol (30-70% V/V) by an appropriate procedure.

Also the monograph of "hawthorn leaf and flower dry extract" exists in the European Pharmacopoeia (2014c):

- Dry extract produced from hawthorn leaf and flower. It contains for aqueous extracts minimum 2.5% of total flavonoids, expressed as hyperoside (dried extract) and for hydroalcoholic extracts minimum 6% of total flavonoids, expressed as hyperoside (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% V/V).

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

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, *Matricaria recutita*, flos, *Salix* spp., cortex, minerals and vitamin E.

1.2. Search and assessment methodology

Databases and other sources used to research available pharmaceutical, non-clinical and clinical data on *Crataegus* spp. or its relevant constituents:

- Relevant articles and references retrieved from databases: PubMed and Toxline. Search term: Crataegus. Publication year: January 2007-April/May 2014. All in all 406 publications were listed.
- Older references were available from a list ("*Crataegus*", provided by the Federal Institute for Drugs and Medical Devices, the national competent authority in Germany) including articles with date of publication until 2007.
- Literature was provided by the Schwabe Company in response to the call for scientific data in October 2011.
- Libraries: EMA library, library of the Federal Institute for Drugs and Medical Devices.
- Textbooks, pharmacopoeias and monographs.

The abstracts of the references found were screened manually and all articles identified that could have a possible impact on the assessment report and monograph were included. This assessment report is based on the summary of the most relevant scientific literature.

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	Regulatory Status
No. 1 *Crataegus* spp., folium cum flore	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)	TU - since 2011 Austria
No. 2 *Crataegus* spp., folium cum flore	see No. 1	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)	TU - since 2013 Austria
No. 3 *Crataegus* spp., folium cum flore	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. (This indication is currently under revision.)	capsule, hard, containing 270 mg hawthorn leaves and flowers adults: 3 times daily 1-2 capsules	TU - Since 1994 Austria
No. 4 quantified liquid extract (1:1); extraction solvent ethanol 45% V/V	see No. 1	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	TU – since 2013 Austria
No. 5 *Crataegus* spp., folium cum flore, fructus extract (1:0.9-1.9); extraction solvent ethanol 49% m/m	Herbal medicinal product used at first signs of reduced cardiac performance with symptoms such as exhaustion and fatigue during exercise.	oral liquid, 100 g containing 75 g extract with 6 mg oligomeric procyanidins (OPC) per gram (1 ml=0.9 g; 1 ml corresponds to approximately 24 drops) adults: 2-3 times daily 15-20 drops	TU – since 1954 Austria
No. 6 *Crataegus* spp., folium cum flore	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	TU – since 1996 Czech Repulic
No. 7 dry extract (4-7:1); extraction solvent ethanol 45% V/V	Herbal medicine for the treatment of mild cardiac failure (NYHA I and II) in adults and elderly.	coated tablet, containing 80 mg extract oral use, 1 tablet 3 times daily, if necessary 2 tablets 3 times daily	WEU – since 2001 Estonia
No. 8 dry extract (DER 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	TU – since 2001 France

Active substance	Indication	Pharmaceutical form	Regulatory Status
No. 9 dry extract (4-5:1); extraction solvent water	see No. 8	hard capsule, containing 250 mg extract 3-4 capsules daily	TU – since 1986 France
No. 10 powder	see No. 8	hard capsule, containing 350 mg powder 1 capsule 3 times daily (up to 5 capsules, if necessary)	TU – since 1981 France
No. 11 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.	tablet, containing 80 mg extract adults and adolescents: 3 times daily 1-2 tablets	WEU – before 1976 Germany
No. 12 dry extract (4-7:1); extraction solvent ethanol 45% V/V	see No. 11	oral liquid, 100 ml contain 20.2 g extract 2 times daily 25 drops (1 ml)	WEU – before 1976 Germany
No. 13 dry extract (4-7:1); extraction solvent methanol 70% V/V	see No. 11	film-coated tablet, containing 600 mg extract adults and adolescents: 3 times daily 0.5 tablet	WEU – before 1976 Germany
No. 14 dry extract (4-7:1); extraction solvent methanol 70% V/V	see No. 11	coated tablet, containing 150 mg extract adults and adolescents: 2-3 times daily 1 tablet	WEU – before 1976 Germany
No. 15 dry extract (4-7:1); extraction solvent ethanol 45% V/V	see No. 11	coated tablet, containing 80 mg extract adults and adolescents: 3 times daily 1 tablet, if required up to 3 times daily 2 tablets	WEU – before 1976 Germany
No. 16; 17 dry extract (4-7:1); extraction solvent methanol 70% V/V	see No. 11	coated tablet, containing 240 mg extract adults and adolescents: 2-3 times daily 1 tablet	WEU – before 1976 Germany
No. 18 dry extract (4-6.6:1); extraction solvent ethanol 45% m/m	see No. 11	film-coated tablet, containing 450 mg extract 2 times daily 1 tablet	WEU – before 1976 Germany
No. 19 dry extract (4-6.6:1); extraction solvent ethanol 45% m/m	see No. 11	film-coated tablet, containing 80 mg extract 3 times daily 1-2 tablets	WEU – before 1976 Germany
No. 20 quantified liquid extract (1:2); extraction solvent ethanol 45% V/V	see No. 11	oral liquid, 10 ml containing 10 ml (9.74 g) extract adults and adolescents: 3 times daily 40 drops (3 x 1.89 ml)	WEU – before 1976 Germany
No. 21 dry extract (4-7:1); extraction solvent ethanol 45% V/V	see No. 11	film-coated tablet, containing 450 mg extract adults and adolescents: 2 times daily 1 tablet	WEU – before 1976 Germany

Active substance	Indication	Pharmaceutical form	Regulatory Status
No. 22 dry extract (4-7:1); extraction solvent ethanol 45% V/V	see No. 11	coated tablet, containing 160 mg extract adults and adolescents: 3 times daily 1 tablet	WEU – before 1976 Germany
No. 23 dry extract (4-7:1); extraction solvent ethanol 45% V/V	see No. 11	coated tablet, containing 175 mg extract Adults and adolescents take 2 times daily 1-2 tablets.	WEU – before 1976 Germany
No. 24 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)	WEU – before 1976 Germany
No. 25 dry extract (4-7:1); extraction solvent ethanol 45% V/V	see No. 11	film-coated tablet, containing 300 mg extract 2-3 times daily 1 tablet	WEU – before 1976 Germany
No. 26 dry extract (4-7:1); extraction solvent ethanol 45% V/V	see No. 11	film-coated tablet, containing 450 mg extract adults and adolescents:2 times daily 1 tablet	WEU – before 1976 Germany
No. 27 dry extract (4-7:1); extraction solvent ethanol 45% V/V	see No. 11	coated tablet, containing 200 mg extract adults and adolescents: 2-3 times daily 1 tablet	WEU – before 1976 Germany
No. 28 dry extract (4-7:1); extraction solvent methanol 70% V/V	see No. 11	coated tablet, containing 300 mg extract adults and adolescents: 3 times daily 1 tablet	WEU – before 1976 Germany
No. 29 dry extract (4-7:1); extraction solvent methanol 70% V/V	see No. 11	Capsules, soft, containing 80 mg extract adults and adolescents:3 times daily 1 capsule	WEU – before 1976 Germany
No. 30 dry extract (4-6.6:1); extraction solvent ethanol 45% m/m	see No. 11	film-coated tablet, containing 80 mg extract 3 times daily 1-2 tablets	WEU – before 1976 Germany
No. 31 quantified liquid extract (1:0.9-1.1); extraction solvent ethanol 45% V/V	see No. 11	oral liquid, 10 g liquid (9.75 ml) contain 10 g extract adults and adolescents:3 times daily 40 drops (1.25 g liquid)	WEU – before 1976 Germany
No. 32 quantified liquid extract (1:1); extraction solvent ethanol 45% V/V	see No. 11	oral liquid no further details	WEU – before 1976 Germany
No. 33 dry extract (4.3-7.7:1); extraction solvent methanol 70% V/V	see No. 11	oral liquid, 100 ml containing 0.9 g extract adults and adolescents:2 times daily 15 ml	WEU – since 1996 Germany

Active substance	Indication	Pharmaceutical form	Regulatory Status
No. 34; 35; 40; 41 dry extract (4-6.6:1); extraction solvent ethanol 45% m/m	see No. 11	film-coated tablet, containing 450 mg extract adults and adolescents: 2 times daily 1 tablet	WEU – since 1998 Germany
No. 36; 38; 39 dry extract (4-6.6:1); extraction solvent ethanol 45% m/m	see No. 11	film-coated tablet, containing 300 mg extract adults and adolescents: 2-3 times daily 1 tablet	WEU – since 1998 Germany
No. 37 dry extract (4-7:1); extraction solvent ethanol 45% V/V	see No. 11	coated tablet, containing 240 mg extract adults and adolescents: 2-3 times daily 1 tablet	WEU – since 1996 Germany
No. 42; 43 dry extract (4-7:1); extraction solvent ethanol 45% V/V	See No. 11	film-coated tablet, containing 300 mg extract adults and adolescents: 2-3 times daily 1 tablet	WEU – since 2000 Germany
No. 44 dry extract (4-7:1); extraction solvent methanol 70% V/V	see No. 11	film-coated tablet, containing 600 mg extract adults and adolescents: 3 times daily 0.5 tablet	WEU – since 2003 Germany
No. 45-50 dry extract (4-7:1); extraction solvent ethanol 45% V/V	see No. 11	film-coated tablet, containing 450 mg extract adults and adolescents: 2 times daily 1 tablet	WEU – since 2003 Germany
No. 51; 54 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. Herbal medicinal product for heart diseases.	film-coated tablet, containing 450 mg extract adults and adolescents:2 times daily 1 tablet	WEU – since 2004 Germany
No. 52, 53 dry extract (4-7:1); extraction solvent ethanol 45% V/V	see No. 51	film-coated tablet, containing 600 mg extract adults and adolescents: 2-3 times daily 0.5 tablet	WEU – since 2004 Germany
No. 55, 56 dry extract (4-6.6:1); extraction solvent ethanol 45% m/m	see No. 11	film-coated tablet, containing 600 mg extract adults and adolescents: 3 times daily 0.5 tablet	WEU – since 2004 Germany
No. 57 dry extract (4-7:1); extraction solvent ethanol 45% V/V	see No. 11	film-coated tablet, containing 600 mg extract adults and adolescents: 3 times daily 0.5 tablet	WEU – since 2006 Germany
No. 58; 63, 64 dry extract (4-7:1); extraction solvent ethanol 45% V/V	see No. 11	film-coated tablet, containing 450 mg extract adults and adolescents: 2 times daily 1 tablet	WEU – since 2005 Germany
No. 59-62 dry extract (4-7:1); extraction solvent ethanol 45% V/V	see No. 51	film-coated tablet, containing 600 mg extract adults and adolescents: 2-3 times daily 0.5 tablet	WEU – since 2005 Germany

Active substance	Indication	Pharmaceutical form	Regulatory Status
No. 65 *Crataegus* spp., folium cum flore; cut	Traditionally used in support of cardiovascular function.	herbal tea, 1 tea bag contains 2 g hawthorn leaves and flowers adults:2-3 times daily 1 cup of freshly brewed tea Duration of use is not limited.	TU – before 1976 Germany
No. 66 *Crataegus* spp., folium cum flore; cut	see No. 65	herbal tea, 1 tea bag contains 1.44 g cut hawthorn leaves and flowers adults: 3-4 times daily one cup of freshly brewed herbal tea Duration of use is not limited.	TU – before 1976 Germany
No. 67 pressed fresh juice; DER 1:0.63-0.9	see No. 65	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.	TU – before 1976 Germany
No. 68 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.	TU – before 1976 Germany
No. 69 pressed fresh juice (1:0.9-1.1)	see No. 65	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.	TU – before 1976 Germany
No. 70 *Crataegus* spp., folium cum flore powder	see No. 65	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.	TU – before 1976 Germany
No. 71 dry extract (4-7.1:1); extraction solvent ethanol 70% V/V	see No. 65	capsule, soft, containing 112.5 mg extract adults: 3 times daily 1-2 soft capsules In the case of complaints of unclear origin self-medication should be stopped after 2 weeks.	TU – before 1976 Germany
No. 72 quantified liquid extract (1:1); extraction solvent ethanol 45% V/V	see No. 65	oral liquid, 100 ml contain 59.8 g extract adults: 3-4 times daily 30 drops (1 ml=32 drops)	TU – before 1976 Germany

Active substance	Indication	Pharmaceutical form	Regulatory Status
No. 73/74 tincture (1:3.5-4.5); extraction solvent ethanol 35% V/V	see No. 65	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.	TU – before 1976 Germany
No. 75 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	WEU – since 2007 Lithuania
No. 76 dry extract, corresponding to 13.88-16.13 mg OPC, estimated as epicatechin(4-6.6:1); extraction solvent ethanol 45% V/V	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.	WEU – since 2008 Lithuania
No. 77 *Crataegus* spp., folium cum flore herbal tea	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	TU – since 1995 Lithuania
No. 78 *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	TU – since 1990 Spain

In Germany the following historical indications are known for the use of hawthorn:

- Historical indications (1978) from Germany [German historical database]

  Herbal tea: tonic for the senile heart, cardiovascular tonic, as cardiovascular remedy acting calming and spasmolytic, regulation of the blood pressure (circulatory stimulant), (mild) nervous cardiovascular disorders.

  Fresh juice: mild form of coronary failure, hypertension, circulatory disorder, senile heart and atherosclerosis, cardiotonic, circulatory stimulant, care product for heart and circulation.

  Fluid extract: to support the heart and circulation, preventive remedy to treat (especially in old age) empirically expected natural fluctuations in the function of organs, to treat exhaustion and increased irritability.

  Powder: nervous cardiac function disorders, regulate blood pressure, palpitations, irritability, exhaustion.

  Dry extract: strengthen the heart and keep it young and powerful.

  Liquid extract: for nervous cardiac disorders and beginning organic cardiac insufficiency, activation of circulation (in circulatory disorders), regulates blood pressure.

  Tinctures: for nutrition/alimentation and invigoration of the myocardium, to support the aging heart.

- Indication of the German Standard Marketing Authorisation (1986)

  Herbal tea: decreasing functional capacity of the heart, sensation of pressure and anxiety in the heart region.

The following additional information is given for different products on the German market:

Risks:
Nausea, fatigue, sweating, rash. Allergic reactions.

Duration of use:
Treatment should last for at least 6 weeks. The physician should determine the further duration of use at the latest after 6 months. Long-term use is possible.

Contraindications:
Hypersensitivity to the active substance. Pregnancy and lactation.

Warnings:
The use should be limited to the functional symptoms of a healthy heart, confirmed by a clinical and electrocardiographic check up.
It is recommended to consult a physician, if symptoms continue unchanged for longer than 6 weeks, or if fluid accumulates in the legs. Immediate medical consultation is absolutely necessary 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 (dyspnea).
There are insufficient data on the use of medicinal products containing hawthorn in children (and adolescents). It must therefore not be used in children (and adolescents) below 18 years.
The user should consult a doctor or another qualified practitioner if the symptoms persist or if adverse events different from those mentioned in the information for use occur.

Interactions:
None known.
Interactions are not investigated so far. Enhancement or attenuation of the effect of other drugs cannot be excluded. The concomitant use of medicinal products with low therapeutic index should be decided on an individual basis.

Pregnancy and lactation:
The medicinal product should not be used during pregnancy and lactation. It should be noted that also the use in women of reproductive age, who do not use a contraceptive, has to be carefully pondered because of a possibly unknown pregnancy.
The widespread use of hawthorn in medicinal products and animal studies gave no evidence of risk during pregnancy and lactation so far.
Not applicable.

Effects on ability to drive and use machines:
Not applicable.
Particular precautions are not required.
The medicinal product has no influence on the ability to drive and use machines.
No studies on the effects on the ability to drive and use machines have been performed.

Adverse effects:
None known.
Gastrointestinal complaints, feeling of weakness or skin rash rarely may occur. These complaints usually disappear within a few days after discontinuation of the medicinal product.
Very rare allergic reactions may occur.
Frequency not known (on the basis of the available data not assessable).

Overdose:
Cases of overdose have not been reported.
Major overdose will cause an increased occurrence of symptoms mentioned in section “adverse effects”. Treatment should depend on the clinical picture.

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

Not applicable.

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

Not applicable

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

As medicine *Crataegus* is mentioned in the European cultural area for the first time in the 1st century AD by Pedanios Dioscurides, a travelling and military doctor during the time of Nero. From that time on it is an integral part of folk medicine as a “cardiotonic” remedy **(Kaul, 1998)**.

Schulz (1919) described the long-lasting usage of tea from dried hawthorn flowers to lower increased blood pressure and therefore for the therapy of atheriosclerosis.

Ripperger (1937) pronounces the usage of hawthorn in cases of light cardiac insufficiency and for the lowering of blood pressure and mentiones also the usage as tonic to regulate the balance between blood pressure and cardiac output and the usage in nervous complaints such as anxiety, sleeplessness and dizziness which are not based on heart or blood vessels diseases.

Madaus (1976, reprint from Madaus 1938) documented that hawthorn is used as medicine since the Middle Ages. At that time the first hint of its effect on the heart originates by Quercetanus (1544-

1609), the personal physician of King Henry IV of France, who produced an “anti-age syrup” from the plant. Léclerc found in the notes from Bonnejoy de Chars the following statement of an unknown author from the 17th century: “There must be an exsanguination when increased motion of the blood causes raised blood supply in blood vessels. The causes of tension could be reduced among other things by hawthorn.”

The plant became famously known only in the second half of the 19th century as a cardiac drug by an Irish doctor named Green. He used hawthorn for treating very successfully numerous heart diseases. Only after his death in 1894 the name of the drug became known. Since then, it is an integrated part of the world of herbal medicinal products.

In Lorraine hawthorn should have always been a common product for treating palpitations and insomnia.

Different traditional indications of preparations from hawthorn flowers are documented. From German folk medicine tea from flowers was recommended, for use lasting for months, to lower pathological increased blood pressure, especially to treat arteriosclerosis. In Polish folk medicine flowers were used as sedative, in Hungary to treat jaundice and as constipating agent.

Dostal (cited in Madaus) reported that the use in Czechoslovakia was as follows: In the non-professional medicine, hawthorn flowers were an excellent product to treat cough (Moravia), diseases of the urinary organs (Silesia), and brewed it was used as warm, pain-relieving compress (Wallachia). According to the author, from dried hawthorn leaves a tea is brewed to treat lung diseases (Moravia).

Since 1896 *Crataegus* has been used (also in America) to treat different heart diseases, angina pectoris, supporting the effect of *Digitalis*, or in cases of irregular heartbeat when *Digitalis* was not tolerated. The use as a tonic preparation for the heart and to regulate circulation was mentioned. It was also used successfully to treat climacteric inconveniences, arteriosclerosis and cardiac neuroses of dyspeptics. *Crataegus*, independent from the above mentioned cardiovascular effects, was also used for treating purely nervous affections.

Furthermore, Madaus (1976) also reported the main effects of *Crataegus* from several sources:

- calming influence on the nervous system, especially on the sympathetic nervous system of the heart and a beneficial influence on increased blood pressure in patients suffering from neural gout
- prophylactic in sense of a care product for the heart
- cardiac and circulatory medication, that proved beneficial for the early form of circulatory insufficiency in older ages, it has a strengthening and slowing effect on heart function
- tea from Crataegus flowers is mentioned as a good diuretic

The general dose of preparations from hawthorn flowers is mentioned for a tincture with 10 drops 3-5 times daily and for the powder with 2-5 g.

Irion (1955) describes the usage of the hawthorn flowers (tea and tincture) as blood pressure lowering agents in cases of heart insufficiency, angina pectoris arteriosclerosis. The author emphasised that a long-lasting usage was needed to achieve such effects (several months).

In former times hawthorn was also combined with different other cardioactive herbal preparations, such as from *Digitalis*, *Strophantus*, *Nerium*, *Atropa* (Gehes Codex, 1953).

On the basis of a long experience, it is explained that long-term use of *Crataegus* is safe due to the lack of any toxicity, even in patients with renal dysfunction, without fearing any accumulation in the organism. Only in high doses of more than 100 drops of tincture a reduction in the pulse rate and mild drowsiness were shown.

Table 2: Overview of historical data

Herbal preparation	Documented Use / Traditional Use	Pharmaceutical form	Reference
tincture, produced from hawthorn leaves and flowers with diluted ethanol (1 + 5)	used to treat heart diseases (has a tonic effect, reduces the pulse rate and dissolve edema)	10 drops 3-5 times daily	Frerichs *et al.* (1925)
standardised *Crataegus*-active agent concentrate	a) mild forms of circulatory disorders performance insufficiency b) coronary and myocardial damages c) arrhythmias d) age-related heart failure	8-15 (up to 25) drops 3-4 times daily	Rote Liste (1949)
Crataegus leaves and flowers (no further details)	a) senile heart b) hypertonic heart c) mild forms of coronary insufficiency d) weakness of the heart after infectious diseases e) arrhythmias f) functional heart disorders (such as palpitations, cardiac neuroses and heart disorders connected to the menopause)	not specified	List & Hörhammer (1973)
Crataegus leaves and flowers (no further details)	a) hypertension b) age-related insufficiency c) cardiac neuroses	not specified	Hoppe (1975)
Crataegus leaves and flowers and/or fruits as well as their preparations	a) decreasing cardiac output as described in functional stages I-II of NYHA b) sensation of pressure and anxiety in the region of the heart c) senile heart (no need of digitalis) d) mild forms of bradycardiac arrhythmias	minimum daily dose: 5 mg flavones, estimated as hyperoside according to DAB 8 or 10 mg total flavonoids (determined as total phenols, estimated as hyperoside) or 5 mg OPC (estimated as epicatechin)	Commission E monograph (1984)
preparations from *Crategus* leaves and flowers (no further details)	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, that do not yet need cardiac glycoside treatment	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	Pharmaceutical form	Reference
	d) sensation of pressure and anxiety in the region of the heart e) mild forms of bradycardiac arrhythmias		
preparations from *Crategus* leaves and flowers (no further details)	a) mild forms of coronary insufficiency (NYHA stages I-II) b) mild forms of arrhythmias	a) as an infusion: 1 g in a cup 3-4 times daily b) minimum daily dose: 5 mg flavones or 10 mg total flavonoids or 5 mg OPC	Hartke & Mutschler (1988)
a) native, hydroalcoholic extract (ethanol 45% V/V or methanol 70% V/V (4-7:1), with defined flavonoid or procyanidine content), corresponding to 30-186.7 mg OPC, estimated as epicatechin, or 3.5-19.8 mg flavonoids, estimated as hyperoside according to DAB 10 b) herbal substance as well as aqueous and hydroalcoholic (others than mentioned above), vinous extracts and fresh plant juice	For a): declining cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA For b): traditionally used for strengthening and invigoration the cardiovascular function	For a): 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 lasts at least for 6 weeks. For b): no details	Commission E monograph (1994)
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 erethism 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)
a) hydroalcoholic preparations b) herbal substance as well as aqueous and hydro alcoholic (other than in the commission E monograph of 1994), ethanolic extracts and fresh plant juice	For a): declining cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA For b): traditionally used for strengthening and invigoration the cardiovascular function Herbal tea is used to treat declining cardiac performance and sensation of pressure and anxiety in the region of the heart	For a): see Commission E monograph b) Herbal tea: ca. 1.5 g hawthorn leaves and flowers in 150 ml boiling water, 10-15 minutes steeping time, 3-4 times daily	Blaschek *et al.* (2011)

2.3. Overall conclusions on medicinal use

From market overview (section 2.1) the following indications and respective herbal preparations were identified for traditional use:

In Germany

- Traditionally used in support of cardiovascular function: comminuted herbal substance; powdered herbal substance; expressed juice from the fresh leaves and flowers (DER1:0.63-0.9) and (DER 1:0.9-1.1); dry extract (DER 4-7.1:1, ethanol 70% V/V); liquid extract (DER 1:0.9-1.1, ethanol 45% V/V) and (DER 1:2, ethanol 45% V/V); tincture (DER 1:3.5-4.5, ethanol 35% V/V).
- Traditionally used for strengthening cardiovascular function: liquid extract (DER 1:19.2-20, sweet wine, flavoured with absinthe herba).
  The extract contains absinthe herb as flavouring to gain bitter taste; therefore absinthe herb is not mentioned in the preparation description in the monograph. 100 ml of sweet wine contains 49.4 mg absinthe herb; the finished product contains 0.049% absinthe herb (or 8.1 mg absinthe herba in max recommended daily dose of 16.5 g extract).
- Declining cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA: dry extract (DER 4-7:1, methanol 70% V/V); dry extract (DER 4-7:1, ethanol 45% V/V); dry extract (DER 4-6.6:1, ethanol 45% m/m); liquid extract (DER 1:2, ethanol 45% V/V); liquid extract (DER 1:0.9-1.1, ethanol 45% V/V).

In France

- Traditionally used in disorders of cardiac erethism in adults (healthy heart).

  The indication is still authorised, but under re-assessment. It will be replaced by the following wording: “Traditional herbal medicinal product used in the symptoms of irritable heart such as palpitations (exaggerated perceptions of heart beating)”: powder.
- Traditionally used in the symptomatic treatment of neurotonic conditions of adults and children, notably in cases of mild disorders of sleep (for the powdered herbal substance).

  The indication is still authorised, but also under re-assesment. It will be replaced by “Traditional herbal medicinal product for relief of mild symptoms of mental stress and to aid sleep”: powder, dry extract (DER 4-5:1, water).

Based on available literature and information provided by Member States on traditional use as well after discussion in the MLWP, the following indications are listed in the monograph:

- 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.

This indication is plausible according to the long-lasting usage in France (more than 30 years) and information found in handbooks. According to the information given in chapter “4. Clinical Data” the treatment of declining cardiac performance is no longer acceptable as indication for *Crataegus*.

- Indication 2:

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

This indication is plausible according to the long-lasting usage in France (more than 30 years) and information found in handbooks.

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
herbal substance, comminuted			
Crataegus spp., folium cum flore; comminuted	Traditionally used in support of cardiovascular function.	herbal tea 1-2 g up to 3-4 times daily (max. 6 g)	before 1976
powder			
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.	solid dosage form 3 x 350 mg (up to 5 x 350 mg possible, if necessary)	since 1981
powder	Traditionally used in support of cardiovascular function.	solid dosage form adults: 3 x 190 mg	before 1976
expressed juice			
expressed juice from the fresh leaves and flowers; (1:0.63-0.9)	Traditionally used in support of cardiovascular function.	liquid dosage form adults: 3 x 7 ml expressed juice	before 1976
expressed juice from the fresh leaves and flowers (DER 1:0.9-1.1)	Traditionally used in support of cardiovascular function.	liquid dosage form adults: 3 x 2.4 ml expressed juice	before 1976
tincture			
tincture (1:3.5-4.5); extraction solvent: ethanol 35% V/V	Traditionally used in support of cardiovascular function.	liquid dosage form adults: 3 x 1.68 g tincture	before 1976
liquid extracts			
liquid extract (1:2); extraction solvent: ethanol 45% V/V	Declining cardiac performance corresponding to Functional Capacity Class II as defined by the NYHA.	liquid dosage form adults and adolescents: 3 x 1.84 g liquid extract	before 1976
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.	liquid dosage form adults and adolescents: 3 x 1.25 g	before 1976

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
liquid extract (1:19.2-20); extraction solvent: sweet wine	Traditionally used for strengthening cardiovascular function.	liquid dosage form adults: 2 x 8.24 g	before 1976
liquid extract (1:1); extraction solvent: ethanol 45% V/V	Traditionally used in support of cardiovascular function.	liquid dosage form adults: 3-4 x 0.56 g	before 1976
dry extracts			
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 form adults and adolescents: single dose 80-300 mg, daily dose: 240-900 mg	before 1976
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.	liquid and solid dosage form adults and adolescents: 240-900 mg devided into 2-3 single doses	before 1976
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.	solid dosage form 240-900 mg divided into 2-3 single doses	before 1976
dry extract (4-7.1:1); extraction solvent: ethanol 70% V/V	Traditionally used for strengthening cardiovascular function.	solid dosage form adults: 3 x 112.5-225 mg	before 1976
dry extract (4-5:1), extraction solvent: water	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.	solid dosage form adults: 3-4 x 250 mg	since 1986

3. Non-Clinical Data

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

Many pharmacological studies have been conducted with extracts and isolated constituents of *Crataegus* spp*. in vivo* and *in vitro*. A systematic review of all of these studies will not be attempted here; rather a selection of studies with emphasis on studies with relevance for the plausibility of traditional use is presented, focussing on more recent publications (after the year 2000 and *in vivo*/*ex vivo* studies).

Sendker *et al*. 2013 claim that flavone-C-glycosides and oligomeric procyanidins are thought to be responsible for the usage of hawthorn preparations, however, since the extracts are classified as "other extracts" according to Ph.Eur. these considerations cannot be followed.

3.1.1. Primary pharmacodynamics

Referring to the indications mentioned in the monograph reflecting the usage of preparations of hawthorn leaves and flowers on mental performance (" … temporary nervous cardiac complaints …" and " mild symptoms of mental stress…") no studies could be found in literature.

3.1.2. Secondary pharmacodynamics

Several cardiac and non-cardiac effects are described for hawthorn preparations. Additionally to the literature reflected below some more reviews also discussing older studies (e.g. Chang *et al*. (2005b); Koch & Malek (2011); Pittler *et al*. (2008); Vogel *et al*. (2005); Frishman *et al*. (2005), and Momekov & Benbassat (2013) are published.

Myocardial contractility (positive inotropic effects + negative chronotropiv effects)

Hawthorn has been found to inhibit the Na^+/K^+ adenosine triphosphatase, which in turn indirectly hampers the activity of the Na^+/Ca^{2+} antiport leading to increased intracellular calcium levels and the positive inotropic effect (Momekov & Benbassat, 2013).

While some authors describe a catecholamine-like activity upon the adenylyl cyclase which leads to an increase in the cAMP-level, which in turn, activates protein kinase A and evokes a series of signal events associated with increased contractility of the cardiomyocytes (Momekov & Benbassat, 2013) other authors could not find such effect (Chang *et al.*, 2005b).

At least some of the cardio-vascular effects of hawthorn extracts are mediated by inhibition of phosphodiesterase as evidenced by different *in vitro* studies. This effect is consistent with reduced rate of cAMP breakdown and hence sustained effects on protein kinase A, and the cAMP–dependent calcium channels and signaling cascades in cardiomyocytes (Momekov & Benbassat, 2013).

Coronary and myocardial perfusion, effects on ischaemia- and reperfusion-induced arrhythmia

Ex vivo

Herbal preparations

Dood *et al.* (2013) measured coronary flow in nonworking perfused rat hearts (Langendorff, constant pressure). The dry extract from hawthorn leafs and flowers tincture (80% aqueous ethanol, no further details) showed an early (30-120 s) vasodilation (5%), followed by a later (3-5 minutes) decrease in

coronary flow (appr. the same rate, dropping below baseline flow). Maximum vasodilation occurred with 240 µg/ml hawthorn extract. Both nitric oxide synthase inhibitors and indomethacin abolished early vasodilation, but they had no effect on the late phase decrease in flow.

In vivo

Herbal preparations

Veveris *et al.* (2004) evaluated the improvement of cardiac function and prevention of myocardial infarction in rats during prolonged ischemia and reperfusion lasting for 240 and 15 minutes, respectively. Oral administration of the 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). The pressure rate product was calculated as the product of mean arterial blood pressure and heart rate. 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%). It was discussed that these pharmacological effects are accounted for by the combined antioxidative, leukocyte elastase inhibiting and endothelial nitric oxide (NO) synthesis enhancing properties of the extract.

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).

Jayachandran *et al.* (2010) evaluated the efficacy and mechanism of a dry extract of *Crataegus oxycantha* (not further specified) in preventing ischemia-reperfusion injury in an *in vivo* rat model of acute myocardial infarction induced by a 30 minutes regional ischemia followed by 72 hours of reperfusion. The test substance used was an ethanolic extract (ethanol 50% V/V) of an unknown extract. 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. At the molecular level, sample administration resulted in a significant attenuation of PTEN (phosphatase and tensin homolog deleted on chromosome 10) and upregulation of phospho-Akt and c-Raf levels in the heart. As a consequence, cleaved caspase-9 and cleaved caspase-7 levels were significantly downregulated, indicating negative regulation of apoptosis by the sample. In part with the hypoxia-inducible factor (HIF) signaling pathway, sample administration significantly upregulated the prolyl hydroxylase-2 level. In contrast, other proapoptotic proteins such as nuclear factor-κB, cytochrome c, apoptosis-inducing factor, and cleaved poly(adenosine diphosphate-ribose) polymerase levels were significantly downregulated in the sample treated group when compared with the untreated control group. It was suggested by the authors that the reduced apoptotic incidence after treatment of rats with the sample is mediated by the regulation of signaling pathways comprising the serine-threonine kinase Akt and hypoxia-inducible factor 1 (HIF-1).

Inhibition of cardiac hypertrophy (caused e.g. by decreased afterload)

In vivo

Herbal preparations

Koch & Spörl-Aich (2006) reported that cardiac hypertrophy (CH) is an adaptive enlargement of the myocardium in response to diverse pathophysiological stimuli such as hypertension, valvular disease or myocardial infarction. Whereas this process is generally a beneficial response that temporarily augments cardiac output, sustained hypertrophy often becomes maladaptive and is a leading cause for the development of heart insufficiency. Activation of the protein phosphatase calcineurin (PP2B) is discussed as a major intracellular signaling pathway that contributes to the growth of cardiomyocytes. Using an *in vitro* test system, it was observed that dry extract from hawthorn leaves and flowers (DER 4-6.6:1, ethanol 45% m/m) inhibits the enzymatic activity of calcineurin. Thus, the effect of *Crataegus* dry extract on the development of CH in animal models of hypertension was investigated. 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 (100 and 300 mg/kg/day). The human equivalent dose (HED) is 16 and 48 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. After euthanisation, the heart was removed and the weights of the entire heart and the left ventricle were obtained. In both experimental models a marked increase of BP as well as enlargement of the heart and the left ventricle were observed. 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.

Hwang *et al.* (2009) determined the effects of hawthorn extract (DER 4-6.6:1; extraction solvent ethanol 45% m/m) on left ventricular remodeling and function in pressure overload-induced heart failure in an animal 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, $p < 0.05$) but not in those given hawthorn 130 mg/kg (<10% increase). After aortic constriction, the velocity of circumferential shortening significantly decreased in the vehicle group but not in the medium- or high-dose groups. In the aortic constriction-vehicle group, the induced increases in messenger RNA expression for atrial natriuretic factor (approximately 1000%) and fibronectin (approximately 80%) were significantly attenuated by high-dose hawthorn treatment by approximately 80% and 50%, respectively.

Fürst *et al.* (2010) aimed to assess the potential of a hawthorn 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.

Antiplatelet activity

In vivo

Herbal preparations (different species)

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 (HED = 16, 32 and 81 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 (HED 161 and 322 mg/kg) and thromboxane B2-levels were increased with 2000 mg/kg.

Endothelial activity

In vivo

Herbal preparations

Bubik *et al.* (2012) investigated the effect of hawthorn extract (DER 4-6.6:1; extraction solvent ethanol 45% m/m) on endothelial barrier-regulating systems. *In vivo*, the extract (100 µg/animal, i.a., bolus) inhibited the histamine-evoked extravasation of FITC-dextran from mouse cremaster muscle venules. In cultured human endothelial cells, this extract blocked the thrombin-induced FITC-dextran permeability. Mechanistically, the extract inhibited the thrombin-induced rise of intracellular calcium (ratiometric measurement), followed by an inactivation of PKC and RhoA (pulldown assay). Moreover, the extract increased endothelial cAMP levels (ELISA), which consequently activated PKA and Rap1 (pulldown assay). It specifically interacts with endothelial permeability-regulating systems by blocking the Ca^{2+}/PKC/RhoA and activating the cAMP/Epac1/Rap1 pathway.

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

In vivo

Herbal preparations

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. The authors discussed the findings in relation to the traditional use of *Crataegus oxyacantha* as a treatment of dyslipidemia and the hyperglycaemia, and related abnormalities in Morocco.

Effects on blood pressure

In vivo

Herbal preparations

Amel *et al.* (2014) investigated the hypotensive effect of an extract of *Crataegus azarolus* leaves (DER 6.9:1; methanol 85%) and several fractions of it (hexane, chloroform, ethylacetate and aqueous) in rats. Animals were treated i.v. (femoral vein) with the methanol extract and ethylacetate fraction (0.04, 0.12, 0.4, 1.2, 4 and 12 mg/kg). The i.v. administration of both preparations decreased the systolic blood pressure, diastolic blood pressure in a dose dependant manner at the range doses of 0.04 to 12 mg/kg body weight. The effect of both preparations was transient, since blood pressure returned to the original baseline after the maximal response was obtained in about 137 ± 3.1 s and 108 ± 5.2 s for ethylacetate fraction and methanol extract, respectively.

3.1.3. Safety pharmacology

A 60% methanol extract of the flowers (no further information) 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, the clinical impact of this data is unknown (Momekov & Benbassat, 2013).

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 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, no further information) and the other was made from the berries only (brand 2, no further information). 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. Information about the extracts were not available, therefore the relevanve of these results was regarded as limited.

3.1.5. Conclusions

No non-clinical studies exist which would support the usage of hawthorn leaves and flowers preparations in conditions related to nervousness or stress. However, some studies on extracts, its fractions and isolated constituents of hawthorn leaves and flowers have been conducted in *in vitro* and in animal models connected to cardiovascular conditions. However, in most of the experiments relatively high concentrations were used and *in vitro* experiments did not take into account pharmacokinetic aspects. However, at least the tests published are not contrary to the usage of preparations from hawthorn leaves and flowers.

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 radioactivy 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. The absorption rate for the OPC total fraction was about 31%, and those for individual substances ranged from 16 to 40%. After repeated oral administration, the accumulation of radioactivity was higher than after a single dose.

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* 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 possible alterations of the pharmacokinetics of a given active herbal substance when administered in an combined form as compared to that when administered as a pure compound. 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 the 2 formulations. The authors discussed that the differences in the pharmacokinetics of the 2 formulations 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).

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) observerd 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 feces 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 feces) for VOG and 89.01% (0.72% in urine; 88.29% in feces) 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.

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) investigated acute oral toxicity by standard methods in a "limit-test" dosing of 3000 mg/kg ethanolic dry extract from hawthorn leaves and flowers (4-6.6:1, ethanol 45% m/m) in 1% carboxymethylcellulose by gavage to groups of five male and five female rats (Sprague-Dawley, CD strain) and five male and five female mice (NMRI).
In these limit tests, 3000 mg/kg could be given to rats and mice by the oral route without causing clinical signs or death. By the intraperitoneal route, sedation, piloerection, dyspnea, and tremor were recorded in both the mouse and the rat; an LD_{50} value of 1170 mg/kg was calculated in the mouse and 750 mg/kg in the rat.

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.

Rats

Dry extract from hawthorn leaves and flowers (4-6.6:1, ethanol 45% m/m) was given to groups of 20 male and 20 female Sprague-Dawley rats (CD strain) at dosage levels of 30, 90, or 300 mg/kg/day. A fourth group receiving the vehicle only served as controls. The compound was given by gavage at a dosage volume of 10 ml/kg in 1% methylcellulose daily for 26 weeks.

Clinical signs as well as food and water consumption were monitored throughout the study. Body weight was determined weekly to week 14 and thereafter at 4-week intervals to week 26. Ophthalmoscopic examinations were carried out after 4, 13, and 26 weeks of compound administration, with hematologic and biochemical examinations at the same intervals. Urinanalysis was conducted. Post-mortem examination included weighing and histological examinations of several organs and tissues.

Dogs

Thirty-two beagles, equally divided with respect to sex, were assigned to four groups, three of which received dry extract from hawthorn leaves and flowers (4-6.6:1, ethanol 45% m/m) at dosage levels of 30, 90, or 300 mg/kg/day, respectively. *Crataegus* dry extract was administered orally in gelatin capsules. A fourth group received empty gelatin 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.

Hematological and biochemical examinations before dosing, as well as after 13 and 26 weeks of dosing.

After six months´ dosage, the dogs from each group were sacrificed. Post-mortem examination included weighing of several organs. A wide range of tissues were prepared for routine histologic examination.

Results

After administration of *Crataegus* dry extract to rats and beagles at doses of 30, 90, or 300 mg/kg/day, respectively, for 26 weeks, no abnormalities in clinical, chemical, hematological, gross morphological, and histological findings were observed.

Kanyonga *et al*. (2011) investigated the effects of the extract of *Crataegus oxyacantha* (DEV 3:1; methanol) in rats by monitoring blood homeostasis and body weight as well as toxicity. 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.

3.3.3. Genotoxicity

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 (4-6.6:1, 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 pretreated male rats) and the experiment was performed twice on separate dates. The results showed that the Ames test was negative.

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 (4-6.6:1, 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 *Crataegus* dry extract has no mutagenic potential in this mammalian gene mutation assay *in vitro*.

In a cytogenetic analysis in cultured human lymphocytes the dry extract from leaves and flowers (4-6.6:1, 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*.

In the mouse micronucleus assay CD-1 mice received a single oral dose of 5000 mg/kg by intra-gastric gavage of the dry extract from leaves and flowers (4-6.6:1, 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.

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 hawthorn leaf preparation (*Crataegus monogyna*) to the developing foetus (*in vivo*) and to whole embryo cultures (*ex vivo*).

For the *in vivo* study a hawthorn leaf 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).

Since the dry extract was dissolved in ethanol 45% m/m the control group was treated with an equal amount of ethanol 45% m/m.

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 fetal observation was a significant effect of treatment on mean fetal 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 relevant data available

3.3.7. Other special studies

No relevant data available

3.3.8. Conclusions

For most extracts listed in the monograph no toxicological data are available.

Only for one monograph relevant hawthorn preparation (*Crataegus* dry extract, DER 4-6.6:1, ethanol 45% m/m) toxicological data were published. Single dose toxicity tests with that extract indicated the following data: no lethality was observed at doses up to 3 g *Crataegus* extract per kg body weight after oral and intraperitoneal administration in rats and mice. Sedation, piloerection, dyspnoea and tremor were observed after intraperitoneal application.

The oral administration of that ethanolic dry extract from hawthorn leaves and flowers in doses up to 300 mg/kg body weight per day for 26 weeks induced no toxic symptoms in rats and dogs.

Tests on genotoxicity have not been performed for all except one preparation listed in the monograph.

The dry extract (4-6.6:1, ethanol 45% m/m) was negative in the AMES assay (TA 1535, TA 1537, TA 1538, TA 98, and TA 100), the the mouse lymphoma assay and the cytogenetic analysis assay (all *in vitro*) and also turned out to be negative in the 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

No studies exist to support the traditional indications in the area of nerveous or stress related conditions. Results from experimental studies on *Crataegus* spp. models connected to cardiovascular diseases exist although the value of the results is very limited, due to the high dosages/concentrations used or the *in vitro* test systems lacking important factors such as absorption. The reported pharmacological effects are not considered contradictory to the traditional uses. None of the reported pharmacological studies constitute any cause for safety concern.

Limited data on pharmacokinetics are available on isolated compounds after intravenous and oral administration. Therfore, no statement on pharmacokinetic of *Crataegus* leaves and flowers preparations can be made.

Toxicological data exist only for the dry extract (DER 4-6.6:1, ethanol 45% m/m). With this extract studies concerning acute and sub-chronic toxicity and genotoxicity (*in vitro* and *in vivo*) have been performed. The genotoxicity testing revealed no concern for this extract.
Tests on carcinogenicity and reproductive and developmental toxicity have not been performed. As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

The oral administration of *Crataegus* leaves and flowers preparations can be regarded as safe under conditions of use that are described in the monograph.

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

Dry extract (4-6.6:1, ethanol 45% m/m):

Brixius *et al.* (1998) investigated the effect of *Crataegus* dry extract (4-6.6:1, 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). *Crataegus* extract significantly increased force of contraction [basal: 1.8 ± 0.2 mN, *Crataegus* 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 *Crataegus* 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, *Crataegus* extract (50 µg/ml) +0.9 ± 0.3 mN).

Schmidt-Schweda *et al*. (2000) analysed the effect of an ethanolic dry extract (4-6.6:1, ethanol 45% m/m) and different sub-extracts for the relative shortening of enzymatically isolated human myocytes ("Chunck"-method) 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). *Crataegus* 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.

Schwinger *et al.* (2000) examined the mode of inotropic action of ethanolic dry extract (4-6.6:1, 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; *Crataegus* 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 Ca2+-transient and force generation. These effects also were observed in the lipophilic ethyl acetate-soluble fraction A, enriched in flavone derivatives.

Vasorelaxation

Ex vivo

Dry extract (4-6.6:1, ethanol 45% m/m):

Brixius *et al.* (2006) investigated the influence of a dry extract (DER 4-6.6:1; extraction solvent ethanol 45% m/m) on the relaxation of human mammarian 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. WS 1442 induced a concentration-dependent vasodilation in isolated vessel rings that had been precontracted by 10 µM phenylephrine (concentration for halfmaximal 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.

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

No relevant data available

4.2. Clinical efficacy

Since many years preparations from hawthorn leaves and flowers are discussed and used as treatment option for chronic heart failure.

Definition

European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure (ESC, 2012):
Heart failure (HF) can be defined as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolising tissues, despite normal filling pressures (or only at the expense of increased filling pressures). For the purposes of these guidelines, HF is defined, clinically as a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated apex beat) resulting from an abnormality of cardiac structure or function. Approximately 1-2% of the adult population in developed countries have HF, with the prevalence rising to ≥10% among persons 70 years of age or older.
The goals of treatment in patients with established HF are to relieve symptoms and signs (e.g. oedema), prevent hospital adminission, and improve survival.

Treatments that are recommended in potentially all patients with systolic heart failure are: an ACE inhibitor, a beta-blocker, and a mineralocorticoid/aldosterone receptor antagonist (MRA). They are commonly used in conjunction with a diuretic given to relieve the symptoms and signs of congestion. Other treatments are valuable in patients with systolic HF that have not been shown clearly to reduce all-cause mortality. Most of these drugs have shown convincing benefits in terms of symptom reduction, HF hospitalisation, or both, and are useful alternative or additional treatments in patients with HF. These are angiotensin receptor blockers (ARBs), ivabradine, digoxin and other digitalis glycosides, combination of hydralazine and isorbade dinitrate and omega-3 polyunsaturated fatty acids.

A Guideline concerning the clinical investigation of medicinal products for the treatment of cardiac failure exist (e.g. CPMP/EWP/235/95 Rev. 1). The preferred primary endpoints in such studies are:

- clinical symptoms
- cardiovascular morbidity
- 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 demontstrate efficacy in relation to symptomatic benefit or cardiovascular morbidity a minimum duration of 6 month is mandatory for such a study.

4.2.1. Dose response studies

See section 4.2.2.

4.2.2. Clinical studies (case studies and clinical trials)

4.2.2.1. Placebo controlled studies

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

Holubarsch *et al.* (2008) investigated the efficacy and safety of *Crataegus* dry extract (4-6.6:1, ethanol 45% m/m) in a randomised, double-blind placebo-controlled and multicenter 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. Nevertheless, cardiac mortality was significantly reduced after 6 (p = 0.009) and 18 months (p = 0.046). 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.

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 *Crataegus* dry extract (4-6.6:1, ethanol 45% m/m) 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 favor 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.

Tauchert (2002) investigated whether long-term therapy with *Crataegus* dry extract is efficacious 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.

Zapfe jun. (2001) investigated the clinical efficacy and safety of *Crataegus* dry extract (4-6.6:1, ethanol 45% m/m) 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.

Weikl *et al*. (1996) treated 136 patients with NYHA II heart failure in a multicenter, randomised, placebo-controlled, and double-blind study with *Crataegus* dry extract (4-6.6:1, ethanol 45% m/m) 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.

Leuchtgens (1993) investigated in a randomised, placebo-controlled and double-blind study *Crataegus* dry extract (4-6.6:1, ethanol 45% m/m) 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 ($p < 0.05$).

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 *Crataegus* dry extract (4-6.6:1, ethanol 45% m/m). Hawthorn extract 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.

O'Conolly *et al*. (1986) tested in a placebo-controlled, double-blind, randomised and cross-over study the efficacy of *Crataegus* dry extract (4-6.6:1, ethanol 45% m/m) versus placebo. 36 multimorbid patients (62-84 years) suffering from chronic congestive heart failure according to NYHA I-II received 3 x 60 mg/day extract 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 active substance 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).

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 (4-7:1, methanol 70% V/V) 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.

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 (4-7:1, methanol 70% V/V) 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.

Bödigheimer & Chase (1994) examined the effectiveness of a dry extract (4-7:1; methanol 70% V/V) at a dosage of 3 x 100 mg per day over a 4-week period. In a randomised, double-blind, placebo-controlled, multicenter 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).

Other extracts

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 and water, standardised to 50 mg oligomeric procyanidin per 250 mg extract) in a a four-period cross-over design. 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. 21 prehypertensive or mildly hypertensive adults completed the study. 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).

4.2.2.2. Reference-controlled studies

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

Tauchert *et al*. (1994) compared the effectiveness of a dry extract (4-7:1, methanol 70% V/V) with the ACE inhibitor captopril in a multicenter, 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.

4.2.2.3. Open, controlled studies

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

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 hawthorn extract/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.

4.2.2.4. Non-controlled studies

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

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 *Crataegus* dry extract (4-6.6:1, 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 multicenter utilisation observational study 1011 patients with NYHA II heart failure. Patients were treated with 2 x 450 mg *Crataegus* dry extract (4-6.6:1, ethanol 45% m/m) per day for 24 weeks. Efficacy parameters evaluated were the clinical symptoms: decline in physical performance, fatigue, exercise-induced dyspnea, 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 dyspnea 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 *Crataegus* dry extract (4-6.6:1, 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.

4.2.2.5. Pooled and meta-analyses

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

Eggeling *et al.* (2011) evaluated in the present 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 *Crataegus* dry extract (4-6.6:1, ethanol 45% m/m) or placebo in 687 patients were pooled. 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, exetional dyspnea, 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 by baseline differences.

Table 5: Clinical studies on humans, in chronic congestive heart failure (NYHA I-III)

Type	**Study**	**Test product(s):**	**Number of subjects**	**Type of** subjects	**Outcomes**	**Statistical analysis**	**Clinical relevance**
Härtel *et al*. (2014)	open, controlled duration: 8 weeks	dry extract (4-6.6:1, ethanol 45% m/m), adjusted to 17.3-20.1% OPC 2 x 450 mg/day	add-on treatment: 70 patients standard treatment: 70 patients age: 62±9.0 add-on 62±7.8 standard drop outs: 5 add-on 8 standard	Chronic congestive heart failure (NYHA II).	no primary endpoint defined improvements of symptoms and quality of life tended to be larger with training and extract compared to training alone; most pronounced difference in subscore "symptoms" (dyspnoea, fatigue, ankle swelling) of the Kansas City Cardiomyopathy Questionnaire (KCCQ)	treatment effects in the training only group = Wilcoxon rank sum test parameters measured at every exercise level = are reported descriptively group differences in treatment effects = explored by repeated measurements ANOVA	Secondary endpoints according to ESC (2012) were examined.
Holubarsch *et al*. (2008)	placebo-controlled, double-blind, randomised, multicenter duration: 2 years	dry extract (4-6.6:1, ethanol 45% m/m), adjusted to 17.3-20.1% OPC 2 x 450 mg/day or placebo	verum: 222 female 1116 male placebo: 213 female 1130 male age: 59.8±10.6 verum 60.4±10.7 placebo drop outs:	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%	Time until first cardiac was evaluataed by Kaplan-Meier survival analysis. Treatment groups were compared using a log-rank test stratified fr countries. This test was performed on the ITT analysis set which	No significant effect on the primary endpoint.

Type	**Study**	**Test product(s):**	**Number of subjects**	**Type of** subjects	**Outcomes**	**Statistical analysis**	**Clinical relevance**
			378 verum 397 placebo			included all randomised patints to confirm the primary hypothesis.	
Zick *et al.* *(*2009)	placebo-controlled, double-blind, randomised duartion: 6 months	dry extract (4-6.6:1, ethanol 45% m/m) 2 x 450 mg/day or placebo	verum: 14 female 46 male placebo: 16 female 44 male age: 54.4±12.6 verum 57.8±9.0 placebo drop outs: 6 verum 3 placebo	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 treadmill exercise testing, NYHA classification, left ventricular ejection fraction, neurohormones, and measures of oxidative stress and inflammation No significant differences between groups in the change in 6 min walk distance (p = 0.61), or on measures of QOL, functional capacity, neurohormones, oxidative stress, or inflammation. A modest difference in LVEF favoured hawthorn (p = 0.04).	Analyses were conducted according to the ITT principle when possible (i.e. fro deaths, hospitalisations and AEs). No imputation was performed for missing values at 6 months.	No significant effect on the primary endpoint.

Type	**Study**	**Test product(s):**	**Number of subjects**	**Type of** subjects	**Outcomes**	**Statistical analysis**	**Clinical relevance**
Tauchert (2002)	placebo-controlled, double-blind, randomised, multicenter duration: 16 weeks	dry extract (4-6.6:1, ethanol 45% m/m), adjusted to 18.75% OPC 2 x 900 mg/day or 2 x 450 mg/day or placebo	verum 1 (1800 mg): 47 female 22 male verum 2 (900 mg): 45 female 25 male placebo: 50 female 20 male age: 67.1±9.0 verum 1 67.4±10.7 verum 2 68.4±8.5 placebo drop outs: 1 verum 1 7 verum 2 4 placebo	Chronic congestive heart failure (NYHA III).; >6 months; exercise capacity ≤75 watts	Change from baseline in the maximal tolerated workload during bicycle exercise. significant increase of maximal tolerated workload: verum 1: 52.2% of patients verum 2: 34.3% of patients placebo 42.9% of patients	The primary analysis was based on the ITT principle.	Secondary endpoints according to ESC (2012) were examined.
Zapfe jun. (2001)	placebo-controlled, double-blind, randomised, parallel-group,	dry extract (4-6.6:1, ethanol 45% m/m), adjusted to 18.75% OPC 3 x 80 mg/day or placebo	verum: 15 female 5 male placebo: 14 female 6 male	Chronic congestive heart failure (NYHA II).	change of exercise tolerance (determined with bicycle exercise testing): verum: increase by 10.8% (from 616.3 to	Confirmatory analysis was performed to the ITT principle.	Secondary endpoints according to ESC (2012) were examined.

Type	Study	Test product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
	multicenter duration: 12 weeks		age: 58.2±10.6 verum 66.5±11.0 placebo drop outs: 1 placebo		682.5 W x min) placebo: decrease by 16.9% (from 623.8 to 527.6 W x min)		
Weikl *et al.* (1996)	placebo-controlled, double-blind, randomised, multicenter duration: 8 weeks	dry extract (4-6.6:1, ethanol 45% m/m), adjusted to 18.75% OPC 2 x 80 mg/day or placebo	verum: 49 female 18 male placebo: 49 female 20 male 40-80 years age: 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 by 5.6 mmHg/min/100 [from 67.0 to 61.4 mmHg/min/100]) placebo: worsening (mean increase by 4.2 mmHg/min/100 [from 63.8 to 68 mmHg/min/100])	Working hypothesis was performed to the ITT principle with Rank-Sum test according to Wilcoxon-Mann-Whitney. CI 95%	Secondary endpoints according to ESC (2012) were examined.
Schmidt *et al.* (1994)	placebo-controlled, double-blind, randomised, multicenter duration: 8 weeks	dry extract (4-7:1, methanol 70% V/V) 3 x 200 mg/day or placebo	verum: 26 female 14 male placebo: 22 female 16 male age: 60.4±6.5	Chronic congestive heart failure (NYHA II).	increase in exercise tolerance (determined with bicycle exercise testing): verum: by 28 W (from 79 to 107 W) placebo: by 5 W (from 71 to 76 W)	Wilcoxon test (Comparison of check-up times in the medication groups) and Mann-Whitney U test (Comparison of medication groups).	Secondary endpoints according to ESC (2012) were examined.

Type	**Study**	**Test product(s):**	**Number of subjects**	**Type of** subjects	**Outcomes**	**Statistical analysis**	**Clinical relevance**
			verum 60.3±7.7 placebo				
Förster *et al.* (1994)	placebo-controlled, double-blind, randomised duration: 8 weeks	dry extract (4-7:1, methanol 70% V/V) 3 x 300 mg/day or placebo	verum: 19 female 16 male placebo: 20 female 14 male age: 49.8±9.1 verum 52.0±10.7 placebo drop outs: 1 verum 2 placebo	Moderately reduced left ventricular ejection fraction (NYHA II).	Oxygen uptake as well as the tolerance period until the patients reached the anaerobic threshold and when exercise was discontinued. increase in exercise time taken to reach the anaerobic threshold: verum: 30 s (from 280 to 310 s) placebo: 2 s (from 275 to 277 s) improvement of the oxygen uptake: verum: by 75% of patients placebo: 42% of patients	Parameters with arithmetic mean values, standard deviations, minima and maxima. Results were examined on significance before and after administration with t-test according to student and chi-squared test (paired comparison).	Secondary endpoints according to ESC (2012) were examined.
Bödigheimer & Chase (1994)	placebo-controlled, double-blind, randomised, multicenter duration: 4 weeks	dry extract (4-7:1, methanol 70% V/V) 3 x 100 mg/day or placebo	verum: 26 female 10 male placebo: 25 female 12 male age: 61.1±10.8	Chronic congestive heart failure (NYHA II).	bicycle ergometry exercise tolerance; in addition, the typical symptoms as well as tolerability and final global assessment by the investogators and patients Exercise tolerance,	Parameters with arithmetic mean, mean values, standard deviations, minima and maxima or rather with absolute or relative frequency.	Secondary endpoints according to ESC (2012) were examined.

Type	**Study**	**Test product(s):**	**Number of subjects**	**Type of** subjects	**Outcomes**	**Statistical analysis**	**Clinical relevance**
			verum 62.1±9.6 placebo drop outs: 6 verum 6 placebo		pressure-rate product and clinical symptomatology showed a trend toward – but no statistically significant – superiority of verum over placebo.		
Leuchtgens (1993)	placebo-controlled, double-blind, randomised duration: 8 weeks	dry extract (4-6.6:1, ethanol 45% m/m), adjusted to 18.75% OPC 2 x 80 mg/day or placebo	verum: 7 female 8 male placebo: 5 female 10 male age: 66.0±8.3 verum female 67.9±6.1 verum male 61.6±5.9 placebo female 66.8±6.6 placebo male drop outs: not specified	Chronic congestive heart failure (NYHA II).	decrease in pressure-heart rate product: verum: by 24% placebo: by 7% improvement of symptoms (von Zerssen symptom score): verum: by 16.5 points (from 38 to 21.5) placebo: by 4 points (from 31 to 27)	Null hypotheses were examined by the adaptive rank tests according to Hogg-Büning.	Secondary endpoints according to ESC (2012) were examined.
O´Conolly *et al.* (1987)	placebo-controlled, double-blind, randomised, cross-over	dry extract (4-6.6:1, ethanol 45% m/m) 3 x 60 mg/day or placebo	group A (verum-placebo): 13 female 5 male	Chronic congestive heart failure (NYHA I-II).	change in the pressure-heart rate product: verum 25 W: −11% placebo 25 W: +3% verum 50 W: −11%	T-test for the statistical analysis of therapyrelated influences on cardiovascular	Secondary endpoints according to ESC (2012) were

Type	**Study**	**Test product(s):**	**Number of subjects**	**Type of** subjects	**Outcomes**	**Statistical analysis**	**Clinical relevance**
	duration: 6 weeks		group B (placebo-verum): 14 female 4 male age: 74.0±4.8 group A 74.0±5.1 group B drop outs: no drop outs		placebo 50W: 0%	parameters. Analysis of variance for changes in NOISE and BPRS scores independent of treatment.	examined.
Tauchert *et al.* (1994)	reference-controlled, double-blind, randomised, multicenter duration: 8 weeks	dry extract (4-7:1, methanol 70% V/V) 3 x 300 mg/day or 3 x 12.5 mg/day captopril	verum: 36 female 32 male reference: 43 female 21 male age: 62±6 verum 63±5 reference drop outs: 3 verum 5 reference	Chronic congestive heart failure (NYHA II).	increase of workload: verum: by 14 W (from 83 to 97 W; $p < 0.001$) reference: by 16 W (from 83 to 99 W; $p < 0.001$)	For measurements arithmetic mean, standard deviation, min. and max. was calculated. For categorisation variables a frequency distribution was specified. For parameters that were collected at several control times only those patients were included that values were available at each measurement	Secondary endpoints according to ESC (2012) were examined.

Type	Study	Test product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
						point. Statistical assurance of differences for the non parametrical varibales was carried out with the Wilcoxon test (comparison of control times in the test group and in the control group) and the Mann-Whitney U test (comparison of treatment groups with each other). For categorisation variables the McNemar test and the chi-squared test was used.	

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

See section 4.2.2.

4.4. Overall conclusions on clinical pharmacology and efficacy

Clinical pharmacology

In clinical *in vitro* investigations the inotropic effect of *Crataegus* dry extract (4-6.6:1, ethanol 45% m/m) and different sub-extracts was observed on the basis of the following results: an increase in force of contraction, an improvement of the frequency-dependent force generation and enhancement of dose-dependent relative shortening of myocytes in the atrium myocardium as well as in the ventricular myocardium.

Clinical efficacy

The indications specified in the above mentioned clinical trials and the reported well-established use for hawthorn extract cannot be regarded as proven by the available data.

Conventional treatment protocols for HF have undergone modifications in the last 15-20 years. By now ESC (2012) states that three neurohumoral antagonists - an ACE inhibitor (or angiotensin receptor blocker), a beta-blocker, and a mineralocorticoid receptor antagonist - are fundamentally important in modifying the course of systolic HF and should at least be considered in every patient (NYHA II-IV). They are commonly used in conjunction with a diuretic given to relieve the symptoms and signs of congestion. Monotherapy or therapy with hawthorn products is not foreseen. Since these recommendations can not be ignored the existing studies concerning efficacy of hawthorn monotherapy have to be evaluated very critically since international and national established guidelines require already in class NYHA II obligatory an effective heart failure therapy (endpoints). A therapy not guideline-conform is already seen as associated with an increased mortality.

It is to point out, that all the studies mentioned in 4.2.2, which used hawthorn extracts as monotherapy, secondary endpoints according to ESC (2012) were examined. However, the goals of treatment should be to relieve symptoms and signs (e.g. oedema), to prevent hospital admission and to improve survival. The studies were not designed to investigate such primary endpoints.

The HERB CHF-trial investigated secondary endpoints according to ESC (2012) in patients receiving conventional medical therapy and hawthorn or conventional medical therapy and placebo. The primary outcome (change in 6 minutes walk distance at 6 months) was not influenced by co-medication with hawthorn (endpoint not conform to ESC 2012). That also applied to the secondary outcomes included quality of life measures, peak oxygen consumption, and anaerobic threshold during maximal treadmill exercise testing, NYHA classification, left ventricular ejection fraction (LVEF), neurohormones, and measures of oxidative stress and inflammation.

The SPICE-study investigated the primary outcome “time until first cardiac event” for a hawthorn preparation in a dosage comparable to the authorised products as add-on therapy to a guideline-conform basic therapy in 2500 patients with chronic heart failure (NYHA II-III) for 2 years. Results of the SPICE-study allow no other assessment that the use of *Crataegus* in patients with chronic heart failure (NYHA II-III) achieves no statistically significant benefit compared to placebo. This applies not only for the primary outcome, but also for symptoms of heart failure and quality of life parameter (secondary outcomes).

Taken together, the results of previous studies, which have also been the basis for the monograph of commission E (1994) and therefore the basis for the well-established use indications of the German

products, can no longer sufficiently prove the efficacy of *Crataegus* in the claimed indication. Justification therefore is that in previous studies only surrogate parameter (ergometer capacity, pressure-rate product etc.) were investigated. These are no longer sufficient to current knowledge and to corresponding guidelines (ESC 2012, CPMP/EWP/235/95 Rev.1).

The fact, that in the SPICE-study *Crataegus* was only tested as add-on leads to no other assessment. It is rather to point out that such a supplemental usage of hawthorn is not explicitely authorised. Also no traditional use exists for such a co-medication.

According to current information a negative benefit/risk balance has to be taken because of the absence of therapeutic efficacy of *Crataegus* treatment in a disease which obligatory requires a therapy, which is afflicted with an extensive mortality; this is already the case in NYHA II.

Traditional use:

Data provided by the Member States and data from text books prove a long history of usage of hawthorn preparations in indications linked to heart. From older monographs, e.g. Commission E monographs on hawthorn flowers and hawthorn leaves (Commission E, 1994), textbooks and products the traditional usage in nervous heart complaints can be deduced. That is also mentioned in more recent publications (e.g. Kraft, 2006) and covered by traditional registrations in the Member States. Therefore, MLWP/HMPC agreed to accept the long-lasting usage (even in the indication bound to "NYHA II") as proof of tradition in the indication "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". Also the second traditional indication based on the traditional use in France refers to the calmative effects of hawthorn "Traditional herbal medicinal product for relief of mild symptoms of mental stress and to aid sleep".

5. Clinical Safety/Pharmacovigilance

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

Fischer *et al*. (1994) assessed the effects of a hawthorn extract (900 mg; DER 4-7:1, 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.

Koller *et al*. (2005) investigated the influence of treatment with *Crataegus* dry extract (4-6.6:1, ethanol 45% m/m) on quality of life and disease specific symptoms (performance impairment, fatigue, exertion dyspnoe 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.

Daniele *et al.* (2006) assessed systematically safety data from 24 clinical studies on hawthorn monopreparations. 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 (4-6.6:1, ethanol 45% m/m) and *Crataegus* dry extract from hawthorn leaves and flowers (4-7:1, methanol 70% V/V). A total of 166 adverse events were reported. Most of these adverse events were, in general, mild to moderate; eight severe adverse events have been reported with the methanolic *Crataegus* extract. 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).

Pittler *et al*. (2008) assessed systematically safety data from 14 clinical studies 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. Most of these studies are already mentioned in this AR.

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 *Crataegus 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 *Crataegus laevigata* group compared to the placebo group. In the *Crataegus 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 ($p < 0.0001$). *Crataegus 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 *Crataegus 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 leas 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.

Table 6: Clinical safety data from clinical trials or observational studies

Type	Study	Test product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
Härtel *et al*. (2014)	open, controlled duration: 8 weeks	dry extract (4-6.6:1, ethanol 45% m/m), adjusted to 17.3-20.1% OPC 2 x 450 mg/day	add-on treatment: 70 patients standard treatment: 70 patients age: 62±9.0 add-on 62±7.8 standard drop outs: 5 add-on 8 standard	Chronic congestive heart failure (NYHA II).	frequency of adverse events: add-on treatment: 13% of patients standard treatment: 17% of patients One serious adverse event (bacterial urogenital infection) was considered unrelated to hawthorn events probably or possibly related to hawthorn or drug interactions were not reported throughout the trial	No significant differences in any specific category of AEs.
Dalli *et al*. (2011b)	reference-controlled, cross-over duration: 15 days each with 2 weeks between treatments	comminuted herbal substance 3 x 800 mg/day or 1 x 100 mg aspirin	verum/reference: 7 female 9 male age: 30±8 drop outs: no drop outs	healthy subjects	no AEs	
Dalli *et al*. (2011a)	placebo-controlled, double-blind, randomised duration: 6 months	comminuted herbal substance 3 x 400 mg/day or placebo added to conventional treatment	verum: 4 female 20 male placebo: 3 female 18 male age: 61.3±8.3 verum	diabetic patients with chronic coronary heart disease (NYHA I)	no AEs	

Type	Study	Test product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
			60.4±8.2 placebo drop outs: 1 verum 3 placebo			
Holubarsch *et al*. (2008)	placebo-controlled, double-blind, randomised, multicenter duration: 2 years	dry extract (4-6.6:1, ethanol 45% m/m), adjusted to 17.3-20.1% OPC 2 x 450 mg/day or placebo	verum: 222 female 1116 male placebo: 213 female 1130 male age: 59.8±10.6 verum 60.4±10.7 placebo drop outs: 378 verum 397 placebo	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%) In both groups the most frequently reported AEs were cardiac disorders (verum 30.3%, placebo 30.7%), metabolic and nutritional disorders (16.5% and 17.2%, e.g., hypercholesterolaemia, hyperlipidaemia), infections (13% and 16.2%, e.g., influenza, bronchitis), and by general disorders (10.2% and 11.9%, e.g., chest pain, pyrexia).	No significant differences in any specific category of AEs that differed in frequency between placebo and hawthorn groups.
Zick *et al.* (2009)	placebo-controlled, double-blind, randomised duration: 6 months	dry extract (4-6.6:1, ethanol 45% m/m) 2 x 450 mg/day or placebo	verum: 14 female 46 male placebo: 16 female 44 male	Chronic congestive heart failure (NYHA II-III).	Significantly more total AEs were reported in the hawthorn group (36 vs. 23, p = 0.02), most were non-cardiac.	No significant differences in any specific category of AEs that

Type	Study	Test product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
			age: 54.4±12.6 verum 57.8±9.0 placebo drop outs: 6 verum 3 placebo			differed in frequency between placebo and hawthorn groups.
Koller *et al.* (2005)	open, observational, multicenter duration: 6 months	dry extract (4-6.6:1, ethanol 45% m/m) 2 x 450 mg/day and/or several commonly used therapy options such as diuretics, acetyl salicylic acid, heart glykosides, clopidrogel etc.	verum: 196 female 155 male references: 201 female 159 male 158 patient pairs after matching age: 67.9 verum 67.7 references	NYHA II cardiac insufficiency and concomitant 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	no direct information about AE quality of life of the patients and cardinal symptoms of CHD improved in the hawthorn cohort to a significantly greater extent than in the comparison cohort direct costs in the hawthorn cohort were appreciably lower due to less frequent hospitalisation	

Type	Study	Test product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
Tauchert (2002)	placebo-controlled, double-blind, randomised, multicenter duration: 16 weeks	dry extract (4-6.6:1, ethanol 45% m/m), adjusted to 18.75% OPC 2 x 900 mg/day or 2 x 450 mg/day or placebo	verum 1 (1800 mg): 47 female 22 male verum 2 (900 mg): 45 female 25 male placebo: 50 female 20 male age: 67.1±9 verum 1 67.4±10.7 verum 2 68.4±8.5 placebo drop outs: 1 verum 1 7 verum 2 4 placebo	Chronic congestive heart failure (NYHA III). >6 months; exercise capacity ≤75 watts	Incidence of AEs was lowest in the verum 1 group. The most marked difference was observed for dizziness and vertigo (1.4% verum 1, 4.3% verum 2, 10% placebo). Difference in the number of AEs reported was statistically significant for both of the verum groups versus the placebo group (23 in verum 1, 30 in verum 2, 54 in placebo).	no serious AEs
Zapfe jun. (2001)	placebo-controlled, double-blind, randomised, parallel-group, multicenter duration: 12 weeks	dry extract (4-6.6:1, ethanol 45% m/m), adjusted to 18.75% OPC 3 x 80 mg/day or placebo	verum: 15 female 5 male placebo: 14 female 6 male age: 58.2±10.6 verum 66.5±11.0 placebo drop outs: 1 placebo	Chronic congestive heart failure (NYHA II).	verum: no AE placebo: One drop out because of an allergic skin reaction.	

Type	Study	Test product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
Weikl *et al.* (1996)	placebo-controlled, double-blind, randomised, multicenter duration: 8 weeks	dry extract (4-6.6:1, ethanol 45% m/m), adjusted to 18.75% OPC 2 x 80 mg/day or placebo	verum: 49 female 18 male placebo: 49 female 20 male age: 65.5 verum 65.3 placebo drop outs: 4 verum 3 placebo	Chronic congestive heart failure (NYHA II).	AEs were mild to moderate (in 6 patients in the placebo group and in 3 patients in the verum group). verum: 1) swelling of the lower ankle, exertional dyspnea, inner agitaion 2) stomach complaints, inner agitation 3) temporary tachycardia with dizziness, dyspnea and hot flush placebo: 1) dizziness, concentration disorders 2) inner agitation, anxiety 3) stomach pain, nausea 4) peeling of the skin on the hands 5) pressure pain in thighs 6) burning left-thoracic without radiation	
Schmidt *et al.* (1994)	placebo-controlled, double-blind, randomised, multicenter duration: 8 weeks	dry extract (4-7:1, methanol 70% V/V) 3 x 200 mg/day or placebo	verum: 26 female 14 male placebo: 22 female 16 male age: 60.4±6.5 verum 60.3±7.7 placebo drop outs primary endpoint: 4 verum 4 placebo	Chronic congestive heart failure (NYHA II).	2 AEs in both groups verum: nausea, once-only heart complaints placebo: dryness of the mouth, agitation	

Type	Study	Test product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
Förster *et al.* (1994)	placebo-controlled, double-blind, randomised duration: 8 weeks	dry extract (4-7:1, methanol 70% V/V) 3 x 300 mg/day or placebo	verum: 19 female 16 male placebo: 20 female 14 male age: 49.8±9.1 verum 52.0±10.7 placebo drop outs: 1 verum 2 placebo	Moderately reduced left ventricular ejection fraction (NYHA II).	No relevant AEs in both groups.	-
Bödigheimer & Chase (1994)	placebo-controlled, double-blind, randomised, multicenter duration: 4 weeks	dry extract (4-7:1, methanol 70% V/V) 3 x 100 mg/day or placebo	verum: 26 female, 10 male placebo: 25 female 12 male age: 61.1±10.8 verum 62.1±9.6 placebo drop outs: 6 verum 6 placebo	Chronic congestive heart failure (NYHA II).	in 4 patients mostly unspecific AEs verum: 1) increased migaine, nausea, flatulence 2) palpitations placebo: 1) stomach pain 2) stomach pressure, abdominal fullness, nausea	no serious AEs
Fischer *et al*. (1994)	reference- and placebo controlled, cross-over duration: single dosage	dry extract (4-7:1, methanol 70% V/V) 1 x 900 mg/day or 0.3 mg medigoxin or pacebo	verum/reference: 7 female, 5 male age: 24.7±4.0 drop outs: no drop outs	healthy subjects	no AEs	

Type	Study	Test product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
Leuchtgens (1993)	placebo-controlled, double-blind, randomised duration: 8 weeks	dry extract (4-6.6:1, ethanol 45% m/m), adjusted to 18.75% OPC 2 x 80 mg/day or placebo	verum: 7 female 8 male placebo: 5 female 10 male age: 66.0±8.3 verum female 67.9±6.1 verum male 61.6±5.9 placebo female 66.8±6.6 placebo male drop outs: not specified	Chronic congestive heart failure (NYHA II).	no AEs	
O´Conolly *et al.* (1987)	placebo-controlled, double-blind, randomised, cross-over duration: 6 weeks	dry extract (4-6.6:1, ethanol 45% m/m) 3 x 60 mg/day or placebo	group A (verum-placebo): 13 female 5 male group B (placebo-verum): 14 female 4 male age: 74.0±4.8 group A 74.0±5.1 group B drop outs: no drop outs	Chronic congestive heart failure (NYHA I-II).	verum group (in 3 patients): dizziness placebo group (in 4 patients): dryness of the mouth, impaired vision, headache, dizziness	no serious AEs

Type	Study	Test product(s):	Number of subjects	Type of subjects	Adverse reactions	Comments
Tauchert *et al.* (1994)	reference-controlled, double-blind, randomised, multicenter duration: 8 weeks	dry extract (4-7:1, methanol 70% V/V) 3 x 300 mg/day or 3 x 12.5 mg/day captopril	verum: 36 female 32 male reference: 43 female 21 male age: 62±6 verum 63±5 reference drop outs: 3 verum 5 reference	Chronic congestive heart failure (NYHA II).	AEs in 3 patients in both groups verum: gastrointestinal complaints (2x) and cardiac pain reference: irritative cough (2x), headache, dizziness	no serious AEs

5.2. Patient exposure

In the above mentioned clinical investigations of approximately 1800 patients and test persons no signs of acute toxicity have been observed. On the basis of the longstanding use in some Member States a significant exposure can be expected.

According to information received during the call for submission of scientific data for *Crataegus* folium cum flore approximately 810 millions defined daily doses of *Crataegus* dry extract from leaves and flowers (4-6.6:1, ethanol 45% m/m) were placed on the European market between 1992 and 2011.

5.3. Adverse events, serious adverse events and deaths

Clinical trials

Except for two studies, Holubarsch *et al.* (2008) and Zick *et al.* (2009), all clinical studies mentioned in section 4.2. are included in the safety analysis review by Daniele *et al.* (2006). Hawthorn was well tolerated by patients. The most frequent adverse events included dizziness/vertigo, gastrointestinal complaints, headache, migraine and palpitation, but the occurrence of these adverse events was typically lower in the treatment groups than in the placebo groups (see section 5.1.).

In the following two studies hawthorn was given as an add-on treatment.

The adverse events observed in Holubarsch *et al.* (2008) were of the same types and occurred at comparable rates in the treatment and placebo group (see section 5.1.).

In Zick *et al.* (2009) adverse events (AE) were divided into cardiac categories and those that most commonly occurred in the trial. There were no differences between placebo and hawthorn for cardiac-related adverse events (e.g. angina and atrial fibrillation) or in common AE categories including infections, rashes, gastrointestinal complaints, or headaches. However, significantly more total adverse events were reported in the hawthorn (as add-on) group (36 vs. 23, $p = 0.02$), although most were non-cardiac. Non-cardiac adverse events were amongst others infections, headache, rash, and gastrointestinal symptoms such as constipation, diarrheoa, loose stool, nausea and vomiting. There were no significant differences between hawthorn and placebo in the number of deaths. As hawthorn was given as an add-on treatment the influence on adverse events of the first-line treatment remains unclear.

Spontaneous reports

In Germany currently (April 08, 2014) over 100 adverse reactions reports are labelled according to the Federal Institute for Drugs and Medical devices (BfArM) database for adverse events. The following adverse events were most frequently mentioned (5 or more reports for each adverse event): chills (n=5), dyspnoea (n=6), headache (n=6), dizziness (n=9) and nausea (n=10).

Market overview

Adverse events are also reported in the SmPC from Member States. Gastrointestinal complaints, feeling of weakness or hypersensitivity reactions may occur. These complaints usually disappear within a few days after discontinuation of the medicinal product. Nausea, fatigue and sweating were reported as well. On the basis of the available data the frequency is not assessable. So the frequency is not known.
These data show that the mentioned adverse events occurred at low rates. An inclusion of any of the advese event in the monograph is not reasonable.

5.4. Laboratory findings

In all studies, mentioned in section 4.2., that investigated laboratory parameters; these parameters were within their normal ranges or did not differ in a clinically significant manner during the study. Furthermore, several mentioned clinical trilas included already the changes in pressure-heart rate as outcome (for details please refer to section 4.2.). In addition, in the extensive systematic review by Daniele *et al*. (2006) no laboratory finding recorded as adverse drug reaction has been mentioned.

5.5. Safety in special populations and situations

The following data on safety are based on results from clinical trials (see section 4.2.2.) and information about products on the market in the Member States (see section 2.1.1.).

5.5.1. Use in children and adolescents

Based on data from clinical trials the use in children and adolescents has not been investigated with respect to indication 1. For indication 2 the use in adolescents is supported by the traditional use.

5.5.2. Contraindications

In accordance with informations from the Member States the contraindication “hypersensitivity to the active substance” is relevant for the monograph.

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 ofconcerns 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 (dyspnea), 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

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 from leaves and flowers (4-6.6:1, ethanol 45% m/m) (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.

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.

Williamson *et al*. (2013) discussed the above mentioned study of Tanakow *et al.* (2003) and concluded that this study appears to be the only evidence reported of an interaction study from hawthorn with digoxin. It suggests 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.

Another clinical interaction study with hawthorn and antihypertensives was analysed but the effect was small. It was stated, as such, it is unlikely that clinically important hypotension would occur if hawthorn is added to existing antihypertensive treatment.

Gruenwald *et al*. (2007) discussed drug interactions for hawthorn with antiplatelet agents, cardiac glycosides, antiarrhytmics and cisapride. The corresponding conclusions reflected hypothetical statements. No clinical evidence was reported.

Daniele *et al.* (2006) included in the review three randomised clinical trials and one observational study which involved concomitant use of cardioactive glycoside medications. None of these studies raised any issues regarding herb/drug interactions.

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 cited to date.

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, however it was discussed, that the evidence is based on pharmacological effects rather on direct investigations.

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

In line with the pharmacodynamic properties of hawthorn and especially the Na^+/K^+ pump and phosphodiesterase inhibitory activities described, it was presumed that it may have a potentiating effect on digitalis glycosides, beta-blockers and other hypertensive and/or vasodilator drugs, when co-administrated (Momekov & Benbassat, 2013). However in various clinical trials (patients received three or more concomitant drugs according to current treatment guidelines, especially ACE-inhibitors, AT-II-antagonists, beta-blockers, diuretics, spironolactone, and digitalis) such effects were not seen.

5.5.5. Fertility, pregnancy and lactation

Taking together information from the Member States, monographs and literature, safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

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

Preparations from *Crataegus* leaves and flowers have a good safety profile. The oral administration of *Crataegus* preparations can be regarded as safe under the informations for use that are described in the monograph.

From clinical trials, spontaneous reports and information from the Member States the most frequently reported adverse events were mild to moderate and occurred in clinical trials typically less in the treatment groups than in the placebo groups or at least in the same range.

On the basis of the available data the frequency is not assessable; therefore the frequency is not known. The data show that the mentioned adverse events occurred at low rates. An inclusion of any of the adverse events in the monograph is not reasonable.

From *in vitro* data and animal experiments a potential drug interaction of hawthorn with digoxin may be assumed and many different theoretical interactions between *Crataegus* and conventional medications have been postulated. However, until now none have been substantiated clinically. Three

randomised clinical trials and one observational study which involved concomitant use of cardioactive glycoside medications were reviewd by Daniele *et al.* (2006). None of these studies raised any issues regarding herb/drug interactions. Furthermore data from a clinical trial in healthy volunteers showed no interaction with digoxin. Also in the clinical trial from Holubarsch *et al*. (SPICE study, see section 4.2.2.) and Zick *et al*. (HERB CHF trial, see section 4.2.2.), hawthorn was administered as add-on treatment to a conventional heart failure regimen (including digoxin), no drug interaction was reported. Therefore the proposed theoretical herb/drug interaction between *Crataegus* preparations and conventional medications remains theoretical since no clinical/human evidence exist.

6. Overall conclusions (benefit-risk assessment)

Products containing *Crataegus* leaves and flowers have been registered as traditional herbal medicinal products in some Member States. The plausibility of usage is given by the long-standing medicinal use in the registered indications.

The requirements of medicinal use for at least 30 years (15 years within the European Union) according to Directive 2004/24/EC as amended is considered fulfilled for the following herbal preparations:

- Indication ”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 1):
  - 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
- Indication “Traditional herbal medicinal product for relief of mild symptoms of mental stress and to aid sleep” (Indication 2):
  - b) Powdered herbal substance
  - k) Dry extract (DER 4-5:1), extraction solvent: water

Use during pregnancy and lactation cannot be recommended.

Clinical safety data identified for preparations from *Crataegus* leaves and flowers present a good safety profile with no harmful signals.
For indication 1 there are concerns on the use in children and adolescents under 18 years of age because of concerns requiring medical advice. In some countries it was recommended to visit a doctor, if symptoms continue unchanged for longer than 6 weeks. For safety reasons this period was reduced to 2 weeks.

For indication 2 insufficient data on the use in children are available. Therefore, products containing hawthorn leaves and flowers are not recommended for indication 1 in children and adolescents under 18 years of age and for indication 2 in children under 12 years of age. The duration of use was restricted to 2 weeks as for similar products.

Toxicological data exist only for the dry extract (DER 4-6.6:1, ethanol 45% m/m). With this extract studies concerning acute and sub-chronic toxicity and genotoxicity (*in vitro* and *in vivo*) have been performed. The genotoxicity testing revealed no concern, however, differences in medical approach, health care customes 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.") and therefore the HMPC agreed not to propose to the European Commission a binding list entry for this extract. Although genotoxicity data are available for the preparation, it was specified that safety concerns don't refer to the herbal substance as such but the indication and use in general.

Annex

List of references