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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Cimicifuga racemosa* (L.) Nutt., rhizoma

Final

Based on Article 10a of Directive 2001/83/EC (well-established use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Cimicifuga racemosa</i> (L.) Nutt., rhizoma (black cohosh)
Herbal preparations	a) Dry extract (DER 5-10: 1), extraction solvent ethanol 58% (V/V) b) Dry extract (DER 4.5-8.5: 1), extraction solvent ethanol 60% (V/V) c) Dry extract (DER 6-11: 1), extraction solvent propan-2-ol 40% (V/V)
Pharmaceutical forms	Herbal preparation in solid dosage forms for oral use.
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List of abbreviations

The acronyms and abbreviations commonly used in the context of EU herbal monograph establishment by the HMPC please refer to the document "Abbreviations used in HMPC agendas/minutes" (EMA/HMPC/441838/2013) available

here: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/11/WC500155666.pdf

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000193.jsp&mid=WC0b01ac0580028e96

AACE	American Association of Clinical Endocrinologists
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	alkaline phosphatase
AST	aspartate aminotransferase
BDI	Beck's depression inventory
CE	conjugated oestrogens
CEE	conjugated equine oestrogens
CGI	clinical global impression scale
CHD	coronary heart disease
CI	confidence interval
CR	CR
CT	computer tomography
CYP	cytochrome p450
DILI	drug induced liver injury
E ₂	oestradiol
ER	oestrogen receptor
ESCOF	European Scientific Cooperative On Phytotherapy
FSH	follicle stimulating hormone
γ-GT / GGT	gamma glutamyl transferase
GCP	Good Clinical Practice
GOT	glutamic oxaloacetic transaminase=AST
GPT	glutamic pyruvic transaminase= ALT
GCS	Greene Climacteric Scale
HAMA	Hamilton anxiety scale
HAMD	Hamilton depression scale
HD	high dose
HDL	high density lipoproteins

HED	human equivalent dose
HILI	herb induced liver injury
HT	hormone therapy
I(i)CR	isopropanolic CR dry extract
IGF-1	Insulin-like growth factor
IM	intramuscular
IP	intraperitoneal
ITT	intention-to-treat
KI	Kupperman Index
LD	low dose
LDH	lactate dehydrogenase
LDL	low density lipoproteins
LH	luteinising hormone
MPA	medroxyprogesterone acetate
MMTV	mouse mammary tumour virus
MRCP	magnetic resonance cholangiopancreatography
MRS I	menopause rating scale I
MRS II	menopause rating scale II
NOAEL	no-observed-adverse-effect level
pg/mL	picogram per millilitre
P-gp	P-glycoprotein
PP	per protocol
Rand-36 QoL	quality of life questionnaire
SAS	statistical analysis system
SDS	self rating depression scale
SERM	selective oestrogen receptor modulator
SRT	symptom rating test
TRH	thyrotropin releasing hormone

1. Introduction

Cimicifuga racemosa is a perennial plant of the Ranunculaceae (buttercup family). It is native to the Eastern US and Canada, from where normally all commercial stocks are derived. Indian tribes used the roots/rhizomes of this plant for medicinal use.

In some European countries specific herbal preparations of Cimicifugae rhizoma (CR) are authorised as herbal medicinal products with well-established use. These products are marketed with an indication for relief of menopausal symptoms, e.g. hot flushes. Additionally, in the United Kingdom, there is a traditional medicinal product used for the symptomatic relief of rheumatic pain.

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

- Herbal substance(s)

There is a monograph with the title 'Cimicifugae rhizoma (black cohosh)' published in the European Pharmacopoeia (2069).

Definition according to Ph. Eur.:

Dried whole or fragmented rhizome and root of *Actaea racemosa* L. (syn. *Cimicifuga racemosa* (L.) Nutt.) containing a minimum of 1.0% of triterpene glycosides, expressed as monoammonium glycyrrhizate (C₄₂H₆₅NO₁₆; Mr 840) (dried drug).

- Herbal preparation(s)

Herbal preparation used as active substance are defined as other extracts and should be declared conform to the guideline EMEA/HMPC/CHMP/CVMP/287539/05 Rev. 1 as follows:

- a) Dry extract from CR (DER 5-10:1); extraction solvent ethanol 58% (V/V)
- b) Dry extract from CR (DER 4.5-8.5:1); extraction solvent ethanol 60% (V/V)
- c) Dry extract from CR (DER 6-11:1); extraction solvent propan-2-ol 40% (V/V)

1.1. Search and assessment methodology

This assessment report revised the first HMPC assessment report on *Cimicifuga racemosa* (L.), Nutt., rhizoma (EMA/HMPC/3968/2008) and is based on the literature on Cimicifugae rhizoma available at the Federal Institute for Drugs and Medicinal Devices in Germany and the publications provided by the AESGP (Association of the European Self-Medication Industry) in response to the EMA HMPC call for data on 14 October 2015. Additionally a literature search in the DIMDI database was performed in January 2017 using the following terms: Cimicifugae rhizoma included in the title, humans, clinical, preclinical, safety, year of publication between 2010 and 2017, language in English or German. A separate literature research was performed for the therapeutic use of Cimicifugae rhizoma in the indication menopausal complaints in the database XMEDALL (terms used: Menopausal complaints, Cimicifugae rhizoma).

Only the articles considered as relevant for the establishment of this assessment report on a well-established use of CR were included in the reference list.

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

The following data are derived from the request for information concerning the marketed products of CR preparations (dated 15 December 2006) and the request for updated market overviews for CR preparations (dated 28 October 2015).

No products were authorized in Iceland, Italy, Norway and Portugal in December 2006.

No products were authorized in Finland, Croatia, Ireland and Slovakia in October 2015.

Table 1: Overview of data obtained from marketed medicinal products (15 December 2006 and 28 October 2015)

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
Liquid extract preparation, DER 1:20-25, ethanol 40% m/m	For the relief of menopausal complaints like hot flushes and profuse sweating	Oral liquid 100 g medicinal product contain 100 g liquid extract preparation 1x20 drops per day, up to 6 months(several changes regarding posology and extract declaration since 1973; information provided here according to most recent SmPC)	WEU (1973, AT)
Dry extract, DER 6-11:1, propan-2-ol 40% V/V	Neurovegetative and psychic climacteric disorders For the relief of menopausal complaints such as hot flushes and profuse sweating	Tablets 2.5 mg dry extract per tablet corresponding to 20 mg of herbal substance 2x1 tablet per day	WEU (1999, AT)
Dry extract, DER 7-12:1, ethanol 50% m/m	For the relief of menopausal complaints such as hot flushes and profuse sweating	Tablets 4.5 mg dry extract per tablet corresponding to approximately 43 mg of herbal substance 1 tablet per day	WEU (2000, AT)
Dry extract, DER 5-10:1, ethanol 58% V/V	Neurovegetative and psychic menopausal complaints	Film-coated tablets 2.8 mg dry extract per film-coated tablet corresponding to 20 mg of herbal substance 2x1 tablet per day	WEU (2002, AT)

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
Dry extract, DER 4.5–8.5:1, ethanol 60% V/V	For the relief of menopausal complaints such as hot flushes and profuse sweating	Film-coated tablets 6.5 mg dry extract per film-coated tablet corresponding to 40 mg of herbal substance 1 tablet per day	WEU (2007, AT)
Dry extract, DER 4.5–8.5:1, ethanol 60% V/V	For treatment of menopausal symptoms such as hot flushes and profuse sweating, sleep disorders, anxiety and irritability	Tablets 6.5 mg dry extract per tablet corresponding to 40 mg of herbal substance 1 tablet per day, maximum 6 months	WEU (2014, BE)
Dry extract, DER 5-10:1, ethanol 58% V/V	For the relief of menopausal complaints such as hot flushes and profuse sweating	Film-coated tablets 2.8 mg dry extract per film-coated tablet corresponding to 20 mg of herbal substance 2x1 tablet per day, maximum 6 months	WEU (2014, BE)
Tincture, DER 1:5, ethanol 60% V/V	Premenstrual syndrome, menopause associated with nervous disorders, painful menstruation	Oral liquid 12 ml tincture (1:5) corresponding to 2.4 g herbal substance in 100 g oral liquid 2x20 drops per day	WEU (2001, BG)
Dry extract, DER unknown, propan-2-ol 40% V/V	Premenstrual syndrome, menopause associated with nervous disorders, painful menstruation	Tablets 0.018-0.026 mg extract per tablet corresponding to 20 mg of herbal substance	WEU (2001, BG)

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
		2x1 tablet per day	
Tincture, DER 1:10, ethanol 69.7% V/V	Premenstrual syndrome, menopause associated with nervous disorders, painful menstruation	Oral liquid 20 ml tincture (1:10) per 100 g oral liquid 1x30-40 drops per day	WEU (2002, BG)
Dry extract, DER 4:1, extraction solvent unknown	Premenstrual syndrome, menopause associated with nervous disorders, painful menstruation	Capsules 5 mg dry extract per capsule corresponding to 20 mg of herbal substance 2x1 capsule per day	WEU (2002, BG)
Dry extract, DER 5-10:1, ethanol 58% V/V	Premenstrual syndrome, menopause associated with nervous disorders, painful menstruation	Film-coated tablets 2.8 mg dry extract per film-coated tablet corresponding to 20 mg of herbal substance 2x1 tablet per day	WEU (2005, BG)
Dry extract, DER 4.1-6.5:1, ethanol 60 % V/V	Mild pre and post-menopausal neurovegetative symptoms such as nervousness, mood swings, irritability, profuse sweating, hot flushes and sleep disorders	Tablets 7 mg dry extract per tablet corresponding to 40 mg of herbal substance 1 tablet per day, up to 6 months	WEU (1999-2009, CZ)
Dry extract, DER 5-10:1, ethanol 58% V/V	Mild to moderate pre and post-menopausal neurovegetative symptoms such as nervousness, mood swings, irritability,	Tablets 2.8 mg dry extract per tablet corresponding to 14-	WEU (2000, CZ)

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
	profuse sweating, hot flushes, sleep disorders and concentration disorders	28 mg of herbal substance 2x1 tablet per day	
Tincture, DER 1:10, ethanol 69.7% (V/V)	For improvement of psychological and neurovegetative complaints due to the menopause	Oral liquid 20 g tincture (1:10) per 100 g oral liquid 2x30-40 drops (1 g=1 ml =33 drops), up to 3 months	WEU (1993, DE)
Dry extract, DER 4.5–8.5:1, ethanol 60% V/V	For improvement of psychological and neurovegetative complaints due to the menopause For the relief of menopausal complaints such as hot flushes and profuse sweating	Film-coated tablets/capsules, hard 6.5 mg dry extract per tablet/capsule corresponding to 40 mg of herbal substance 1 tablet/capsule per day, up to 3-6 months	WEU (16 authorised medicinal products since 1997, DE)
Tincture, DER 1:5, ethanol 50% (V/V)	For the relief of menopausal complaints such as hot flushes and profuse sweating	Oral liquid 12 g tincture (1:5) per 100 g oral liquid 2x30 drops per day, up to 6 months	WEU (1998, DE)
Dry extract, DER 4–9:1, ethanol 58% V/V	For improvement of psychological and neurovegetative complaints due to the menopause	Film-coated tablets 6 mg dry extract per tablet corresponding to 40 mg of herbal substance 1 tablet per day up to 3 months	WEU (1998, DE)

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
Dry extract, DER 4.1-6.5:1, ethanol 60% V/V	For improvement of psychological and neurovegetative complaints due to the menopause	Film-coated tablets 7 mg dry extract per tablet corresponding to 40 mg of herbal substance 1 tablet per day, up to 3 months	WEU (1999, DE)

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
Dry extract, DER 6.6–8.7:1, ethanol 60% V/V	For improvement of psychological and neurovegetative complaints due to the menopause	Capsules, hard 2.675 mg dry extract per capsule corresponding to 20 mg of herbal substance 2x1 capsule per day, up to 6 months	WEU (2005, DE)
Dry extract, DER 5-10:1, ethanol 58% V/V	For the relief of menopausal complaints such as hot flushes and profuse sweating	Film-coated tablets 2.8 mg dry extract per film-coated tablet corresponding to 20 mg of herbal substance 2x1 tablet per day, up to 6 months	WEU (2005, DE)
Dry extract, DER 6-11:1, propan-2-ol 40% V/V	For improvement of psychological and neurovegetative complaints due to the menopause such as hot flushes, sweating and sleep disorders For the relief of menopausal complaints such as hot flushes and profuse sweating	Tablets 2.5/5 mg dry extract per tablet corresponding to 20 mg/40 mg of herbal substance 2x1/1x1 tablet per day, up to 3-6 months	WEU (3 authorised medicinal products since 2005, DE)

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
Dry extract, DER 6-11:1, propan-2-ol 40% V/V	For the relief of hot flushes and sweating in the menopause	Tablets 2.5 mg dry extract per tablet corresponding to 20 mg of herbal substance 2x1 tablet per day, up to 6 months	WEU (1999, DK)
Dry extract, DER unknown, ethanol 58% V/V	For the relief of hot flushes and sweating in the menopause	Tablets unknown amount of dry extract per tablet corresponding to 20 mg of herbal substance 2x1 tablet per day, up to 6 months	WEU (2000, DK)
Dry extract, DER 6-11:1, propan-2-ol 40% V/V	For the relief of menopausal neurovegetative complaints such as hot flushes, profuse sweating, sleeping problems, nervousness and depressive mood	Tablets 2.5 mg dry extract per tablet corresponding to 20 mg of herbal substance 2x1 tablet per day, up to 6 months	WEU (2000, HU)
Dry extract, DER 7-12:1, ethanol 58% V/V	For the relief of menopausal neurovegetative complaints	Film-coated tablets 1.66-2.86 mg dry extract per tablet corresponding to app. 20 mg of herbal substance 2x1 tablet per day, up to 6 months	WEU (2004, HU)
Dry extract, DER 4-9:1, ethanol 50% w/w	For the relief of menopausal neurovegetative complaints such as hot flushes, profuse sweating, sleeping problems, nervousness	Tablets 4.5 mg dry extract per tablet corresponding to approximately 40 mg of herbal substance	WEU (2004, HU)

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
	and depressive mood	1 tablet per day, up to 6 months	
Dry extract, DER 6.6-8.7:1, ethanol 60% V/V	For improvement of psychical and neurovegetative disorders caused by the menopause	Capsules, hard 2.675 mg dry extract per capsule corresponding to 20 mg of herbal substance 2x1 capsule per day, up to 6 months	WEU (2001, HU)
Dry extract, DER 4.5–8.5:1, ethanol 60 % V/V	For the relief of menopausal neurovegetative complaints such as hot flushes, profuse sweating, sleeping problems, nervousness and depressive mood	Film-coated tablets 6.5 mg dry extract per tablet corresponding to 40 mg of herbal substance 1 tablet per day	WEU (2001 and 2007, HU)
Dry extract, DER 4.5–8.5:1, ethanol 60% V/V	Symptomatic treatment of menopausal complaints	Capsules 6.5 mg dry extract per capsule corresponding to 40 mg of herbal substance 1 capsule per day, up to 3 months	WEU (2004, HU)
Dry extract, DER and extraction solvent unknown	Climacteric complaints; premenstrual disorders; dysmenorrhoea	Pharmaceutical form unknown 5 mg dry extract 2 times per day	WEU (no date given, LT)
Dry extract, DER 6.6-8.7:1, ethanol 60% V/V	For improvement of psychological and neurovegetative complaints due to the menopause	Capsules 2.675 mg dry extract per capsule corresponding to 20 mg of herbal substance	WEU (2003, LV)

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
		2x1 capsule per day	
Dry extract, DER 4.5–8.5:1, ethanol 60% V/V	For symptomatic treatment of menopausal complaints	Tablets 6.5 mg dry extract per tablet corresponding to 40 mg of herbal substance 1 tablet per day	WEU (2007, LV)
Dry extract, DER 5-10:1, ethanol 58% V/V	For the relief of menopausal complaints such as hot flushes and profuse sweating	Film-coated tablets 2.8 mg dry extract per film-coated tablet corresponding to 20 mg of herbal substance 2x1 tablet per day	WEU (2011, LV)

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
Tincture, DER 1:10, ethanol 50% (V/V)	For the relief of menopausal complaints such as hot flushes, profuse sweating, sleeping disorders, mood swings and irritability	Oral liquid 1x26 drops per day, up to 6 months	WEU (2005, PL)
Dry extract, DER 5-10:1, ethanol 58% V/V	For the relief of menopausal complaints such as hot flushes and profuse sweating	Film-coated tablets 2.8 mg dry extract per film-coated tablet corresponding to 20 mg of herbal substance 2x1 tablet per day, up to 12 months	TU 2006; reclassified WEU 2012; SE
Dry extract, DER 6-11:1, propan-2-ol 40% V/V	For the relief of menopausal complaints such as hot flushes and profuse sweating	Tablets 2.5 mg dry extract per tablet corresponding to 20 mg of herbal substance 2x1 tablet per day, up to 6 months	TU 1998; reclassified WEU 2012; SE
Liquid extract, DER and extraction solvent unknown	An herbal remedy traditionally used for the symptomatic relief of rheumatic pain	5 ml contain aqueous alcoholic extractive from black cohosh 5 g	TU (since before 1968, UK)

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

Since publication of the European Union herbal monograph on *Cimicifuga racemosa* (L.) Nutt., rhizoma (EMA/HMPC/600717/2007) on 20 January 2011, the wording of the indication for the authorised medicinal products has usually been adapted to the monograph.

Further data regarding the safe administration of CR were provided by the two countries:

Belgium

Drug interactions and other forms of interaction

- In a case description CR seemed to antagonise the immune-suppression after transplantation with concomitant use of azathioprine and cyclosporine.
- CR extract may amplify the effects of tamoxifen.

Fertility, pregnancy and lactation

- CR can display oestrogen activity and may disturb the conservation of the pregnancy.
- There are no data from the use of ethanolic extracts from CR in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). CR is not recommended during pregnancy.
- Women of childbearing potential should consider using effective contraception during treatment. It is unknown whether ethanolic extracts from CR or metabolites thereof are excreted in human milk. A risk to the suckling child cannot be excluded. CR should not be used during breast feeding.

Germany

Special warnings and precautions for use/undesirable effects

- Since 9 June 2009 a graduated pharmacovigilance plan is effective in Germany concerning the risks of hepatotoxicity and the consumption of CR containing medicinal products.

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

Combinations with Hypericum can be found on the market. This monograph refers exclusively to CR.

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

Extracts that are listed in the USP 39, NF 34 Volume 4 (The United States Pharmacopoeia; The National Formulary, Official from May 1, 2016. Dietary Supplements: Black Cohosh pp 6 501-6 511) were not taken into account. The USP is not relevant for the preparation of the European Union herbal monograph on CR. There are no herbal medicinal products marketed in the European Union with the specification of the USP. Studies on efficacy and safety have not been performed with these preparations.

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

Cimicifuga racemosa (L.) Nutt. (syn. *Actaea racemosa* L.) is a perennial plant of the Ranunculaceae (buttercup family). It is native to the Eastern US and Canada. The roots and rhizomes have been used

medicinally by Native Americans since pre-Columbian times, to treat malaise, kidney disorders, rheumatism, snakebites, nervous disorders, including gynaecologic disorders, especially as a uterine stimulant and labour-inducing aid. CR was first listed in 1830, in the US pharmacopoeia under the name "black snakeroot".

In Germany CR is used since 1940 as a natural agent for treating premenstrual, dysmenorrhoeal and menopausal neurovegetative symptoms and the Commission E established a monograph (Commission E (Germany), Bundesanzeiger No. 43, published 2 March 1989) including the indications mentioned before. Since the medicinal use and efficacy in the treatment of premenstrual and dysmenorrhoeal symptoms have not been sufficiently documented, these indications were excluded in the revised Commission E monograph (14 December 1994) and only the use for the relief of menopausal symptoms, e.g. hot flushes was considered relevant.

For the following specified preparations clinical data are available:

- a) Dry extract from CR (DER 5-10:1); ethanol 58% (V/V)
- b) Dry extract from CR (DER 4.5-8.5:1); ethanol 60% (V/V)
- c) Dry extract from CR (DER 6-11:1); propan-2-ol 40% (V/V)

Table 2: Overview of historical data

Herbal preparation	Documented use / Traditional use	Pharmaceutical form Strength Posology Duration of use	Reference
Cimicifugae racemosae rhizoma, ethanolic extracts, 40-60% V/V	WEU: Premenstrual, dysmenorrhoeal and menopausal neurovegetative symptoms	Herbal preparations for oral use, daily dose corresponding to 40 mg herbal substance, up to 6 months	Monograph of the Commission E (Blumenthal <i>et al.</i> 1998)
Cimicifugae racemosae rhizoma, ethanolic extracts, 40-60% V/V	WEU: Relief of menopausal symptoms, e.g. hot flushes	Herbal preparations for oral use daily dose corresponding to 40 mg herbal substance, up to 6 months	Monograph of the Commission E (revised 14 December 1994, unpublished)

2.3. Overall conclusions on medicinal use

CR is a well-known herbal substance which has been used worldwide for decades in many herbal medicinal products, as for example since 1940 in Germany. To date, 24 preparations have been in use for more than 10 years in Germany. A very high number of daily dosages of CR preparations have been sold worldwide over the years. CR is positively described in a Monograph of the German Commission E (Bundesanzeiger Nr. 43) published 2 March 1989 (Blumenthal *et al.* 1998), revised 14 December 1994 (not published) and in ESCOP Monographs, second edition 2003. Furthermore, the scientific interest in the use of the substance reflects the importance of CR preparations for treatment of menopausal complaints. The following preparations and indications were accepted for the

monograph: Relief of menopausal complaints such as hot flushes and profuse sweating (for assessment of the clinical data see chapter 4).

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Dry extract from CR (DER 5-10:1); ethanol 58% (V/V)	Neurovegetative and psychic menopausal complaints	Single dose: 2.8 mg dosage frequency: 2 times daily daily dose: 5.6 mg	since 2002
Dry extract from CR (DER 4.5-8.5:1); ethanol 60% (V/V)	For improvement of psychological and neurovegetative complaints due to the menopause	Single dose: 6.5 mg dosage frequency: 1 single daily dose daily dose: 6.5 mg	since 1997
Dry extract from CR (DER 6-11:1); propan-2-ol 40% (V/V)	For improvement of psychological and neurovegetative complaints due to the menopause such as hot flushes, sweating and sleep disorders	Single dose: 2.5 mg or 5.0 mg dosage frequency: 1-2 times daily daily dose: 5.0 mg	since 1998

In Austria, a herbal preparation has been on the market since 1973 in the indication treatment of menopausal symptoms (first position in Table 1). Over the years however, the preparation has been changed (e.g. posology, extract declaration). Therefore, it is not possible to derive an exact posology and extract declaration from the available data.

There is a formal tradition for a product which is traditionally used for treatment of rheumatism in the UK (last position in Table 1). Data on tradition in the treatment of rheumatism are limited.

There are several products on the market with the indication 'premenstrual syndrome'. The data on the traditional use of these medicinal products are considered not sufficient. Furthermore, bibliographical or expert evidence, i.e. the revised Commission E monograph (1994) in which this indication was excluded, was taken into account.

Overall, the available data are considered insufficient to justify an indication for traditional use.

3. Non-Clinical Data

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

Human clinical studies support the efficacy of CR in treating menopausal symptoms. The exact mechanism by which CR elicits its effects, however, has not yet been fully elucidated. Around 1980, the first investigations were performed in order to examine the binding to oestrogen receptors and the influence on breast cancer cells and endometrium.

3.1.1. Primary pharmacodynamics

Binding to oestrogen receptors and influence on breast cancer cells and endometrium

In vitro tests

In vitro experiments have examined the effect of CR on proliferation of various -mostly oestrogen receptor positive- breast cancer cell lines. A number of studies have shown that CR did not cause cell proliferation and in some cases even inhibited proliferation:

- No proliferative virility was observed with the breast cancer cell line MDA-MB 435 in concentrations from 0.0025-0.25 µg/ml; dosages greater than 2.5 µg/ml led to an inhibition of proliferation (Nesselhut *et al.* 1993). No information on extracts is available.
- Zava *et al.* (1998) showed that a 50% hydroethanolic extract of CR did not stimulate cell proliferation in T-47D cells in steroid-depleted serum.
- Dixon-Shanies and Shaikh (1999) showed that a 0.1% ethanolic extract of *Cimicifuga* had significant growth inhibitory effects on serum stimulated T-47D cells.
- For one extract with isopropanol an inhibition of proliferations from MCF-7 cells could be shown for dilutions between 100 µg/ml and 1 ng/ml (Freudenstein *et al.* 1999).
- An inhibitory effect on cell proliferation was shown for the human breast adenocarcinoma MCF-7 cells with an ethanolic extract of CR (Ze 450). According to the authors modulation of cyclin D1 promoter activity and transcription activity of the p21 gene promoter may be involved as possible mechanism of anti-proliferative effects of the CR extract (Garita-Hernandez *et al.* 2006).

Other studies have indicated a proliferative effect:

- Different ethanolic extracts (more information not available) in very low concentrations caused a significant increase in cell number of oestrogen dependent MCF-7 cells (Löhning 1999).
- Liu *et al.* (2001) observed oestrogen-like proliferation at low CR concentrations, but anti-oestrogen-like inhibition at high concentrations in human breast cancer MCF cells (CR extract; active ingredient, 2.5%; Pure world Botanicals Ltd., Bedminster, NJ, USA).

Similarly, studies examining the binding of CR to oestrogen receptors have shown conflicting results:

- Endocrine activity and binding at oestrogen receptors extracted from rat uteri and rat pituitary glands were tested in an early study. Binding could be demonstrated for a methanolic extract. A dose-dependent displacement of labelled estradiol from antibody could be shown for two ethanolic extracts (Jarry *et al.* 1985, a+b).
- Subsequent studies with the ethanolic CR extract BNO 1055, on the other hand, could not demonstrate any binding activity to ER-α or ER-β receptors by the extract (Jarry *et al.* 2003).
- Amato *et al.* (2002) observed neither stimulation of MCF-cell proliferation in an oestrogen-depleted environment nor transactivation of ER-α or ER-β in a cell reporter assay upon treatment with an alcoholic extract (more information not available).

In vivo tests

Increased uterine weight and/or decreased LH (luteinising hormone) levels are used as evidence of a possibly present oestrogenic activity in rats and mice (typically ovariectomised animals) after administration of CR:

- Serum levels of pituitary hormones FSH (follicle-stimulating hormone), prolactin and LH did not change after a 14 day treatment in ovariectomised rats with a 50% ethanolic CR extract. After a three day treatment however, LH and prolactin levels were significantly reduced; after a one day treatment prolactin levels were increased (Jarry & Harnischfeger 1985b).
- Treatment with a 50% ethanolic CR extract for three days did not affect the weight of uteri of juvenile mice. There was also no effect on vaginal cytology (Einer-Jensen *et al.* 1996).
- Ovariectomised DA/Han rats were treated with an isopropanolic CR extract alone or in combination with the anti-oestrogen fulvestrant in comparison to estradiol and controls. Uterine and vena cava gene expression were investigated. CR extracts had no uterotrophic effects and did not seem to act as an oestrogen agonist, but possibly as a weak anti-oestrogen (Kretschmar *et al.* 2005).
- These results have been confirmed by a more recent investigation on ovariectomised rats treated with BNO 1055 (Kapur *et al.* 2010). In this study no uterotrophic effect could be detected, as uterus weights remained as low as in the sham controls.

Furthermore, the following studies with additional endpoints were conducted:

Ovariectomised (ovx) rats were treated with the ethanolic CR extract BNO 1055 = 33 mg per day for 3 months; 3 parallel groups were treated with 0.325-0.35 mg E₂ or 12.5 mg soy extract containing 0.6 mg genistein and 1.3 mg daidzein or placebo. The study was performed to demonstrate the pharmacology of the CR extract on bones, fat and uterus of the treated rats. Conclusion of the authors: The extract BNO 1055 exerted oestrogenic effects in the bone (particularly in osteoblasts) and in fat tissue, but not in the uterus of ovx rats. The extract appears to contain rat organ-specific selective oestrogen receptor modulators (SERMs). If these findings can be confirmed in human, it may be an alternative to hormone therapy (HT) (Seidlová-Wuttke *et al.* 2003).

An *in vivo* investigation of a clinically tested isopropanolic extract showed that treatment with CR extract did not stimulate cancer growth, the hormone levels, and organ weights and endometrial proliferation. Mammary tumours were induced in Sprague Dawley rats (n=75) by the application of dimethylbenz (a) anthracene. Five to nine weeks later the animals were ovariectomised, allowed to recover, and daily doses of the extract (0.714, 7.14 or 71.4 mg/kg body weight per day) or control substances (oestrogen/positive control 450 µg/kg per day mestranol) or extract vehicle/negative control were administered. The animals were sacrificed 6 weeks later and tumours (number and size), plasma hormone levels and the weight of oestrogen sensitive organs were analysed. In contrast to the oestrogen treatment the CR extract did not stimulate cancer growth. The hormone levels, organ weights and endometrial proliferation were unaffected (Freudenstein *et al.* 2002).

Dopaminergic effects and serotonin-binding properties

Properties other than oestrogenic activity are discussed in several publications. Dopaminergic effects and serotonin-binding properties could be responsible for reduction of vasomotor and psychological symptoms under treatment with CR preparations.

Dopaminergic effects of CR extracts were demonstrated *in vitro* and *in vivo*:

- 10 µg/ml and 100 µg/ml CR extract reduced significantly basal prolactin and thyrotropin releasing hormone (0.04 µg/ml) stimulated prolactin secretion in primary pituitary cell cultures. As effects of the extract on prolactin secretion were clearly reduced by the D₂/D₄-antagonist haloperidol, a dopaminergic activity of the extract was assumed. The same extract (100 mg/kg, oral application) caused in mice a fall in body temperature comparable to the effect of a D₂-agonist (bromocriptine, 5 mg/kg) given i.p. This fall in body temperature following CR application was inhibited by pre-

treatment with a D2/D3-receptor antagonist and was unchanged after application of a selective D1-receptor antagonist (Löhning *et al.* 1998, 1999a).

- The dopaminergic activity of the CR extract BNO 1055 could be demonstrated in a D2-receptor assay (recombinant dopamine D2-receptor protein). Unknown dopaminergic components have been suggested to contribute to the pharmacological profile of the extract (Jarry *et al.* 2003).

Serotonin-binding properties were examined in the following studies:

- The ethanolic CR extract BNO 1055 demonstrated concentration dependent binding to the serotonin receptors 5-HT 1A and 5-HT 7 *in vitro* with EC₅₀ (half maximal effective concentration) values of 1.67 and 6.5 µg/ml, respectively. Binding results in the activation of these serotonin receptors as demonstrated measuring the cAMP (cyclic adenosine monophosphate) levels in CHO-K1 cells recombinantly expressing human 5-HT 1A (EC₅₀ = 20.7 µg/ml) or 5-HT 7 (EC₅₀ = 4.1 µg/ml). Furthermore, the presence of compounds with strong binding properties to the 5-HT 1A, 5-HT 1D, and 5-HT 7 subtypes was observed in a 40% 2-propanol CR extract at a concentration of 250 µg/ml. Analysis of ligand binding data indicated that components of a methanolic CR extract at concentrations of 10 and 20 µg/ml functioned as a mixed competitive ligand of the 5-HT 7 receptor which are thought to be involved in the development of hot flushes (Burdette *et al.* 2003).
- Powell *et al.* (2008) showed that crude CR extracts displayed 5-HT 7 binding activity and induced cAMP production. N ω -methylserotonin was identified by fractionation to display 5-HT 7 binding, cAMP induction and blockage of serotonin re-uptake. In contrast, CR triterpenoids did not induce these effects. The reduction in serotonin turnover in the striatum and the increase in dopamine concentration suggest an inhibition of monoamine oxidase. Clinically, this may result in an improvement of mood in depressed climacteric patients.

Dopaminergic and serotonergic effects of CR extracts were demonstrated *in vitro* and partly *in vivo*. These data suggest that reductions of hot flushes observed in women taking CR may be induced by pharmacodynamic properties other than the oestrogenic activity discussed so far.

None of the investigations described above, however, provide a sufficient explanation of the therapeutic action or allow a translation into clinical practice. Rather, they are intended to give a mechanistic explanation of the pharmacological activity of CR. Furthermore, it remains to be clarified whether CR compounds penetrate the blood-brain-barrier for efficient dopamine- and serotonin-receptor modulation *in vivo*.

3.1.2. Secondary pharmacodynamics

Prevention of bone loss / Osteoprotective effects

Some studies have reported pharmacological properties of CR extracts that are indirectly linked to the pathology of menopausal complaints, e.g. osteoprotective effects:

In vitro, an ethanolic CR extract increased the bone nodule formation in mouse MC3T3-E1 pre-osteoblast cells and increased expression of osteoblast-specific markers (Chan *et al.* 2008).

In a five weeks feeding study, in CR treated ovariectomised rats (isopropanolic extract, no dosage given) the overall bone turnover was significantly reduced as compared with the untreated controls over the course of the treatment. The pycnometric bone density values in CR treated animals and the fracture resistance of the femurs (head) were higher than in the control group at the end of the treatment period (Nisslein and Freudenstein 2003).

The effects of BNO 1055 on uterus, bone and serum luteinising hormone (LH) were compared to the effects of 17 β -oestradiol (E₂) under acute (6 hours; 3.5 μ g extract/animal, IV application) and chronic (3 months; 2-1 000 mg extract/animal; oral application) conditions in ovariectomised rats. When given acutely, both E₂ and the BNO 1055 inhibited LH secretion and stimulated slightly gene expression of IGF-1, collagen-1 α -1, osteoprotegerin and osteocalcin (all osteoblast products), and of tartrate-resistant acid phosphatase (TRAP, an osteoclast product) in the metaphysis of the femur. Within 3 months of ovariectomy, control rats had lost more than 50% of the metaphyseal bone mass of the tibia, an effect prevented by E₂ and, partially, by BNO 1055 supplementation (Seidlova-Wuttke *et al.* 2003).

A triterpenoid glycoside isolated from CR, i.e. 25-acetylcimigenol xylopyranoside (ACCX), was shown to block osteoclastogenesis *in vitro* (Qiu *et al.* 2007). ACCX interfered with the RANKL (receptor activator of nuclear factor kappa-B ligand, member of the tumour necrosis factor (TNF) cytokine family that functions as a key factor for osteoclast differentiation and activation) and the TNF α signalling pathway thereby preventing the expression of proteins necessary for osteoclast differentiation. ACCX significantly reduced TNF α -induced osteoclastogenesis *in vivo* (12 mg/kg, IP application).

3.1.3. Safety pharmacology

Hepatotoxicity

Animal studies, predominantly in rats, investigating the hepatotoxic potential of CR have given mixed results.

An ethanolic CR extract was administered orally to rats. Liver sections were analysed by electron microscopy. Tests for cytotoxicity, mitochondrial toxicity and apoptosis/necrosis were performed using HepG2 cells. Mitochondrial toxicity was studied using isolated rat liver mitochondria. *In vivo*, microvesicular steatosis was found in rats treated with >1000 mg/kg body weight CR extract. *In vitro*, cytotoxicity with HepG2 cells was observed at 75 μ g/ml, and mitochondrial β -oxidation was impaired at 10 μ g/ml. The mechanism of cell death was predominantly apoptosis. These findings might be compatible with an idiosyncratic hepatotoxicity as observed in patients treated with CR extracts. The authors concluded that the ethanolic CR extract is associated with hepatic mitochondrial toxicity both *in vivo* in rats and *in vitro* using cell cultures and isolated rat liver mitochondria. According to the authors, this toxicity is only clinically relevant for patients with underlying risk factors, because toxic concentrations can most probably not be reached in humans treated with the recommended doses (Lüde *et al.* 2007 and 2010).

Campos *et al.* (2012) tried to overcome the gaps of the publication by Lüde *et al.* (high dosages used) and calculated the animal doses according to the recommended human dosage (calculation via HED). The authors reported that treatment with an undefined *C. racemosa* extract induced oxidative stress and impaired fatty acid β -oxidation in ovariectomised rats with induced renovascular hypertension. The verum group was treated daily with 0.6 mg/kg of an unspecified CR extract. The treatment increased the reactive oxygen species (ROS) generated by mitochondria. The increased mitochondrial ROS generation was expected to lead to lipid peroxidation. Thus, lipid peroxidation levels were assessed in the livers from these animals by thiobarbituric acid reactive substances (TBARS) measurements. TBARS were significantly increased only in the *C. racemosa* extract treated group. The authors concluded from this study that *C. racemosa* extract may make women more susceptible to toxic effects of other drugs.

3.1.4. Pharmacodynamic interactions

The purpose of the *in vitro* study by Einbond *et al.* (2006, 2007 a, b) was to determine whether the triterpene glycosides present in CR enhance the growth inhibitory effects of specific breast cancer chemotherapy agents in the MDA-MB-453 cells. Actein enhanced the growth inhibitory effects of both the anthracycline doxorubicin and the antimetabolite 5-fluorouracil; the ethyl acetate fraction enhanced doxorubicin.

3.1.5. Conclusions

Non-clinical research has been directed mainly to detect the substances responsible for the effects reported in clinical trials and to investigate, in *in vitro* and animal models, the main pharmacological effects that lead to therapeutic efficacy in clinical trials. Although early preclinical studies indicated that CR constituents were able to bind to oestrogen receptors *in vitro*, this is not supported by recent data. Available non-clinical and clinical data suggest that CR does not have an oestrogenic effect mediated through the oestrogen receptor. Dopaminergic and serotonergic effects of CR extracts were demonstrated *in vitro* and partly *in vivo*.

None of the investigations described above provide a sufficient explanation of the therapeutic action or allow a translation into clinical practice. The constituents relevant for the improvement of menopausal complaints are not known.

Several studies have been carried out and different models were used to test the pharmacological activity of CR. However, most concentrations/dosages used do not correlate with the human dosage and the numbers of animals used did not rely upon statistical sample size considerations. With regards to the dosages used in non-clinical investigations, no study has been planned to consider translation of the results into clinical settings. Clinical daily routine dosing and the indication for which CR is used rely mainly on its historically established use and the results of clinical trials.

Known risks are especially associated with hepatotoxicity. In an *in vivo* study in rats microvesicular steatosis was found in animals treated with >1000 mg ethanolic extract/kg body weight. This can be calculated to a human equivalent dosage of ~200 mg/kg body weight. The therapeutic dose in humans in contrast is ~0.08 mg/kg body weight. Altogether the available non-clinical data examining the effects of CR on hepatic parameters do not support the reported hepatotoxicity in humans. It could be of relevance, however, to understand the potential toxicity in patients with underlying risk factors.

The results of the non-clinical studies on the potential osteo-protective effects of CR extracts must be considered of preliminary nature. Additional *in vitro* and *in vivo* studies are needed to support this pharmacological activity, which would require clinical studies on its own.

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

There is no specific information on pharmacokinetics of CR. Only few non-clinical studies are available on pharmacokinetic drug-to-drug interactions.

Li *et al.* (2011) showed an interaction between tamoxifen and CR through inhibition of CYP2D6 and CYP3A4 *in vitro*. A 75% ethanolic extract of black cohosh was found to have the potential to interfere with the metabolic conversion of tamoxifen into its active metabolites. According to the authors the clinical significance needs to be determined in a well-designed clinical trial.

Huang *et al.* (2010) reported for ethanolic CR extracts (75% and 80% ethanol) and a 40% isopropanolic extract to inhibit *in vitro* CYP1A2, CYP3A4, CYP2C9 and CYP2D6 at concentrations

between 21.2 µg/ml and 76.7 µg/ml. Since none of the extracts inhibited the growth of Hep-G2 cells at concentrations up to 50 µg/ml the authors concluded that potential hepatotoxic effects may occur due to herb-drug interactions rather than through direct hepatotoxicity.

Non-clinical results suggest that interactions between CR components and other drugs might be possible. Clinically relevant interactions have not been reported so far.

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

3.3.1. Single dose toxicity

There are no studies on acute toxicity.

3.3.2. Repeat dose toxicity

There is a 6 month oral toxicity study with the isopropanolic extract, followed by an 8 week recovery period in Wistar rats. The daily doses were 3.125, 22.5 and 62.5 mg/kg body weight (equals to 250, 1800 and 5000 mg granulate/kg body weight). Animals in the extract test group were found to consume slightly more food. In the high dose group several effects were noted: increased relative liver weight, increased ovary weight and significant changes in the heart. These values returned to normal after 8 weeks of recovery. The NOEL was therefore defined with 22.5 mg/kg body weight (Korn 1991; Freudenstein 1997).

3.3.3. Genotoxicity

The mutagenicity of the isopropanolic extract was studied in an Ames test. The test was conducted with the *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538. The highest concentration was 1000 µg per plate. In this setting no evidence for genetic mutation was found (Hillmann 1990). The test procedure however, does not conform to the current guidelines regarding the used test strains and the highest concentration.

A Guideline-conform (EMA/HMPC/107079/07 with reference to OECD 471) Ames test (5 test strains of *Salmonella typhimurium* in the presence and absence of a metabolizing system, highest concentration of native extract 5000 µg/plate) was provided for the ethanolic extract (4.5-8.5:1, ethanol 60% (V/V)). For concentrations higher than 1000 µg/plate however, precipitations were observed (King and Harnasch 2002). Therefore, these concentrations cannot be assessed and the test does not fulfil the recent criteria of such a testing. Hence the results of this test are of limited value.

3.3.4. Carcinogenicity

The *in vitro* studies using human cancer cell lines and *in vivo* studies using animal tumour models suggested that CR has no effects, but data are not sufficient for a final conclusion (Nesselhut *et al.* 1993; Zava *et al.* 1998; Dixon-Shanies *et al.* 1999; Freudenstein *et al.* 1999, 2002; Liu *et al.* 2001; Amato *et al.* 2002; Einer-Jensen *et al.* 1996; Einbond *et al.* 2006).

A study with MMTV-neu transgenic mice was performed in order to investigate the effects of CR on mammary tumour development and progression. In this model the female mice developed primary and metastatic mammary tumours by spontaneous activation of the proto-oncogene neu (erbB2, HER2), the most common oncogene in breast cancer. CR (isopropanolic extract) was provided via diet in order to mimic the oral route of application in women. CR did not alter the latency or incidence of mammary tumours compared to MMTV-neu females maintained under control diet. The lack of any effect on

mammary tumour development in this experiment suggests that CR would not modify women's risk of developing breast cancer either beneficially or adversely. In contrast to its lack of effect on primary mammary tumour development, CR negatively influenced the progression of metastatic disease. In CR-treated female mice, the percentage of mice with detectable lung tumours at necropsy was increased compared to those on the control diet (26.5% n=110, versus 10.7%, n=116, of females with primary mammary tumours) (Davis *et al.* 2003 and 2008).

An *in vivo* test in four groups of 5-6 female ovariectomised DA/Han rats was performed in order to examine the concomitant administration of an isopropanolic extract of CR and tamoxifen in a tumour model of implanted RUCa-I rat endometrial adenocarcinoma cells. Ectopic growth of the primary tumour as well as the incidence and localisation of metastases were analysed. CR did not promote further growth or metastatic potential of the primary tumour. Pulmonary metastases were frequently found in all groups (Nisslein and Freudenstein 2004).

3.3.5. Reproductive and developmental toxicity

There are no studies on reproductive and developmental toxicity.

3.3.6. Local tolerance

No studies investigating the local tolerance of CR extract have been identified.

3.3.7. Other special studies

Not applicable

3.3.8. Conclusions

There are some studies which address toxicology of herbal preparations from CR. With a 6-month study in rodents a NOEL of 22.5 mg/kg body weight for the isopropanolic extract could be found (human equivalent dose of 3.6 mg/kg body weight). The daily dosage of the isopropanolic extract is about 0.08 mg/kg body weight (for a 60 kg adult).

For this isopropanolic extract an Ames test was performed which does not fulfil all requirements of the current guidelines. A guideline-conform Ames test was provided for the ethanolic extract (4.5-8.5:1, ethanol 60% (V/V)). For concentrations higher than 1000 µg/plate however, precipitations were observed which precluded an assessment.

A number of in-vitro and in-vivo pharmacological studies have shown that CR did not influence the latency or development of breast cancer, while other studies indicated a proliferative effect.

In a study with MMTV-neu transgenic mice CR negatively influenced the progression of metastatic disease (Davis *et al.* 2003 and 2008).

There are no conclusive studies on carcinogenicity with CR extracts.

3.4. Overall conclusions on non-clinical data

The pharmacological studies do not clarify the mode of action. Neither the mechanism of action nor the constituents relevant for the improvement of menopausal complaints are known.

Although early *in vitro* preclinical studies indicated that CR constituents bind to oestrogen receptors, this is not supported by recent evidence. Dopaminergic and serotonergic effects of CR extracts were observed *in vitro* and partly *in vivo*.

There is no specific information on pharmacokinetics of CR. Only few non-clinical studies are available on pharmacokinetic drug-to-drug interactions. Further studies are needed to assess the clinical relevance.

Known risks are especially associated with hepatotoxicity. In an *in vivo* study in rats microvesicular steatosis was found in animals treated with >1000 mg ethanolic extract/kg body weight. This can be calculated to a human equivalent dosage of ~200 mg/kg body weight. The therapeutic dose in humans is ~0.08 mg/kg body weight. Therefore, toxic concentrations are most likely not reached in humans at the recommended daily doses. Altogether the available non-clinical data examining the effects of CR on hepatic parameters do not support the reported hepatotoxicity in humans. It could be of relevance, however, to understand the potential toxicity in patients with underlying risk factors.

In vitro and *in vivo* studies on carcinogenicity suggested that CR has no effects, but data are not sufficient for a final conclusion.

In a study with MMTV-neu transgenic mice CR negatively influenced the progression of metastatic disease (Davis *et al.* 2003 and 2008).

Studies on reproductive and developmental toxicity have not been performed.

The Ames tests of the isopropanolic extract and ethanolic extract (4.5-8.5:1, ethanol 60% (V/V)) are not conclusive because of the indicated deficiencies.

4. Clinical Data

Menopausal complaints/symptoms

Menopausal complaints are caused by a decrease in oestrogen production and are characterised by neurovegetative, somatic and emotional complaints. Hot flushes represent the leading symptom. The theory of the cause of hot flushes is that there is a dysfunction in the central thermoregulatory set point in the hypothalamus as a result of decreased oestrogen, decreased gonadal steroid levels, and exaggerated LH pulsatility. Norepinephrine is the primary neurotransmitter responsible for lowering the thermoregulatory set point. Serotonin might also have an important role. Thermoregulation seems to be dependent on the balance of these factors; an imbalance might trigger hot flushes (Boekhout *et al.* 2006). In addition, excitability, irritability and sleep disturbances are reported.

Hormone therapy (HT) is generally accepted as the treatment of choice for the amelioration of severe climacteric symptoms. However, clinical trials such as the Women's Health Initiative (WHI) Study have shown serious health concerns associated with use of HT, including heart disease, stroke, invasive breast cancer and venous thromboembolic disease (Rossouw *et al.* 2002; Umland 2008; AACE 2011; Hall *et al.* 2011).

The use of HT remains limited due to existing risks ("Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women"; EMEA/CHMP/021/97 Rev. 1). Affected women are therefore in search of therapeutic alternatives like many other patients who prefer herbal medicines.

4.1. Clinical pharmacology

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

Climacteric complaints include neurovegetative symptoms (hot flushes, fits of perspiration, night sweats, sleep disorders), psychological symptoms (nervousness, mood swings, depressed mood,

physical and mental fatigue), disturbances of the menstrual cycle and urogenital symptoms (dyspareunia, vaginal dryness and itching) (Palacio *et al.* 2009).

Hot flushes affect two thirds of postmenopausal women, and 10%-20% of all postmenopausal women find them nearly intolerable (Boekhout *et al.* 2006).

The role of oestrogen or rather the lack of it appears to be crucial and is underlined by the clinical effects of hormone therapy (HT). Due to the fact that potentially serious adverse effects have been associated with this treatment, products containing preparations of CR are of interest for alternative treatment of climacteric complaints.

The use for the alleviation of women's menopausal symptoms such as hot flushes has been interpreted frequently as being due to the presence of phyto-oestrogens or phyto-SERM (selective oestrogen receptor modulators) in CR. Furthermore, triterpenes - besides phenolics and flavonoids one of the major natural product groups contained in an extract of the root and rhizome - show a structural relationship to steroidal hormones. However, pharmacological evaluation has not provided the required evidence for this mode of action.

Recent reviews summarise the existing knowledge concluding that the mode of action of CR still remains unknown (Fritz *et al.* 2014; Drewe *et al.* 2015). This also reflects the inconsistent results of numerous preclinical and clinical investigations.

Since the constituents relevant for the improvement of menopausal complaints are not known, the herbal preparation as a whole is the effective principle.

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

CR weakly inhibits CYP2D6 in a human pharmacological study, however the magnitude of this result may not be clinically relevant. Clinically relevant interactions with further CYP P450 enzymes were not found (Gurley *et al.* 2005). This was confirmed in a further study (Gurley *et al.* 2006a). Here, CR does not seem to have a clinically relevant effect on CYP3A activity in healthy humans. Whether this lack of effect is a function of dose, solubility, bioavailability or a combination of factors remains to be investigated.

Furthermore, CR is not a potent modulator of P-glycoprotein (P-gp) activity in healthy humans and therefore does not pose a significant interaction risk with digoxin (Gurley *et al.* 2006b).

Patel and Derkits (2007) report a possible increase in liver enzymes secondary to combined atorvastatin and CR administration. A 53 years old woman with a history for atypical chest pain, family history of coronary artery disease and menopause discontinued oral hormone therapy (HT) and started CR. The patient also took atorvastatin, aspirin, glucosamine/chondroitin and vaginal oestradiol. Routine laboratory results revealed an acute elevation of liver enzymes. After discontinuing CR, her liver enzymes decreased within one month. As a possible explanation the authors state that atorvastatin is a known HMG-CoA reductase inhibitor and major substrate of CYP P450 phenotype 3A4. Inhibition of CYP3A4 by CR could elevate levels of atorvastatin, causing an elevation of liver enzymes. However, additional medication was used and a clear allocation of the seen adverse events to the concomitant use of CR with atorvastatin is not possible.

In the study by van Breemen *et al.* (2010), a 75% ethanolic black cohosh extract prepared from botanically authenticated plant material was standardized to total triterpene glycosides and tested in a phase I clinical trial in women to evaluate the maximum tolerated dose and pharmacokinetics of one of its triterpene glycosides, 23-epi-26-deoxyactein. Single doses of black cohosh extract corresponding to 32, 64, or 128 mg of herbal substance and containing 1.4, 2.8, or 5.6 mg of 23-epi-26-deoxyactein

were administered to 15 healthy menopausal women. Serial blood samples and 24-hours urine samples were obtained; blood chemistry, hormonal levels, and 23-epi-26-deoxyactein levels were determined. No acute toxicity or oestrogenic hormone effects were observed. Pharmacokinetic analyses of 23-epi-26-deoxyactein in sera indicated that the maximum concentration and area under the curve increased proportionately with dosage, and that the half-life was ~2 hours for all dosages. Less than 0.01% of the 23-epi-26-deoxyactein was recovered in urine 24 hours after administration. No phase I or phase II metabolites were observed either in clinical specimens or *in vitro*. The pharmacological significance of 23-epi-26-deoxyactein for the indication menopausal complaints however, is still unclear.

4.2. Clinical efficacy

4.2.1. Dose response studies

Information on posology is derived from clinical studies and includes the long-standing use as well as recommendations contained in the German Commission E monograph (daily dose: 40 mg herbal substance).

One study has been performed comparing a daily dosage of a CR dry extract (40% isopropanol) corresponding to 39 mg herbal substance with 127.3 mg herbal substance per day (Liske *et al.* 2002). The duration of this study was up to 6 months. The investigation showed the same effects in both treatment groups: the Kupperman Index decreased from 31.0 to 7.0 in the high dose group after 3 months of treatment compared to 31.5 to 8.0 in the low dose group.

Another study was performed with a high dose of CR preparation standardised to 27-deoxyactin, 160 mg daily (Newton *et al.* 2006). Information whether this dosage refers to the amount of extract or drug is not given. The results of the high dose group are comparable with the placebo treated group.

As in both studies no benefit of higher dose treatment could be demonstrated, the results support the recommended daily dose of 40 mg herbal substance.

In a third study (Brattstroem 2005; Kaiser *et al.* 2008; Schellenberg *et al.* 2012), 180 female outpatients with climacteric complaints were treated for 12 weeks in a randomized, double-blind, placebo-controlled, 3-armed trial (CR dry extract Ze 450, DER 4.5-8.5:1, ethanol 60%, 6.5 mg (LD) or 13.0 mg (HD) corresponding to 40 mg or 80 mg of herbal substance daily, or placebo). The extract Ze 405 proved to be superior versus placebo in the Kupperman Index (mean absolute differences 17.0 (95% CI 14.65–19.35) score points, $P < 0.0001$ for 13.0 mg; mean absolute differences 8.47 (95% CI 5.55–11.39) score points, $P = 0.0003$ for 6.5 mg). For patients with severe symptoms (total KI > 35), however, only the high dose (13.0 mg) of Ze 450 was effective. For premenopausal patients, only the HD showed a significant ($P < 0.001$) decrease in average total KI scores compared to the placebo group (20.9 (7.6 SD) versus 1.1 (7.8 SD) score points, resp.). The low dose (6.5 mg) was superior to placebo in the early and late postmenopausal stage. In the late postmenopausal subgroup no superiority for the HD over the LD group could be established. The study results indicate a possible dose dependency of the effect especially in patients with severe symptoms. But the numbers are rather small and a confirmation for other extracts is missing.

4.2.2. Clinical studies (case studies and clinical trials)

For assessment of efficacy in the clinical studies predominantly the modified Kupperman Index (KI) or the Menopause Rating Scale I (physician) or II (patient) were used (Kupperman *et al.* 1953).

Table 4: Kupperman Index (modified)

Kupperman Index (modified)						
Symptoms	None (0)	mild (1)	moderate (2)	severe (3)	multiplicator (factor)	numerical conversion = factor x
Vasomotor					4	
Paresthesia					2	
Insomnia					2	
Nervousness					1	
Melancholia					1	
Vertigo					1	
Weakness					1	
Arthralgia & Myalgia					1	
Headache					1	
Palpitation					1	
Formication					1	
Assessment: < 20 = mild; 20 – 35 = moderate; > 35 = severe					Index	

(Kupperman *et al.* 1953)

The Kupperman Index (KI) has also been used for the characterisation and quantification of menopausal symptoms. A quantitative assessment of symptoms is achieved by a grading according to their severity:

3 = severe

2 = moderate

1 = mild

0 = not present

Useful categories for describing clinical relevance of the index are (Schneider *et al.* 2000b):

No symptoms	0
Minor symptoms:	1-14
Mild symptoms:	15–19
Moderate symptoms:	20–34
Severe symptoms:	>=35

To overcome the limitations of this rather simple symptom questionnaire of the late 1950s and in order to include urogenital symptoms the Menopause Rating Scale I (performed by physician) and Menopause Rating Scale II (performed by patient, one additional item: anxiety) were developed and validated in the late 1990s (Schneider *et al.* 2000b).

The Menopause Rating Scale (MRS I) comprises the following 10 items:

- (1) hot flushes, sweating
- (2) cardiac symptoms
- (3) sleep disorders
- (4) depressive mood
- (5) nervousness, irritability
- (6) impaired performance / memory
- (7) disorders of sexuality
- (8) urinary symptoms
- (9) vaginal dryness
- (10) joint and muscle symptoms

The individual degree of severity of an item in MRS I is defined as follows (Schneider *et al.* 2000a):

Mild:	0.1-0.3
Moderate:	0.4-0.5
Severe:	0.6-0.7
Very severe:	0.8-1.0

Four dimensions (sub-scores) of symptoms/complaints can be discerned:

- a) Hot flushes (items 1 und 3)
- b) Psyche (items 4, 5 und 6)
- c) Soma (items 2 und 10)
- d) Atrophy (items 7, 8 und 9)

Whereas MRS I is completed by the physician who does the interview with the patient, MRS II is a self-administered questionnaire. It consists of a list of 11 items to be answered. A five-point rating of severity is applied to each of the 11 items.

Table 5: Menopause Rating Scale II

Menopause Rating Scale II					
Symptoms score	none 0	mild 1	moderate 2	severe 3	very severe 4
1. Hot flushes, sweating (episodes of sweating)					
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)					
3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through, waking up early)					
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)					
5. Irritability (feeling nervous, inner tension, feeling aggressive)					
6. Anxiety [MRS II] (inner restlessness, feeling panicky)					
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)					
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)					
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)					
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)					
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)					

(Heinemann *et al.* 2003, International versions of the menopause rating scale)

For MRS II, three dimensions of symptoms/complaints were identified:

- a) Psychological domain: four symptoms (items 4-7: depressive mood, irritability, anxiety, exhaustion)
- b) Somato-vegetative domain: four symptoms (items 1-3: hot flushes/sweating, heart discomfort, sleep problems and item 11: joint and muscular discomfort)
- c) Urogenital domain: three symptoms (items 8-10: sexual problems, bladder problems, dryness of vagina)

The term “climacteric (menopausal) complaints” refers to the period of menopausal transition from fertility to sterility. The most important climacteric symptoms are vasomotor symptoms (hot flushes). The severity of hot flushes is defined clinically as follows:

Mild: sensation of heat without sweating

Moderate: sensation of heat with sweating, able to continue activity

Severe: sensation of heat with sweating, causing cessation of activity

Due to lack of guidelines concerning herbal medicinal products for diagnosis and treatment of menopausal complaints it is appropriate to use the guideline for hormone replacement therapy (EMEA/CHMP/021/97, Rev. 1) and other diagnostic instruments, derived from other established therapies.

For planning and conduction of adequate studies, the study population has to be predefined precisely. Only comparable complaints in comparable groups of patients can provide acceptable results concerning efficacy, safety and tolerability. Therefore, the target groups should be investigated separately, for example pre-and perimenopausal women on the one hand and postmenopausal women on the other hand. Additionally, breast cancer patients with and without other therapies except surgery should be included in the considerations about the conduct of studies. Different results are to be expected for the subgroups.

Basic parameters have to be predefined for the use of herbal medicinal products in order to achieve reliable results; i.e. character, severity, duration and improvement of complaints have to be measured and compared from baseline over treatment up to follow up. Although the Kupperman Index, the different MRS scales and the guideline for hormone replacement therapy (EMEA/CHMP/021/97, Rev. 1) are generally accepted instruments, they were not developed for herbal medicinal products. The large variety of different study protocols, inclusion and exclusion criteria, interpretation of results and conclusions thereof shows the need for validated and commonly used instruments.

The scientific data all in all indicate an efficacy of CR extracts in patients with menopausal symptoms even though none of the clinical studies available completely showed a significant improvement of the total Kupperman Index or the total Menopause Rating Scale Score. Partly results were not shown in the publications, the sample sizes were too small or the Kupperman Index and the Menopause Rating Scale were not validated for the study population (Asians). Therefore, the trials could not be accepted in their entirety.

Unfortunately, in some publications correct specifications of solvent and drug-extract ratio (DER) are missing. Herbal extracts contain a large number of different substances. The clinical effects of the CR dry extracts cannot be attributed to a specific individual constituent and the whole extracts represent the active substance. The number of diverse extracts with different quality standards used in the clinical efficacy studies hampers the evaluation additionally.

In the 1980s and 1990s several clinical studies investigated efficacy and safety of different CR preparations. These studies which were conducted prior to the introduction of good clinical practice (GCP) criteria provided a basis for the publication of the monograph for *Cimicifuga racemosa* rhizoma by the German Commission E.

In addition to the Kupperman Index (KI) and the Menopause Rating Scale (MRS) the following assessment tools were used in the clinical trials:

- GCS: Greene Climacteric Scale
- HAMD: Hamilton Depression Scale
- HAMA: Hamilton Anxiety (rating) Scale

- CGI: Clinical Global Impression
- SDS: Self Rating Depression Scale
- SRT: Symptom-Rating Test (depression, anxiety)
- BDI: Beck's Depression Inventory
- Diary
- Rand-36 QoL: Quality of life questionnaire
- Cervantes QoL: Quality of life questionnaire (intended to be used in Spanish women aged between 45 and 64 years) (Palacios *et al.* 2004).

Stolze (1982): A non-interventional study, multicentre, n=629, on average 51 years old, 6-8 weeks treatment. Improvement of menopausal symptoms was shown in 80% of women; no severe, only gastrointestinal adverse events. Medication used: Oral liquid (12 ml tincture, 1:5, corresponding to 2.4 g herbal substance in 100 g oral liquid, extraction solvent ethanol 60 % V/V), 2 times 40 drops, lack of placebo group, no validated scales. Descriptive improvement of symptoms (%) was shown in detail. Neurovegetative complaints such as hot flushes: 86.6%, sweating: 88.8%, headache: 81.9%, dizziness 86.6%, palpitations: 90.4%, tinnitus: 92.9%. Emotional complaints such as nervousness: 85.6%, sleep-disorders: 76.8%, depressive disorders: 82.5%.

Daiber (1983): An open, uncontrolled study, n=36, 45-62 years old, 3 months duration. Significant decrease of KI from moderate (19) to light (11) after 12 weeks; decrease in hot flushes, sweating, nervousness, depressive disorders and sleep disorders (graphically shown without details); also significant decrease in CGI, good tolerance; medication used: Oral liquid (12 ml tincture, 1:5, corresponding to 2.4 g herbal substance in 100 g oral liquid, extraction solvent ethanol 60 % V/V), 2 times 40 drops; lack of placebo group.

Vorberg (1984): An open, uncontrolled study, n=50, 38 postmenopausal women with contraindication for hormone therapies, 45-60 years old, 3 months treatment. Significant decrease of KI from moderate to light, significant improvement of mood profile, no serious adverse events, only mild gastrointestinal adverse events. Medication used: Oral liquid (12 ml tincture, 1:5, corresponding to 2.4 g herbal substance in 100 g oral liquid, extraction solvent ethanol 60 % V/V), 2 times 40 drops; lack of placebo group.

Warnecke (1985): An open, controlled, randomised study, n=60 (20/20/20 treated with oral liquid (12 ml tincture, 1:5, corresponding to 2.4 g herbal substance in 100 g oral liquid, extraction solvent ethanol 60 % V/V), 2 times 40 drops, or conjugated oestrogen 0.625 mg per day or 2 mg diazepam), 3 months, under Cimicifuga treatment significant decrease of KI and HAMA, somatic disease under diazepam not influenced, tendentious increased proliferation of the vaginal epithelia under oestrogen as well as under Cimicifuga. Withdrawal from the study in 5 cases because of non-amelioration of emotional symptoms; lack of placebo group.

Pethö (1987): An open study, n=50, change in therapy (Pre-treatment: oestrogen), age on average 49 years, 6 months treatment. Significant decrease of KI from 17.6 to 9.2 after 6 months, no adverse events. Medication used: ICR dry extract, DER 6-11:1, propan-2-ol 40% (V/V), 2 times 2 tablets; lack of placebo group.

Stoll (1987): A double-blind, randomised, placebo and reference controlled study, n=80 (30/30/20) treated with ICR dry extract, DER 6-11:1, propan-2-ol 40% (V/V), 2 times 2 tablets, conjugated oestrogen or placebo, 46-58 years old, 3 months, predominance of Cimicifuga compared to placebo, decrease of KI below 15 (p<0.001) and HAMA, vaginal cytology, all three parameters had significantly improved, 13 withdrawals because of ineffectiveness in the oestrogen group. The administered

oestrogen dose proved to be too low and yielded no effect compared to placebo. Three adverse effects of weight gain were reported without details.

Lehmann-Willenbrock (1988): An open, controlled, randomised study, n=60 hysterectomized women. 4 treatment groups: ICR dry extract, DER 6-11:1, propan-2-ol 40% (V/V), 2 times 2 tablets, conjugated oestrogen 1.25 mg per day, estriol 1 mg per day, oestrogen/gestagen combination, 6 months treatment. In all groups significant decrease of KI; no influence of LH, FSH, no adverse events; lack of placebo group.

Georgiev and Jordanova (1997): An open uncontrolled study, n=50 postmenopausal women, 6 months treatment, decrease of KI and HAMA, no change in endometrium thickness. No data on medication and adverse events. Very poor data available.

Mielnik (1997): An open uncontrolled study, n=34 postmenopausal women, 6 months treatment, after 1 month clinically relevant decrease of KI from >20 to <10, 4 drop outs, no more information on medication. Very poor data available.

Nesselhut and Liske (1999): A non-interventional study, n=28, postmenopausal women, age on average 56.4 years, 3 months treatment, after 1 month clinically relevant decrease of KI, no influence on LH, FSH and Prolactin, no hormonal effects (or oestrogen agonistic activities) could be verified; no ovarian stimulation could be shown. Good efficacy in neurovegetative symptoms, no adverse events. Medication: ICR dry extract, DER 6-11:1, propan-2-ol 40% (V/V), tablets corresponding to 136 mg herbal substance per day, which is approximately the threefold recommended daily dose; lack of placebo group.

An overview on more recent clinical studies in menopausal complaints investigating dry extracts from CR is provided in Table 6.

Table 6: Clinical studies in menopausal complaints investigating dry extracts from CR (CR)

a) Isopropanolic extract (iCR): DER 6-11:1, extraction solvent propan-2-ol 40% (V/V)

- Double-blind randomised study, placebo controlled

Reference	Design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Osmer <i>et al.</i> 2005	Randomised, double-blind, placebo-controlled, multicentre	iCR dry extract, DER 6-11:1, propan-2-ol 40% (V/V), 2x2.5 mg per tablet, equivalent to 40 mg herbal substance per day, 3 months	304 post-menopausal German women iCR: 153 patients, mean age 53 years placebo: 151 patients, mean age 54 years	Climacteric complaints as defined by MRS \geq 0.4 in at least 3 items; \geq 12 months since last regular menstruation or \geq 6 months plus FSH \geq 50 U/l	Efficacy: Significant improvement of the total score of MRS I (=primary endpoint) by 0.03-0.05 MRS units (p=0.01), better efficacy in the early menopause, claimed improvement of the MRS I sub scores hot flushes (p=0.007), atrophy (p=0.012) and psyche (p=0.019) (secondary endpoints), data not shown in publication Safety: no significant difference, no serious adverse events in both groups, no clinically relevant changes of liver function tests (ALT, AST, GGT)	Primary endpoint analysed in a linear regression model, advanced primary model used for analysing secondary endpoints	Study results support the use of dry extracts of CR for relief of menopausal complaints. Good tolerance of study medication

- Double-blind randomised studies, comparator controlled

Reference	Design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Nappi <i>et al.</i> 2005	Randomised, comparator-controlled	iCR dry extract, DER 6-11: 1, propan-2-ol 40% (V/V), 2x2.5 mg per tablet, equivalent to 40 mg herbal substance per day Comparator: low dose transdermal estradiol (25 µg + progesterone 10 mg), 3 months	64 post-menopausal Italian patients iCR: 32 patients., mean age 50.5 years Comp.: 32 patients, mean age 50.9 years	Spontaneous menopausal status of at least 6 months with FSH>30 U/l, at least 5 hot flushes per day and endometrial thickness<5 mm	Primary endpoints: -number of hot flushes per day (diary) -climacteric complaints (GCS) -anxiety, depression (SRT) Efficacy results: Identical improvement under both treatments, Safety results: no changes in laboratory parameters (FSH, LH, Prolactin, 17β-estradiol, cortisol, lipid profile, liver function) and endometrial thickness	Paired Student <i>t</i> test, one way analyses of variance	Lack of placebo group, no inferiority of iCR compared to HT
Liske <i>et al.</i> 2002	Randomised, double-blind parallel group	iCR standard dose: dry extract DER 6-11: 1, propan-2-ol 40% (V/V), 1 tablet equivalent to 39 mg herbal substance per day iCR high dose: dry extract, DER 6-11: 1, propan-2-ol 40% (V/V), 1 tablet equivalent to 127.3 mg herbal substance per day, 3 months up to 6 months	152 (76/76, mean age 49.7/50.2 years) patients randomised, 149 patients in ITT population, 123/116 included in PP data set (12/24 weeks)	Peri-and post-menopausal Polish patients, Kupperman Index (KI)≥20	Efficacy: Significant decrease of KI in both groups from moderate to normal range, no differences in SDS (self-depression scale), CGI (clinical global impression scale) and in vaginal cytology between treatment groups; Safety: 19 mild to moderate adverse events without definite causal relationship to iCR, no serious adverse events in both groups, no changes in laboratory parameters (FSH, LH, Prolactin, 17β-estradiol)	Wilcoxon-Mann-Whitney-test, CI 95%, responder analysis of patients with KI<15 after treatment	Lack of placebo group, but significant improvement of KI in both groups (no benefit of higher dose treatment)

- Open study, controlled

Reference	Design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Briese <i>et al.</i> 2007	Non-interventional study, comparator controlled, multicentre	iCR dry extract, DER 6-11:1, propan-2-ol 40% (V/V), 2x2.5 mg per tablet, equivalent to 40 mg herbal substance per day Comparator: combination preparation containing 3.75 mg iCR extract and 70 mg of an ethanolic extract from 245 to 350 mg St. John's wort (<i>Hypericum perforatum</i>), 2x1 or 2 tablets, equivalent to 60-120 mg herbal substance (iCR) per day, 6 months	6 141 German outpatients, iCR: 3027 comp: 3114 mean age: 52.7 years	Climacteric complaints	Significant decrease in MRS I in both groups in all items (MRS total score and sub scores soma, psyche, atrophy and hot flushes); rate of possibly treatment-related adverse events was 0.16%, all non-serious	Covariance analysis	Improvement of MRS in both groups, good tolerance of study medications, lack of placebo group

- Open studies, uncontrolled

Reference	Design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Schmidt <i>et al.</i> 2005	observational	iCR dry extract, DER 6-11:1, propan-2-ol 40% (V/V), 2x2.5 mg per tablet equivalent to 40 mg herbal substance per day, 3 months	502 Swiss patients, mean age: 56 years	Climacteric complaints	Improvement in KI	Descriptive statistics only	Supportive, limited relevance for efficacy because uncontrolled
Vermes <i>et al.</i> 2005	observational	iCR dry extract, DER 6-11:1, propan-2-ol 40% (V/V), 2 x 2.5 mg per tablet equivalent to 40 mg herbal substance per day, 3 months	2016 post-menopausal Hungarian women	Climacteric complaints	Improvement in KI	Descriptive statistics only	Supportive

b) Ethanolic extracts

- Double-blind randomised studies, placebo- and/or comparator controlled

Reference	Design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Wuttke <i>et al.</i> 2003, 2006	Randomised, double-blind, placebo and comparator controlled, multicentre	CR BNO 1055 dry extract, DER 5-10:1, ethanol 58% (V/V), 2xdaily 2.8 mg per tablet, equivalent to 40 mg herbal substance per day, CE: conjugated oestrogens 0.6 mg per day, 3 months	95 Czech patients randomised and treated for 3 months, 33 patients excluded from ITT analysis due to protocol violations [<3 hot flushes per day, signs of (un-) ovulatory cycles, body mass index >30 kg ²], 62 patients included in the per-protocol analysis: CR: 20, mean age 52.25 years CE: 22, mean age 52.3 years Placebo: 20, mean age 54.05 years	Postmenopausal patients, age 40-60, with a minimum of three hot flushes per day, postmenopausal hormone values (17 β -estradiol ≤ 40 pg/ml, FSH ≥ 25 U/l)	<p>Primary endpoint MRS I total score: comparable improvement under CR and CE and superiority vs placebo, but statistically just below level of significance.</p> <p>Secondary endpoints:</p> <p>Sub score 'hot flushes' significantly improved under CE, similar effect under CR, but statistically not significant.</p> <p>Sub score 'psyche' improved by CR and CE, but statistically not significant.</p> <p>Sub score 'atrophy' significantly improved by CR, similar but statistically not significant effect by CE.</p> <p>Significantly increased serum levels of alkaline phosphatase in CR group, no effect on endometrium (trans-vaginal ultrasound) in contrast to CE, increased number of superficial cells in vaginal smears, but in contrast to CE group statistically not significant.</p> <p>Safety: No serious adverse events, clinical laboratory data including liver enzymes remained unaffected. No changes in FSH, LH, 17β-estradiol</p>	Multiple comparisons of treatment groups by analysis of covariance. Calculation of point estimators for baseline- and centre-adjusted mean values, CI and p-values. Statistical analyses with SAS	Improvement in MRS score under CR comparable to CE vs placebo; results show significant predominance of CR vs placebo in the MRS sub score 'atrophy' without effects on the endometrium, positive influence on bone markers and vaginal cytology; however: small sample size

Reference	Design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Frei-Kleiner <i>et al.</i> 2005	Randomised, double-blind, placebo-controlled, multi-centre	CR 99 dry extract, DER 4.5-8.5: 1, ethanol 60% (V/V), 1x6.5 mg per capsule daily, equivalent to 40 mg herbal substance per day, 3 months	122 peri-and postmenopausal Swiss patients CR: 81, mean age 52.5 years Placebo: 41, mean age 52.2 years	At least 3 hot flushes per day	Efficacy: No significant difference of mean decrease in weekly weighted score of hot flushes (37% CR group, 30% placebo group) and in KI (26% CR group, 17% placebo group); Significant treatment difference in subgroups (peri-menopausal patients, KI \geq 20) Safety: no significant difference, no serious adverse events in both groups, no clinically relevant changes of liver function tests (ALT, AST)	Wilcoxon-Mann-Whitney-test, using the percentage change between end of treatment and baseline values	The results indicate a superiority of CR compared to placebo in patients with menopausal disorders of at least moderate intensity according to a KI \geq 20, but not in the whole population.
Brattstroem 2005, Kaiser <i>et al.</i> 2008, Schellenberg <i>et al.</i> 2012	Randomised, double-blind, placebo-controlled, 3-armed	Ze 450 dry extract, DER 4.5-8.5: 1, ethanol 60% (V/V), 6.5/13 mg per 2 tablets once daily (double-dummy, parallel group design) equivalent to 40 mg (LD) or 80 mg (HD) herbal substance per day or placebo, 3 months	180 Swiss patients randomised, mean age 51.7 years, 166 patients included in ITT population, LD: 57 HD: 55 Placebo: 54	Pre, early and post-menopausal patients (age \geq 40 years) suffering from menopausal syndrome	Efficacy: Significant decrease of KI in both groups (LD and HD) compared to placebo Significant decrease of KI in HD group compared to LD group (esp. for patients with KI>35 and premenopausal patients) Safety: no serious adverse events, no significant differences between groups, no dose relation	Two-sided Mann-Whitney test, predefined hierarchical test procedure	The results indicate a possible dose dependency of the effect especially in patients with severe symptoms. Small numbers, confirmation for other extracts is missing

- Open studies, uncontrolled

Reference	Design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Rauš <i>et al.</i> 2006	open label, non-comparative, prospective, multicentre and multinational	CR BNO 1055 dry extract, DER 5-10:1, ethanol 58% (V/V), 2x2.8 mg per tablet, equivalent to 40 mg herbal substance per day, 52 weeks	400 Czech and Polish patients enrolled, 375 patients completed, mean age 56.38 years	Postmenopausal patients, age 50-75, with symptoms related to estrogen deficiency; intact uterus; BMI ≤ 28 kg/m ² ; last spontaneous menstrual period at least 2 years ago; FSH ≥ 35 U/l; 17 β -estradiol ≤ 40 pg/ml; endometrial thickness ≤ 5 mm	Primary endpoint: Proof of endometrial safety: No case of hyperplasia or more serious adverse endometrial outcome Secondary endpoints: MRS II/4-week weighted scores of hot flushes: Number of hot flushes decreased	Point estimator for primary endpoint and its upper limit of 95% CI were calculated, descriptive statistics were used to assess the secondary endpoints	The study results indicate that the investigated product has no oestrogenic or oestrogen like effects on the endometrium within a 12 months treatment period.
Lopatka <i>et al.</i> 2007	Observational	Ze 450 dry extract, DER 4.5-8.5:1, ethanol 60% (V/V), 1x6.5 mg per tablet, equivalent to 40 mg herbal substance per day, 4 months	584 Swiss patients included, 541 patients completed, mean age 53.2 years	Peri-and postmenopausal patients with menopausal complaints	Improvement in MRS II score, no change in body weight and BMI	Descriptive statistics only	Supportive
Drewe <i>et al.</i> 2013	Observational	Ze 450 dry extract, DER 4.5-8.5:1, ethanol 60% (V/V), 1x13 mg per tablet equivalent to 80 mg (HD) herbal substance per day, 3 months, continuation	442 Swiss unselected outpatients, mean age 52.3 years	Menopausal complaints	Improvement in KI especially in HD group	Descriptive statistics only	Patients treated according to the preference of their private physicians and not per randomisation

Reference	Design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		over additional 6 months or switch to 1x6.5 mg per tablet equivalent to 40 mg (LD) herbal substance per day					The results support a possible dose dependency of the effect. Good tolerability

c) Non-European Studies

- Double-blind randomised studies, (placebo) controlled

Reference	Design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Bai <i>et al.</i> 2007	Randomised, double-blind, multicentre, comparator-controlled	iCR dry extract, DER 6-11: 1, propan-2-ol 40% (V/V), 2x2.5 mg per tablet, equivalent to 40 mg herbal substance per day; Comparator: 2.5 mg tibolone, 1 tablet per day, 3 months	244 post-menopausal Chinese patients, iCR: 122, mean age 51.8 years Comp.: 122, mean age 50.9 years	Spontaneous menopausal status of at least 4 weeks and KI \geq 15	Primary endpoints, efficacy: combination of the Mann–Whitney values (MWV) of the KI with significant reduction of KI in both groups, Safety: frequency of adverse events at end of treatment with significant lower incidence of adverse events in iCR group, no clinically relevant changes of liver function tests (ALT, AST, GGT)	MWV=0.479% CI= 0.39-0.54; p)=0.002 (non-inferiority) showing statistical significant non-inferiority of iCR to tibolone	Non-European study population, KI not validated for Asian women
Li <i>et al.</i> 2011	Randomised, double-blind,	iCR dry extract, DER 6-11: 1, propan-2-ol 40% (V/V), 2x2.5 mg per	89 perimeno-pausal Chinese patients, 12 dropouts,	Spontaneous menopausal status of at least	Primary endpoint/efficacy results: Significant	Paired Student <i>t</i> test	Non-European study population,

Reference	Design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
	placebo-controlled	tablet, equivalent to 40 mg herbal substance per day, 3 months	iCR: 45 patients, mean age 51 years Placebo: 32 patients, mean age 50.4 years	3 months with FSH>40 U/l and 17 β -estradiol <20 pg/ml, age 45-55 years, KI \geq 17	improvement of KI Secondary endpoints / safety results: No changes in laboratory parameters (FSH, LH, 17 β -estradiol, lipid profile, liver function), endometrial thickness and vaginal maturation index (VMI)		KI not validated for Asian women
Oktem <i>et al.</i> 2007	Prospective, randomised, open, comparator-controlled	- CR: extraction solvent and DER not known, 40 mg per day - fluoxetine: 20 mg per day	120 Turkish patients CR: 60, mean age 53.1 years fluoxetine: 60, mean age 52.7 years	Postmenopausal patients (no bleeding within 12 months or FSH>40 U/L) with menopausal complaints	Improvement in KI in CR group Improvement in Beck's depression scale in Fluoxetine group	1-way analysis of variance (ANOVA), Mann-Whitney U test	No valid information on CR, lack of placebo group
Newton <i>et al.</i> 2006, Reed <i>et al.</i> 2008	Randomised, double-blind, placebo-controlled, 5-armed	- CR: Dry extract, ethanol 70%, DER not known, , 160 mg per day standardized to 2.5% triterpene glycosides - Multibotanical with Cimicifuga 200 mg per day - Multibotanical plus soy diet counseling - Conjugated equine	351 patients mean age 52.2 years CR: 80 Multi+CR: 76 Multi+Soy: 79 CEE: 32 Placebo: 84	Late menopausal transition (1 skipped menses within the preceding 12 months) or postmenopausal (no bleeding within 12 months or FSH>20 U/L) 2 or more	No difference in vasomotor symptoms per day between the herbal interventions and placebo at 3, 6 and 12 months	Multivariate mixed model	CR: No medicinal product (USA), comparability of CR and daily dose unclear

Reference	Design	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		estrogens 0.625 mg per day with or without medroxyprogesteron acetate - Placebo 12 months		vasomotor symptoms per day over 2 weeks			
Geller <i>et al.</i> 2009	Randomised, double-blind, placebo-controlled, 4-armed	- CR: Dry extract, DER 20:1, ethanol 75%, 128 mg per day standardized to 7.27 mg triterpene glycosides - Red clover - Conjugated equine estrogens (CEE) 0.625 mg per day with 2.5 mg medroxyprogesteron acetate (MPA) - Placebo 12 months	89 patients mean age 53 years CR: 22 Red clover: 22 CEE/MPA: 23 Placebo: 22	Peri- or post-menopausal patients with at least 35 vasomotor symptoms per week (hot flashes and night sweats) in the 2 weeks before study enrollment	Efficacy: No difference in vasomotor symptoms per day between the herbal interventions and placebo after 12 months Safety: no serious adverse events, no significant differences between groups, no clinically relevant changes of liver function tests (ALT, AST) and FSH, LH, 17 β -estradiol in CR group	Multivariate mixed model	CR: No medicinal product (USA), comparability of used CR and daily dose unclear
Mohammad-Alizadeh-Charandabi <i>et al.</i> 2013, Shahnazi <i>et al.</i> 2013	Randomised, double-blind, placebo-controlled	CR: 6.5 mg dry extract per tablet, DER and extraction solvent not known, standardized to 0.12–0.18 mg 27-deoxyactein, 1 tablet per day, 2 months	84 early post-menopausal Iranian patients CR: 42 patients, mean age 51.4 years Placebo: 42 patients, mean age 51.7 years	Greene climacteric scale (GCS) scores of 15 to 42, no menstrual cycle in the last 12 months	Efficacy: Significant improvement in GCS, Safety: no adverse events	T-test for comparison of the baseline scores, linear model for comparison of the follow up scores	Non-European study population, no information on CR

For various reasons non-European studies are listed separately. The perception of menopausal symptoms depends on cultural factors or the symptoms show real differences in prevalence. Thus, direct comparisons of menopausal symptom scores between Europe/North America on the one side and regions in Latin America and Asia are not recommended. In US-American studies CR preparations without marketing authorisation as medicinal products are used. Information on DER and/or extraction solvent is often missing and the dosage information in the publications does not always clearly indicate whether it refers to the amount of extract or drug. Therefore, the relevance of the study results for European patients seems questionable.

Other indications

Amsterdam *et al.* (2009): Randomized, double-blind, placebo-controlled trial of CR in women with anxiety disorder due to menopause. No statistically significant anxiolytic effect of CR (vs. placebo) was found.

Bebenek *et al.* (2010): The aim of this study was to determine the effect of periodised exercise training with and without CR (CR) on bone mineral density (BMD) and 10-year coronary heart disease (CHD) risk in early postmenopausal women. The authors concluded that the exercise program favourably affected BMD, menopausal symptoms, lean body mass, and, to a smaller extent, 10-year CHD risk in early postmenopausal women. Adjuvant supplementation of CR did not enhance these positive effects.

Meta-analyses

There are several reviews which have reached different conclusions.

Borrelli and Ernst (2008) performed a meta-analysis in order to evaluate the efficacy of CR in relieving menopausal complaints. Six randomised-controlled trials with a total of 1163 peri and post-menopausal women (352 participants in verum group, 811 participants in control group) met the inclusion criteria: Stoll (1987), Wuttke *et al.* (2003), Osmers *et al.* (2005), Frei-Kleiner *et al.* (2005), Newton *et al.* (2005) and Bai *et al.* (2007). The authors found the study results conflicting. The scores used in the trials (e.g. KI or MRS) determined the severity but not the frequency of menopausal symptoms and not all studies evaluated the frequency of vasomotor symptoms using a self-report daily diary. Therefore, the data seemed to suggest that CR could reduce the intensity but probably not the frequency of climacteric symptoms. The authors stated that the evidence from these trials did not consistently demonstrate an effect of black cohosh on menopausal symptoms, but would not exclude a beneficial effect of CR on peri and post-menopausal women.

The meta-analysis performed by Shams *et al.* (2010) used the results of seven randomised-controlled trials for calculation of the combined estimate for the change in menopausal vasomotor symptoms. Five trials of the seven included trials had used CR in combination with other products and are therefore not further mentioned here. Only two studies, Frei-Kleiner *et al.* (2005) and Newton *et al.* (2005), had used CR in the intervention group. Overall, CR containing preparations were found to be efficacious in reducing the symptoms of menopause in comparison to placebo. The heterogeneity of the selected studies regarding the study medication however, does not allow a definite attribution and an evaluation of the efficacy of CR in relieving menopausal complaints.

Sixteen randomized-controlled trials, recruiting a total of 2 027 peri-or postmenopausal women, were identified in the Cochrane Review by Leach and Moore (2012): Amsterdam *et al.* 2009; Bai *et al.* 2007; Bebenek *et al.* 2010; Frei-Kleiner *et al.* 2005; Geller *et al.* 2009; Jacobson *et al.* 2001; Lehmann-Willenbrock 1988; Nappi *et al.* 2005; Newton *et al.* 2006; Oktem *et al.* 2007; Osmers *et al.* 2005; Pockaj *et al.* 2006; Stoll 1987; Wuttke *et al.* 2003. In addition to the studies which are already mentioned above following trials were included in the review:

Carlisle and Jessup (2008): Effect of black cohosh on biochemical markers of bone remodeling in postmenopausal women. Dissertation, University of Florida, USA, 2008

Kronenberg *et al.* (2009): Effect of black cohosh extract on hot flashes and other menopausal symptoms. Poster presentation, 20th Annual Meeting, North American Menopause Society, San Diego, CA 2009 (original reference not available)

All studies used oral mono-preparations of CR at a median daily dose of 40 mg, for a mean duration of 23 weeks. According to the authors, only four studies (Amsterdam *et al.* (2009), Frei-Kleiner *et al.* (2005), Geller *et al.* (2009), Newton *et al.* (2006)) were suitable for pooling to assess the efficacy of CR in improvement of menopausal symptom scores. Pooling of the study data showed no statistically significant difference in menopausal symptom scores between CR and placebo. Three out of these four studies were conducted in the USA (Amsterdam *et al.* (2009), Geller *et al.* (2009), Newton *et al.* (2006)) and the non-uniformity of the used preparations makes an evaluation problematic. Furthermore, one study (Amsterdam *et al.*, 2009) examined the efficacy of CR in a different indication (anxiety disorder).

Beer *et al.* (2013) comment on major statements of the Cochrane Collaboration report 2012: "The authors' negative conclusions are questionable and call for reply and clarification. Our careful reconsideration of all appropriate placebo-controlled clinical studies reveals a standardized mean difference of 0.385 in favor of black cohosh ($p < 0.0001$)." Beer *et al.* (2013) criticize that several relevant placebo-controlled trials were excluded from the evaluation or have not been identified. Furthermore, quality of the herbal extracts, dose, duration of treatment and accepted therapeutic indications have been ignored. About 40% of the assessed black cohosh preparations had no marketing authorisation.

The review by Beer and Neff (2013) was the first to differentiate by extract types. Nine studies with a total of 9391 patients investigating the isopropanolic extract (iCR), DER 6-11:1, extraction solvent propan-2-ol 40% (V/V) were included: Osmers *et al.* (2005), Liske *et al.* (2002), Bai *et al.* (2007), Nappi *et al.* (2005), Vermes *et al.* (2005), Schmidt *et al.* (2005), Mollá *et al.* (2009), Briese *et al.* (2007), Uebelhack *et al.* (2006). The authors concluded that best evidence of efficacy of iCR was provided especially by the four randomised-controlled trials: Osmers *et al.* (2005), Bai *et al.* (2007), Nappi *et al.* (2005), Uebelhack *et al.* (2006). It has to be stated however, that one of the studies (Bai *et al.*, 2006) was conducted in a non-European study population and another one (Uebelhack *et al.* 2007) used a combination of iCR and Hypericum as study medication. The studies on the ethanolic extract BNO 1055, DER 5-10:1, extraction solvent ethanol 58% (V/V) with a total of 420 patients (Wuttke *et al.* 2003; Rauš *et al.* 2006) showed exploratory evidence. For three further CR medicinal products, each with one publication of a randomised-controlled study, according to the authors exploratory evidence was demonstrated: Kaiser *et al.* (2008), Frei-Kleiner *et al.* (2005), Oktem *et al.* (2007). The study by Oktem *et al.* however, was conducted in a non-European study population and no valid information on the used CR product has been provided. For three US-American CR preparations without marketing authorisation as medicinal product two randomized controlled (Newton *et al.* (2006) and Geller *et al.* (2009)) and one open, uncontrolled study (Ruhlen *et al.* 2007) could be identified which provided no evidence for the efficacy of the used preparations. The authors concluded that a positive benefit-risk profile was stated and limited to CR products holding a marketing authorisation for treating climacteric complaints.

Overall, attempts at meta-analyses of the clinical studies have been complicated by the use of different preparations and result parameters.

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

No data are available for use in children, adolescents and men. Due to the indication (menopausal symptoms) children, adolescents and men are excluded and studies are not necessary. In some of the studies the examined women had an age up to 70 years, but no special studies for elderly have been performed.

Menopausal symptoms in patients with breast cancer

Especially women undergoing breast cancer therapy are looking for alternatives to HT, which is contraindicated in these patients. Furthermore, tamoxifen which is established as adjuvant therapy for breast cancer patients induces an artificial menopause, named "chemopause" by some authors. Several clinical studies were conducted, investigating the efficacy of CR in patients with breast cancer suffering from complaints caused by menopause and/or tamoxifen therapy:

Controlled clinical trials

Jacobson *et al.* (2001): A randomised, placebo controlled, double blind trial (USA); of 85 patients (59 on tamoxifen, 26 not on tamoxifen) enrolled in the study, 42 were assigned to CR treatment and 43 to placebo. The extract of CR is not identified. Duration of the study was only 60 days. Both, the treatment group and the placebo group experienced a benefit in terms of reduced number and intensity of hot flushes. No significant improvement of other menopausal symptoms except sweating was observed. No significant changes in LH or FSH levels were found overall or between groups.

Pockaj *et al.* (2006): A randomised, crossover, double-blinded trial (USA) with two 4-week crossover periods in 132 patients with a history of breast cancer or perceived increased risk of breast cancer, 4 weeks therapy with black cohosh or placebo, then crossover without a wash-out period. Treatment: 20 mg extract of CR (twice daily), which is supposed to be similar to the isopropanolic dry extract of CR, DER 6-11:1, extraction solvent propan-2-ol 40% (V/V), standardised to 1 mg triterpene glycosides or placebo. No significant difference for hot flushes or quality of life, no adverse event. This trial failed to provide any evidence that CR reduces hot flushes more than placebo and did not confirm the preliminary information provided by the pilot study in 2004 (see below: Uncontrolled clinical trials). No data on safety aspects were published.

Muñoz and Pluchino (2003): 136 young (35-52 years) premenopausal breast cancer survivors were involved (usual care group on tamoxifen: n=46, intervention group on tamoxifen plus CR BNO 1055: n=90) in an open label, randomly assigned study (Venezuela) to examine the effect of CR on hot flushes caused by tamoxifen adjuvant therapy. The treatment presents an off-label use of an ethanolic dry extract of CR, DER 5-10:1, extraction solvent ethanol 58% (V/V) (=CR BNO 1055), 2 tablets, equivalent to 40 mg herbal substance per day, plus tamoxifen 20 mg daily. The duration of treatment for tamoxifen was 5 years and for tamoxifen plus CR 12 months. The combined administration of tamoxifen plus CR for a period of 12 months allowed satisfactory reduction in the number of hot flushes. No statement is given about the influence on breast cancer.

Uncontrolled clinical trials

Pockaj *et al.* (2004): A pilot study (USA), open-label, non-randomised, non-blinded, 23 patients (21 evaluable), 13 of them had a history of breast cancer, 4 week treatment with isopropanolic dry extract of CR, DER 6-11:1, extraction solvent propan-2-ol 40% (V/V) corresponding to 20 mg herbal substance twice daily. Results: Significant reduction of hot flushes, one report of joint pain. Lack of placebo group, small sample size, short treatment period; no safety data available.

Rostock *et al.* (2011), Fischer (2006): This prospective trial (Germany) examined the association of CR use and hot flush severity among 50 women with recent breast cancer diagnoses. These women had

"severe" hot flashes as assessed by the Menopause Rating Scale (MRS II). Patients receiving isopropanolic dry extract of CR DER 6-11:1, extraction solvent propan-2-ol 40% (V/V) corresponding to 20 mg herbal substance (1 to 4 tablets daily plus tamoxifen 10-40 mg) daily for 6 months had a significant reduction of the total MRS II score from 17.6 at baseline to 13.6 at the end of the study ($P < 0.001$). Hot flashes, sweating, sleep problems, and anxiety improved, whereas urogenital and musculoskeletal complaints did not change. Lack of placebo group; dose adjustment according to patients' requirements (after 4 weeks standard dosage of 40 mg): 1-4 tablets, equivalent to 20 mg up to 80 mg herbal substance daily; 4 patients switched to CR/Hypericum combination; 35 patients continued medication for 6 months.

Nine more overview articles covering the same studies have been published:

- Moyad (2002) reported about the study by Jacobson (2001); he found that more studies relating to safety and mechanism of action are necessary.
- Chlebowski *et al.* (2003) reported about the study by Jacobson (2001).
- Simpson (2004) reported about the study by Jacobson (2001).
- Hickey *et al.* (2005) reported about the study by Jacobson (2001), and the study by Muñoz & Pluchino (2003); she found that there are no convincing data to show a benefit greater than placebo.
- Carpenter (2005) reported about the study by Jacobson (2001); he found that CR has been shown to act as a mixed competitive ligand and partial agonist of the 5-HT-7 receptor.
- Boekhout (2006) reported about the study by Jacobson (2001), the study by Muñoz & Pluchino (2003), and the study by Pockaj (2004); she found that the data on the effect of CR in the treatment of hot flashes are conflicting.
- Bruno and Feeney (2006) reported about the study by Jacobson (2001) and the study by Osmer (2005); they found that CR can be used in an attempt to control menopausal symptoms, provided that patients are vigilant about possible hepatotoxicity and their use during the active antineoplastic treatment is avoided.
- Bordeleau *et al.* (2007) reported about the study by Jacobson (2001) and the study by Pockaj (2006).
- Antoine *et al.* (2007) found that very few data are available on the safety of CR in breast cancer patients.

There are only two randomised, controlled trials in patients with breast cancer available. One of them showed no statistical significance for the ability of CR to relieve hot flashes associated with menopause in women with breast cancer. The other study showed a reduction of symptoms of menopause, whether it was statistically significant or not was not reported.

The data on the effect of CR in the treatment of hot flashes in patients with breast cancer are conflicting with some benefits seen when compared with baseline, but not when compared with placebo.

There are no randomised controlled trials assessing the efficacy of CR for breast cancer.

4.4. Overall conclusions on clinical pharmacology and efficacy

Pharmacodynamics

To date, the most widely accepted explanation for climacteric or menopausal complaints is still a decrease of oestrogens. As CR extracts have been used to alleviate the adverse symptoms of menopause, the assumption that one or more constituents probably have phyto-oestrogenic activity may seem logical. In some early pharmacological experiments CR extracts exhibited organ specific effects, which resembled effects caused by oestrogen. This is not supported by newer evidence. Knowledge and experimental data are not consistent enough to characterise CR as a so-called selective oestrogen receptor modulator (SERM). Furthermore, dopaminergic effects and serotonin-binding properties could be responsible for reduction of vasomotor and psychological symptoms under treatment with CR preparations. Clinical studies in humans concerning the influence of CR preparations on CNS located receptors, neurotransmitters or hormones are not available so far.

Overall, data from clinical studies on pharmacodynamics are not consistent to establish a single model on the mode of action of CR.

Neither the mode of action nor the constituents relevant for the improvement of menopausal complaints are known yet, but clinical studies indicate that climacteric symptoms can improve under treatment with medicinal products containing CR.

Since the mode of action is not clearly identified, possible effects on the hormone sensitive tissue cannot be excluded.

To date, there are no clinical studies in humans concerning the influence of CR preparations on CNS located receptors, neurotransmitters or hormones.

Pharmacokinetics

There is only poor information on the pharmacokinetics of CR. There are some data concerning interactions, e.g. with atorvastatin, but a causal relationship cannot be clearly confirmed.

Efficacy

A total of about 20 clinical trials with approximately 6300 patients treated with CR in menopausal symptoms can be taken to support the efficacy in the proposed indication "Herbal medicinal product for the relief of menopausal complaints such as hot flushes and profuse sweating". In accordance with Article 10a of Directive 2001/83/EC, only studies were considered, which demonstrated that the active substance of the medicinal products fulfil the criteria of a well-established medicinal use.

The large variety of different study protocols, inclusion and exclusion criteria, interpretation of results and conclusions thereof shows the need for validated and commonly used instruments for further clinical studies and assessments of efficacy. None of the GCP conform conducted studies showed unambiguous results for the predefined improvement of menopausal complaints regarding the Kupperman Index or validated Menopause Rating Scale.

The reasons for the vast variety of results are multifactorial:

- a) The complaints which are intended for treatment are not precisely defined.
- b) The groups of patients to be treated are not precisely defined.
- c) Instruments used for measurement of treatment benefits might be insufficient.

Ad a) Lists of complaints composed of 10 or more single symptoms do not reflect the symptoms of an individual. The symptoms of the individual depend on many factors, most of them are not known. In

case of menopausal complaints, e.g. age, hormonal status, ethnicity (Heinemann *et al.* 2004), coincidences of diseases have to be taken into consideration. Regarding the "Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMA/CHMP/021/97 Rev. 1, 13 October 2005)" which defines the vasomotor symptoms as main criteria, it seems to be beneficial to investigate these symptoms as the primary efficacy endpoint.

Ad b) The only group of women with menopausal complaints that is precisely defined is represented by the postmenopausal women (last regular menstruation > 12 months ago, FSH level > 40 U/l). In this defined group valid study results could be expected. For the other stages of menopause, i.e. pre-menopause and peri-menopause a precise definition is difficult. The stages are not distinct, but rather overlap. Menopause can only be confirmed a year or more after the final menstrual cycle. Therefore, the whole transition period has to be investigated carefully for CR preparations to grant efficacy and safety for affected women. The term "climacteric" refers to the period of menopausal transition, and this period between fertility and sterility is defined by: subfertility, accelerated loss of follicles after 38 years of age, increasingly anovulatory cycles with luteal phase defects, initial shortening of the cycle, thereafter longer irregular cycles, increase in early follicular FSH; often low progesterone levels in the second half of the cycle; contraception needs and climacteric complaints; i.e. empty nest situation; midlife crisis (Kenemans).

As shown above, the first symptoms of menopausal complaints start still during the fertile period of women. Therefore, contraception is absolutely needed and pregnancy should be excluded before starting with CR treatment because up to now possible hormonal properties of this herbal substance cannot be excluded and sufficient data on exposed pregnancies with known outcome are not available

Ad c) All investigations until now showed incoherent results due to the extended variety of diagnostically used instruments. The attempt was to cover almost all symptoms that appear in the menopause. As mentioned above, for assessing hormone therapies, only the hot flushes and secondarily the sweating and sleep disturbances are evaluated. This procedure would support claimed indications (hot flushes, sweating and sleep disturbances/disorders) for CR preparations.

As there is no controlled clinical study of good quality which covers all relevant symptoms of the validated total scales to substantiate efficacy, it is necessary to proceed in a case-by-case assessment, to prove efficacy in accordance with the "Guideline on the assessment of clinical safety and efficacy in the preparation of European Union herbal monographs for well-established use and of European Union herbal monographs/entries to the European Union list for traditional herbal medicinal products/substances/preparations (EMA/HMPC/104613/2005)" (Chapter "Elements of the clinical documentation supporting a monograph"). 20 studies were taken into account supporting the indication proposed. In these investigations most of the menopausal symptoms were influenced more or less positively by the treatment with CR preparations. As no study of high quality has demonstrated significant results for the used scores in total or in particular for "hot flushes", the positive results of all studies were taken into account and summarised in the indication "Herbal medicinal product for the relief of menopausal complaints (such as hot flushes and profuse sweating)". The long standing use of these herbal medicinal products and the high sales numbers in the European Union and worldwide are accepted as indicators for efficacy in the framework of a well-established use.

The duration of treatment in the studies varied from:

6-8 weeks: Jacobson *et al.* 2001 [n=85]; Stolze 1982 [n=629]

3 months: Brattstroem 2005, Kaiser *et al.* 2008, Schellenberg *et al.* 2012 [n=180, n=112 on CR]; Frei-Kleiner *et al.* 2005 [n=122, n=83 on CR]; Nappi *et al.* 2005 [n=64, n=32 on CR]; Osmers *et al.* 2005 [n=304, n=153 on CR]; Stoll 1987 [n=80, n=30 on CR]; Wuttke *et al.* 2003, 2006 [n=62, n=20]

on CR]; Daiber 1983 [n=36]; Liske *et al.* 2000 [n=152]; Nesselhut and Liske 1999 [n=28]; Schmidt *et al.* 2005 [n=502]; Vorberg 1984 [n=50]; Warnecke 1985 [n=60]

4 months: Lopatka *et al.* 2007 [n=584]

6 months: Briese *et al.* 2007 [n=6141, n=3027 on CR]; Hirschberg *et al.* 2007 [n=74]; Lehmann-Willenbrock and Riedel 1988 [n=60]; Pethö 1987 [n=50]; Rostock *et al.* 2011, Fischer 2006 [n=50]

9 months: Drewe *et al.* 2013 [n=442]

Up to 12 months: Rauš *et al.* 2006 [n=375].

Overall, more than 6 300 patients were treated with CR preparations in clinical studies. About 4000 patients were treated with CR preparations in eight clinical trials between six and twelve months. The clinical studies with treatment durations of six months and longer did not reveal any safety concerns (see section 5. 'Clinical Safety/Pharmacovigilance'), no signs of tolerance were observed. The duration of use for 6 months is supported by these trials (majority of study patients treated up to 6 months).

Whereas the majority of clinical data has been provided for the dry extract from CR (DER 6-11:1), extraction solvent propan-2-ol 40% (V/V), some clinical data are also available for specified ethanolic extracts (Beer and Neff, 2013).

Altogether, it can be concluded that there is sufficient evidence to accept a well-established use for the following specified herbal preparations of CR:

- a) Dry extract from CR (DER 5-10:1); ethanol 58% (V/V)
- b) Dry extract from CR (DER 4.5-8.5:1); ethanol 60% (V/V)
- c) Dry extract from CR (DER 6-11:1); propan-2-ol 40% (V/V)

The indication is as follows: "Herbal medicinal product for the relief of menopausal complaints such as hot flushes and profuse sweating."

The terms 'neurovegetative' (used in the Monograph of the German Commission E) and 'psychological' (see Table 2: Overview of historical data and Table 3: Overview of evidence on period of medicinal use) are not clearly defined, easy to misinterpret and therefore not useful for the wording of the indication. Hot flushes and profuse sweating on the other hand belong to the most prominent menopausal symptoms.

Results for efficacy of CR preparations in women with breast cancer and menopausal complaints with or without tamoxifen treatment are conflicting with some benefits seen when compared with baseline, but not when compared with placebo. As to date women with breast cancer or other hormone dependent tumours are excluded from the use of CR containing preparations, the results claimed for efficacy are not relevant. For safety assessment, the number of included patients is too small to yield sufficient results.

Patients with breast cancer and hormone dependent tumours should be excluded from treatment with CR preparations for safety reasons.

Sufficient data which support the well-established use in the indication 'for the relief of menopausal complaints' of other than the specified extracts are not available.

There are no clinical data regarding the indications 'premenstrual syndrome' or 'rheumatism'.

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5. Clinical Safety/Pharmacovigilance

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

There are three safety concerns regarding the use of CR preparations: The question of general safety, safety aspects with regard to oestrogen-sensitive tissue including risk of breast cancer and the risk of recurrence and liver safety.

Liver toxicity associated with the use of CR containing products is addressed in section 5.3. 'Adverse events, serious adverse events and deaths'.

Studies on risk of breast cancer or risk of recurrence are listed in section 5.5. 'Safety in special populations and situations'.

In addition to Table 6 in section 4.2.2., where clinical studies investigating the efficacy of dry extracts from CR in menopausal complaints are listed, the following table provides an overview of clinical trials which investigated mainly aspects relevant for safety.

Table 7: Clinical safety data from clinical trials

Reference	Design	Test Product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
1. Isopropanolic extract (iCR): DER 6-11:1, extraction solvent propan-2-ol 40% (V/V)						
Schmidt <i>et al.</i> 2005	Observational study	iCR dry extract, DER 6-11:1, propan-2-ol 40% (V/V), 2x2.5 mg per tablet equivalent to 40 mg herbal substance per day, 3 months	502 post-menopausal Swiss patients, mean age: 56 years	Menopausal complaints	No adverse events were reported; therapy was generally classified as very well tolerated.	Good tolerability of study medication
Vermes <i>et al.</i> 2005	Observational study	iCR dry extract, DER 6-11:1, propan-2-ol 40% (V/V), 2x2.5 mg per tablet equivalent to 40 mg herbal substance per day, 3 months	2 016 peri-and post-menopausal Hungarian women, age range: 40-65 years	Menopausal complaints	12.1% rate of possibly treatment related adverse events (specified by n=35); mostly stiffening of extremities, gastric pain, allergic reactions	Good tolerability of study medication
Hirschberg <i>et al.</i> 2007	Prospective, open, uncontrolled; primary endpoint safety	iCR dry extract, DER 6-11:1, propan-2-ol 40% (V/V), 2x2.5 mg per tablet equivalent to 40 mg herbal substance per day, 6 months	74 post-menopausal Swedish patients, age range: 50-70 years, 65 patients completed	Menopausal complaints	No change in mammographic breast density, no breast cell proliferation (fine needle aspiration biopsies), no change in endometrium thickness (transvaginal ultrasound examination)	Small numbers
2. Ethanolic extracts						
Rauš <i>et al.</i> 2006	Open label, non-comparative,	CR BNO 1055 dry extract, DER 5-10:1, ethanol 58% (V/V),	400 post-menopausal Czech and Polish patients	Menopausal complaints, intact uterus; BMI ≤ 28	Primary endpoint: Proof of endometrial safety: No case of hyperplasia or	No oestrogenic or oestrogen like effects on the endometrium

Reference	Design	Test Product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
	prospective, multicentre and multinational	2x2.8 mg per tablet, equivalent to 40 mg herbal substance per day, 52 weeks	enrolled, 375 patients completed, mean age 56.38 years, age range 50-75 years	kg/m ² ; last spontaneous menstrual period at least 2 years ago; FSH≥35 U/l; 17 β - estradiol≤40 pg/ml; endometrial thickness≤5 mm	more serious adverse endometrial outcome; no changes in LH, FSH, 17β-estradiol Secondary endpoint: MRS II/4-week weighted scores of hot flushes: Number of hot flushes decreased	within a 12 months treatment period
Lopatka <i>et al.</i> 2007	Open, observational prospective, multicentre	Ze 450 dry extract, DER 4.5-8.5:1, ethanol 60% (V/V), 1 x 6.5 mg per tablet equivalent to 40 mg herbal substance per day, 4 months	584 peri-and postmenopausal Swiss women with a mean age of 53.2±6.6 years enrolled, 541 of them completed the study as planned	Menopausal complaints	35 adverse events reported by 25 patients, most of them unspecific and affecting the gastrointestinal system; body weight and BMI remained constant	Good tolerance of study medication, no effect on body weight observed
Drewe <i>et al.</i> 2013	observational	Ze 450 dry extract, DER 4.5-8.5:1, ethanol 60% (V/V), 1x 13 mg per tablet equivalent to 80 mg (HD) herbal substance per day, 3 months, continuation over additional 6 months or switch to LD (1x6.5 mg per tablet, 40 mg herbal substance per day)	442 unselected Swiss outpatients with menopausal complaints, mean age 52.3 years	Menopausal complaints	18 patients experienced 24 adverse events (16 under therapy with HD and 2 under therapy with LD). Adverse events under CR therapy were predominantly gastrointestinal symptoms	Good tolerability of study medication

Reference	Design	Test Product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
3. Non-European studies						
Ruhlen <i>et al.</i> 2007	Prospective, open, uncontrolled; primary endpoint safety	CR dry extract, extraction solvent and DER not known, equivalent to 40 mg herbal substance, standardised to 1 mg 23-epi-25 deoxy-actein per capsule, twice daily one capsule 12 weeks followed by a 12 week wash-out period	61 peri- and post-menopausal US American patients, median age 53+/- 0.7 years	Menopausal complaints	Primary endpoint: no effect of CR on oestrogenic markers in serum and nipple aspirate fluid Secondary endpoint: reduction of menopausal symptoms by at least 1 point in the KI	Study results suggest that CR has no systemic or breast specific oestrogenic effects

5.2. Patient exposure

Overall, more than 6300 patients were treated with CR preparations in clinical studies. See also sections 4.2, 4.3, 5.1 and 5.6.

There are no concrete data concerning sales volume, but it must be assumed that a huge amount of patients have used CR preparations due to Europe-wide market presence.

5.3. Adverse events, serious adverse events and deaths

Adverse events

Liver toxicity

Liver toxicity has been associated with the use of CR containing products. The frequency is not known.

The HMPC document EMEA/HMPC/269258/2006 Rev. 1, dated 8 May 2007 on the assessment of case reports linked to herbal medical products containing CR reported cases with liver damages, either reported as undesirable effects or taken from the literature. Out of 44 partially poorly documented cases, four show coherence between liver damage and intake of CR, whereof in two cases the coherence is probable and the patients developed an autoimmune hepatitis. Until now, there is no known dose dependence. A correlation to a pathophysiological mechanism is not known. Fifteen further cases have been reported; nearly all are poorly documented and are not assessable. Meanwhile, four new cases of liver injury have been reported; two spontaneous reports in the German pharmacovigilance database in 2010 and two more cases from the literature (Guzman *et al.* 2009). Three of these cases were assessed as “probable” using the RUCAM Score; one was “unrelated” due to insufficient data. In 2010, there were five cases assessed as “probable”.

To commemorate the history and rationale for choice of the RUCAM Score in the assessments of hepatotoxicity of CR, the following text might be helpful, which was published in EMEA/HMPC/269258/2006, Rev. 1.:

“RUCAM Score (Roussel UCLAF causality assessment method)

At the request of CIOMS (Council of International Organisations of Medical Sciences), international meetings were organised by Roussel UCLAF. Eight international experts formed a group dealing with hepatotoxicity: Benhamou JP, Danan G (France), Bircher J (Germany), Maddrey WC, Zimmermann HJ (USA), Neuberger J (UK), Orlandi F (Italy) and Tygstrup N (Denmark). In 1993, the international group of experts published the so-called RUCAM Score to evaluate cases of hepatotoxicity (Danan & Benichou 1993). The score was validated and the results published (Benichou *et al.* 1993).”

An update of the RUCAM Score was published in 2015 (Danan and Teschke 2015). As mentioned by the authors, the practical experience with the original version, emerging new data of drug-(DILI) and herb induced liver injury (HILI) characteristics, and questions in domains such as alcohol use and exclusions of non-drug causes like hepatitis E virus (HEV) led to the update of RUCAM.

Since 2010, further case reports have become known either reported as undesirable effects or published in literature.

Literature:

- Subacute liver failure secondary to black cohosh leading to liver transplantation, Lim *et al.* (2013)

This is a case report of a sixty-year-old woman who presented to her general practitioner with pruritus and dark urine after a 2-week period of taking black cohosh for menopausal symptoms. She had a

medical history of hypothyroidism and migraine which was managed with levothyroxine 100 µg daily and propranolol 20 mg daily. She had no risk factors for acquiring a viral hepatitis. On presentation at hospital, she was deeply jaundiced. Her blood results showed elevated bilirubin and liver enzymes, the abdominal computer tomography (CT) showed a collapsed liver and ascites without any signs of malignancy and pre-existing chronic liver disease. With a working diagnosis of subacute liver failure she was referred to a liver transplant unit. Three weeks after admission the patient deteriorated rapidly, becoming confused with grade 3 encephalopathy, requiring intensive care treatment and intubation. She was listed for a liver transplant and had a liver transplantation 48 hours after listing. After a successful recovery she was discharged from hospital 2 weeks later. In the RUCAM classification system, this case had a score of 6 (probable adverse drug reaction). The publication does not state the origin and quality of the CR preparation used.

- Mechanism of hepatotoxicity due to black cohosh (*Cimicifuga racemosa*), Enbom *et al.* (2014)

Enbom *et al.* (2014) describe two cases of troxis necrosis (i.e. necrosis that occurs in fragments) in patients taking a not further described CR preparation as part of their postmenopausal regimen. Both patients presented with acute elevation of liver enzymes, cholestasis, absence of reactivity to hepatitis A, B and C antibodies, and weak non-specific positivity for autoimmune serological markers. Both patients underwent CT-guided liver biopsy. They gradually recovered without further complication. No information is given on other medication, quality of the CR preparation used or duration of use.

- Black cohosh and liver toxicity: Is there a relationship?, Adnan *et al.* (2014)

This report describes a case of a 44-year-old female who developed subacute liver injury, as demonstrated by CT scan and liver biopsy, within a month of taking a not further characterised CR extract. The authors discussed the possible temporal and causal association between CR use and the liver disease observed in the patient. They acknowledge that the causal relationship is highly probable according to the RUCAM/CIOMS criteria, but they warn about the need to know the exact composition of the extract used before a firm causal assessment is made.

A major limitation in evaluating the above mentioned case reports is the lack of information concerning the quality of the products that allegedly caused the reaction. CR preparations are available in the USA and UK as dietary supplements or unlicensed herbal remedies and are consumed without professional advice. There is usually no patient information leaflet provided with such products. The additional case reports -even if poorly documented- present a clear signal of safety concern and show the need for regulation via marketing authorisation with guarantee of quality and clear specification and adequate labelling.

Spontaneous reports in the German pharmacovigilance database (2017):

- DE-BFARM-16406139: A 58-year old patient took CR dry extract, DER 4.5-8.5: 1, ethanol 60% (V/V), film-coated tablets (daily dosage: 1x6.5 mg every evening corresponding to 40 mg of the herbal substance) from 23 September 2016 to 08 November 2016 for treatment of climacteric discomfort. At the end of October total fatigue and pain of muscles started. The diagnosis acute hepatitis was given. The symptoms were symptomatically treated with physical rest and elimination of medication until 15 December 2016. At mid of December, after initial recovering of values and stabilisation of general condition, renewed worsening and starting of treatment with Prednisolone. Magnetic resonance cholangiopancreatography (MRCP), liver biopsy and blood sampling were performed (maximum rise of ALT, i.e. alanine aminotransferase 35,85 µmol/l.s = 2151 U/L on 20 November 2016, last ALT value 28.58 µmol/l.s = 1715 U/L on 28 November 2016) and the following causes were excluded: Hepatitis A, B, C, E, Cytomegalovirus, Epstein-Barr virus, cardiopulmonary diseases, autoimmune hepatitis, haemochromatosis and rare intoxications (e.g. cocaine, ecstasy, other amphetamines). According to medical report of liver biopsy the

following diagnosis was made: Samples of moderate hepatitis with fibrosis level 2. Histomorphological aspect compatible with drug-induced, toxic hepatitis. Medical history: the patient's medical history was not specified, but no alcohol intake was reported. Concomitant therapy: The patient took magaldrate stomach gel symptomatically for existing disorders and pantoprazole as needed (since end of October). Outcome: The outcome was stated as recovering/resolving. In the RUCAM Score (both, original und updated version) this case had a score of 7 (probable adverse drug reaction). Unfortunately, there is no initial ALT value reported. It is stated however, that ALT values increased even after cessation of medication (maximum on 20 November 2016).

- CN-BFARM-16251777: A 37 year old Chinese patient started treatment with CR dry extract, DER 6-11:1, propan-2-ol 40% (V/V) (no information on dosage, dosage form and date) as an add-back therapy for endometriosis. On an unspecified date, reported as before injection of triptorelin acetate=gonadotropin releasing hormone agonist, the patient's lab results revealed ALT (alanine aminotransferase) at 25, while AST (aspartate aminotransferase) was also at 25 (units and normal values not reported). On 21 March 2016, the patient started treatment with 3.75 mg triptorelin acetate every 28 days via IM injection for endometriosis. On 21 May 2015, 61 days after starting the treatment, the patient developed drug-induced liver injury and chocolate cyst at the left ovary. The patient's lab results revealed increased values of ALT at 201, while AST were at 130 (units and normal values not reported). The treatment with triptorelin acetate was maintained and the patient received next injection on 05 July 2016. At the time of follow up reporting on 21 July 2016, the events were still persisting. The event of supposed DILI (liver enzyme elevation) is considered possibly related. The event of chocolate cyst is considered not related as most probably this effects from disease under treatment. Information on start and end of therapy with CR dry extract is missing.
- DE-BFARM-13253468: 57-year-old patient with increased liver values and very strong tiredness since starting ferrous (II) glycine sulphate and CR dry extract, DER 6-11:1, propan-2-ol 40% (V/V), 2x2.5 mg per tablet corresponding to 40 mg of the herbal substance per day from 1 July 2013. After discontinuation of CR extract on approximately 17 July 2013, the symptoms abated permanently after 1-2 days. Concomitant medication: amitriptyline hydrochloride (tricyclic antidepressant). The case was considered possibly related to use of CR.
- DE-BFARM-14247842: 63-year-old patient with abnormal liver function test after intake of CR (DER 4.5-8.5:1, ethanol 60% V/V) tablets over 17 days (May 2014), no further information.
- DE-BFARM-14192249: 57-year-old patient with medical history of recurrent mildly increased hepatic enzymes and hysterectomy. Concomitant medications included L-Thyroxin (levothyroxine sodium). The patient received CR (60% ethanolic extract, DER 4.5-8.5:1) film-coated tablet for the treatment of menopausal symptoms at an unreported daily dose (oral) from an unknown start date for the duration of 10 years. In April 2014 the patient experienced increased liver enzymes (GGT, ALT, and AST). Hepatic steatosis was diagnosed in ultrasound. Treatment with suspect drug was discontinued in mid of June 2014. The following lab tests showed an improvement. Information on ultrasound is not available. The event 'Hepatic enzyme increased' was reported with a plausible temporal relationship to suspect drug. The causal role of the medication could not be ruled out.
- DE-BFARM-13213675: 54-year-old patient with epigastric discomfort and increased transaminases after use of CR (60% ethanolic extract, DER 4.5-8.5:1) film-coated tablets, treatment duration 14 days in April 2013. Treatment with suspect drug was discontinued and symptoms improved. The events were regarded as possibly related to CR use.

- CH-BFARM-13033043: 55 year-old female patient who experienced mixed hepatocellular-cholestatic injury and pruritus, which were medically significant and required intervention, following treatment with atorvastatin, CR (60% ethanolic extract, DER 4.5-8.5:1) film-coated tablets and Rheum rhaponticum root. All medications were discontinued (30 August 2012). On 25 October 2012, the patient's liver enzymes were normalised (ALT 34 U/L and AP 59 U/L). The case was considered serious and possibly related to concomitant use of CR and atorvastatin. See also section 5.5.4.

Conclusion

Due to limited data, patients have to be carefully observed for signs of liver toxicity. Patients are advised to pay particular attention to symptoms of a possible liver injury (such as tiredness, loss of appetite, yellowing of skin and eyes or severe upper stomach pain with nausea and vomiting, or dark urine). To date based on available preclinical or clinical data, liver toxicity of CR preparations cannot be excluded. Case reports have to be assessed thoroughly using the RUCAM Score which can be considered to be the most practicable one for spontaneous adverse event report systems.

Taking into account the possible association between the use of CR and hepatotoxicity *Cimicifuga racemosa* (L.) Nutt., rhizoma was put on the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs). The PSUR cycle is 5 yearly, the procedure is still ongoing during revision of the assessment report at hand. PSURs are required for products referred to in Articles 10(1), 10a, and 16a of Directive 2001/83/EC. Any new information gained from the PSUR evaluation will be included in the next revision.

Other adverse events

Allergic reactions of the skin (urticaria, itching of the skin, exanthema), facial oedema, peripheral oedema and gastrointestinal symptoms (i.e. dyspeptic disorders, diarrhoea) have been reported. The frequency is not known.

There are two literature reports of as yet unknown adverse events:

- Muscle damage induced by black cohosh, Minciullo *et al.* (2006)

This is a case report about a 54-year old woman with severe asthenia. Some days after the appearance of symptoms, the patient underwent under medical counselling blood laboratory exams showing: CPK 237 and 230 U/l (normal 24-170 U/l), LDH 504 and 548 (normal 230-460 U/l, total cholesterol 277 and 282 mg/ml (normal 120-250), all samples were repeated after 9 days. Other parameters such as blood cell count, AST, ALT, GGT, kidney and thyroid functionally indexes were in the normal range. The same laboratory exams including muscle enzymes, performed three months before, had shown no alteration. The patient reported to take a CR product for ameliorating menopause vasomotor symptoms; each tablet contains 20 mg of dried rhizome and root extract. The patient had taken 1 tablet twice daily for 1 year and then discontinued the therapy. She restarted the same therapy 2 months later. Asthenia appeared 2 months after the restart of the medication. The patient did not change life, did not exercise and did not take other drugs. The author hypothesised a causative role for CR.

- Cutaneous Pseudolymphoma induced by *Cimicifuga racemosa*, Meyer *et al.* (2007)

There is a report about a 56 year-old female patient with asymptomatic, localized erythematous plaques on arms and legs. Histologically, the diagnosis of pseudolymphoma was confirmed. Because of menopausal complaints the patient has taken a product containing CR for 1 year. Six months after initial administration, first skin lesions appeared. Withdrawal of the product resulted in complete

remission of the lesions within 12 weeks. This is the first report of a pseudolymphoma. However allergic skin reactions have been reported.

Serious adverse events and deaths

There was one death according to hepatic failure and consecutive liver transplantation. The causal relationship to CR seems to be plausible. It is important to add that interaction of concomitant fluoxetine, paracetamol and propoxyphene, together with alcohol abuse may have contributed to the hepatic failure (Teschke & Schwarzenboeck, 2009).

5.4. Laboratory findings

If examined, there were no significant changes in laboratory values. Patients suffering from hepatic disorders showed an increase in liver enzymes.

Spangler *et al.* (2007) performed a secondary analysis to the study by Newton *et al.* (2006) to examine the laboratory parameters in 45-55 years old, peri or postmenopausal women experiencing vasomotor symptoms. 351 women participated in a 3-months, double blind trial randomized to CR alone (160 mg daily), a multibotanical with CR 200 mg daily and 9 other ingredients, a multibotanical plus dietary soy counselling, a conjugated equine oestrogen 0.625 mg daily, with or without medroxyprogesteron acetate 2.5 mg daily, and finally placebo. Baseline and month 3 total cholesterol, high density lipoprotein (HDL) cholesterol, low density (LDL) cholesterol, triglyceride, insulin, glucose and fibrinogen serum concentrations were measured in 310 women. There were no statistically significant differences in the adjusted mean change from baseline to 3 months between the herbal groups and placebo in total cholesterol, high density lipoprotein (HDL) cholesterol, low density (LDL) cholesterol, triglyceride, insulin, glucose. Adjusted fibrinogen levels appear to increase in the multibotanical treatment group in comparison with the other herbal groups and placebo. Liver enzymes have not been examined.

5.5. Safety in special populations and situations

Studies on risk of breast cancer or risk of recurrence

Becher *et al.* (2005), Henneicke-von Zepelin *et al.* (2007): A pharmaco-epidemiological German cohort study in patients with breast cancer, including hormone-receptor-positive tumours; 18.861 patients with breast cancer were examined, 1102 of them were treated with iCR dry extract, DER 6-11:1, propan-2-ol 40% (V/V), 2x2.5 mg per tablet, equivalent to 40 mg herbal substance per day or a combination preparation containing 3.75 mg iCR extract and 70 mg of an ethanolic extract from 245 to 350 mg St. John's wort (*Hypericum perforatum*), 2x1 or 2 tablets, equivalent to 60 to 120 mg herbal substance (iCR) per day. 35.8% of the treatment group was taking tamoxifen. There are no clear results for efficacy and safety of iCR. A minimised risk of 17% for a relapse is claimed for patients under treatment with iCR with or without St. John's wort compared with the control group by the authors in this abstract. The result remains unproven and has to be verified. This pharmaco-epidemiologic observational retrospective cohort study was later published by Henneicke-von Zepelin *et al.* (2007). Objective: "To investigate the influence of an isopropanolic *Cimicifuga racemosa* extract (iCR) on recurrence-free survival after breast cancer, including estrogen-dependent tumours." In conclusion, the authors summarized that an increase in the risk of breast cancer recurrence for women having had iCR treatment, compared to women not treated with iCR is unlikely. "Our study provides some evidence that the isopropanolic black cohosh extract (iCR) does not increase the risk of breast cancer recurrence, even among patients with oestrogen-dependent tumours".

Rebbeck *et al.* (2007): A retrospective US American case-control study; in 949 cases of women with breast cancer and 1524 controls without breast cancer, interviews were performed about use of any hormone-related supplements, including CR. The exact number of patients using CR is not listed. The reported use of CR (brand names, specific compounds, time of treatment and dosage are unknown) was found to have a significant protective effect for breast cancer (as cited in the preface of this publication). Additional confirmatory studies are required to determine whether CR can be used to prevent breast cancer. There is only poor information concerning the use of CR alone or in combination with tamoxifen in the patient group. Consequently, the authors conclude: "Substantial additional research must be undertaken before it can be established that black cohosh, or some compound found in black cohosh, is a breast cancer chemopreventive agent. Furthermore, women may wish to seek guidance from their physician before using these compounds, and the data presented here do not suggest that the use of black cohosh is an appropriate substitute for standard hormone therapy".

Obi *et al.* (2009) (The Mamma carcinoma Risk factor Investigation = MARIE study): Title: "The Use of Herbal Preparations to Alleviate Climacteric Disorders and Risk of Postmenopausal Breast Cancer in a German Case-Control Study". Herbal preparations (HEP) investigated in this study: iCR dry extract, DER 6-11: 1, propan-2-ol 40% (V/V), iCR in combination with an ethanolic extract from St. John's wort, other CR extracts, St. John's wort, phytoestrogens (soy isoflavones and red clover), *Agnus castus* fruit, other specified HEP (including *Pulsatilla* and *Rheum rhaponticum*), unknown HEP. A German case-control study including 10121 postmenopausal women (3464 cases, 6657 controls). 409 patients (6.1%) treated with CR [n=320 iCR or iCR in combination with St. John's wort; n=89 other CR extracts] in the control group, 146 invasive breast cancer cases (4.4%) under the same medication [112+34] in the case group. Author's conclusion: "In summary, we conclude that in postmenopausal women HEP use may exert a protective effect on risk for invasive breast cancer, irrespective of histologic type and receptor status. The specific ingredients responsible for this potential benefit need to be further elucidated".

Assessor's comments

Confusing study design with many confounders.

The author's hypothesis still has to be verified and cannot be accepted to support the claimed protective effects of HEP (herbal preparations) against breast cancer in postmenopausal women particularly with regard to CR preparations.

Brasky *et al.* (2010): A prospective US American case-control study in 35,016 post-menopausal women without a history of breast cancer to investigate the association between the use of nonvitamin, nonmineral "specialty" supplements and breast cancer risk. 985 women reported use of different CR preparations (brand names, specific compounds, time of treatment and dosage are unknown). Incident invasive breast cancers were diagnosed in 880 women from 2000 to 2007. 21 of the diagnosed patients were in the CR subpopulation. Compared with non-use, regular use of CR (HR, 1.17; 95% CI, 0.75-1.82) was not associated with risk.

Conclusions on the use in breast cancer patients

Especially women undergoing breast cancer therapy are looking for alternatives to HT, which is contraindicated in these patients. Furthermore the antihormonal therapy of breast cancer patients with the anti-oestrogen tamoxifen often induces or aggravates menopausal complaints.

In some early pharmacological experiments CR extracts exhibited organ specific effects, which resembled effects caused by oestrogen. This is not supported by current evidence.

Neither the mode of action nor the constituents relevant for the improvement of menopausal complaints are known yet. Since the mechanism of action is not clearly identified, possible effects on the hormone sensitive tissue cannot be excluded.

Based on the preliminary observational data, CR does not appear to adversely impact the risk of breast cancer recurrence or incidence in women with or without a history of breast cancer. However, in contrast to these findings, one *in-vitro* study using transgenic mice expressing c-erbB2 (MMTV-neu mouse model) showed that CR significantly increased the incidence of lung metastases in tumour-positive animals when compared to those on the control diet (Davis *et al.* 2008). In the same experimental model, no effect on primary mammary tumour development was observed. Clinical evidence supporting the potential to promote progression of metastatic disease is not available from studies in patients with breast cancer, but influence on breast cancer cannot be completely excluded.

If examined, CR does not influence circulating levels of oestradiol, FSH or LH or appear to exert oestrogenic effects on breast, endometrial or vaginal tissues.

Clinical studies indicate that climacteric symptoms improve under treatment with medicinal products containing CR. Only limited data regarding the efficacy of CR in women with breast cancer are available which do not allow a final assessment. The small number of patients and the short term duration of the few studies are not sufficient to prove safety of CR preparations in patients with breast cancer.

On the basis of available data, the use of CR preparations or combined therapy with tamoxifen for patients with a history of or treated breast cancer or hormone dependent tumours is not recommended and should be avoided.

5.5.1. Use in children, adolescents and men

There are no data available for use of CR in children, adolescents and men. Due to the indication (menopausal complaints), children, adolescents and men are excluded from use, and studies are not necessary.

5.5.2. Contraindications

Hypersensitivity to the active substance.

5.5.3. Special warnings and precautions for use

Liver toxicity (including hepatitis, jaundice, disturbances in the liver function tests) is associated with the use of CR containing products. Patients with a history of liver disorder or liver diseases should take CR preparations with caution. Patients should stop taking CR preparations and consult their doctor immediately if they develop signs and symptoms suggestive of liver injury (tiredness, loss of appetite, yellowing of skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine).

In case of vaginal bleeding or other unclear symptoms patients should consult their doctor.

Data on co-medication of CR preparations and oestrogens are not available. Due to safety considerations and lack of indication for both treatments in combination, CR preparations and oestrogens should not be used together unless advised by a doctor.

Patients who have been treated or who are undergoing treatment for breast cancer or other hormone-dependent tumours should not use CR preparations without medical advice.

5.5.4. Drug interactions and other forms of interaction

Drug interaction studies in healthy volunteers showed no clinically relevant influence in the safety of CR. CR weakly inhibits CYP 2D6. Although there is evidence for an interaction potential with tamoxifen which is primarily metabolised by CYP 2D6, the clinical data indicate no impact of the combined therapy on the risk of cancer recurrence. No adverse event related to the combination of CR and tamoxifen was reported by any of the trials. Since the use of CR preparations is not recommended for patients who have been treated or are undergoing treatment of breast cancer or other hormone dependent tumours, an additional labelling does not seem necessary.

Clinically relevant interactions with drugs metabolised by the CYP P450 enzymes were not found (Gurley *et al.*, 2005, Gurley *et al.*, 2006). CR is not a potent modulator of P-glycoprotein activity (Gurley *et al.*, 2005).

Patel and Derkits (2007) report a possible increase in liver enzymes secondary to atorvastatin and CR administration. A 53 years old woman with a history of atypical chest pain, familial history of coronary artery disease and menopause discontinued oral HT, started CR. The patient also took atorvastatin, aspirin, glucosamine/chondroitin and topical vaginal estradiol. Routine laboratory results revealed an acute elevation of liver enzymes. After discontinuing CR her liver enzymes decreased within one month. As a possible explanation the authors state that atorvastatin is a known HMG-CoA reductase inhibitor and major substrate of CYP P450 phenotype 3A4. Inhibition of CYP3A4 by CR could elevate levels of atorvastatin, causing an elevation of liver enzymes.

Another case concerning the use of CR concomitantly with atorvastatin has been reported in 2012 (case report: US-BFARM-14019176, see also section 5.3). A 55 year-old female patient experienced mixed hepatocellular-cholestatic injury and pruritus, which were medically significant and required intervention, following treatment with atorvastatin, CR film-coated tablets (60% ethanolic extract, DER 4.5-8.5:1) and *Rheum rhaponticum* root. All medications were discontinued and the patient's liver enzymes were normalised (ALT 34 U/L and AP 59 U/L) within six weeks.

In both cases additional medication was used and a clear allocation of the seen adverse events to the concomitant use of CR with atorvastatin is not possible. Furthermore, statins have been associated with biochemical abnormalities of liver function and adequate warnings are included in the informative texts. Liver toxicity is already included in the safety relevant sections 4.4. 'Special warnings and precautions for use' and 4.8. 'Undesirable effects' of the monograph. An additional labelling does not seem necessary.

5.5.5. Fertility, pregnancy and lactation

Pregnancy and breast-feeding

There are no data on the use of dry extracts from CR in pregnancy and lactation. Taking into account the indication "menopausal symptoms" in the literal sense the use in pregnancy and lactation is excluded. As described above these symptoms often occur before menopause and do not entirely rule out the possibility of becoming pregnant. Therefore, women of childbearing potential should consider using effective contraception during treatment. Animal studies are insufficient with respect to reproductive and developmental toxicity. CR is not recommended during pregnancy. It is unknown whether dry extracts from CR or metabolites thereof are excreted in human milk. A risk to the suckling child cannot be excluded. CR should not be used during breast feeding.

Fertility

No studies on fertility have been performed.

5.5.6. Overdose

As mentioned in Hager (Blaschek 2007), in unspecified doses vertigo, nausea, headache, stiffness and tremor of limbs could occur. In lower doses, not further specified, gastrointestinal discomfort may occur. These symptoms are listed under undesirable effects. No information is given on doses, herbal preparations or co-medication. The evidence is not sufficient to include an additional labelling in the monograph. No case of overdose has been reported in the data-bases.

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

No studies on the effects on the ability to drive and use machines have been performed.

5.5.8. Safety in other special situations

Not applicable

5.6. Overall conclusions on clinical safety

Whereas data from clinical trials with defined herbal preparations from CR demonstrate an acceptable safety profile, several case reports on liver damage associated with the use of CR containing products present a clear signal of safety concern. The possibility of hepatotoxic reactions (including hepatitis, jaundice, disturbances in the liver function tests) has to be taken into consideration during treatment. Patients with a history of liver disorder or liver diseases should take CR preparations with caution. Patients should stop taking CR preparations and consult their doctor immediately if they develop signs and symptoms suggestive of liver injury (tiredness, loss of appetite, yellowing of skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine).

Possible effects on the hormone sensitive tissue cannot be excluded. Patients who have been treated or who are undergoing treatment of breast cancer or other hormone dependent tumours should not use CR preparations without medical advice.

Allergic reactions of the skin (urticaria, itching of the skin, exanthema), facial oedema, peripheral oedema and gastrointestinal symptoms (i.e. dyspeptic disorders, diarrhoea) have been reported. The frequency is not known.

Patients with hypersensitivity to the active substance have to be excluded from the use.

As a precautionary safety measure, CR should not be taken for more than 6 months without medical advice.

In summary, the use of CR containing medicinal products can be considered a safe and well tolerated treatment under the conditions lined out in the EU herbal monograph.

6. Overall conclusions (benefit-risk assessment)

CR is a well-known herb which has been used worldwide for decades in many herbal medicinal products, as for example since 1940 in Germany. To date, 24 preparations have been in use for more than 10 years in Germany. In several other member states products have obtained marketing authorisations. A high number of daily dosages of CR preparations have been sold worldwide over the years. CR is positively described in a Monograph of the German Commission E (Blumenthal *et al.* 1998) and in ESCOP Monographs, second edition 2003. Furthermore, the scientific interest in the use of the substance reflects the importance of CR preparations for treatment of menopausal complaints.

The efficacy of CR preparations on climacteric symptoms has been demonstrated in several randomised controlled and observational studies that complied with GCP criteria and used validated rating scales for menopausal symptoms. As there is no single controlled clinical study of good quality which covers all relevant symptoms of the validated total scales to substantiate efficacy, the positive results of all studies and scientific data available were taken into account. Evidence from the clinical trials is sufficient to use the following specified herbal preparations of CR with the indication:

Herbal medicinal product for the relief of menopausal complaints such as hot flushes and profuse sweating.

- a) Dry extract from CR (DER 5-10:1); ethanol 58% (V/V)
- b) Dry extract from CR (DER 4.5-8.5:1); ethanol 60% (V/V)
- c) Dry extract from CR (DER 6-11:1); propan-2-ol 40% (V/V)

In accordance with Article 10a of Directive 2001/83/EC, only studies were considered, which demonstrated that the active substance of the medicinal products fulfils the criteria of a well-established medicinal use. Data on usage of other than the specified extracts in the treatment of menopausal symptoms are limited and do not fulfil the mentioned requirements.

Based on the clinical data available and supported by the marketing overviews the posology is recommended as follows:

Female adults:

- Herbal Preparation A:
 - Single dose: 2.8 mg, dosage frequency: 2 times daily, daily dose: 5.6 mg
- Herbal preparation B:
 - Single dose: 6.5 mg, dosage frequency: 1 single daily dose, daily dose: 6.5 mg
- Herbal Preparation C:
 - Single dose: 2.5 mg or 5.0 mg, dosage frequency: 1-2 times daily, daily dose: 5.0 mg

Comparing the high number of daily dosages of CR preparations sold worldwide with the small number of reported adverse events, the use of CR can be considered to be safe under appropriate labelling. Allergic reactions of the skin (urticaria, itching of the skin, exanthema), facial oedema, peripheral oedema and gastrointestinal symptoms (i.e. dyspeptic disorders, diarrhoea) have been reported. The frequency is not known. Patients with hypersensitivity to the active substance have to be excluded from the use.

The possibility of hepatotoxic reactions (including hepatitis, jaundice, disturbances in the liver function tests) has to be taken into consideration during treatment. Patients with a history of liver disorder or liver diseases should take CR preparations with caution. Patients should stop taking CR preparations and consult their doctor immediately if they develop signs and symptoms suggestive of liver injury (tiredness, loss of appetite, yellowing of skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine).

Possible effects on the hormone sensitive tissue cannot be excluded. Patients who have been treated or who are undergoing treatment of breast cancer or other hormone dependent tumours should not use CR preparations without medical advice.

The benefit/risk assessment comes to a favourable conclusion regarding the WEU indication 'relief of menopausal complaints' for the specified herbal preparations listed above.

WHO ATC: G02CX04

No constituent with known therapeutic activity or active marker can be recognised by the HMPC .

Available data are considered not sufficient to support an indication for traditional use in other indications.

Annex

List of references