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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Hypericum perforatum* L., herba and *Cimicifuga racemosa* (L.) Nutt., rhizoma

Draft

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Fixed combinations of *Hypericum perforatum* L., herba (St. John's Worth) and *Cimicifuga racemosa* (L.) Nutt., rhizoma (Black Cohosh)
Herbal preparation(s)	Dry extracts from Hyperici herba (DER 3.5-6:1), extraction solvent ethanol 60% (V/V) and Cimicifugae rhizoma (DER 6-11:1), extraction solvent propanol 40% (V/V)
Pharmaceutical form(s)	Herbal preparations in solid dosage forms for oral use
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Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Hypericum perforatum* L., *herba* and *Cimicifuga racemosa* (L.) Nutt., *rhizoma.* It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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Introduction

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

- Herbal substance(s)

Hyperici herba consists of the whole or fragmented, dried flowering tops of *Hypericum perforatum* L., harvested during flowering time. It contains not less than 0.08% of total hypericins expressed as hypericin calculated with reference to the dried drug (European Pharmacopeia 01/2017:1438).

According to the Ph. Eur., black cohosh consists in the 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 ($C_{42}H_{65}NO_{16}$; Mr 840) (dried drug) (European Pharmacopoeia 04/2014:2069).

- Herbal preparation(s)

There is a European Pharmacopoeia Monograph for St. John's Wort Dry Extract, Quantified - Hyperici herbae extractum siccum quantificatum (European Pharmacopoeia 01/2017:1874).

The phytochemical composition of both Hyperici herba and Cimicifugae rhizoma and their preparations have been discussed in the corresponding assessment reports on:

Hyperici herba (EMA/HMPC/244315/2016) (EMA, 2022; Revision 1)

Cimicifugae rhizoma (EMA/HMPC/48744/2017) (EMA, 2018)

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

The herbal preparations with marketing authorizations consist of fixed combinations of dry extracts (prepared with ethanol/propanol, ethanol/ethanol) of Hyperici herba and Cimicifugae rhizoma (Table 1).

1.2. Search and assessment methodology

Scientific databases: Scifinder, Scopus, PubMed; search date 02.09.2022. Search terms: Hypericum perforatum, hyperici, St John's Worth, Cimicifuga racemose, cimicifugae, black cohosh combination.

Publications in other languages than English, French, German and Spanish (at least abstract in English, French or Spanish available) were precluded from the assessment.

Pharmacovigilance resources: Data from EU and non-EU regulatory authorities, European database for suspected adverse drug reaction reports. Search terms: Hyperici herba plus Cimicifugae rhizoma; St John's wort plus black cohosh.

Other resources: Libraries: University Complutense of Madrid, Faculty of Pharmacy.

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

A complete overview of the marketed medicinal products containing Hyperici herba or Cimicifugae rhizoma is included in the corresponding assessment reports (EMA/HMPC/244315/2016 (Revision 1) and EMA/HMPC/48744/2017, respectively).

Table 1: Overview of data obtained from marketed medicinal products

Active substance	**Indication**	**Pharmaceutical form** **Strength (where relevant)** **Posology** **Duration of use**	**Regulatory Status (date, Member State)**
Dry extracts from Hyperici herba (3.5-6:1); extraction solvent: ethanol 60% (V/V) and Cimicifugae rhizoma (6-11:1); extraction solvent: propanol 40% (V/V)			
3.75 mg dry extract from Cimicifugae rhizoma (6-11:1); extraction solvent: propan-2-ol 40% (V/V) and 70 mg dry extract from Hyperici herba, (3.5-6:1); extraction solvent: ethanol 60% (V/V)	Herbal medicinal product for the relief of menopausal complaints such as hot flushes and profuse sweating, if these symptoms are associated with additional psychological menopausal complaints such as depressive mood, nervousness and irritability	Coated tablets Female adults Beginning of treatment (during the 1st 8 weeks): 2 times daily 2 film-coated tablets (SD 140 mg / 7.5 mg) From week 9: 2 times daily 1 film-coated tablet (SD 70 mg / 3.75 mg)	WEU, 1976, Germany
	Treatment of climacteric complaints with pronounced psychovegetative symptoms like depressed mood, nervousness, irritability and problems to concentrate.	Coated tablets Climacteric women 2 x 1 film-coated tablet	WEU, 2003, Austria
Dry extracts from Hyperici (DER 3.5-6:1); extraction solvent ethanol 60% V/V and Cimicifugae rhizoma (DER 4.5-8.5:1); extraction solvent ethanol 60% V/V			
6.4 mg of dry extract from Cimicifuga rhizoma (4.5-8.5:1); extraction solvent: ethanol 60% (V/V) and 300 mg of dry extract from Hypericum herb (3.5-6:1); extraction	THMP for the relief of mild climacteric complaints like hot flushes, sweating and slightly depressed mood	Coated tablets 1 tablet daily	THMP, 2012, Austria
	THMP for the relief of symptoms of the menopause, including hot flushes, night sweats, slightly low mood and mild anxiety.	Coated tablets 1 tablet daily	THMP, 2012, Hungary

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
solvent: ethanol 60% (m/m)	THMP for the relief of symptoms of the menopause, including hot flushes, night sweats, slightly low mood and mild anxiety.	Coated tablets 1 tablet daily	THMP, 2016, Latvia
	THMP for the relief of symptoms of the menopause, including hot flushes, night sweats, slightly low mood and mild anxiety.	Coated tablets 1 tablet daily	THMP, 2018, Norway
	THMP for the relief of symptoms of the menopause, including hot flushes, night sweats, slightly low mood and mild anxiety.	Coated tablets 1 tablet daily	THMP, 2019, Sweden
	THMP for the relief of symptoms of the menopause, including hot flushes, night sweats, slightly low mood and mild anxiety.	Coated tablets 1 tablet daily	THMP; 2016, Hungary, Bulgaria, Czech Republic, Slovakia, Estonia, Lithuania, Romania
	THMP for the relief of symptoms of the menopause, including hot flushes, night sweats, slightly low mood and mild anxiety.	Coated tablets 1 tablet daily	2003-2010, UK, a section 12(2) herbal medicine (without written recommendation for its use). *THMP, 2011, UK (since 2020 UK not part of EU)*

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

Not applicable.

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

Not applicable.

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

The historical use of Hyperici herba and Cimicifugae rhizoma has been discussed in the corresponding assessment reports on Hyperici herba (EMA/HMPC/244315/2016 (Revision 1)) and Cimicifugae rhizoma (EMA/HMPC/48744/2017).

In summary, Hypericum herba has been used for treatment of psychovegetative disturbances, depressive unpleasantness, depression, anxiety and/or nervous restlessness. Cimicifuga rhizoma has

been used to treat, among others, disorders of the female reproductive tract such as amenorrhoea, dysmenorrhea, ovarian pain and menorrhagia), as well as menopausal symptoms.

One combination product has been of low dosage in its early beginnings in Germany. It is still used against menopausal complaints. Nowadays it is a liquid homoeopathic preparation. 100 g of the product (102 ml) contain 3 g Cimicifuga Urtinktur ("mother tincture") and 3 g Hypericum Urtinktur ("mother tincture"), 2 g, Lachesis mutus D8 and 2 g of Sanguinaria canadensis D3. The number of active components has been reduced over time from 10 to 4.

Assessor's comments:
This homeopathic product is marketed at least since 1978 and proves the continuous medicinal use of a fixed combination of ethanolic preparations of Cimicifuga rhizoma and Hypericum herba (3 g mother tinctures of each in 100) *over decades for menopausal complaints.*

2.3. Overall conclusions on medicinal use

The evidence of traditional use of the fixed combination of Hyperici herba and Cimicifugae rhizoma included in the monograph is based on:

- Licenced products: The product containing dry extract from Hyperici herba (DER 3.5-6:1; extraction solvent ethanol 60% (V/V)) and dry extract from Cimicifugae rhizoma (DER 6-11:1; extraction solvent propan-2-ol 40% (V/V)) has been marketed in Germany for over 30 years continuously and in Austria since 2003.

Since 1990, the product in the market in Germany contains both dry extracts. 1 coated tablet contains 2.5-5 mg Cimicifugae rhizoma extract (DER 6-11:1; extraction solvent: 2-propanol 40% (V/V),) and 58-85 mg Hyperici herba extract (DER 3.5-6:1; extraction solvent: ethanol 60% (V/V)). The recommended daily dose is 2 coated tablets equal to 5-10 mg Cimicifugae rhizoma extract and 116-170 mg Hyperici herba extract. According to the SmPC, up to 4 coated tablets are possible: 10-20 mg Cimicifugae rhizoma extract; 232-340 mg Hyperici herba extract. The accepted indication is "Herbal medicinal product for the relief of menopausal complaints such as hot flushes and profuse sweating, if these symptoms are associated with additional psychological menopausal complaints such as depressive mood, nervousness and irritability".

Taking in consideration all the above, historical data and documented period of use in the EU support the evidence of traditional use of the fixed combination Dry extract from Hyperici herba (DER 3.5-6:1;, extraction solvent: ethanol 60% (V/V)) and dry extract from Cimicifugae rhizoma (DER 6-11:1;, extraction solvent propan-2-ol 40% (V/V)).

Table 2: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	**Indication**	**Posology, Strength**	**Period of medicinal use**
Dry extract from Hyperici (DER 3.5-6:1); extraction solvent ethanol 60% (V/V) and Dry extract from Cimicifugae (DER 6-11:1); extraction solvent propan-2-ol 40% (V/V)	Herbal medicinal product for the relief of menopausal complaints such as hot flushes and profuse sweating, if these symptoms are associated with additional psychological menopausal	Beginning of treatment (during the 1st 8 weeks): SD: 140 mg/7.5 mg, twice daily DD: 280 mg/15 mg From week 9: SD: 70 mg/3.75 mg, twice daily DD: 140 mg/7.5 mg	Since 1976

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
	complaints such as depressive mood, nervousness and irritability.		

The fixed combination containing the Dry extract from Hyperici herba (DER 3.5-6:1, extraction solvent ethanol 60% (V/V)) and dry extract from Cimicifugae rhizoma (DER 4.5-8.5:1, extraction solvent ethanol 60% (V/V)), which has been registered in AT and HU (2012) and later on in several other EU MS partly based on confidential information that could not be disclosed and therefore the period of use of this preparation in the EU could not be substantiated and thus, traditional use is not supported.

3. Non-Clinical Data

The pharmacology, pharmacokinetics and the toxicology of both Hyperici herba and Cimicifugae rhizoma and their preparations have been discussed in the assessment reports on Hyperici herba (EMA/HMPC/244315/2016 (Revision 1) (EMA, 2022) and Cimicifugae rhizoma (EMA/HMPC/48744/2017) (EMA, 2018).

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

3.1.1. Primary pharmacodynamics

No information available for the combination.

3.1.2. Secondary pharmacodynamics

No information available for the combination.

3.1.3. Safety pharmacology

No information available for the combination.

3.1.4. Pharmacodynamic interactions

No information available for the combination.

3.1.5. Conclusions

There are no studies available regarding the fixed combination of Hyperici herba and Cimicifugae rhizoma.

According to the "Guideline on non-clinical documentation in applications for marketing authorisation/ registration of well-established and traditional herbal medicinal products" (EMEA/HMPC/32116/2005 Rev.1) (EMA, 2018), where there is, in terms set out by the Directive 2001/83/EC, sufficient and well-documented experience available in humans pharmacological tests including primary and secondary pharmacology, safety pharmacology and pharmacokinetics are not necessary, if there are no reasons to expect a specific risk.

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

There are no studies available regarding pharmacokinetic data of the fixed combination of Hyperici herba and Cimicifugae rhizoma.

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

No toxicological data are published for the combination.

3.4. Overall conclusions on non-clinical data

Results from experimental studies on the fixed combination of Hyperici herba and Cimicifugae rhizoma are not available and not required.
Specific data on pharmacokinetics and interactions are not available.
Since there is no non-clinical information on the safety of the combination available, non-clinical safety data included in the individual monographs on Hyperici herba and Cimicifugae rhizoma have been included in the monograph on the combination.

As there is no information on reproductive and developmental toxicity on the combination, the use during pregnancy and lactation cannot be recommended. In line with the monograph on Cimicifugae rhizoma women of childbearing potential should consider using effective contraception during treatment with the combination taking into consideration interactions related to Hyperici herba.
Tests on reproductive toxicity, genotoxicity and carcinogenicity on the combination have not been performed.

4. Clinical Data

All clinical aspects of both Hyperici herba and Cimicifugae rhizoma and their preparations have been discussed in the assessment reports on Hyperici herba (EMA/HMPC/244315/2016 (Revision 1) (EMA, 2022) and Cimicifugae rhizoma (EMA/HMPC/48744/2017) (EMA, 2018).

4.1. Clinical pharmacology

No data available.

4.2. Clinical efficacy

Three clinical trials have been performed for combinations of Hyperici herba and Cimicifugae rhizoma (see Table 3).

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

Two clinical studies have been performed with the preparation Dry extracts from Hyperici herba (3.5-6:1); extraction solvent: ethanol 60% (V/V) and Cimicifugae rhizoma (6-11:1); extraction solvent: propanol 40% (V/V).

The study by Briese *et al.* (2007) was a large-scale observational study aimed to assess the superiority of Cimicifugae rhizoma + Hyperici herba versus Cimicifuga alone on psychological symptoms in women with menopausal symptoms. After 6 months of treatment, women receiving the fixed combination (3.75 mg cimicifuga extract and 70 mg hypericum extract, 1-2 twice daily) significantly improved when pronounced psychological symptoms such as nervousness/irritability and depressive mood were present.

Assessor's comments:
Although the number of patients included and the duration of treatment can be considered as adequate, this study was a non-randomized, observational study and thus, can not be taken in account as a proof of efficacy of the fixed combination in the claimed indication.

The study by Übelhack *et al.* (2006) was a double-blind randomized placebo-control study including 301 women experiencing climacteric complaints with psychological symptoms. The treatment consisted of the fixed combination of Hyperici herba + Cimicifugae rhizoma (3.75 mg cimicifuga extract and 70 mg hypericum extract, 2 tablets twice daily (weeks 1 to 8) and 1 tablet twice daily (weeks 9 to 16)) or a matched placebo for 16 weeks. Climacteric complaints were evaluated by means of the Menopause Rating Scale mean score, and psychological complaints were evaluated using the Hamilton Depression Rating Scale sum score. After 16 weeks of treatment, a statistically significant improvement in alleviating climacteric complaints, including the related psychological component was shown.

Assessor's comments:
Although the number of patients included, the duration of treatment and the study design can be considered as adequate, this study does not fulfil the "Guideline on clinical investigations for Hormone Replacement Therapy of oestrogen deficiency symptoms in postmenopausal women" (EMEA/CHMP/021/97 Rev. 1) (EMA, 2005), and thus it can not be taken in account as a proof of efficacy of the fixed combination.

The study conducted by Chung *et al*. (2007) aimed to investigate the efficacy of one combination of Cimicifuga racemosa and Hypericum perforatum (1 tablet- 264mg - contains 0.0364 ml Cimicifuga extract equivalent to 1 mg terpene glycosides and 84 mg of hypericum dried extract equivalent to 0.25 mg of hypericin, with 80% methanol) in women with climacteric symptoms, and to assess their effects on vaginal atrophy, hormone levels and lipid profiles during 12 weeks. It was a double-blind randomized, placebo-controlled, multicentre study including 89 peri- or postmenopausal women (77 women concluded the study) experiencing climacteric symptoms. Climacteric complaints were evaluated by the Kupperman Index (KI); vaginal maturation indices, serum ostradiol, FSH, LH, total cholesterol, HDL- cholesterol, LDL-cholesterol, and triglyceride levels were measured before and after treatment. Mean KI scores and hot flushes after 4 and 12 weeks were significantly lower in the treated group. Differences in superficial cell proportion were not statistically significant. The lipid metabolism profile improved in the treated group (p=0.04).

Assessor's comments:
This study included a low number of patients, the exact composition and posology of the fixed combination is not known, and it does not fulfil the "Guideline on clinical investigations for Hormone Replacement Therapy of oestrogen deficiency symptoms in postmenopausal women"

(EMEA/CHMP/021/97 Rev. 1) (EMA, 2005), in particular regarding the proposed primary endpoint for efficacy trials which should be the frequency of moderate to severe hot flushes (enrolled subjects should have a defined minimum of hot flushes per day at baseline to justify a need for treatment - at least 5 moderate to severe hot flushes). The Kupperman index could be accepted as a secondary endpoint to assess efficacy) and thus it can not be taken in account as a proof of efficacy of the fixed combination.

Table 3: Clinical studies on humans, in Clinical studies on humans, in climacteric complaints with psychovegetative symptoms

Type	**Study**	**Test Product(s)**	**Number of Subjects)**	**Type of subjects**	**Outcomes**	**Statistical analysis**	**Clinical relevance**
Superiority of Cimicifugae rhizoma + Hyperici herba versus Cimicifuga alone on psychological symptoms in women with menopausal symptoms Briese *et al*., 2007	Large-scale, non-randomized, observational study 6 months	Dry extract from Cimicifugae rhizoma DER 6-11:1, extraction solvent propan-2-ol 40% V/V Dry extract from Hyperici herba, DER 3.5-6:1, extraction solvent ethanol 60% V/V 1 film-coated tablet contains 3.75 mg cimicifuga extract and 70 gm hypericum extract. Posology: 1-2 tablets twice daily Oral route 6 months + additional 6 months	6141 patients: 3027 received monotherapy; 3114 received the combination preparation 768 drop put Women 52 ± 7 years	Women with any menopausal symptom	Pre-defined primary effectiveness variable: change in the Psyche subscore from baseline to month 3 (ITT) Secondary variables: changes in the total MRS score and other subscores Main outcomes: Both treatments had effects on all three components of the subscore PSYCHE: depressive moods; nervousness and irritability; and general impairment of performance and memory. Greater effectiveness of the combination therapy on the MRS subscore "PSYCHE", relevant in the total MRS-score and greater effects on the items depressive mood swings and nervousness/irritability	Soma ANOVA (significant when $p<0.05$) Cohen's *D*	None (non-randomized, observational study)
Efficacy of Cimicifugae rhizoma + Hyperici herba in women with	Randomized, placebo-control 16 weeks	Dry extract from Cimicifugae rhizoma DER 6-11:1, extraction solvent propan-2-ol 40% V/V	301 patients: 151 treated group 150 placebo	Women with climacteric complaints with a pronounced psychological component	Main outcome: Decrease of the MRS by 30.4% points. Superiority of the treatment compared	Non-parametric tests (Mann-Whitney *U* test; Wilcoxon test). Student	None, "Guideline on clinical investigations for Hormone Replacement

Type	Study	Test Product(s)	Number of Subjects)	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
climacteric complaints with pronounced psychological component Uebelhack *et al*., 2006		Dry extract from Hyperici herba, DER 3.5-6:1, extraction solvent ethanol 60% V/V 1 film-coated tablet contains 3.75 mg cimicifuga extract and 70 gm hypericum extract. Posology: 2 tablets twice daily (weeks 1 to 8) and 1 tablet twice daily (weeks 9 to 16) Oral route 16 weeks	Women 45-60 years		with placebo was observed for all 10 items Secondary outcome: decrease in the Hamilton Depression Rating Scale (HDRS) score	*t* tests for metric data. *(adjusted according the EMEA- Points to Consider on Adjustment for Baseline Covariates)*	Therapy of oestrogen deficiency symptoms in postmenopausal women" (EMEA/CHMP/021/97 Rev. 1) not followed
Efficacy of Cimicifugae rhizoma + Hyperici herba in women with climacteric symptoms Chung *et al*., 2007	Double-blind randomized, placebo controlled 12 weeks	Cimicifugae rhizoma (equivalent to 1mg terpene glycosides), Hyperici herba (equivalent to 0.25mg hypericine) 1 tablet (264mg) contains 0.0364 ml cimicifuga extract and 84 mg hypericum extract	42 treatment group 35 control group 45-60 years	Healthy menopausal women with climacteric symptoms, intact uteruses, abstention from hormone therapy within previous 3 months	Primary: KI score reduction of 20.09 ± 9.75 in the treatment group *vs* 8.24 ± 7.57 in the control group ($p < 0.001$), hormone levels, lipid profile, vaginal maturation indices (VMIs) Secondary: adverse events: no significant differences between groups: mastalgia, bloating. Liver damage in the treated group, casual relationship unclear	Kupperman index (statistical significance =0.05) -Student's t-test -Web chi square calculator for changes in vaginal cytology distribution	Not clinically relevant: low number of patients, posology and exact composition of the medication not reported.

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

No data available.

4.4. Overall conclusions on clinical pharmacology and efficacy

There are no clinical pharmacology studies available regarding the fixed combination of Hyperici herba and Cimicifugae rhizoma.

Three clinical studies have been published with two different combinations of Hyperici herba and Cimicifugae rhizoma. The first two ones (Briese *et al*., 2007; Uebelhack *et al*., 2006) have been conducted with the fixed combination "Dry extracts from Hyperici herba (3.5-6:1) extraction solvent: ethanol 60% (V/V) and Cimicifugae rhizoma (6-11:1) extraction solvent: propanol 40% (V/V)", which corresponds to the product in the EU market since 1978. Nevertheless, none of these studies can be taken in account as a proof of efficacy of the fixed combination because of a) a not adequate design or b) not fulfilment of the "Guideline on clinical investigations for Hormone Replacement Therapy of oestrogen deficiency symptoms in postmenopausal women" (EMEA/CHMP/021/97 Rev. 1) (EMA, 2005) regarding the primary endpoint (decrease in the frequency of moderate to severe hot flushes) and justification of the minimum episodes of hot flushes per day at baseline, among others.

The third study (Chung *et al.,* 2007) was conducted with a different combination for which the exact composition and posology is unknown, and thus it can not be taken in account for the assessment of the fixed combination of Hyperici herba and Cimicifugae rhizoma.

5. Clinical Safety/Pharmacovigilance

All clinical safety aspects of both Hyperici herba and Cimicifugae rhizoma and their preparations have been discussed in the assessment reports on Hyperici herba (EMA/HMPC/244315/2016 (Revision 1)) (EMA, 2022) and Cimicifugae rhizoma (EMA/HMPC/48744/2017) (EMA, 2018).

The Hypericum herba extract used in the combination product is the dry extract from Hyperici (DER 3.5-6:1), extraction solvent ethanol 60% V/V (SD=140 mg/DD=280 mg; SD=70 mg/DD=140 mg). Similar extracts [c) Dry extract (DER 2.5-8:1), extraction solvent ethanol 50-68% V/V] are described in the monograph on Hypericum herba with single dosage of 250-600 mg and daily dosages of 500-1200 mg. Thus, the daily dose of the hypericum partner in the combination is much lower as for the mono preparation.

The Cimicifuga rhizoma extract used in the combination product (SD=7.5 mg/DD=15 mg; SD=3.75 mg/DD=7.5 mg) is described in the monograph on Cimicifuga rhizoma with single dosage of 2.5-5.0 mg and daily dosages of 5.0 mg. The daily dosage of the Cimicifuga partner in the combination product is far above the single/daily dosage of the mono preparation.

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

The data from the clinical trials conducted with the fixed combination of Hyperici herba and Cimicifuga rhizoma (Briese et al., 2007; Uebelhack et al., 2006) revealed no safety concerns up to six months of continuous treatment.

In the study by Briese et al. (2007), the overall rate of adverse events was 2.2% (138 cases) and the rate of possibility treatment-related adverse events was 0.16% (10 cases, 3 of them, in the combination group). Overall, 4 patients (0.07%) reported gastrointestinal complaints and 2

patients (0.03%) reported climacteric complaints as an adverse event; 2 patients in the combination group (0.06%) reported skin complaints. 1 case of allergic conjunctivitis and 1 reported bleeding of an uterine myomatosis were recorded. No case of liver dysfunction was reported.

In the study by Uebelhack et al. (2006), a total of 35 (23.2%) adverse events were reported in the treated group (151 women), with no statistically significant difference with the placebo group. Among them, 18 patients (11.9%) reported infections and infestations, 6 patients (4.0%) reported musculoskeletal and connective tissue disorders and 2 patients (1.3%) reported metabolism and nutrition disorders. A significant difference between the 2 groups regarding the intensity of the adverse events could not be observed; in some patients, the adverse events were judged as being unlikely related to the intake of the investigational product. In all other cases causality with the intake of the investigational product was excluded.

A third study (Chung et al., 2007) was conducted with a different combination of Cimicifuga racemosa and Hypericum perforatum (1 tablet- 264mg - contains 0.0364 ml cimicifuga extract and 84 mg hypericum extract), but can be taken in account for the safety profile. After 12 weeks of treatment, the most common adverse events were gastrointestinal complaints (12.8% in the treatment group. 9.5% in the placebo group), 1 patient discontinued the medication due to chest discomfort.

Results from these studies are summarized in Table 4.

Table 4: Clinical safety data from clinical trials in climacteric complaints with psychovegetative symptoms

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
Superiority of Cimicifugae rhizoma + Hyperici herba versus Cimicifuga alone on psychological symptoms in women with menopausal symptoms Briese *et al*., 2007	Large-scale, non-randomized, observational study 6 months	Dry extract from Cimicifugae rhizoma DER 6-11:1, extraction solvent propan-2-ol 40% V/V Dry extract from Hyperici herba, DER 3.5-6:1, extraction solvent ethanol 60% V/V 1 film-coated tablet contains 3.75 mg Cimicifuga extract and 70 gm Hypericum extract. Posology: 1-2 tablets twice daily Oral route 6 months + additional 6 months	6141 patients: 3027 received monotherapy (Cimicifuga rhizoma); 3114 received the combination preparation 768 drop put Women 52 ± 7 years	Women with any menopausal symptom	Rate of possibility treatment-related adverse events: 0.16% (3 cases in the combination group) GI complaints, Skin complaints	Adverse events already reflected in the combination monograph
Efficacy of Cimicifugae rhizoma + Hyperici herba in women with climacteric complaints with pronounced psychological component	Randomized, placebo-control 16 weeks	Dry extract from Cimicifugae rhizoma DER 6-11:1, extraction solvent propan-2-ol 40% V/V Dry extract from Hyperici herba, DER 3.5-6:1, extraction solvent ethanol 60% V/V	301 patients: 151 treated group 150 placebo Women 45-60 years	Women with climacteric complaints with a pronounced psychological component	36 (23.2%) adverse events in the treated group (no statistically significant difference to placebo) Eye disorders 1 (0.7%) Gastrointestinal disorders 1 (0.7%) General disorders and	No clinically relevant, as no statistically significant difference with placebo After 8 weeks of treatment, 31 not serious adverse events: there was no (n=30) or unlikely

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
Uebelhack *et al*., 2006		1 film-coated tablet contains 3.75 mg Cimicifuga extract and 70 gm Hypericum extract. Posology: 2 tablets twice daily (weeks 1 to 8) and 1 tablet twice daily (weeks 9 to 16) Oral route 16 weeks			administration site cond. 1 (0.7%) Infections and infestations 18 (11.9%) Injury, poisoning and procedural complications 2 (1.3%) Investigations 3 (2.0%) Metabolism and nutrition disorders 2 (1.3%) Musculoskeletal and connective tissue disorders 6 (4.0%)	(n=1) relationship to the study medication. After 16 weeks of treatment, 36 not serious adverse events: no significant difference between the 2 groups regarding the intensity of the adverse events was observed. In 4 patients within the treatment group and in 3 patients within the placebo group, the adverse events were judged as being "unlikely" related to the intake of the investigational product. In all other cases causality with the intake of the investigational product was excluded.
Efficacy of Cimicifugae rhizoma + Hyperici herba in women with	Double-blind randomized, placebo controlled 12 weeks	Cimicifugae rhizoma (equivalent to 1mg terpene glycosides), Hyperici herba (equivalent to 0.25mg hypericine)	42 treatment group 35 control group 45-60 years	Healthy menopausal women with climacteric symptoms, intact uteruses, abstention from hormone therapy	GI complaints: 12.8% in the treatment group, 9.5% in the placebo group Chest discomfort: 1 patient	GI events reflected in the combination monograph

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
climacteric symptoms Chung *et al*., 2007		1 tablet (264mg) contains 0.0364 ml Cimicifuga extract and 84mg Hypericum extract		within previous 3 months		

5.2. Patient exposure

In the clinical trials conducted with the fixed combination, more than 3000 patients were included and treated for up to six months. No serious adverse events were reported. The total percentage of adverse events was similar to the one observed for the mono therapy or control groups (See also sections 4.2, 4.3, 5.1 and 5.6).

Aside from market presence and data from studies, there are no concrete data concerning patient exposure.

5.3. Adverse events, serious adverse events and deaths

Data for clinical trials conducted with the fixed combination of Hyperici herba and Cimicifugae rhizoma revealed no safety concerns after 6 months of continuous use. The main adverse events were gastrointestinal disorders/complaints.

Table 5. Safety information from products marketed in the EU/EEA.

Herbal substance/ preparation	**SmPC section**	**Safety information**
Dry extracts from Hyperici herba (3.5-6:1); extraction solvent: ethanol 60% (V/V) and Cimicifugae rhizoma (6-11:1); extraction solvent: propanol 40% (V/V)	4.8	Restlessness, dyspeptic disorders, diarrhoea. Liver damage, transaminases increased. Allergic skin reactions (urticaria, itching, exanthema). Fair-skinned individuals may react with dysesthesia (e.g. tingling, sensitivity cold or pain, burning sensation) and intensified sunburn-like symptoms under intense sunlight. Fatigue, facial oedema, peripheral oedema. Weight gain.
Dry extracts from Hyperici (DER 3.5-6:1); extraction solvent ethanol 60% V/V and Cimicifugae rhizoma (DER 4.5-8.5:1); extraction solvent ethanol 60% V/V	4.8	Restlessness, anxiety, mania. Headache, neuropathy, dizziness. Dyspepsia, diarrhoea. Liver toxicity (including hepatitis, jaundice, disturbances in the liver function tests). Fatigue, facial oedema, peripheral oedema. Weight gain.

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

A search in the EudraVigilance database was done on 8 October 2024. Related to the search terms Hypericum perforatum, hyperici, St John's wort AND Cimicifuga racemosa, Cimicifuage, black cohosh 66 reports were found. Most of the reports were related to hypersensitivity reactions where the reaction PTs listed belong to the SOC 'Skin and subcutaneous tissue disorders'. Also, several reports where the PTs were related to gastrointestinal disorders and the PT dizziness could be found. Symptoms related to climacteric complaints were also frequently reported e.g., palpitations and sleep disorders. There were six case reports related to hepatobiliary disorders, two of these reports from healthcare professionals were classified as serious and no concomitant drug was reported. Overall, there were no new safety issues identified.

Assessor's comment:

From available safety data, the following adverse reactions are listed in the monograph section 4.8 with a statement that the frequency is not known:

Psychiatric disorders: Restlessness, anxiety, mania

Nervous system disorders: Headache, neuropathy, dizziness

Gastrointestinal disorders: Nausea, abdominal pain, diarrhoea, dyspepsia

Hepatobiliary disorders: Liver toxicity (including hepatitis, jaundice, disturbances in the liver function tests)

Skin and subcutaneous tissue disorders: Allergic skin reactions (urticaria, itching, exanthema). Fair-skinned individuals may react with dysesthesia (e.g. tingling, sensitivity cold or pain, burning sensation) and intensified sunburn-like symptoms under intense sunlight.

General disorders and administration site conditions: Fatigue, face oedema, peripheral oedema

Investigations: Weight gain

5.4. Laboratory findings

There are no data available regarding the fixed combination.

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

There is no relevant indication for children and adolescents. There are no data available.

5.5.2. Contraindications

It has been shown that hypericum dry extract induces the activity of CYP3A4, CYP2B6, CYP2C9, CYP2C19 and P-glycoprotein. The concomitant use with coumarin-type anticoagulants, cyclosporine, everolimus, sirolimus, tacrolimus for systemic use, fosamprenavir, indinavir and other protease inhibitors, nucleoside reverse transcriptase inhibitors, irinotecan, imatinib and other cytostatic agents metabolised by CYP3A4, CYP2B6, CYP2C9, CYP2C19 or transported by P-glycoprotein is contraindicated.

5.5.3. Special warnings and precautions for use

The following warnings and precautions of use have to be considered:

- Patients with an existing or previous liver disorder should use this combination with caution.
- Patients should stop the use and consult their doctor immediately if they develop signs and symptoms suggestive of liver injury (icterus, dark urine, severe upper stomach pain, nausea, loss of appetite, tiredness).
- Patients who have been treated or who are undergoing treatment for breast cancer or other hormone-dependent tumours should not use this combination without medical advice.
- If vaginal bleeding occurs or other symptoms occur, a doctor should be consulted.
- Not to used together with oestrogens unless advised by a doctor.
- During the treatment intense UV-exposure should be avoided.

5.5.4. Drug interactions and other forms of interaction

Hyperici herba

A great number of clinical trials have consistently shown that St. John's wort induced P-glycoprotein as well as several enzymes of the CYP-family. Induction of CYP enzymes and P-

glycoprotein is most probably caused by hyperforin via activation of the pregnane X receptor. For further details, see assessment report on Hyperici herba (EMA/HMPC/244315/2016) (EMA, 2022).

- Daily dose of hyperforin ≤ 1 mg:
    - As the daily intake of hyperforin is less than 1 mg~~,~~ no clinically relevant interactions are reported for concomitantly administered drugs, which are metabolised via CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4 or transported by P-glycoprotein. Pharmacokinetic interactions with drugs, which are metabolised via other CYP-enzymes have not been investigated.
- Daily dose of hyperforin > 1 mg:
    - Hyperici herba preparations induce the activity of CYP3A4, CYP2B6, CYP2C9, CYP2C19 and P-glycoprotein. Concomitant use with coumarin-type anticoagulants, cyclosporine, everolimus, sirolimus, tacrolimus for systemic use, fosamprenavir, indinavir and other protease inhibitors, nucleoside reverse transcriptase inhibitors, irinotecan, imatinib and other cytostatic agents metabolised by CYP3A4, CYP2B6, CYP2C9, CYP2C19 or transported by P-glycoprotein is contraindicated.
    - Special care should be taken in case of concomitant use of all drug substances the metabolism of which is influenced by CYP3A4, CYP2B6, CYP2C9, CYP2C19, or P-glycoprotein (e.g., amitriptyline, fexofenadine, alprazolam, diazepam, midazolam, methadone, simvastatin, digoxin, finasteride), because a reduction of plasma concentrations is possible.
    - The reduction of plasma concentrations of hormonal contraceptives may lead to increased intermenstrual bleeding and reduced safety in birth control. Women using hormonal contraceptives should take additional contraceptive measures.
    - Prior to elective surgery possible interactions with products used during general and regional anaesthesia should be identified. If necessary, the herbal medicinal product should be discontinued. The elevated enzyme activity returns within 1 week after cessation to normal level.
    - Pharmacodynamic interactions: Hyperici herba preparations may contribute to serotonergic effects when combined with antidepressants such as serotonin reuptake inhibitors (e.g. sertraline, paroxetine) or buspirone. Very rarely undesired effects (serotonin syndrome) with autonomic dysfunctions (such as perspiration, tachycardia, diarrhoea, fever), mental alterations (such as agitation, disorientation), and motor alterations (such as tremor or myoclonias) can occur in combination with serotonin-uptake inhibitors or other serotonergic active substances.

<u>Cimicifugae rhizoma</u>

Cimicifugae 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 black cohosh and tamoxifen was reported by any of the trials. Since the use of this preparation 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. For further details, see assessment report on Cimicifugae rhizoma (EMA/HMPC/48744/2017) (EMA, 2018).

5.5.5. Fertility, pregnancy and lactation

Data on the effects of both Hyperici and Cimicifugae on Fertility, pregnancy and lactation are included in the corresponding assessment reports (EMA/HMPC/244315/2016 (EMA, 2022) and EMA/HMPC/48744/2017 (EMA, 2018), respectively).

Nevertheless, due to the therapeutic indication, the use of the fixed combination is not intended during pregnancy and lactation. Women of childbearing potential should consider using effective contraception during treatment.

5.5.6. Overdose

No case of overdose has been reported.

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

No data available.

5.6. Overall conclusions on clinical safety

Data for clinical trials conducted with the fixed combination of Hyperici herba and Cimicifugae rhizoma revealed no safety concerns after 6 months of continuous use. The main adverse events were gastrointestinal disorders/complaints. Undesirable effects listed in monograph section 4.8 derive from the individual monographs on Hyperici herba and Cimicifugae rhizoma and their preparations and from products on the market.

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

The contraindications, warnings, interactions for this fixed combination are obtained from marketed products and also from the use of each active principle alone, taking in account the final content of hyperforin in the fixed combination

The use of the fixed combination of Hyperici herba and Cimicifugae rhizoma proves not to be harmful in the specified conditions of use (recommended indications and sections lined out in the HMPC monograph) on the basis of the information on its long-standing use.

6. Overall conclusions (benefit-risk assessment)

Fixed combinations of dry extracts of Hyperici herba and Cimicifugae rhizoma have been used for more than 30 years in the EU for the relief of mild climacteric complaints like hot flushes, sweating and slightly depressed mood.

Two clinical studies have been found with the fixed combination of Hyperici herba and Cimicifugae rhizoma (dry extract from Hyperici herba (DER 3.5-6:1), extraction solvent ethanol 60% (V/V) and dry extract from Cimicifugae rhizoma (DER 6-11:1), extraction solvent propan-2-ol 40% V(/V)). The quality and clinical outcome of these studies is not adequate to substantiate efficacy according the requirements in the current "Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products" (EMA/HMPC/104613/2005–Rev. 1).

The clinical studies have also shown that combination products of Hyperici herba and Cimicifugae rhizoma dry extracts are well-tolerated except for, gastrointestinal disorders (nausea, abdominal pain, diarrhoea) and skin and subcutaneous tissue disorders (mainly allergic skin reactions). . Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended. Women of childbearing potential should consider using effective contraception during treatment.

The fixed combination dry extract from Hyperici herba (DER 3.5-6:1), extraction solvent ethanol 60% (V/V) and dry extract from Cimicifugae rhizoma (DER 6-11:1), extraction solvent propan-2-ol 40% (V/V) has been in medicinal use in the EU for more than 30 years.

Thus, the following TU indication *Traditional herbal medicinal product used for the relief of mild climacteric complaints like hot flushes and sweating when associated with temporary mental exhaustion* can be accepted.

The product is a traditional herbal medicinal product for use in the specified indications exclusively based upon long-standing use."

The content of hyperforin of the herbal preparation should be specified in the dossier.

A European Union list entry is not supported due to lack of data on genotoxicity data.

Annex

List of references