



European Medicines Agency  
Press office

London, 18 July 2006  
Doc. Ref.: EMEA/269259/2006

**EMEA PUBLIC STATEMENT ON HERBAL MEDICINAL PRODUCTS CONTAINING  
*CIMICIFUGAE RACEMOSAE RHIZOMA* (BLACK COHOSH, ROOT)  
- SERIOUS HEPATIC REACTIONS -**

The European Medicines Agency (EMA) and the Committee on Herbal Medicinal Products (HMPC) have been made aware of a number of case reports of hepatotoxicity (liver injuries) in patients using *Cimicifugae racemosae rhizoma* (Black Cohosh, root).

Following review of all available data, the HMPC considered that there is a potential connection between herbal medicinal products containing *Cimicifugae racemosae rhizoma* (Black Cohosh, root) and hepatotoxicity.

The EMA therefore wishes to give the following advice to patients and healthcare professionals:

**Advice to patients:**

- **Patients should stop taking *Cimicifugae racemosae rhizoma* (Black Cohosh, root) and consult their doctor immediately if they develop signs and symptoms suggestive of liver injury (tiredness, loss of appetite, yellowing of the skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine).**
- **Patients using herbal medicinal products should tell their doctor about it.**

**Advice to healthcare professionals:**

- **Health care professionals are encouraged to ask patients about use of products containing *Cimicifugae racemosae rhizoma* (Black Cohosh, root).**
- **Suspected hepatic reactions should be reported to the national adverse reaction reporting schemes.**

Within the EU, *Cimicifugae racemosae rhizoma* (Black Cohosh, root) is widely used, sometimes in combination with other plants, in different licensed and unlicensed herbal medicinal products. The licensed products have a wide range of indications but *Cimicifugae racemosae rhizoma* (Black Cohosh, root) is currently most commonly used to treat minor climacteric (peri- and post-menopausal) symptoms such as hotflushes, sweating, sleep disturbances and nervous tension. In some Member States, *Cimicifugae racemosae rhizoma* (Black Cohosh, root) is also used in a range of other indications, such as: symptomatic relief of rheumatic pain, cough, stomach cramps, period pains/bloatedness, tenseness/irritability. The number of unlicensed herbal medicinal products containing *Cimicifugae racemosae rhizoma* (Black Cohosh, root) marketed in the Europe is not known.

The HMPC evaluated 42 case reports of hepatotoxicity, collected from European National Competent Authorities (34 cases) as well as literature case reports (8 cases). Of these, only 16 cases were considered sufficiently documented<sup>1</sup> to allow the Committee to assess if use of *Cimicifugae racemosae rhizoma* (Black Cohosh, root) could be linked to the liver injuries. As a result of the assessment, 5 cases were excluded and 7 cases were considered unlikely to be related. In the remaining 4 cases (2 autoimmune hepatitis, 1 hepatocellular liver injury and 1 fulminant hepatic failure), there was a temporal association

<sup>1</sup> Case reports evaluated according to RUCAM score (Roussel UCLAF causality assessment method), a well-established method used to assess cases of hepatotoxicity. [Danan G. and Benichou C. (1993) J Clin Epidemiology Vol.46 (11): 1323-1330] . [Benichou C. et al (1993) J Clin Epidemiology Vol.46 (11): 1331-1336]

between the start of treatment with *Cimicifugae racemosae rhizoma* (Black Cohosh, root) and the occurrence of hepatic reaction.

The HMPC will continue to review all new safety information relating to this issue and if necessary will release a further updated statement. Further details regarding the case reports are provided in the Annex 1: “Assessment of case reports connected to herbal medicinal product containing *Cimicifugae racemosae rhizoma* (Black Cohosh, root)”, which can be found [here](#).

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For further information contact:

Mr Martin Harvey

Press Office (Tel: +44 20 74 18 86 99, Fax: + 44 20 74 18 84 09)



London, 18 July 2006  
Doc Ref: EMEA/HMPC/269258/2006

**COMMITTEE ON HERBAL MEDICINAL PRODUCTS  
(HMPC)**

**ANNEX 1**

**ASSESSMENT OF CASE REPORTS CONNECTED TO HERBAL MEDICINAL PRODUCTS  
CONTAINING *CIMICIFUGAE RACEMOSAE RHIZOMA* (BLACK COHOSH, ROOT)**

<b>DISCUSSION IN HMPC</b>	November 2004 January 2005 November 2005 March 2006
<b>TRANSMISSION TO PhVWP FOR CONSIDERATION</b>	January 2005 June 2006
<b>RE-DISCUSSION IN HMPC</b>	13 July 2006
<b>ADOPTION BY HMPC</b>	13 July 2006

This document contains an assessment of a number of case reports connected to herbal medicinal products containing *Cimicifugae racemosae rhizoma* (Black Cohosh, root). It has been prepared by the HMPC and commented on by the CHMP<sup>1</sup> Pharmacovigilance Working Party (PhVWP). The HMPC decided at its meeting in July 2006 to publish the assessment report as a public statement that provides recommendations to Health care professionals and patients.

<sup>1</sup> Committee for Medicinal Products for Human Use.

**Annex 1**  
**Assessment of case reports connected to herbal medicinal products**  
**containing *Cimicifugae racemosae rhizoma* (Black Cohosh, root)**

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## 1. Introduction

The Committee on Herbal Medicinal Products (HMPC) has been confronted with a number of case reports on hepatotoxicity connected to *Cimicifugae racemosae rhizoma* (Black Cohosh, root). The HMPC has therefore collected further cases from National Authorities as well as cases published in literature, and used as a basis for this assessment.

Before analysing the pharmacovigilance case reports in the EU and the published cases in literature related to the intake of herbal medicinal products containing *Cimicifugae racemosae rhizoma* (Black Cohosh, root), it would be relevant to briefly introduce the method used in the evaluation process.

Draft recommendations of the Scientific Advisory Panel Subgroups on Hepatotoxicity (2004) could not be used except for the case discussed by Cohen (Cohen, 2004) due to poor documentation of the other cases.

## 2. RUCAM Score (Roussel UCLAF causality assessment method)

At the request of CIOMS, 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 et al 1993). The score was validated and the results published (Benichou et al. 1993).

Liver injuries are classified in three categories and defined as follows:

- Hepatocellular liver injuries: ALAT rises above 2 N (normal range) or R (ratio serum activity ALAT/serum activity AP)  $\geq 5$ , measured together at time of recognition
- Cholestatic liver injuries: AP  $> 2$  N or R  $\leq 2$
- Mixed liver injuries: ALAT  $> 2$  N and an increase in AP and  $2 < R < 5$

The data received at 37°C were used as reference ranges for the liver enzymes.

### Seven criteria are to be assessed:

#### I. Time of onset:

The reaction is unrelated:

- if the reaction has started before the treatment or
- if the reaction has started more than 15 days after the cessation of the drug in case of a hepatocellular reaction or
- if the reaction has started more than 30 days after the cessation of the drug in case of a cholestatic or mixed type.

If information on the time frame is not ascertainable, the case report is insufficiently documented.

#### II. The course of the reaction:

It is inconclusive, if the liver test abnormalities return to normal while the suspected drug is continued.

#### III. Risk factors:

- Age of the patient older than 55 years
- Alcohol consumption for the hepatocellular type of reaction
- Alcohol consumption and/or pregnancy for cholestatic or mixed type

#### IV. Concomitant drugs:

- With a compatible/incompatible time of onset
- With known hepatotoxicity

- With a positive role in this case (positive rechallenge or validated test)

#### V. Non-drug related causes:

- 1) IgM anti HAV Ab recent Hepatitis A  
IgM anti HBc Ab recent Hepatitis B  
Anti Hepatitis C Ab (HCV);  
Administration of blood or blood products 1-6 months earlier,  
Recent travels to hepatitis endemic areas  
Alcohol induced injury is suggested when ASAT/ALAT  $\geq 2$   
Ultrasound excludes cholelithiasis and biliary tract abnormalities  
Recent acute hypotension leading to ischemic liver necrosis
- 2) Diagnostics of the following causes are optional:  
Natural history of the underlying disease and recent infections with CMV, EBV or Herpes virus

#### VI: Previous information on toxicity:

Previous information on the hepatotoxicity of the suspected drug has to be considered.

#### VII: Response to re-administration:

Confirmation of the reaction either in vivo (positive rechallenge or in vitro (tests or assays) is requested.

Theoretically, the range of the global score would be -9 to +15; in practice it was -5 to +13 after evaluating several hundred cases. It may be classified in five degrees:  $\leq 0$  "excluded"; 1-2 "unlikely"; 3-5 "possible"; 6-8 "probable"; above 8 "highly probable"  
With 5 as a cut off point, sensitivity was 78%, specificity 68%.

Please be aware that norm ranges for laboratory methods of liver enzymes have changed due to a change of reference-temperature and that they are used on the basis of a temperature of 37°C.

### **3. Assessment of the EU cases collected from European National Competent Authorities**

1. **unrelated**: patient with underlying cirrhosis already treated with spironolacton, furosemid, lactulose and multiple other drugs developed after intake of 15 different drugs an Stevens Johnson syndrome.
2. RUCAM Score 1 (**unlikely**); Cholestatic Hepatitis; case poorly documented, underlying breast cancer, insufficient differential diagnosis.
3. RUCAM Score -2 (**excluded**); mixed type hepatitis; case poorly documented, Rhapontic rhubarb is known as a possibly hepatotoxic agent, the onset of reaction was five weeks after the commencement of Rapontic rhubarb, *Cimicifugae racemosae rhizoma* (Black Cohosh, root) was taken for 3 month without problems.
4. **unrelated** according to the reporting hospital: hepatocellular hepatitis due to ethyltoxic reaction after alcohol abuse for decades, the intake of *Cimicifugae racemosae rhizoma* (Black Cohosh, root) had been without problems for more than several months.
5. **unrelated** according to the reporting senior medical doctor: autoimmune hepatitis Type 1, recovery after immunosuppressant therapy; additionally, known hepatotoxicity of Dilatrend and Coversum (concomitant drugs); dechallenge not assessable due to immunosuppressant therapy.
6. **unrelated** due to increased liver enzymes (ALAT 46 U/l  $\Rightarrow$  2N before use of *Cimicifugae*

*racemosae rhizoma* (Black Cohosh, root), six weeks after commencement of *Cimicifugae racemosae rhizoma* (Black Cohosh, root), ALAT was 86 U/l, three weeks after cessation of *Cimicifugae racemosae rhizoma* (Black Cohosh, root), ALAT was still 51 U/l; RUCAM Score would be 1 (unlikely).

7. RUCAM Score -1 (excluded): mixed type reaction, 4 weeks after TEP, concomitant therapy (diclofenac) known to be hepatotoxic, dose and period of administration of *Cimicifugae racemosae rhizoma* (Black Cohosh, root) containing product unknown; differential diagnosis insufficient
8. not assessable because no laboratory data available: after discontinuation of Remifemin cholestatic reaction; time of onset of reaction five months after commencement of intake of Remifemin; known hepatotoxicity of Ketorprofen (concomitant drug); no data on the time frame between medication and onset of reaction.
9. RUCAM Score -1 (excluded); the values are too discreetly elevated to qualify for a hepatotoxic reaction and to be classified as possible.
10. unrelated: acute phase of a chronic hepatitis on an autoimmune basis; the acute phase started five months after discontinuation of Remifemin but four weeks after the beginning of a treatment with oestrogen/gestagen.
11. RUCAM Score 1 (unlikely); type not assessable due to a lack of information on cholestatic parameters; overall assessment possible, before intake of Remifemin all laboratory parameters had been in a normal range, after 6 days Remifemin ALAT 3 N, six weeks later unchanged, recovery documented in September, no information on cholestatic parameters, on differential diagnosis or concomitant drugs etc.
12. RUCAM Score 2 (unlikely); assessment possible due to possible time relationship; improvement after cessation, ALAT decreases but not AP, limited information overall, no data on differential diagnosis, AP three months after discontinuation of Remifemin unchanged, i. e. still elevated.
13. RUCAM Score 1 (unlikely); mixed type; the relationship between the period of the intake of the drug and the onset of reaction is discussed; liver biopsy: chronic active hepatitis or toxic liver injury; no suspicion of alcohol; lack of information on hepatitis serology, ultrasound, differential diagnosis; recovery after dechallenge; AP is still elevated 276 U/l four weeks after dechallenge.
14. hepatocellular reaction; not assessable because of insufficient information, the duration of drug intake is not known so that the time frame of onset of reaction is not assessable; according to RUCAM, the case is insufficiently documented, other causes for acute hepatitis were not excluded; the reporting person assumes a drug induced hepatitis
15. not assessable because of insufficient information, the duration of drug intake is not known, therefore the time frame of onset of reaction is not assessable, according to RUCAM, the case is insufficiently documented
16. RUCAM Score -1 (excluded); hepatocellular reaction not assessable because of insufficient information; sonographically probably cirrhotic, although exclusion of infiltrative metastatic disease not possible; histologically severe active chronic hepatitis (B+C serologically excluded); Cimicifuga was discontinued on 11 Sept. 2003; ASAT increasing till 11 Oct. 2004; if the drug is the trigger, it is impossible to identify cirrhotic changes as early as four weeks after the intake of the drug. In addition, green tea extract was taken which is known to be hepatotoxic (FR;SP: Exolise), time frames concerning the intake of green tea extract and the reaction are not available.

17. RUCAM Score 2 (unlikely); not assessable because of insufficient information; the only information is the time of onset two weeks after discontinuation of *Cimicifugae racemosae rhizoma* (Black Cohosh, root); there are no laboratory data available, no information on concomitant drugs or on differential diagnosis etc.
18. not assessable because of insufficient information, the duration of drug intake is not known, therefore the time frame of onset of reaction is not assessable, according to RUCAM, the case is insufficiently documented; the reporting person did not classify the reaction as serious.
19. not assessable because of insufficient information; the period of intake of the drug is not known, therefore the time frame of onset of reaction is not assessable, according to RUCAM, the case is insufficiently documented; no information at all except that liver function tests were abnormal.
20. not assessable because of insufficient information, the duration of drug intake is not known, the time frame of onset of reaction is therefore not assessable; according to RUCAM, the case is insufficiently documented; no information on laboratory tests, concomitant drugs, differential diagnosis, morphology etc.
21. RUCAM Score 2 (unlikely); not assessable because of insufficient information, reaction started three months before discontinuation of intake of *Cimicifugae racemosae rhizoma* (Black Cohosh, root), mixed type of reaction; values are just 2 N elevated on the border to be classified as possible; it is unclear whether laboratory values had been elevated before drug intake.
22. unrelated, patient developed autoimmune hepatitis, recovery after treatment with corticosteroids; the duration of drug intake is not known, the time frame of onset of reaction is therefore not assessable, according to RUCAM, the case is insufficiently documented.
23. an isolated elevation of GGT up to 206 U/l is reported, which normalised three weeks after dechallenge; not assessable because of insufficient information, there are no further information available, neither of concomitant drugs, nor of differential diagnosis, nor other laboratory parameters, not even an ultrasound.
24. not assessable, because of insufficient information, the time of medication is not known, the date of onset of reaction is not known, the case following RUCAM insufficiently documented, there are no further information available, neither of concomitant drugs, nor of differential diagnosis, nor other lab parameters, not even ultrasound.
25. not assessable because of insufficient information, the duration of drug intake is not known, the time frame of onset of reaction is therefore not assessable, according to RUCAM, the case is insufficiently documented; Hepatocellular reaction with weak positive ASMA and ANA and a massively elevated Ca19-9 (533 kU/l); the patient's liver parameters return to normal with CA 19.9, ALAT, Gamma GT, albumin and globulin all entirely back within normal limits.
26. unrelated; abnormal liver function tests noted before the intake of *Cimicifugae racemosae rhizoma* (Black Cohosh, root).
27. not assessable because of insufficient information, the duration of drug intake is not known, the time frame of onset of reaction is therefore not assessable, according to RUCAM, the case is insufficiently documented. The patient observed pruritus six weeks after cessation of *Cimicifugae racemosae rhizoma* (Black Cohosh, root), which she had taken for about two months in 2002. Late 2003, elevated liver function tests (ALAT just 2 N) were observed, concomitant drugs NSAID; the long time of nearly two years between discontinuation of the drug and the onset of reaction makes a connection unlikely.

28. RUCAM SCORE 4 (possible), the connection is possible because time of onset of reaction is related to drug exposure. The admitted amount of 80 mg/day is twice the dose laid down in respective the Commission E monograph. Since results of or further information on differential-diagnostic assessment are not available, we consider the connection between the intake of black cohosh and the adverse event as possible. According to RUCAM, the liver injury can be classified as hepatocellular. However, it should be pointed out that Bilirubin is elevated.
29. RUCAM SCORE 2 (unlikely), an isolated elevation of ALAT up to 334 U/L which decreased more than 6 times during nearly 2 weeks. Patient additionally took Diclofenac and Amitriptyline, two substances known to be hepatotoxic. There is no further information about the daily dose of intake of black cohosh.
30. RUCAM SCORE 0 (excluded), the patient had taken black cohosh for 6 weeks and received a fulminant hepatic failure requiring liver transplantation. She also took Ibuprofen, known to be hepatotoxic. The test of Paracetamol was in a range of being of possible hepatic toxicity. The hepatitis serology was negative, but the test of Epstein-Barr virus antibody was positive. There is no further information about the daily dose of intake of black cohosh.
31. not assessable because of insufficient information, the duration of drug intake is not known, the time frame of onset of reaction is therefore not assessable, according to RUCAM, the case is insufficiently documented. The patient showed an increase of ALAT and Bilirubin, recovering within 1 month.

## 6. Assessment of Non-EU cases received from European National Competent Authorities

1. not assessable, because information is lacking about laboratory data, onset of reaction 5 month after starting the *Cimicifugae racemosae rhizoma* (Black Cohosh, root) containing product, the period of intake is not defined, data on any differential diagnosis are missing, patient had nephrectomy due to renal cancer 2000. The case report is not validated by a medical professional.
2. unrelated: pre-existing liver disease of unknown origin, continuously increasing bilirubin, patient was waiting for a liver transplant and was evaluating with MAH whether *Cimicifugae racemosae rhizoma* (Black Cohosh, root) is attributing to the situation. There is no information about the period and daily dose of *Cimicifugae racemosae rhizoma* (Black Cohosh, root) intake. The casereport is not validated by a medical professional.
3. unrelated: increasing liver enzymes on the first day of intake of the product containing *Cimicifugae racemosae rhizoma* (Black Cohosh, root), improvement of the liver enzymes despite continuing Cimicifuga with the same dose, liver enzymes normalised after 2 weeks. The casereport is not validated by a medical professional.

## 7. Assessment of the cases published in literature

1. Cohen, Stanley M. MD et al. (2004) *Menopause*. 11(5): 575-577  
RUCAM Score 7 (probable); 57 year old multimorbid woman suffering from a polymyositis, diabetes mellitus, hypertension and obstructive sleep apnoea; time of onset of hepatocellular damage may be related to the intake of *Cimicifugae racemosae rhizoma* (Black Cohosh, root), brand and dose unknown, could as well be multi system autoimmune disease. According to the SPC, concomitantly administered Verapamil may cause allergic hepatotoxic reactions. However, in this case it had been administered over a period of approx. two years before the onset of reaction.

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]



Hepatotoxicity (2004), the case would be classified as idiosyncratic liver necrosis (criteria page 12).

Case n. 8 presented in Section 7 of this report, was first published at a Workshop on the Safety of Black Cohosh in Clinical Studies: NIH Bethesda, Maryland, November 22, 2004 (Cohen SM et al.: Auto-immune hepatitis associated with the use of black cohosh (Case 2). A second report is published in LIVER TRANSPLANTATION 12: 989-992, 2006 (Ch. R. Lynch, et al: Fulminant Hepatic Failure Associated With the Use of Black Cohosh: A Case Report). To some extent the information in both reports seem to be contradictory. However, there is no doubt, that both articles report on the same case.

As assessed in the initial report (Cohen) the ADR was serious (patient died during a liver transplant procedure due to uncontrollable hemorrhage) and unexpected for the manufacturer's *Cimicifuga* containing products.

The causal relationship to Black Cohosh in the present case was first assessed as "unclassifiable" as information provided concerning the reaction was regarded as incomplete and contradictory. The follow-up publication includes more (although to some extent contradictory) therapy information. The case presentation, the laboratory values and its history, the liver biopsy and finally the liver histology leave no doubt on the pathological liver process. Histology was suggestive of drug and/or toxin-related liver failure. The authors assessed the causality as "probably" drug-induced, based on 2 different algorithms.

According to the information given in the follow-up report (Lynch) the 54 years old female patient took Black Cohosh (product not mentioned) for 8 months and was symptomatic for 8 weeks before hospitalized. It is assumed that she developed symptoms (e.g. fatigue, forgetfulness, weight loss) after intake of Black Cohosh for only about 3 months. Assuming that the patient took Black Cohosh for 8 months, the temporal relationship between intake of Black Cohosh and the development of hepatic failure seems to be plausible. The MAH assessed the causal relationship to Black Cohosh as "possible". It is also important to add, that interaction of concomitant fluoxetine, paracetamol and propoxyphene, together with alcohol use, may have contributed to the hepatic failure in this case.

Levitsky et.al (2005) report a well-documented case (RUCAM Score 6). The connection is possible, because the time frame of onset of reaction is related to the drug exposure. The admitted amount of 500 mg drug/day is 12 fold the provided dose of the Commission E Monograph. The reaction is hepatocellular, other causes for acute hepatitis have been excluded. The provisional clinical diagnosis was autoimmune hepatitis. Therapy was started with 60mg prednisone/d for 5 weeks. Liver enzymes improved, but due to worsening coagulopathy and encephalopathy the patient underwent an orthotopic transplantation. In the explanted organ, histologically features of acute hepatitis, fibrous linkage of portal tracts and cholestasis were seen after 5 weeks on corticoids.

## 9. Conclusions

In summary, the connection of herbal medicinal products containing *Cimicifugae racemosae rhizoma* (Black Cohosh, root) and hepatotoxicity should be seen as a signal. The Herbal Medicinal Product Committee would like to draw the attention of the public to the potential serious hepatic reactions that may occur in patients using herbal medicinal products containing *Cimicifugae racemosae rhizoma* (Black Cohosh, root). The HMPC endorse the publication of this assessment document as an Annex to a Public Statement document, in which the following is recommended:

### Advice to patients:

- **Patients should stop taking *Cimicifugae racemosae rhizoma* (Black Cohosh, root) and consult their doctor immediately if they develop signs and symptoms suggestive of liver injury (tiredness, loss of appetite, yellowing of the skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine).**
- **Patients using herbal medicinal products should tell their doctor about it.**

### Advice to healthcare professionals:

- **Health care professionals are encouraged to ask patients about use of products containing *Cimicifugae racemosae rhizoma* (Black Cohosh, root).**

- **Suspected hepatic reactions should be reported to the national adverse reaction reporting schemes.**

## 9. References

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Workshop on the Safety of Black Cohosh in Clinical Studies two cases: case#1= Cohen (2004) Menopause. 11(5):575-577 = DE-03901129;

Workshop on the safety of Black Cohosh in Clinical Studies in Bethesda Maryland, November22, 2004 (see above)