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**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
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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 =>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 Amytriptyline, 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.

#### 4. 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.
4. RUCAM SCORE 5 (possible). Increased liver enzymes serum activities in a patient with pre-existing liver disease of unknown origin suggestive of mild hepatocelular liver injury 5 weeks after starting on *Cimicifuga racemosae rhizoma* (Black Cohosh, root) with positive dechallenge for cimicifuga and atenolol. Concomitant drugs (Flurazepam 15 mg/night + 7.5 mg on demand, partial abuse up to 60 mg/night ; Lorazepam 2.5 mg/d; Lithium 660 mg/tabl from ½ - 2 tbl/day; Atenolol 50 mg/day) might have contributed, as well as patient's underlying diseases (gallstones, psychiatric disorders including intentional self injuries). Risk factors included age over 55 and abuse of benzodiazepines.
5. RUCAM SCORE 1 (unlikely). Increased liver enzymes serum activities and conjugated bilirubin suggestive of cholestatic liver injury 3-4 weeks after starting on *Cimicifuga racemosae rhizoma* (Black Cohosh, root). Patient took diclofenac 100 mg/d orally at the same

time. Positive dechallenge of both cimicifuga and diclofenac products within a few days.

## 5. 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.
2. **Lontos S, Jones RM, Angus PW, Gow PJ. MJA 2003; 179: 390-391.**  
The reported case of acute liver failure resulting in transplantation is associated with the use of a herbal preparation containing several ingredients (5) including *Cimicifugae racemosae rhizoma* (Black Cohosh, root) over a period of three months. The patient took no other medications and had no risk factors for viral hepatitis. Because of the known hepatotoxic potential of Ground ivy (*Glechoma hederacea*: pulegone is one of its ingredients) and the lack of detailed information, it is not possible to conclude that Black Cohosh is the relevant cause of liver failure.
3. **Thomsen M. et al. (2004) MJA 180 (11): 598-600**  
This is a comment on the above reported case of a liver failure resulting in transplantation. The author takes into consideration that the known hepatotoxic herb Ground ivy containing the liver toxin pulegone is much more suspected than Black Cohosh and should have been better analysed.
4. **Whiting PW et al (2002) MJA 177 (8):432-435**  
This is a report about six patients with hepatitis after the use of herbal medicinal products, five patients with jaundice, fatigue and pruritus after intake of herbal combination products without Black Cohosh and one patient with a fulminate hepatitis and liver transplantation related to Black Cohosh.  
Five of them took different combinations of herbs in varied doses. Because of the combination of different herbs that have not been analysed for their constituents and the lack of further information, it is not possible to assess the cause of liver failure. Among these combinations were herbal drugs with known hepatotoxic potential: Greater celandine, Chaparral, and Skullcap (possible adulteration with *Teucrium* species).  
Only one woman developed a liver failure with following transplantation after one week of intake of Cimicifuga. Histologically, an early cirrhosis was seen. A relation to the intake of *Cimicifugae racemosae rhizoma* (Black Cohosh, root) is improbable, because of the short time between intake of drug and transplantation.
5. **Whiting PW et al (2002) MJA 177 (8):440-443**  
The same author covers the same subject. It is not possible to assess whether or not Black Cohosh is the reason for the described hepatotoxic reaction.
6. **Levitsky et al. (2005), Digestive Diseases and Sciences 50 (3); 538-539**  
RUCAM Score 6: probable. 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 60 mg 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.

According to Ref 3-4-5-6-8-9-10-11 BlackCohosh NebraskaCt Testimony1.pdf, page 20/61: the patient admitted in front of court that she drank 1-2 glasses of wine on Fridays, Saturdays and Sundays, which is modifying the data from the publication, where alcohol consumption was denied. As concomitant medication Valtrex (valaciclovir) 1,000 mg ½ tab p.o. daily for over two years, calcium 500 mg 3x1 p.o.daily, ferrosulfate 325 mg p.o. daily and Sudafed (pseudoephedrine) three tablets a week are noted. 4 month before she had stopped taking erythromycin. 9 years before she took ibuprofen in amounts causing an anaemia due to bleeding from a gastric ulcer.

For valaciclovir very rare reversible increases in liver function tests are labelled, for ibuprofen single cases of liver damages especially under long term treatment are labelled. Nevertheless, the gastroenterologist according to Ref 7 BlackCohosh NebraskaCt Testimony2.pdf pages 10/37 ff. did not consider these factors responsible for the liver failure of the patient.

Conclusions for the update 22.12.2006:

Worst case RUCAM Score would be 4 if the comments of the expert would not be taken into account. Because of the clinical experience of the expert and the requested obligatory causality in front of an American court the HMPC prefers to keep the RUCAM Score as 6. Both scorings would not change conclusions, because the case was assessed as an overdose.

7. **Cohen: Hepatitis Associated with Black Cohosh Bethesda Maryland Nov. 22, 2004** Workshop on the Safety of Black Cohosh in Clinical Studies (case #1) = Cohen (2004) Menopause. 11(5):575-577 = DE-03901129; Workshop on the safety of Black Cohosh in Clinical Studies in Bethesda Maryland, November 22, 2004 (see above)

8. **Cohen: Hepatitis Associated with Black Cohosh Bethesda Maryland Nov. 22, 2004** Workshop on the Safety of Black Cohosh in Clinical Studies (case #2)

NOTE: A follow-up of the same ADR was reported in literature: **Lynch CR et al. Fulminant Hepatic Failure Associated with the Use of Black Cohosh – A case Report, Liver Transplantation 12:989-992, 2006.** Subsequently, an expedited follow-up report was reported in June 2006.

RUCAM Score 3 (based solely on the publication of Lynch et al.): possible.

A 54-year-old woman with history of hypothyroidism, fibromyalgia, osteoarthritis and depression had taken 1000 mg black cohosh (no information available) daily for several months. The patient was on fluoxetine, propoxyphene and paracetamol (acetaminophen) concomitantly, moreover, she admitted drinking one or two glasses of wine a day. Known interaction between fluoxetine, propoxyphene and paracetamol is leading to increase of the drugs serum levels that particularly in combination with contraindicated alcohol use may lead to significant hepatotoxic effect. According to Cohen, laboratory diagnostics showed a positive test for hepatitis B surface antibody and a low positive test for Herpes simplex virus IgM. However, according to Lynch et al., no biochemical marker for the cause of her liver disease (including Hepatitis A, B and C serology tests and herpes simplex polymerase chain reaction) could be identified At hospital admission, the patient complained about an 8 weeks history of fatigue, forgetfulness and a 10 pound unintentional weight loss. Laboratory studies revealed an elevated ALAT of 1001 U/L, ASAT of 1014 U/l, Gamma-Gt of 504 mg/dl and Bilirubin of 2.4 mg/dl. All markers for liver disease were negative, liver core biopsies demonstrated severe planlobular inflammation with predominantly lymphocytes, collapse with bridging necrosis and moderate piecemeal necrosis. Prednisolon was started for possible autoimmunehepatitis. By hospital day 15, she developed encephalopathy, ALAT and ASAT increased to more than 2000 U/L, Bilirubin up to 20.6 mg/dl.

The patient underwent orthotopic liver transplantation, but died in the operation room, due to uncontrollable haemorrhage. Postmortem analysis revealed extensive centrilobular and bridging necrosis and severe canalicular and ductular cholestasis.

Since there is no further information on the herbal preparation, the case report is not of great relevance in the assessment of cimicifuga-related hepatotoxicity.

It should be highlighted that the RUCAM Score might change if information provided by Cohen is taken into account. Moreover, his report on the case is partially inconsistent compared with the information provided by Lynch et al.: different data concerning duration of

intake of black cohosh, additional concomitant medication, different information on laboratory evaluation. Because of these inconsistencies, the case report should not be included in the overall assessment.

## 6. Summary

Overall, all discussed cases of literature and pharmacovigilance reports are poorly documented. In many cases there is not even information about the time frame of treatment with Cimicifuga containing products or about the relation to the onset of reaction available. Therefore, they are insufficiently documented according to RUCAM. The Non-EU cases are not validated by a health care professional but reported by patients, as far as coming from the US (Swiss cases are validated):.

With regard to the RUCAM Score points, it can be summarized that

- five cases have to be excluded (RUCAM Score range between 0 and -2);
- eight cases are unlikely (RUCAM Score range between 1 and 2)
- three cases can be classified as possible: RUCAM Score 5, 4 and 3
- two can be classified as probable. RUCAM Score 7 and 6

In terms of similarities, disregarding the RUCAM Scores, there are two cases of autoimmune hepatitis, one of Type I (ANA ASMA) (EU case n. 5), and one case (EU case n. 23) with weak ANA and ASMA, but massively elevated Ca19-9 (533kU/l normal <36kU/l), but they are all not assessable due to a lack of information about the time of onset of reaction related to drug exposure.

Cohen, Stanley M. MD et al. (2004), case 1, report the best documented case (RUCAM Score 7). A 57-year-old multimorbid woman with a history of polymyositis had developed an autoimmune hepatitis about three weeks after the first intake of Cimicifugae racemosae rhizoma (Black Cohosh, root) (brand and dose unknown; no information if it was a combination product). After cessation of the drug and commencement of a therapy with steroids and azathioprine, the patient recovered. The autoimmune hepatitis could have been as well a manifestation of a multisystem autoimmune disease. According to the draft recommendations of the Scientific Advisory Panel Subgroups on Hepatotoxicity (2004), the case would be classified as idiosyncratic liver necrosis (criteria page 12).

Case n. 8 presented in Section 5 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 60 mg 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.

According to Ref 3-4-5-6-8-9-10-11 BlackCohosh NebraskaCt Testimony1.pdf page 20/61, the patient admitted in front of court that she drunk 1-2 glasses of wine on Fridays, Saturdays and Sundays, which is modifying the data from the publication, where alcohol consumption was denied. This is very close to hepatotoxic risk amount of chronic alcohol intake (more than 7 units per week for women). As concomitant medication Valtrex (valaciclovir) 1,000mg ½ tab p.o. daily for chronic herpetic infection over two years, calcium 500 mg 3x1 p.o.daily, ferrosulfate 325 mg p.o. daily and Sudafed (pseudoephedrine) three tablets a week are noted. 4 month before she had stopped taking erythromycin. 9 years before she took ibuprofen in amounts causing anaemia due to bleeding from a gastric ulcer.

For valaciclovir very rarely reversible increases in liver function tests are labelled, for ibuprofen single cases of liver damages especially under long term treatment are labelled. Nevertheless, the gastroenterologist according to Ref 7 BlackCohosh NebraskaCt Testimony2.pdf pages 10/37 did not consider these factors responsible for the liver failure of the patient. Chronic herpetic infection might have contributed to the hepatic failure.

Worst case RUCAM Score would be 4 if the comments of the expert would not be taken into account. Because of the clinical experience of the expert and the requested obligatory causality in front of an American court the HMPC prefers to keep the RUCAM Score as 6. It is recognised that the data the patient reported during the hearing do not fulfil requirements of unbiased medical history. The questions clearly aimed at shedding doubts over the causal relationship between the liver failure and the intake of Black cohosh. This would not change conclusions, for the case was assessed as an overdose.

## 7. Adverse drug reactions from clinical studies

From overall 15 clinical studies (controlled clinical trials and post-marketing studies from 1983-2005) only two covered laboratory controls of liver function. The controlled dose finding trial of Wober (1997) lasted over 6 months with 152 patients and revealed no liver damages in both dosage groups (127 mg drug daily/39 mg drug daily). Some of the patients started with slightly elevated enzymes without increase within half a year. The placebo controlled study of Osmers (2004) covered three months with laboratory controls covering liver dysfunction in 134 patients (PP) receiving 40mg drug daily. 4 patients started here as well with slightly elevated transaminases (<50 U/l) under verum and under placebo without significant differences between beginning and end of the study and in between both groups. Overall, in 15 clinical studies no case regarding significant liver dysfunction was observed.

It should be noted that long term safety of *Cimicifuga racemosa* rhizome was not studied.

## 8. 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 HMPC 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.**

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