

This is a translation from the original German-language document, as downloaded from the following link:
http://www.bfarm.de/de_ver/arzneimittel/amrisiken/stufenplan/Besch-Kava-Final.pdf.

Translation by: Petra G. Hartmann, 10920 West 65th Way, Arvada, CO 80004 (303) 422-3474, petra@industriallabs.net
BfArM: Bundesinstitut fuer Arzneimittel und Medizinprodukte / Federal Institute for Drugs and Medicinal Products

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Bonn, June 14th, 2002

Rejection of Drug Risks, Step II

As related to: Kava-Kava (*Piper methysticum*)-containing, and kavain-containing drugs, including homeopathic preparations with a final concentration up to, and including D4.

Reference: Hearing document of Step II, dated August 11th, 2001

Medications: see attachment

Dear Ladies and Gentlemen,

With this, we are giving the following

Notification

1. The permits for the above-mentioned medications are withdrawn, effective immediately. As per § 30, section 3, clause 2, AMG, this order can be executed immediately.
2. For the affected medications, an immediate recall is ordered, as per § 69, section 1, clause 2, number 4, and clause 3, AMG.
3. Not affected by these measures are
 - Medications, which are produced using a process technology that is described in the homeopathic section of the Medication Code and that contain Kava-Kava preparations whose final concentrations are less than the fourth decimal potency.
 - Medications, which are produced in a "spargyric" process technology as per Zimpel (Regulation 25 and 26).

Justification:

This order rests on the regulations of § 30, section 1 i.V.m. § 25, section 2, number 5, as well as § 39, section 2, number 4 of the Medication Laws dated August 24th 1978 (BGBl S. 2445), last

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changed through article 3 of the second law for the Change of the Medicinal Products Law (2. MPG-AendG) dated December 13th 2001 (BGBl. I S. 2704) - AMG-.

On the basis of the documents and results available to us, the Federal Institute for Medications and Medicinal Products does not consider the continued commerce of the above-mentioned medications as defensible, because justified suspicion exists that these medications when used as indicated can have harmful effects, and that these effects, are in excess of the justifiable norm as based on medical science known today, according to § 5, section 2 und § 25, section 2, number 5, AMG. The order of the above-named measures is thus necessary to avoid the possible dangers associated with the use of the above-named medications.

1. Risks associated with the use of Kava-Kava- and kavain-containing medications

Kava-Kava- and kavain-containing medications are able to induce major hepato-toxic reactions, which exceed the justifiable norm as based on medical science known today. These risks are not balanced by sufficiently documented therapeutic efficacy. This can be determined on the basis of information from several sources.

1.1 Domestic spontaneous reports

1.1.1 Undesirable effects on the liver

BfArM has evidence of a total of 39 spontaneously reported suspect cases of undesirable medication effects (**UAW**) with liver involvement that relate to Kava-Kava- mono- and combination preparations, of which 3 cases ended in death.

The spectrum of hepato-toxic effects ranges from transitorily elevated liver enzyme values and jaundice to cholestatic and necrotic hepatitis to hepatic coma with hepatic failure and necessary liver transplant. Approximately half of the cases are well documented, the other half are not sufficiently documented for a detailed evaluation.

1.1.1.1 Spontaneous reports with well-documented serious UAW's

Following we will elaborate on those cases involving serious side effects on the liver (n=18) for which clinic documentation, liver histology, and physician's reports are available and for which a well-founded causality evaluation is possible. In this report we have divided these cases into those reported to the BfArM prior to, and those reported after the hearing document of November 8, 2001.

1.1.1.1.1 Reports known to the BfArM prior to the hearing document

1. BfArM 93015209: Medication hepatitis caused by Kava-Kava-containing medications

39-year old female patient. Hospital admission due to nausea, upper abdominal discomfort, loss of appetite, jaundice. Symptoms appeared 12 weeks after ingestion of 3 x 1 capsule Laitan® 100 (Challenge). No allergic disposition, no history of alcohol. Liver histology: drug-induced toxic hepatic damage.

Known co-medication: oral contraceptive (OC; in this case ethinylestradiol/levonorgestrel). The pharmaceutical manufacturer (pU) additionally asserts the use of diazepam as needed. This could not be supported by the primary report or through the clinic physician's report. Following discontinuation of Laitan® a reverse tendency and normalization of transaminase values and jaundice (Dechallenge positive).

Case Evaluation by pU and Associations

The pU [1] in his position paper does not pursue a possible Kava-Kava causality, but rather only comes to the conclusion that "...two of the medications used concurrently by the patient have the potential of hepatic toxicity". The position paper by the Association arrives at the same conclusion [2]. It finds it questionable that the cause is assigned to Kava-Kava, given the asserted co-medication with diazepam and the oral contraceptive.

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Case Evaluation BfArM

The co-medication with oral contraceptive should not be considered cause for the hepatic toxicity, because the patient used hormonal contraceptives for a 16-year period prior to the above-mentioned UAW's. During this time no side effects as related to liver function were determined that could be attributed to the contraceptive. The diazepam medication, which the pU and the Associations listed as a possible reason but which apparently and in reality was not even taken, can also be ruled out as an alternative cause, due to the fact that it was only used as needed and did not exhibit the Dechallenge pattern, as was the case with the UAW and the OC-use. This pattern only exists in relation to the Kava-Kava ingestion. Because Challenge and Dechallenge match and no alternative causes can be identified, the causal connection can be viewed as probable. This also agrees with the assessment rendered in the discharge report of the hospital.

2. BfArM 94006568: Severe toxic liver parenchyme damage

69-year old female patient. Ingestion of Laitan® 100 2-3 x 1 capsule for depression over a period of 2 years. Additional co-medication with St. John's Wort (Neuroplant®) for the past year, and Maaloxan as needed. Hospital admission with idiopathic jaundice with elevated levels of bilirubin, SGOT, SGPT, and gamma-GT. Liver biopsy showed a severe, toxic cholestatic hepatic parenchymal damage.

Case Evaluation by pU:

The firm [1] does not see a causal connection between Kava-Kava medication and toxic liver reaction, because the time period between ingestion and reaction was unusually long; in fact longer than the period between Hypericum ingestion and the reaction.

Case Evaluation BfArM:

The argument of the manufacturer regarding the co-medicated St. John's Wort as also hepato-toxic, is not plausible. Neither in Martindale's "The Complete Drug Reference" or in Hager's Handbook (2001) or Meyler's Side Effects of Drugs" or in other literature searches can any reference be found to hepatotoxic effects of St. John's Wort.

The elapsed time period between initial ingestion of Kava-Kava and the occurrence of the event (2 years) may be longer than the "average" 5-90 days claimed by the manufacturer, but this fact weighs only partially in light of the fact that other causes (inherent disease, co-medication) are not present. This case is thus classified as a possible causal connection with Kava-Kava.

3. BfArM 94901308: Acute hepatitis with jaundice

50-year old female patient. After a 6-week period of ingesting Laitan® 100 (3 x 1 capsule) (Challenge) an acute toxic hepatitis developed. No history of alcohol. Co-medications: furosemide, atenolol, terfenadine.

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Liverbiopsy: the histological picture supports a drug-induced hepatitis.

Case Evaluation pU:

The manufacturer arrives at the conclusion [1] that the histology of the liver tissue (drug damage of the hepatitic type) also gave evidence of a long-term hepatitis, which means that the liver damage could possibly have been present prior to the application of Kava-Kava. The acute damage was caused by the co-medication.

Case Evaluation BfArM:

It is unfortunate that the critical pathological evaluation did not include a statement about the earlier case of Hepatitis A. The etiology of the current hepatitis cannot be resolved without doubt due to the anamnestic allergic state, which was also noted by the industry association [2]. It can be determined, however, that the patient did not have clinically apparent liver anamnesis up until the time of Kava-Kava ingestion and that current immunological and serological laboratory data do not indicate an auto-immune hepatitis.

The co-medications furosemide/ atenolol/terfenadine, presented as “potentially hepatotoxic” by the pU, must be considered individually: no hepato-toxicity has been shown for furosemide. The beta-blocker atenolol had been tolerated for 5-6 years without any significant UAW's. After an initial discontinuance during the acute phase, it (atenolol) was placed into use again while still in the hospital, and the liver values continued to drop (Dechallenge). It is unlikely that the hepatic reaction was caused by the antihistamine terfenadine, as the medication has been tolerated well for 12 years. At a minimum, this medication was apparently not acting “above threshold”, so that at the most it could have contributed to the manifestation of the hepatic reaction from the additional Kava-Kava medication.

Because Challenge and Dechallenge were positive and because no alternative causes are apparent, the causal connection is categorized as probable.

4.BfArM 98004297: Hepatic failure followed by death

81-year old female patient. Presented with generalized jaundice three months after ingestion of Kavatio® (120 mg daily of Kava-Kava extract). Co-medication with hydrochlorothiazide and Crataegus-extract.

Admitted to hospital due to acute cholestatic hepatitis. Laboratory: limited synthesis of coagulatory proteins. Condition worsened in spite of immediate intense medical measures, reaching a state of acute hepatic failure. Complications due to subarachnoid bleeding. Patient died three days after admittance. Autopsy showed an acute hepatic dystrophy with massive hepatic cell necrosis as the base for a histologically proven toxic hepatopathy.

Case evaluation by pU and Association:

In their statement, the Associations and the pU come to the conclusion that in this fatality a pre-damaged liver due to alcohol abuse cannot be ruled out, and that the causal connection to Kava-Kava is either unlikely[2] or questionable[3], i.e. cannot be evaluated [4], or in any case, based on the autopsy, they conclude that the patient died due to alcohol consumption "....*but in any case, death was due to liver failure.*"

Case evaluation BfArM:

This line of reasoning cannot be followed by BfArM. The physician's report explicitly mentions that the patient did not abuse alcohol. Although the autopsy report shows residues of chronic pancreatitis, no alcohol-typical results are present and nothing suggests that the severe liver atrophy (weight 570 g) can be attributed to a possible alcohol noxe(?).

The listed co-medication (hydrochlorothiazide / Crataegus extract) has not been associated with a fulminating liver toxicity as occurred in this case. Three months prior, the patient had been accepted into the SCOPE-study (Candesartan vs. placebo, patient in the placebo group). From this, it follows that the admittance studies did not show any liver function disturbances or correlating clinical signs.

BfArM considers the causal connection to Kava as probable. In their final critical evaluation the attending physicians as well came to the determination that "..*the side effects of the other medications could not be reconciled with the disease state.*"

5. BfArM 99006005: Acute toxic necrotizing hepatitis

33-year old female patient. Admitted to hospital with acute hepatitis 4 months after ingestion of Kavatino® capsules with 60 mg kavapyrone (3 x 1 per day) and co-medication of Cisaprid (Propulsin®, 3 x 1). No alcohol abuse or other documented risk factors. Liver histology: extended toxic damage of hepatic parenchyma. Based on the presence of antibodies, the first stage of autoimmune hepatitis can be assumed. After high-dose treatment with corticoid medication, the liver parameters normalized.

Case Evaluation BfArM:

Because Kava-Kava and Cisaprid were taken concurrently (the start and duration of ingestion are almost identical), it is impossible to assign the hepatotoxic effects to one of the two medications. The cause of the hepatitis is due to ingestion of Kava-Kava or Cisaprid, according to the hospital report.

The causal connection between Kava-Kava medication and hepatotoxicity can be viewed as probable in the sense of triggering or co-involvement together with Cisaprid.

6. BfArM 99006200: Elevated transaminase activity, suspicion of acute hepatitis

35-year old female patient. Because of symptoms of depression, 1 x 1 Tbl Antares® 120 mg per day. After 3 months, elevation of transaminases, suspicion of acute hepatitis. Concurrently with Kava-Kava, administration of a Hypericum preparation (2 x daily). Transaminase levels reversed after discontinuation of medications.

Case evaluation by pU:

The pU [4] themselves evaluate the causal connection between the occurring undesirable reactions and Kavapyrones as likely and adds in their statement "..*however, a medication polytherapy (Rose of Sharon preparation) existed, which could have contributed two or also caused the development of a toxic liver disease.*"

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Case Evaluation BfArM:

As was already stated in the discussion of BfArM No. 94006568, the lack of data or evidence that attributes liver toxicity to Hypericum applies here as well. Because of this, Kavapyrones are to be considered the sole cause of the hepatotoxic reaction in this case. Because Challenge and Dechallenge are positive, and alternative causes cannot be determined, the BfArM evaluation of causal connection is: probable.

7. BfArM 00005994: Fulminating liver failure with hepatic transplant

50-year old female patient. Ingestion of 60 mg daily of kavapyrones over a time period of seven months. Following this, icterus with bilirubin values of approximately 400 µmol/l and transaminase values of 1000 U/l. An initial liver biopsy showed liver cell necrosis affecting approx. 45% of the organ. Based on subsequent clinical worsening, urgent registration for liver transplant. A transjugular liver biopsy prior to liver transplantation showed evidence of only 15% sustained liver cells with continuing toxic cell damage. After occurrence of hepatic coma, an orthotopic liver transplantation was done. Post-surgically, a marked improvement of overall condition without considerable complications was noted.

The patient's co-medications included hormone replacement therapy (estradiolvalerat / levonorgestrel), as well as Metformin and Glimepirid.

Case Evaluation by the Associations:

Although the Associations [2] in their statement discuss the certainty of some of the reported data and other possible, but not stated, potential causes and the "late" diagnosis, they do finally come to the conclusion that histological proof of a causal relation indeed exists.

Case evaluation BfArM:

The concurrent application of Kava-Kava with the above-mentioned co-medication complicates the assignment of the liver-damaging effect to one of the medications, because all of the medications possess hepato-toxic properties.

Kava-Kava, however, is considered to be the probable initial trigger of the fulminating liver failure with subsequent liver transplant of the patient, according to the attending and reporting physician's from the Transplant Center Rostock, which published this case [27]: "...histological evidence of a connection between the liver changes and ingestion of Kava after exclusion of other causes." BfArM also considers it probable that Kava-Kava caused the toxic liver changes, at least in the sense of a synergistic effect with the co-medication.

8. BfArM 00008627: Fulminating liver failure with transplant

23-year old female patient. Acute liver failure after medication with Antares® 120 mg, 2 x 1 Tbl, for 4 months, which necessitated a transplant. This was initially successful, but then viral hepatitis occurred. The patient died. Histopathology: massive liver necrosis with extensive destruction of the liver parenchyme.

The patient had an inconspicuous internal anamnesis, hepatitis serology and tests for Wilson's Syndrome were negative, a portal fibrosis and cirrhosis were ruled out. Patient was under Physician's care during the Kava-Kava medication.

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Co-medication with Rizatriptan (as needed), as well as a contraceptive (ethinylestradiol + norgestimate) followed. The initial course of the case was published as an abstract [26], the fatal conclusion of the case was not known yet at the time of publication.

Case Evaluation by pU and Associations:

The pU [4] points out that 240 mg is the twice the recommended daily dose. Additionally they discuss a preexisting infection with Cytomegalo-Virus. In their statement, the pU [5] also asserts, that in this case, a regular consumption of pain medication (with hepato-toxic effects) took place.

The statement by the Associations [2] also speculates about accompanying self-medication for migraine and symptoms of anxiety, with a potential for hepatotoxicity on its own or as a potentiator.

Case evaluation BfArM:

The reference to the elevated dose on the part of the pU is correct, however, this does not rule out a causal connection between Kava-Kava medication and the hepato-toxic reaction, but rather shows that higher doses of Kava-Kava can cause higher hepatotoxicity. The possible prior Cytomegalo-virus infection discussed by the pU, causing either primary or additional viral liver damage, occurred only after the transplant. Accordingly the physician's report reads: "... *in spite of an initially successful transplant, the course was unfortunately complicated by multiple complications of the LTX. Recidivating soft-organ infections were joined by various opportunistic infections under immune suppression (PCP, CMV, invasive aspergillosis)...*"

An interaction between Kava-Kava and Rizatriptan on cytochrome P450-2D6-isoenzyme with subsequent elevated Kava-Kava concentrations and potentiated hepatotoxicity cannot be ruled out. However, no supporting positive pharmacokinetic proof exists. The continuous therapy with Rizatriptan suspected by the pU and the Associations has no basis as well: Documentation clearly demonstrates that this medication was only used as needed.

On the basis of the chronological connection between Kava-Kava medication and the occurrence of hepatotoxicity, the causal connection between Kava-Kava medication and hepatotoxic reaction is evaluated as possible to probable.

9. and 10. BfArM 01003950/51: Reoccurrence of Kava-Kava induced hepatitis. (Re-exposure)

56-year old female patient. In 1993 and also in January of 2001, elevated asymptomatic transaminase activities were determined following ingestion of Kava-Kava-containing medications (positive Rechallenge). The co-medications in 2001 included various cold medications, L-thyroxine, estradiol patches, omeprazol, Candesartan and Losartan. The disease state normalized with glucocorticoid therapy.

A liver biopsy raised suspicion back in 1993 of a drug-induced toxic genesis. Another liver biopsy was done in March of 2001. The histological report clearly established a drug-induced toxic damage to the parenchyma. Indicators of HCV-, CMV- or EBV-infection were absent, and antibody tests for ANA and dsDNA were negative.

Case evaluation by pU and Associations:

The pU [4] judged the causal connection to be probable. Another pU [5] and the Associations [2] however, expressed doubt regarding the re-exposure.

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Case evaluation by BfArM:

This involves an assured positive re-exposure, with the limitation that the Kava-Kava product ingested in 1993 cannot be named. Doubts regarding the re-exposure are removed by the re-evaluation of attending physicians (see epicrisis(?) dated June 12, 2001 by Prof. Layer in the final report) and the patient letter dated July 13, 2001.

The co-medications are dominated by cold medications lacking hepatotoxic effects (acetylcysteine, dolo-dobendan®, Otriven®, Pimafucin®, Salviathymol®) and thus do not play a role in the causality discussion.

Further co-medications used by the patient included omeprazol (as needed), Candesartan (ended 5 months prior to the event), Losartan/HCT, as well as L-thyroxine® and an estradiol patch; all medications for which liver-damaging side effects have been described. However, these medications differ from Kava-Kava in that none had a positive re-exposure. It is possible though, that the co-medicated preparations for which hepato-toxic effects have been described could have led to an additive effect. None of the medications were contraindicated for use with Kava-Kava, however. In light of the fact that re-exposure with Kava-Kava led to a second incident of the hepato-toxic reaction, we find the causal connection of this UAW with Kava-Kava medication to be certain.

11. **BfArM 01006229:** Severe necrotizing hepatitis with liver transplant.

32-year old male patient. After ingestion of 2 x 1 Tbl Antares® 120 mg for 3 months, a severe necrotizing hepatitis with highly pathological transaminase- and bilirubin values around 300 µmol/l. Co-medication consisted of a Valerian root preparation (occasional). Previous liver disease is unknown.

A viral hepatitis and autoimmune hepatitis were ruled out by serology. Liver damage due to disturbances with copper, i.e. iron metabolism could not be demonstrated. Upon time of hospital admittance a reduced synthesis capability (Quick value 49%) with a progradient course was already present. The liver transplant was followed by transplant failure due to occlusion of the aortic interponate (thrombosis of the arteria hepatica); a re-transplant was successful. Histology of the removed liver showed a markedly advanced fibrosis, bridging parenchyme necrosis, as well as lobe-centralized necrosis.

Case evaluation by pU and Associations:

While the Phytopharmaca Cooperative [3] considers the connection with Kava-Kava administration as probable, pU [4] points to the high dose of 240 mg kavapyrones. The Associations[2] feel that the case information is partly insufficient and does not allow for a conclusion. In addition the statement by the Associations speculates regarding questionable co-medications (*"...experience shows that especially panic disorders generally go hand-in-hand with part long-term, part multiple treatment attempts by the patient him/ herself and by physicians."*)

Case evaluation BfArM:

A viral hepatitis as well as autoimmune hepatitis was ruled out. A relevant basic disease was not present, and, in contrast to the speculation on the part of the Associations regarding further co-medications, the Valerian root extract was only administered as needed. This preparation is not even hepato-toxic. In light of the fact that BfArM and the evaluators had access to detailed documentation in the form of Physician's reports from the treating hospital with detailed laboratory- and diagnosis reports

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1.1.1.1.2 Reports received by BfArM after the Hearing Document

12. BfArM 01006939 Severe necrotizing hepatitis

36-year old male patient. Developed necrotizing hepatitis after a 6-week period of ingestion of 1 x 1 Tbl. Laitan® (100 mg) which could be treated conservatively.

With the exception of pneumonia (6 years prior) no previous diseases of the liver and no co-medications were known. A liver histology confirmed the presence of necrotizing hepatitis with a toxic damage pattern. A viral genesis and autoimmune disorders were ruled out and no indications of other toxins were present.

Case Evaluation by BfArM:

Based on the well-documented clinical file, which show the absence of co-medications and other risk factors and in agreement with the histological report, a causal connection is considered probable regarding Kava-Kava medication.

13. BfArM 01010536: Acute necrotizing hepatitis with signs of liver failure.

45-year old female patient. After a period of several months of daily ingestion of 1 Tbl. Maoni® 120 mg, a diagnosis was made of acute necrotizing hepatitis with signs of hepatic failure.

With the exception of an occasional co-medication with an artichoke-preparation, the patient had not received any co-medications in the previous 4 months. Excessive alcohol consumption was not present. The results of serological testing were negative. After discontinuation of the Kava-Kava preparation the patient was released with an overall improved condition.

Case Evaluation by the pU:

The pU only noted that "...this singular case should be classified as an UAW", but does not evaluate the causality any further.

Case evaluation by BfArM:

In light of the chronological connection between the Kava-Kava preparation and the hepato-toxic reaction, the improvement of condition after discontinuation of the preparation (Dechallenge) and missing alternative risk factors, the causal connection between the Kava-Kava preparation and the undesirable medication effect is considered probable.

14. BfArM 02000370: Symptoms of liver cirrhosis

50-year old female patient. Worsening of general condition following a 3 ½ month ingestion of 2 Tbl daily of Antares® 120 mg for depression. After admittance to the hospital, a diagnosis was made of liver cirrhosis with Child-Pugh classification A (5 points). Infection and autoimmune disorders were ruled out. Co-medications were determined to be a long-term estradiol/levonorgestrel preparation and Cylandelat (for migraine interval treatment). After discontinuation of all medications the overall condition improved slowly, and further data regarding the clinical course are still being determined at this time.

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Case evaluation by pU:

The pU [4] evaluates the factual contents of the case as "...based on the lack of significant data, causally several risk factors for the development of liver disease are joined together" , in spite of the fact that the patient showed no prior problems of possible side effects related to her, in part long-term co-medication, and cites, additionally to the estradiol-medication, the elevated Kava-Kava dosage, medication interaction possibilities, a possible acute migraine treatment, and a potential earlier professional mercury exposure.

Case evaluation BfArM:

The interaction possibilities cited by the pU are speculations without any basis, the migraine treatment is not documented, and the earlier mercury exposure is not assured. From the existing documentation it is clearly determined that the patient showed no earlier possible side effects from her existing medication prior to the Kava-Kava ingestion. The time period of 3 ½ months is surely too short for the development of liver cirrhosis; the evaluation for the causality determination can thus only be based on the acute manifestation of clinical symptoms. Under consideration of the fact that an infection and autoimmune disorder were ruled out during the hospital stay, the manifestation of the undesirable medication effects must be assigned to the Kava-Kava medication, even if one assumes liver damage without clinical manifestation from the estradiol preparation. Causality is thus considered probable in the sense of a joint involvement, and possible in the sense of sole cause. The dosage of 2 x 120 mg was higher than the upper limit (120 mg) of the range stated in monographs.

15. **BfArM 02001414**: Drug-induced acute hepatitis

46-year old female patient. Development of sclerenicterus with elevated transaminase values after a 4 week period of ingesting Antares® (360 mg daily). With appropriate treatment the liver values declined again. No co-medications. Hepatitis A, B, and C, as well as Epstein-Barr virus were ruled out serologically. Cytomegalo IgG was present in the threshold range, the presence Cytomegalo IgM was not detectable.

Case evaluation by the pU:

In their statement, the pU [4] comes to the conclusion that the available information points to a probable causal connection to the ingestion of the Kava-Kava preparation.

Case evaluation by BfArM:

Due to the existing chronological connection and the positive Dechallenge reaction, lack of any co-medications and exclusion of other causes, the causal connection is judged to be probable. The dosage was markedly above the range given by monographs (upper limit 120 mg), indication of low therapeutic breadth.

16. **BfArM 02002090**: Elevated transaminase activity

Female patient of unknown age. Preexisting condition of Bechterew's Reflex. Massive elevation of transaminase activity following ingestion of 4-6 capsules daily of Kavasedon® over a time period of approx. 1 week, leading to hospital admission. The liver enzyme values normalized after discontinuation of the Kava-Kava preparation as well as discontinuation of all co-medications (Sulfasalazin, Diclofenac, Buscopan as needed, Medroxyprogesterone, Omeprazol). Normal liver values were determined after re-exposure to Sulfasalazin, Diclofenac and Omeprazol for treatment of Bechterew's Reflex.

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Case evaluation by pU:

The pU [8] judges the UAW as due to Diclofenac ("....suspected NSAID-transaminitis due to Diclofenac. ").

Case evaluation by BfArM:

The active ingredient of Buscopan, butylscopolamine, is unremarkable as related to UAW's on the liver. As far as Medroxyprogesterone is concerned, its hepatotoxicity is considered not marked. Damage from this medication also would manifest itself more as a cholestasis (elevated bilirubin) than as damaging to hepatocytes (with transaminase elevation). This is why the existing reports do not fit the UAW-pattern of Medroxyprogesteron. In the face of positive Challenge- and Dechallenge reactions with regard to the Kava-Kava preparation, the absence of an effect after Sulfasalazin/Diclofenac/Omeprazol re-exposure, and other not recognizable alternative causes, the causal connection between the ingestion of the Kava-Kava-containing medication and the symptoms of illness by the patient should be classified as possible to probable.

17. **BfArM 02002378:** Hepatic failure followed by death after transplant

61-year old female patient. Fulminating hepatic failure after ingestion of a Kava-Kava-containing medication (120 mg per day) for a period of 12 weeks. Hospital admittance, during which multi-organ failure occurred. After an initially successful liver transplant, multiple complications developed that eventually led to the death of the patient.

Case evaluation BfArM:

The causal connection between Kava-Kava ingestion and the liver failure eventually leading to death is considered to be probable by BfArM, because the UAW occurred approx. 12 weeks after ingestion began and because the accompanying medications (Omeprazol, Cholspasmin, Gingko-biloba extract) had been taken for a long time (some for as long as 10 years) without any side effects.

The physicians of the Clinic Rechts on the Isar in Munich evaluate the causal connection the same ("..very likely").

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18. **BfArM 02003010:** Liver failure with hepatic encephalopathy of the first degree

40-year old female patient. No significant prior illnesses. Ingestion of Kava-Kava-containing medications for 6 months, possibly at an elevated dosage. Then increasing intolerance of food, discolored stools (for approx. 10 days prior) and dark urine. Hospital admittance. Initial laboratory parameters showed a bilirubin level of 25 mg/dL, elevated transaminase levels (SGOT 720, GPT 620), ammonia level of 125 mg/dL and a Quick-value of 33%. Beginning useage(?) -coagulopathy, hepatic encephalopathy of the first degree. Serological examinations for antibodies (HAV, HBV, HCV), CV-PCR and Cytomegalo-virus-antibodies were unremarkable. The patient was placed on the transplant list with fulminating liver failure.

Case evaluation BfArM:

BfArM is currently in the process of trying to obtain additional information regarding co-medications and the course and outcome of the UAW. On the basis of currently available documentation the ingestion of Kava-Kava-containing medication (in this case Kavasporal®) is considered to have been at least possible as the cause of the liver failure.

1.1.1.2 Spontaneous reports of UAW's considered not severe.

In addition to the reports of UAW's shown above, 21 other reports of less-severe liver disorders have been received, of which two occurred following ingestion of Kava-Kava-containing combination preparations. With regard to a causality connection, the majority (14) of cases were evaluated as "possible", two as "unlikely", and five reports were not evaluated on the basis of insufficient documentation.

1.1.2 Spontaneous reports of UAW's affecting other organ systems

BfArM has had reports of side effects on other organ systems in addition to the UAW's affecting the liver-bile system, especially urticaria, skin rashes of varying severity, vision problems, tachycardia, dizziness, dyspnea, and agitation.

1.2 Published case reports from Germany

The occurrence of liver cell damage from Kava-Kava preparations has been displayed in several publications and casuistries.

1.2.1 Strahl et. al. [12]

Described are the anamnesis and course of liver damage of a 39-year old female patient without any remarkable prior illnesses, who was admitted to the hospital due to elevated transaminase values following ingestion of a Kava-Kava preparation. The co-medication (an ovulation-inhibitor with desogestrel/ethinylestradiol) had been used for 6 years without any side effects, in addition the patient occasionally used St. John's Wort and various other anti-depressants. Liver biopsy showed a marked diffuse and necrotizing hepatitis. After discontinuation of all medications the transaminase values at first continued to rise, and hepatic insufficiency developed. After 7 days the transaminase values reversed and then became fully normal. After 2 weeks another transaminase elevation occurred. A detailed medication history showed that the patient ingested kavapyrones again, this time without any co-medications. After discontinuation of this renewed kavapyrone medication ingestion and without further specific therapy the patient was released clinically improved.

The authors feel that kavapyrones were responsible for the necrotizing hepatitis as an exogenic agent. Supporting data for this includes the changes in transaminase values with complete normalization in a chronologically tight correlation with the

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start, end, and renewed start time of Kava-Kava medication. Because of this the authors assume a causal connection. Even though synergistic effects are possible from the concurrent ingestion of other potential hepato-toxic preparations, in this case ovulation inhibitors, the second bout of hepatitis after re-exposure to Kava-Kava-containing medication by itself supports the causal connection theory.

The pU [4] judges the causal connection in this case as probable and talks about the positive re-exposure. The pU [5] is basing his evaluation on a well-documented suspicious case in which a causal connection existed between ingestion of a Kava-Kava-containing medication in conformance with monograph-recommended dosages, although in combination with other medications. BfArM is in agreement with the assessment that the causal connection can be viewed as certain, at least in the sense of an additive effect together with the ovulation-inhibitor.

1.2.2 Kraft et.al.

The report involves a 60-year old female patient who was admitted to the hospital due to weight loss and jaundice following therapy with a Kava-Kava preparation (Antares® 120 mg in changing dosage concentrations over the course of 1 year). Alcohol use was denied. Co-medication consisted of occasional ingestion of Etilefrin-HCl and Piretanid. Laboratory reports upon admittance: sharply elevated transaminase values (GOT and GPT >1000 U/l) and strongly reduced liver synthesis ability (Spontaneous Quick value of 23%, PTT of 57 s, antithrombin III not measurable, fibrinogen level <80 mg/dL). Because of progradient encephalopathy, respiratory insufficiency requiring intubation, and strongly decreasing liver synthesis capability, a liver transplant had to be executed. Hepatitis serology, as well as HIV, Cytomegalovirus, Epstein-Barr Virus, Herpes simplex and Varicella-Zoster diagnostics, and results from the determination of anti-mitochondrial antibodies and antibodies against microsomal antigen of liver and kidney were all negative. There was no evidence of a₁-antitrypsin deficiency or copper or iron metabolic disorders. Liver histology gave the result of an extensive, partly confluent hepato-cellular necrosis with intra-hepatic cholestasis, but no grounds for a cirrhotic change.

The authors come to the conclusion that "*... on the basis of the existing results...a causal connection between the fulminating hepatic failure and the ingestion of the phytotherapy Kava-Kava must be assumed*". However, they add that it cannot be ruled out with certainty that co-medication with Piretanid played a role as a possible cofactor in the pathogenesis of the coma induced by hepatic failure. The pU [5] judges the causal connection with Kava-Kava as "*possible*". BfArM considers the causal connection as probable in light of the chronology and the lack of alternative causes (Piretanid has not been considered hepatotoxic).

1.3 Summary of the cited UAW-reports (Spontaneous reports / Literature reports from Germany)

As a total, we are currently overseeing 41 cases of liver-toxic reactions that occurred in Germany. Twenty of these had sufficiently good documentation allowing for a well-based causality evaluation, of these, 18 were spontaneously reported and 2 were from literature.

Among the 20 cases the hepato-toxic reaction was so severe in seven cases, that a liver transplant was necessary. Two of these seven patients died in spite of this (Case 8 and 17). In addition, another female patient died, who did not have a liver transplant. (case 4).

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In two cases (Spontaneous report 9/10 and the case published by Strahl) the liver toxic reaction reversed itself after discontinuation of the Kava-Kava preparation and occurred again after re-exposure, so that the causal connection can be considered sure according to standard criteria. With 12 spontaneously reported cases and the case published by Kraft, a causality nexus to the Kava-Kava treatment must be assumed based on a clear chronological connection between the start of Kava-Kava medication and the occurrence of symptoms or pathological changes (Challenge), the recidivation of liver disease after discontinuation of Kava-Kava medication (Dechallenge) and / or the absence of liver toxic factors such as a co-medication that could be considered a sole alternative cause. In a few of the twelve cases a synergistic involvement of other medications (for instance an estrogen) is considered possible, but this does not justify the assumption that Kava-Kava medications were not involved with the hepato-toxic reaction.

The chronological connection between the beginning of Kava-Kava medication and the occurrence of a hepato-toxic reaction showed a characteristic distribution: In those 15 cases where the time course was described in sufficient detail, the latency was 3-4 months in 9 cases, in 3 cases the latency was shorter and in 3 cases the latency was longer.

The dosage of the Kava-Kava extracts i.e. substances was not clearly described in three of the 18 spontaneously reported cases, in six cases the dosage was within the range of 60-120 mg/day recommended by the monographs, in one case it was below, and in eight cases above.

Under the assumption that the majority of patients treated with Kava-Kava preparations remained within the recommended standard dose, which was only exceeded by a minority, the distribution of the reported cases on to the two exposure groups shows that the assumption of a higher risk of liver toxicity lies with the higher Kava-Kava dosage. A longer exposure appears to have unfavorable effects: In case Nr. 7, which had a low dose of only 60 mg of kavapyrone per day, the signs of severe hepato-toxic reaction requiring transplantation, occurred only after exposure for 7 months. This is exactly opposite to three of the 18 spontaneously reported cases, which were individually discussed, in which the hepato-toxic reaction did not appear too severe (generally only a reversible transaminase elevation, possibly sclerenicterus). In case 16 the dosage was low, in case 6 the dosage was within standard range, and in case 15 the length of exposure was short.

As a total, the described cases show that Kava-Kava clearly has the potential for severe liver toxicity and that the effect has a characteristic pattern with a time peak of 3-4 months after start of the medication and a probable higher toxicity with higher doses.

1.4 Reports from other countries

1.4.1 Switzerland

From Switzerland through April 2002 we had a total of 7 spontaneous reports describing hepatocellular damage (histologically confirmed in three cases) in connection with the ingestion of Kava-Kava-containing medication. Six of these cases were reported following ingestion of medications containing acetone extract and one case after the application of a medication containing D/L-kavain. The connection between these undesirable medication effects and Kava-Kava treatment was evaluated by the IKS (InterCanton Control Office) and judged to be "probable" in two of the six cases occurring following Kava-Kava acetone extract, and "possible to probable" in one case. With the remaining three cases the causal connection with Kava-Kava treatment is evaluated as "possible", because co-medication must be considered as a trigger. A viral hepatitis, alcohol consumption, or obstruction of the diverting

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bile ducts was definitely ruled out in four of the six cases. The patient treated with D/L kavain had a finding of Hepatitis C with positive serology. The occurrence of this UAW correlated chronologically with the ingestion of the medication.

The dosage of the Kava-Kava-containing medications in four cases was in part significantly above the high dose of 120 mg of kavapyrones per day as recommended in Germany. In two cases the dosage was within the recommended range of 60 - 120 mg per day. The patient receiving the D/L-kavain containing medication received a dose of only 50 mg per day.

Two of the six cases receiving acetone extract required a liver transplant. One of the transplant cases was preceded by icterus with coagulopathy, which remained progradient in spite of discontinuation of Kava-Kava treatment. In this case a differential diagnosis of primary biliary cirrhosis must be considered in the evaluation.

The second case concerns a 50-year old male who quickly developed jaundice after treatment for approx. 6-8 weeks with 300 - 400 mg of Laitan® daily (corresponds to 210 - 280 mg of kavapyrones). After emergency admittance he rapidly developed liver failure with massive transaminase increases, Quick value decrease, and encephalopathy. Death from acute liver failure could only be prevented through a liver transplant within 48 hours. Histology showed severe confluent necrosis, and a portal and lobular inflamed infiltrate with lymphocytes and eosinophils. Relevant hepato-toxic co-medications were ruled out, as well as obstruction of the diverting bile ducts and the presence of viral, autoimmune or circulatory causes. The histology of the explanted liver and the clinical course spoke against regular alcohol consumption. This case was published by Escher and Desmeules [28] and was presented in the overview by Stoller [10]. The causal connection was considered "probable".

1.4.2 Canada [41]

The Canadian Medication Surveillance Office (Health Canada) is currently reviewing nine suspicious cases of UAW in connection with ingestion of Kava-Kava containing medication. Two of these cases affect the organ system liver-bile. One case categorized as severe involved "abnormal liver function". This female patient displayed symptoms of hepatic involvement, as well as unusual fatigue, weakness, painful abdomen, and loss of appetite. After discontinuation of the Kava-Kava preparation the symptoms disappeared. The dosage and length of ingestion in this case are not known.

In a second case categorized as severe, the reported symptoms included liver enlargement, elevated liver enzyme values and bilirubin concentrations, accompanied by jaundice, vomiting, exhaustion, and weight loss. These symptoms reversed after discontinuation of the Kava-Kava-containing preparation. The circumstances surrounding the case that must be taken into consideration include alcohol misuse associated with hepatitis, as well as the consumption of St. John's Wort and other phytopharmaceuticals.

In the opinion of the attending physician the Kava-Kava containing preparation should be viewed as the cause for the liver disease.

1.4.3 USA

Here a total of 15 cases are known, of which one has been well documented and published [11]: A previously healthy 14-year old female patient was admitted to the hospital with fulminating hepatic failure and pathological liver function values. After several unsuccessful attempts at treatment, a liver transplant became necessary. Biopsy showed a liver cell necrosis, which was classified as "chemical" hepatitis. A Kava-Kava product was the only medication the patient had been using for a total duration of six months. After a one-month break the patient resumed ingestion of Kava-Kava. Doctors were unable to find any alternative causes that could have caused the damage, and concluded on the grounds of the chronological

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connection and the lack of other possible causes that the UAW had been triggered by Kava-Kava.

The FDA has had reports of 14 other cases of undesirable medication effects as related to the organ system liver-bile, with some cases taking a severe, life-threatening course [42], including a second case of liver transplant. Detailed information is currently not available.

1.4.4 Great Britain

In Great Britain one case of liver problems in connection with the ingestion of a Kava-Kava containing medication has become known [43], detailed information is currently not available.

1.5 Studies with information on UAW's (except for those from 1.2)

1.5.1 Clinical studies

Prospective studies with data regarding the type and frequency of side effects of Kava-Kava are not available. In 15 published studies, in which the overall tolerance was determined, no UAW's with hepatic involvement are found.

1.5.2. Epidemiological studies

In a retrospective compatibility study (Title: "Demonstration of tolerability depending on the level of the implemented Kavapyrone dosages") conducted by a pharmaceutical company [1], 15 UAW's with liver involvement were registered out of approx. 60 million daily doses (TD). Six UAW's occurred with dosages of 120 mg / TD Kava-Kava extract or less (number of TD's = 24.6 million), and nine with dosages above 120 mg/TD (number of TD's = 34.8 million). The UAW's involved cases of toxic hepatitis with transaminase elevation, and in some cases icterus and partly pathological liver function.

2. Hypothesis and data with regard to the effect mechanism of the UAW

The mechanism of the undesirable effects of Kava-Kava containing medications on the liver is unknown [12]. According to current scientific knowledge, allergic [14] or dose-dependant toxic medication reaction [13] is assumed. One hypothesis states that in rare cases of genetic predisposition a connection with a CYP2D6- deficiency might be involved. As shown in 1.3 above, the dosage used in the cases reported to BfArM tend to speak more for the dose-dependant toxic mechanism. A possible genetic predisposition may also play a role [15].

Results from two submitted positive lymphocyte transformation tests after exposure to Kavapyrones support the possibility of immuno-induced genesis. Kavapyrones are partially metabolized in the human and excreted in the urine [16]. It can be assumed that metabolism occurs in the liver, where the metabolites could exert a direct toxic effect or may induce hypersensitivity reactions. The described, in part severe hepato-toxic reactions followed by death or liver transplant have been histologically confirmed as toxic drug reactions. In almost all of these cases the dosage exceeded the recommended standard range of 60-120 mg as per Commission E [9]. BfArM thus assumes that the hepatic damage is due to both dose-independent idiosyncratic reactions and dose-dependant reactions.

In the position paper by one pU [5], the latter conclusion is discussed because of the higher number of incidents related to side effects occurring with higher dosages (*"If Kava-Kava is assigned a hepato-toxic effect, then it can be assumed that it is very possible that the main mechanism is a dose-dependant intrinsic toxicity"*). In reference to an in-vitro toxicity test by Gebhardt, it states: *".... The 6 examined kavapyrones showed a dose-dependant intrinsic toxicity on rat hepatocytes..."*

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Stickel and Seitz [6] come to the conclusion that Kava-Kava containing medications come into question as the cause of liver damage and then go on to say ".... *the most likely is a dose-independent, immuno-allergic mechanism.*" In summary they conclude: "*Kava-Kava containing medications carry a clear hepato-toxic risk.*" May [7] also arrives at this conclusion and writes: "*...Kava-Kava containing medications have hepato-toxic potential.*" Cooperation Phytopharmaka [3] and one pU [4] note that the risk of toxic liver damage is low, but in the end, do not exclude the risk: "*.... the risk of side effects, including liver damage, is low.*" One pU [5] concludes in his position paper that Kava-Kava associated hepato-toxicity must be considered: "*.... the mechanisms of Kava-Kava associated hepato-toxicity are apparently heterogenous.*"

3. Relevance of production and different extract-types

Undesirable effects of Kava-Kava containing medications have been reported with alcohol-based and acetone-based extracts and synthetic kavain. The following distribution of the reported numbers is shown for UAW's with liver involvement: ethanol extract: 27 cases, methanol-extract: 2 cases, acetone-extract: 7 cases, D/L kavain: 3 cases. It is currently not known if those kavapyrones considered to be active, such as dihydrokavain, dihydromethysticin, kavain, methysticin, desmethoxyyangonin and yangonin or other components also contained in the plant extract of Piper methysticum, such as chalcones(?) or cinnamic acid derivatives, may be responsible for the undesirable effects. The UAW cases for cases involving synthetic D/L kavain agree with the results of the in-vitro testing by Gebhardt, which showed that kavain displays the greatest toxicity among the Kavapyrones.

According to calculations by Loew [17] the total content of kavapyrones and the distribution pattern of the various kavapyrones in the different extracts is comparable, aside from natural deviances. In the acetone-extracts the Kavapyrone content is approx. 70% and is greater than in ethanolic extracts (approx. 40 - 60%). Acetone and ethanol extracts differ only slightly in regard to co-extracted substances.

In the opinion of BfArM, a differentiation of the ordered measures based on the method of production is currently not sufficiently justifiable.

4. Determination of a threshold-dose for Kava-Kava extracts, i.e. kavapyrones

Specific examinations to determine a dosage of Kava-kava extracts, i.e. kavapyrones, which is without toxic effects in humans, are not available. From data available in literature, as well as the position papers by pharmaceutical companies, a threshold dose can be estimated, below which liver-toxic reactions should not be expected:

4.1 Toxicity data from literature and in-vivo studies

Data from in-vivo studies are presented in the position paper from Cooperation Phytopharmaka [3].

According to these toxicity studies conducted by the manufacturer, the NOEL (No Observed Effect Level) in the rat is approx. 24 and in the dog approx. 20 mg Kavapyrone / kg of body weight.

From a toxicological point of view, the following security factors must be considered when extrapolating these numbers to humans: A factor of 10 for the possible species difference (rat / human), another factor of 10 for the protection of hypersensitive persons, and 10 for chronic applications, which totals a factor of 1000. On the basis of the toxicity study on rats and dogs a dosage of approx. 1.5 mg kavapyrones per day should be considered safe.

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In a neurophysiological in-vivo examination on rats, Boone et.al. [20] observed that, under chronic ingestion of 10.8 mg kavain/kg/day in the feed, the animals in the kavain group had significantly reduced weight gain compared to the animals in the control group. This observation leads to the possibility that the NOEL could be lower than what was determined in the above study. As a limitation to the report by Boonen et.al., it must be mentioned that this study did not involve an examination of the chronic toxicity of kavain.

In the position paper of the Associations [2], two studies of the toxicity of kavain and Kava-containing medications with repeated application on rats are cited. With dosages of 7.3 and 73 mg of Kava-Kava total extract / day/ kg over the course of 3 / 6 months, no chronically toxic effects were determined. These studies (Sorrentino, 1990) were done internally at the manufacturers and were not available to BfArM and could thus not be evaluated properly.

In the opinion of Commission D, the lowest concentration at which liver-toxic reactions may still be possible is at the homeopathic dilution step of D6. The Commission recommends that registrations for Kava-kava containing homeopathic remedies should only be accepted for dilutions starting at D4. Information about contraindications, side effects, and random effects should be included in the package inserts for dilutions of up to D6.

Under consideration of the above-mentioned, a threshold dose for humans can be assumed that is equal in concentration to that ingested with a homeopathic D4 dilution. A D-4 dilution is equal to a Kavapyrone concentration of 0.04 to 0.08 mg/day, under the manufacturing rules of the HAB and dosage regulations for acute dosing (5-8 Tr./h). An upper limit of 7% kavapyrone content for Kava-Kava was used as a basis for these calculations, as per HAB.

4.2 Studies by Gebhardt

In-vitro toxicity studies on liver cells have their place primarily with the screening or ranking (Toxicity comparison) of test substances, i.e. with the identification of the mechanism that is the basis of the toxicity. At the request of the IKS (Intercantonal Control Office), Gebhardt [18] executed an in-vitro study of kavapyrones as well as Kava-Kava extracts in an "MTT-Test" on rat hepatocytes. This test determines the cytotoxicity of chemical compounds or extracts from biological material through the reduction of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide). EC_{50} is given as the parameter. An EC_{50} in this case gives that concentration of a substance in the test set-up that leaves 50% viable rat hepatocytes at the time of measure. The test resulted in an EC_{50} of 45 $\mu\text{g}/\text{mL}$ for kavain. For methysticin, another kavapyrone, an EC_{50} of 65 $\mu\text{g}/\text{mL}$ was determined. Gebhardt assumes that kavain accumulates in the liver, leading to higher exposure there. However, studies of the accumulation of kavain or kavapyrones in the liver are lacking.

The EC_{50} values determined by Gebhardt [19] are not suitable for threshold dose estimation in humans. To determine a threshold dose, the study at best can be used as an adjunct to existing in-vivo toxicity studies. Gebhardt made several assumptions for the derivation of a threshold dose that is without concern for humans (complete accumulation of kavapyrones in the liver, transfer of in-vitro data from animal cells to in-vitro conditions with humans, etc.) and it is unknown if and if so, how much, these assumptions are relevant. Additional and further safety factors are inalienable:

A safety factor of 10 as the minimum distance from the EC_{50} determined in the MTT test,

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ten for the possible species difference between rat / human

an additional ten for the transfer of in-vitro data to in-vivo conditions.

Another limitation to the test results of the MTT-test is due to method deficiencies and factors that could influence the results (the low solubility of the examined kavapyrones in the test medium as mentioned by Gebhardt, filtration method, etc.). According to the data by Gebhardt, it can be suspected that the actual exposure of rat hepatocytes to kavapyrones was lower by an unknown factor than what was used in the calculation.

5. Efficacy

According to the monograph from Commission E [9], Kava-Kava is suitable for use with nervous fear-, tension, and anxiety conditions.

The evaluation of therapeutic efficacy in this case also considers the state of scientific knowledge at the time of the early 90's; an evaluation of therapeutic usefulness however, must orient itself to the current state of scientific knowledge especially when it comes to the evaluation of concretely named risks. The state of scientific knowledge is fixed in a specific CPMP-Guideline for the clinical trials of medications for treatment of panic disorders in revised form from the years 1993 and 1994 (Clinical investigation of medicinal products in the treatment of generalized anxiety disorder, panic disorder and obsessive-compulsive disorder [Clinical Investigation of Anxiolytics/III/3673/92]).

A significant portion of this guideline consists of the demand for trials using random sampling on a homogenous group of patients with differential diagnoses in the panic disorder group (DSM III-R, ICD-10) - especially because of the increasing medical realization that medications from differing pharmacological classes can be applied for treatment of various forms of panic disorders.

For this reason we would not subject older studies of kavain-containing medications to these standards, and we would at this time relinquish executing a lege artis (?) differential diagnosis of various forms of panic disorder, with the assumption that the target population for treatment with kavain-containing medications can still be sufficiently characterized. However, it must be expressly noted the pharmaceutical manufacturer still has the duty to bring their examinations up to date.

What applies here instead, are the older "Basic rules for the execution of clinical trials for medications" as published in the Federal register in December 1987 with the goal of improving the quality of clinical trials. Essentially these rules were designed to make concrete the "legal demand for a test plan that is in accordance with the current state of scientific knowledge" (§ 40, section 1 AMG).

Only when such a study protocol is commonly known, can a plausible reconstruction of the stringency of planning, execution, and evaluation / reporting be done.

5.1 Kava-Kava extracts

In the context of evaluating the efficacy studies, only randomized, controlled studies will be reviewed, because these are available in greater numbers and are relevant to decision-making in light of the indications.

5.1.1 Studies with dosages that are in accordance with monographs

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The following studies / publications are based on dosages in accordance with monographs of 60-120 mg kavapyrones per day, but will not be considered proof of efficacy for the following reasons:

5.1.1.1 Bhate et.al. [29]

The examined Kava-Kava preparation was used as oral pre-medication in epidural anesthesia prior to surgery. Significant improvement of sleep quality and significant reduction of fear and tension are described. This study cannot be used as proof for the monograph-indications because no criteria are described that determined fear-, tension-, or anxiety conditions. Additional deficiencies in this study were: no calculation of binomial distribution (?), no justification for the choice of evaluation instruments, no clarification of statistical methods.

5.1.1.2 Warnecke et.al. [30]

The Kava-Kava preparation was used for treatment of menopausal symptoms with excessive panic and vegetative disorders. A significant improvement is noted. Even the evaluation of this specific indication cannot be used as sole proof for monograph-indications. In addition, no testing for significance was possible at the end of the test phase after 12 weeks, because 14 out of 20 patients in the placebo-group had left the study. Additional deficiencies of this study were: no calculation of binomial distribution (?), no clarification of the statistical methods used, no follow-up phase.

5.1.1.3 Geier [31]

The significance of results could only be shown in the per-protocol-attempts (?), and not in the decisive intent-to-treat analysis. In addition, the decrease of scores in the Hamilton Rating Scale for Anxiety (HAMA) by 15 points from 26 to 11 under Verum application, and by 13.5 points from 28 to 14.5 points under placebo application, calls into question the clinical relevance of group differentiation. An additional deficiency was: no clearly defined panic disorders as per DSM-III-R or ICD-10 as an inclusion criteria in the test protocol, but only in the publication manuscript.

During review of final data from this study, it was noted that 4 patient using Verum showed a slight elevation of gamma-GT values. Another patient showed an increase in alkaline phosphatase value from 126 to 207 U/l.

5.1.1.4 Becker et.al. [32]

A significant difference in the intra-individual differences in values of the total score of the Anxiety Status Inventory (ASI) could only be evaluated under consideration of the central effects, which were not further elaborated. With an improvement of the median by 10.5 points from 47.5 to 37.0 under Verum therapy, and by 9 points from 48.0 to 39.0 points under placebo therapy, the clinical relevance of differentiation comes into question again. Additional deficiencies were: no clearly defined panic disorders per DSM-III-R or ICD-10 as inclusion criteria in the test protocol, but only in the manuscript for publication.

As a total, the studies examined are not sufficient for supportive efficacy proof for the indications and dose recommendations named in monographs.

5.1.2 Studies using dosages above those named in monographs

The following studies are based on higher doses than those given in monographs, but cannot be used as supportive proof of efficacy for the following reasons:

5.1.2.1 Warnecke et.al. [33]

The Kava-Kava preparation was used for treatment of psychovegetative and psychosomatic complaints during menopause. After 8 weeks a significant

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reduction of the HAMA total scores from 31.10 to 5.50 and from 30.15 to 22.50 was achieved. Once again, the evaluation of this specific indication cannot be used as sole proof of efficacy for the monograph-indications. Additional deficiencies of this study: no clearly defined panic disorders per DSM-III-R or ICD-10 for the inclusion criteria, no follow-up phase.

5.1.2.2 Lehmann [34]

In this study the efficacy of a Kava-Kava extracts was tested on women suffering from relative anxiety disorder because of a suspicious breast exam. Significant results in favor of Verum are given, but numerous data important for the evaluation is missing: Inclusion- and exclusion criteria, dropouts, confidence intervals. The originally planned, i.e. calculated binomial distribution (?) could not be achieved.

5.1.2.3 De Nicola [35]

This study was done on 70 hospitalized patients with panic disorder. Use of Verum resulted in a reduction of HAMA scores, one of the main study goal criteria, from 27.55 to 16.12, and use of placebo resulted in a reduction from 29.25 to 25.28. Significance values and confidence intervals are missing, however. For the second major study goal criteria (State-Trait-Anxiety-Inventory), it is merely stated that the suspicion arose that the study was not properly conducted and thus led to conspicuously favorable values for the preparation. An evaluation was thus not done. Additional deficiencies were: no clearly defined panic disorders per DSM-III-R or ICD-10 as inclusion criteria, the statistical process was not stipulated in the study protocol, no justification of the binomial distribution (?), no follow-up phase.

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5.1.2.4 Kinzler et.al. [36]

A significant difference in favor of the Kava-Kava extract is calculated for the HAMA-Total Score: Verum: from 25.3 to 12.6, Placebo: from 24.3 to 21.0. The confidence intervals however, are not mentioned. Additional deficiencies: no clearly defined panic disorders as per DSM-III-R or ICD-10 as inclusion criteria, no binomial distribution calculation, no follow-up phase.

5.1.2.5 Woelk [37]

In this equivalency study (Laitan, Bromazepam, Oxazepam) a clinically relevant reduction of HAMA-scores is determined for all preparations: Laitan: from 27.29 to 15.55, Bromazepam: from 27.29 to 13.4, Oxazepam: from 27.73 to 16.55. Possible differences between the centers are not discussed. Clearly defined panic disorders as per DSM-III-R or ICD-10 as inclusion criteria are not available.

5.1.2.6 Volz and Kieser [38]

A significant difference in HAMA Total score is determined: Verum: from 30.7 to 9.7, Placebo: from 31.4 to 15.2. Confidence intervals are not mentioned. Significant differences exist between the centers. A binomial distribution (?) calculation is absent.

5.1.2.7 Malsch [39]

Significant improvement in HAMA Total score after 36 days and under gradually decreasing benzodiazepine dosage, with only slightly overlapping confidence intervals: Under Verum the difference is 7.5, under placebo -1. The follow-up observation showed that reoccurrence of panic symptoms is likely after discontinuation of therapy. Deficiencies were: no reproducible binomial distribution calculation, no follow-up phase.

5.1.2.8 Lehrl [40]

Statistically significant group differences in favor of the Kava-Kava preparations could be calculated for the subscales "quality of sleep" and "recuperative effects after sleep". However, the confidence intervals overlap. Only minor additional plausibility for the determined significance can be found in the given information.

As a summary it can be noted that the decisive studies for indications and in dosages that are in agreement with monographs for Kava-Kava preparations, cannot be considered proof of efficacy. The study of higher dosages does give some indication of possible anxiolytic efficacy, but the study methodology is too far removed from the current scientific state of knowledge with regard to differentiation and differential therapy of panic disorders, methods of psychometric quantification, and the biometric execution of meaningful studies, so that these study cannot be considered proof of efficacy.

5.2 Kavain

The kavain studies to be evaluated were from the years 1989 to 1992.

Without knowledge of the corresponding study protocols and extensive data, a sound evaluation of the studies solely on the basis of abbreviated publications was possible only on a limited basis. It could also not be assessed to what extent a publication-bias existed and studies with negative results were simply not reported, a practice that is not allowed per AMG and the Guidelines for Testing Medications. The submitted scientific findings addressing the therapeutic efficacy are assessed with the restrictions listed above, as follows:

5.2.1 Lehmann et.al.[22]

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29 resp. 27 patients with panic disorder, generalized anxiety, adaptability problems or phobic disorders were treated over the course of 4 weeks with 2 x 200 mg / day kavain or placebo. The HAMA Total score and clinical global rating are named as the main study goal variables; both showed significant group differences. Some secondary variables support the results.

The authors conclude that kavain, as a support to psychotherapeutic measures, can be useful as an alternative to benzodiazepines in the treatment of slight to medium grade panic disorder, especially when sleep disturbances and psychovegetative disturbances are present concurrently.

The publication, a dissertation, appears plausible. According to the authors, anxiolytic efficacy can be assumed, but requires further solidification.

5.2.2 Lindenberg & Pitule-Schoedel [23]

A total of 38 patients with "panic disorders in connection with neurotic and psychosomatic disturbances" were studied to compare kavain (3 x 200 mg/day) and Oxazepam (2 x 10 mg/day) for the course of 4 weeks. The study was done in the office of an internist.

The inclusion diagnosis of 28 out of 38 patients listed in the original publication (page 50/32) were not reproducible. This involved:

- nicotine abuse (3 patients)
- cannabis abuse (7 patients)
- hallucinogen abuse (12 patients)
- abuse of morphine-type substances (6 patients)

In an otherwise identical special printing by the literature service of the Klinge Company, the ICD-diagnoses shown above were exchanged as follows:

- Muscular-skeletal system (3 patients)
- Respiratory organs (7 patients)
- Heart / circulatory system (12 patients)
- GI tract (6 patients)

When describing the patient random sampling in the statistical report, contrary to normal expectations, no information is given as to the ICD diagnoses.

The study used external and self-evaluation scales. However, to derive "equality of efficacy" from this, as was done by the authors, cannot be done due to the small number of study subjects (insufficient "power") and the missing placebo-group.

In the clinical comprehensive judgement, the assessment of efficacy as "very good" as it is described, falls in favor of oxazepam (71% vs. 55%).

Because of flaws in the study design and a study group that is too small, this study does not render a strong statement

5.2.3 Moeller & Heuberger [24]

40 patients with neurotic or psychosomatic disorders were treated in a double-blind manner by their private physician on an ambulatory basis with 3 x 200 mg of kavain per day, or with placebo.

The efficacy study was obtained through application of external and self-evaluation instruments. The study was conducted for 4 weeks, with one additional week of placebo

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administration. Significant differences were present in the external and self-evaluation (ASI, Self-Rating Anxiety Scale, Global evaluation).

The authors conclude that the therapeutic effect should be secured through further studies and that further attempts should be made to find differential indications for application, which should be done as a comparison with other medications from other substance-groups that can also be used for the treatment of panic disorders.

5.2.4 Moeller et. Al.[25]

The authors studied kavain as a support during benzodiazepine-withdrawal. Prerequisite for study inclusion was a minimum of 6-weeks of benzodiazepine therapy. On a total of 83 patients, withdrawal was done gradually over the course of 3 weeks with randomized kavain 3 x 200 mg/day or placebo, and then follow-up observation for 3 more weeks. Nothing is known about the type of benzodiazepine pre-treatment, especially about the half-life of the administered medications. The merely descriptive statistical report, which was delivered later, does not list any information in this regard.

After initial worsening of panic symptoms and the appearance of withdrawal symptoms in both groups, the kavain-subjects improved successively globally and in the panic scale, while the appearance of specific withdrawal symptoms apparently did not differ among the groups.

Differential data especially, is missing. The publication only gives results in an abbreviated form, and the statistically descriptive tables in the report do not add anything to a quest for information. The study allows for the hypothesis that kavain possesses anxiolytic potential and that it can ease the withdrawal of benzodiazepines under low dose dependency.

Summarized evaluation of the therapeutic use of kavain

Two short-term studies of 4 weeks duration [23,25] give the indication that kavain-containing medications may possibly have therapeutic use for the treatment of panic disorders. However, the dosage question remains unanswered: One time, 2 x 200 mg were administered, the other time 3 x 200 mg. For a permit a multi-armed, placebo-controlled dose finding study would be required.

Furthermore, for proof of efficacy done lege artis, the following would be obligatory: three-pronged studies with active controls on a sufficiently large binomial distribution (?) over a longer test period, as well as studies for Relapse Prevention Design and studies of behavior after discontinuation. As mentioned earlier and as was also discussed by Moeller & Heuberger [24], differential indications should be examined in comparison to other anxiolytic substances (it must be noted here that benzodiazepines do not represent the only possible alternative anymore).

In summary then, we conclude that based on current scientific knowledge and the existing permit practices, no suitable proof of therapeutic efficacy exists for kavain-containing medications.

6. Efficacy and risks of alternative therapies

For the treatment of panic disorder, substances from other groups are available (some benzodiazepines, buspirone, and some Serotonin Re-Uptake Inhibitors like paroxetine and citalopram). It must be taken into consideration that various panic disorders can be differentiated from each other on the basis of differential diagnostics. For the treatment of various panic disorders, varying substances may be suitable. In any case, it no longer applies that panic disorders can only be treated with one substance type. The submitted position papers solely named the benzodiazepine group (even here, no differentiation was made between those benzodiazepines that are suitable for anxiolytic treatment and those that are not), and this does not represent the sole therapeutic alternative to Kava-Kava-containing medications. Aside from drug treatment, non-drug based treatment should always be considered.

The efficacy of some benzodiazepines, some SSRI's and buspirone for the treatment of various forms of panic disorder has been examined and proven in several clinical studies. These substances are permitted and available in Germany. Following a recall of Kava-Kava-containing medications, no supply gap will result for patients.

The frequency of UAW's with benzodiazepines is minor, in one comprehensive capture project ("AMUEP"), it was about 1-2%. For benzodiazepines with a permit for the indication anxiolysis, for which the treated number of patients is extraordinarily high, the BfArM has only 60 spontaneous reports with regard to the organ system liver/gall bladder. In almost all these cases the UAW's were not threatening, instead, they only consisted of an increase in transaminase values, gamma-GT, or bilirubin with sclerenicterus. In 3 cases a severe hepatotoxic reaction existed, however, 2 of the patients had received comprehensive co-medications with potentially hepato-toxic effects. With regard to buspirone, no spontaneous reports regarding significant hepato-toxic reactions are known.

Without doubt, a certain dependency potential exists with benzodiazepines. This, however, is compensated by the fact that the medication requires a prescription. Attempts to circumvent the corresponding limitations occur on a repeating basis, however, BfArM is of the opinion that these limitations do not represent a large burden for the affected products, and that any potential burden does not come close in gravity to the risk of severe hepato-toxic reaction of kavapyrones and could thus not represent an argument for the preference of Kava-Kava-containing medications in certain situations.

For the comparison of UAW's, especially those affecting the liver, caused by Kava-Kava-containing medications and benzodiazepines, a study by Schulze and Siegers [14] was presented. The authors base their calculations on case reports from the IMS MEDIPLUS databank and sales figures from medications that are Kava-Kava preparations or contain benzodiazepines. The number of patients with reported liver dysfunction is tied into the number of packages sold, or DDD's. From this, the authors calculate "incidences" of toxic liver reactions under Kava-Kava containing medications and benzodiazepine-containing medications (0.89 versus 0.90-2.12 per 1,000,000 DDD's).

This method of calculation has such grave deficiencies that the results cannot be considered valid evidence for the frequency of application-dependent liver function disorders in relation to the use of both groups. Results could easily be off by a factor of 10. For an incidence evaluation the number of treated patients and the actual number of patients with the undesirable effect being examined are necessary within a certain time period. Both data sets cannot be deduced from the utilized data sources, neither for the Kava-Kava containing medications or for benzodiazepines.

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Neither the various benzodiazepines, nor the differing areas of use with the correspondingly different user numbers, or the differing time periods of the marketing of medications from both groups were taken into consideration. In addition, it was not possible to include Kava-Kava containing medications that were obtained for self-medication, as was noted by the authors themselves.

There are still no data available regarding the frequency of liver function disorders in connection with the use of Kava-kava containing medications, i.e. for the relative frequency of these undesirable effects in comparison to alternative therapies.

7. Combination medications

For medications that contain other active substances besides Kava-Kava no study results or specific objective justifications exist that would support any advantages of these preparations over preparations containing Kava-Kava as the sole, efficacious component. With this, the demands of §22, section 3 a i.V.m. §105, section 4 AMG are not met. Its usefulness / damage relationship is thus unfavorable

8. Measures by other Drug Agencies

The **Swiss** Medication Office (IKS) recalled the permit for Laitan®, an acetone special extract of Piper methysticum, in April 2001, due to cases of severe liver damage which were only reported there in connection with this medication. Alcoholic extracts so far have not been affected by this recall. However, they are now only available through pharmacies, and are under special observation by the IKS for hepatic side effects.

The **French** authorities have suspended the sale and permits of all Kava-Kava containing products, with the exception of homeopathic preparations with a dilution of D5 or greater, for a period of 1 year, effective January 8, 2002.

Portugal joined the French example and suspended market permits of all Kava-Kava containing preparations with exception of homeopathic remedies with a dilution factor of D5 or greater.

The **British** Medicines Control Agency (MCA) and the Committee on Safety of Medicines (CSM) reported on December 21, 2001, about the preliminary voluntary market recall of Kava-Kava containing "remedies" by several pharmaceutical businesses and commercial enterprises.

The **Irish** Medicines Board reports that in Ireland, all licensed and unlicensed Kava-Kava products have been removed from the market on a voluntary basis.

The Health Sciences Authority of **Singapore** reported on January 15, 2002, that an agreement had been reached with dealers of Kava-Kava containing products, that these products will be removed from the market as soon as possible.

Health Canada notified all manufacturers of Kava-Kava associated UAW's, and then proceeded to recall 15 out of 18 preparations from those manufacturers who did not respond to the notification with a position paper, and Health Canada also warned consumers regarding further ingestion of Kava-Kava.

The **Australian** Therapeutic Goods Association issued a warning about the effects of Kava-Kava containing products on March 7, 2002, which the **New Zealand** Ministry of Health did on January 16, 2002.

The FDA in the **USA** has asked medical professionals to look for cases of liver damage that may be connected to the ingestion of Kava-Kava containing nutritional supplements, and to report such cases to the FDA.

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The **Malta** Department of Health on March 28, 2002, issued a warning about the effects of Kava-Kava containing products.

In Germany, the Association of the Pharmaceutical Industry has applied for moving Kava-Kava and kavain-containing medications in dosage forms as listed in the monographs of Commission E and higher dosages under physician supervision and prescription requirement. The Committee of Experts for Prescription Requirements has reviewed and supported this application in its January 2002 meeting. The suggestion was taken up by the BMG, and the Federal Council of Ministers agreed to a corresponding ordinance draft. As a consequence, as of July 1, 2002, only those Kava-Kava containing medications that are of a concentration that is equivalent to a homeopathic dilution greater than D4 may be purchased without prescription.

9. Summary

The hepato-toxic effects occurring under the use of Kava-Kava containing preparations represent a substantial health risk. This risk is not compensated by a documented therapeutic effect for the applicable indications and for the dosages used. On the other hand, therapeutic alternatives exist, whose efficacy has been demonstrated for the conditions discussed here, and whose liver toxic potential is apparently far less. For this reason, BfArM finds the risk/benefit relationship for the use of Kava-Kava containing medications unfavorable.

In light of the risk of occurrence of severe, life-threatening UAW's on the liver (acute toxic necrotizing hepatitis, fulminating hepatic failure requiring transplantation, or fatal conclusion) further market availability cannot be justified based on the Handicap in §5, section 2 AMG. More importantly, patients must be protected from the risks associated with ingestion of Kava-Kava containing medications.

The recall order of medications in the market rests on §69, section 1, clause 2, Nr. 4 and clause 3, AMG. The affected medications are questionable in the sense of §5, section 2, AMG. Questionable medications are not allowed in the market. This ban extends to the entire supply chain. The continued sale in pharmacies or the use of the affected medications cannot be justified medically based on the reasons named above. This order is thus necessary to prevent that medications that have already been placed into traffic may possibly be delivered and used, possibly out of ignorance of the implicated measures.

It must be expressly noted that this step-plan process does not only extend to ready-made medications requiring a permit, on the basis of §5, section 1, AMG. It also affects, among others, those medical drugs sold loose, as well as those homeopathic medications that are not required to register per the rules of §38, section 1 AMG, if they are brought into the market in amounts up to 1000 packages per year. The affected pharmaceutical companies must execute an immediate market recall for these medications as well. The appropriate agencies will conduct surveillance of this process.

Information on legal rights

Objections to this notification may be raised within one month following publication. The objection must be made in writing or noted on record to the Federal Institute for Medications and Medicinal Products, Kurt-Georg-Kiesinger Allee 3, 53175 Bonn.

The cost decision related to this official action will follow in a separate Notification.

Sincerely,

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Dr. J. Beckmann

P.S.: We apologize for an editorial mistake on page 13, last section: the number of cases requiring liver transplant ("seven") should be replaced with "six"

Enclosure

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