

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 5, 2002

FROM: Lauren Lee, Pharm.D., Safety Evaluator
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THROUGH: Julie Beitz, M.D., Director
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TO: Lee Simon, M.D., Director
Division of Anti-inflammatory, Analgesics and Ophthalmic Drug Products, HFD-550

SUBJECT: ODS Post-Marketing Safety Review (PID# D020462)
➤ Drug: Arava® (leflunomide); NDA 20-905; Aventis Pharmaceuticals
➤ Reaction: Liver failure (foreign cases)

Confidential: contains data obtained from the Therapeutic Goods Administration (TGA); not to be used outside of the FDA without permission from the TGA.

I. EXECUTIVE SUMMARY:

During the summer and fall of 2002, the Office of Drug Safety (ODS) reviewed the domestic post-marketing cases of liver failure in association with leflunomide use in response to a consult from the Division of Anti-inflammatory, Analgesics and Ophthalmic Drug Products (DAAODP), primarily to address the concerns expressed in the March 28, 2002 citizen's petition, which requested the withdrawal of leflunomide, citing the risk of liver failure and its effect on public safety. The review of FDA's AERS database revealed 54 US cases of severe hepatic injury in association with leflunomide, including 16 cases of acute liver failure (ALF) and eight ALF deaths (see PID # D020157). In light of this finding, a subsequent request was made by DAAODP to review foreign AERS cases for additional clinical insight of this issue. On September 30, 2002, the AERS database was searched for all foreign reports of liver injury in association with leflunomide, and 12 cases of liver failure were selected for further review. One additional case of liver failure was received directly from the Australian Therapeutic Goods Administration (TGA), and thus, a total of 13 cases were reviewed in this consult.

All 13 cases in this series met the case definition for liver failure, including three with concurrent encephalopathy and one with hepatic coma. One patient, however, was diagnosed with toxic hepatitis and nonspecific multi-organ failure. Nine patients died, two cases did not provide outcomes, and in the remaining two cases, recovery was uncertain at the time of the report. Liver failure was the cause of death in four cases, and in five other cases, the cause of death was pulmonary embolism, necrotic pancreatitis, sepsis, pulmonary insufficiency, and unknown, respectively.

In this case series, gender was reported in 12 of 13 reports, 11 of which were females. The patient's age was reported in 11 of 13 cases and ranged from 19 to 76 years. The mean and median ages were 51.3 and 59 years, respectively. Nine cases reported that the administered doses did not exceed the recommended range specified in the US labeling (unknown in four). Nine of 13 cases provided the estimated time to onset of symptoms, which ranged from five days to 16 months. The mean and median onsets were 4.9 and three months, respectively. Four of 13 patients with underlying hepatic conditions (*e.g. chronic*

hepatitis (2), cirrhosis, and elevated transaminases) received leflunomide, which is not recommended in patients with significant hepatic impairment or evidence of infection with hepatitis B virus (*per labeling*). Even though the severity of the hepatic impairment was not clear in these cases, the development of liver failure suggests that these patients had either significant hepatic impairment or that the use of leflunomide could have contributed to the event. Although the leflunomide labeling also states that increased side effects may occur when leflunomide is given concomitantly with hepatotoxic substances, 12 of 13 patients in this case series received one or more concomitant medications that have been associated with or labeled for hepatic failure, fibrosis, necrosis, coma, or fatal hepatitis.

Since leflunomide has been associated with hepatotoxicity (*per labeling*), the progression to liver failure is a possible risk with its use. This case series of 13 liver failures, including four liver failure deaths, provides plausible evidence of such risk. In one case, a liver biopsy concluded that the hepatic injury was drug-induced. Four other cases were confounded by underlying hepatic impairment, six lacked clinical details, and two had closer temporal relationship to other drugs that have been associated with liver failure or fatal hepatic necrosis, respectively. Despite these confounding factors, a possible association between the use of leflunomide and the development of liver failure could not be excluded in these cases. The above data are consistent with the findings in 16 US liver failure cases that addressed the possible risk of liver failure with leflunomide use.

II. DRUG INFORMATION AND US LABELING¹:

Drug Product	NDA	Applicant	FDA Approval	Approved Strengths	Date of Last Approved Labeling
Arava (leflunomide)	20-905	Aventis	9/10/98	10, 20, & 100 mg	4/00

Warnings: hepatotoxicity, elevations of liver enzymes and bilirubin

ALT (SGPT) should be performed at **baseline** and **monitored initially at monthly intervals**. For ALT elevations >2-fold ULN, **dose reduction** to 10 mg/day may allow continued administration of ARAVA. If elevations persist despite dose reduction, **liver biopsy** is recommended. If elevations >3-fold ULN, ARAVA should be discontinued and cholestyramine should be administered.

ARAVA is not recommended in patients with **significant hepatic impairment or evidence of infection** with hepatitis B or C viruses. **Increased side effects may occur when leflunomide is given concomitantly with hepatotoxic substances.**

Adverse Reactions: abnormal liver enzymes

III. SELECTION OF CASE SERIES:

As of 9/30/02, AERS contained a total of 1450 domestic adverse event reports and 970 foreign reports in association with leflunomide. Additional AERS searches were conducted using the following criteria to identify any foreign reports of liver failure in association with leflunomide:

	Drug Names	MedDra Search Terms	Selected Outcomes	Crude Counts	Receipt Dates
#1	Arava% Leflunomide%	Hepatic and hepatobiliary disorders (HLGT) Hepatobiliary investigations (HLGT) Liver transplant (PT)	Serious*	134	From: N/A To: 9/26/02
#2	Arava% Leflunomide%	Jaundice cholestatic (PT) Jaundice hepatocellular (PT) Jaundice NOS (PT)	Other	6	From: N/A To: 9/26/02

* Serious: death, life-threatening, hospitalization, disability, & congenital anomaly

Twelve of 140 reports were selected in this case series. The remaining 128 reports were excluded from further analysis based on the following:

One or more of the following:	108
• Primary event unrelated to hepatotoxicity	
• Did not meet the definition* of liver failure	
• Other adverse events reported (<i>e.g. increased transaminases, jaundice, hepatitis, hepatic insufficiency</i>) without liver failure	
• Duplicate reports	18
• Liver failure secondary to underlying medical condition	2
Total	128

***Definition: Liver failure**

Death, liver transplantation, or evidence of altered mental status (encephalopathy) in the setting of acute liver injury (elevated transaminases, bilirubin, or jaundice). Reported clinical signs and symptoms may include coagulopathy or renal function impairment. This category will also include reports with a diagnosis of liver failure without supporting clinical or laboratory data.

One additional case of liver failure was received directly from the Australian Therapeutic Goods Administration (TGA), and thus a total of 13 liver failure cases were reviewed in this consult. Leflunomide was the primary suspect drug in six cases and co-suspect in seven cases.

IV. SUMMARY OF CASES:

The following table contains the demographics and other miscellaneous data from the 13 selected cases:

Age [years]:	Range 19-76, Median 59, Mean 51.3, Not reported (n=2)
Gender:	Male (1), Female (11), Not reported (1)
Indication for use:	Rheumatoid arthritis (10), Chronic polyarthritis (2), Not reported (1)
Estimated loading dose:	60 mg, 100 mg, Not reported (n=11)
Estimated maintenance dose:	Range 5-20 mg/day, Mean 15 mg/day, Median 20 mg/day Not reported (n=4)
Estimated duration of use:	Range 5 days-16 mos, Median 2.3 mos, Mean 4.6 mos Not reported (n=2)
Estimated onset of symptoms:	Range 5 days-16 mos, Median 3 mos, Mean 4.9 mos, Not reported (n=3)
Estimated onset of LFT changes:	Range 5 days-16 mos, Median 2.8 mos, Mean 5.4 mos, Not reported (n=5)
Jaundice at diagnosis:	23% (3/13), Not reported (10)
Liver function tests:	ALT: range 113-6950 U/L, Mean 2012 U/L, Not reported (n=8) AST: range 105-5940 U/L, Mean 1658 U/L, Not reported (n=7) *Total bili: Elevated 31% (4/13), Not reported (n=9) *Alk Phos: Elevated 31% (4/13), Not reported (n=9)
Onset of symptoms or jaundice to encephalopathy, liver failure, transplant, or death within 12 weeks	Yes (10), No (1), 4 mos, Not stated (2)
Cholestyramine washout:	Performed (6), Not reported (7)
Outcomes:	Death (9), Not recovered as of report date (2), Not reported (2)
Dechallenge/Rechallenge:	Positive Dec (1), Not reported (12)

Year of event: (or if unavailable, year of report)	2000 (7), 2001 (4), 2002 (2)
Type of report:	15-day (12), Direct from the Australian Therapeutic Goods Administration (TGA) (1)

* Exact numerical values for total bilirubin and alkaline phosphatase could not be compared among the cases because the foreign reference ranges varied with the country of origin.

Twelve cases were received as 15-day reports, one of which was a published case.² One additional case was received directly from the Australian Therapeutic Goods Administration. Gender was reported in 12 of 13 cases, 11 of which were females. The reported ages ranged from 19 to 76 years (two unknown). The mean and median ages were 51.3 and 59 years, respectively. Leflunomide oral tablets were prescribed for rheumatoid arthritis in ten patients and for chronic polyarthritis in two patients (unknown in one). Leflunomide loading doses were provided in two of 13 cases (60 mg, 100 mg, respectively), and the length of therapy was three days in both cases. The reduced loading dose of 60 mg was used in an elderly patient (69 yo) who weighed 119 lbs. The maintenance doses were provided in nine of 13 cases and ranged from five to 20 mg with the estimated mean and median of 15 mg and 20 mg, respectively. The 5 mg dose was used in a 19 year-old patient. The estimated total length of leflunomide therapy was available in ten cases and ranged from five days to 16 months. The mean and median duration were 4.6 and 2.3 months, respectively.

The estimated onset of symptoms was available in 10 of 13 cases and ranged from 5 days to 16 months. The mean and median onsets were 4.9 and three months, respectively. The presenting symptoms were vomiting, jaundice/icterus, rash, abdominal pain, fever, nausea, anemia, anorexia, asthenia, dehydration, loss of appetite, peripheral edema, and weakness. The estimated onset of abnormal liver function tests (LFT) was available in eight cases and ranged from five days to 16 months. The mean and median onsets were 5.4 and 2.8 months, respectively. Six of 13 cases reported elevated AST levels (range: 105-5940 U/L, mean 1658 U/L), and five cases reported abnormal ALT levels (range: 113-6970 U/L, mean 2012 U/L). Four of 13 cases (31%) reported elevated total bilirubin. The time between the onset of symptoms or jaundice to the occurrence of encephalopathy, liver failure, transplant, or death was within 12 weeks in 10 cases and unknown in two cases. This interval was four months in one patient, and therefore, the liver failure in this patient could be categorized as subacute rather than an acute event.

All 13 cases in this series met the case definition for liver failure, including three with concurrent encephalopathy and one with hepatic coma. One patient, however, was diagnosed with toxic hepatitis and nonspecific multi-organ failure. Liver biopsy findings were available in two cases, and the autopsy results were available in one other case. The liver biopsy in one patient revealed pericentrolobular necrosis, cholestasis, and microvesicular steatosis compatible with acute cytolytic hepatitis of drug origin, and in the second patient, the biopsy findings included micronodular cirrhosis, steatosis, cholestasis, and fibrotic liver. There was no mention of drug-induced toxicity in the second case. An autopsy of one patient revealed acute necrotic pancreatitis with hemorrhage, ascites, and peripancreatic steatonecrosis. Although this patient died from necrotic pancreatitis, she had concurrent hepatic failure with signs of encephalopathy and hepatorenal syndrome. The reporting physician of this case noted that drug toxicity could not be excluded. The remaining ten cases did not provide this information, and therefore, the type of hepatic injury (e.g. cholestatic, hepatocellular, mixed) could not be determined.

Twelve of 13 patients used one or more concomitant medications that have been associated with or labeled for various forms of liver toxicity, including hepatocellular necrosis, fibrosis, or hepatitis. Concomitant medications included: acetaminophen, celecoxib, ciprofloxacin, diclofenac, enalapril, hydroxychloroquine, itraconazole, meloxicam, methotrexate, naproxen, omeprazole, pantoprazole, phenprocoumon³, pravastatin, ranitidine, rofecoxib, sulfasalazine, and venlafaxine. Most of these drugs

have only been very rarely associated with progression to acute liver failure, coma or death. Small numbers of case reports in scientific journals reflect the very rare association of ciprofloxacin, diclofenac, enalapril, hydroxychloroquine, naproxen, ranitidine, and sulfasalazine with severe hepatocellular necrosis or acute liver failure. In contrast, acute liver failure is well described in association with acetaminophen overdose.

In four cases, the actual therapy dates of the above concomitant drugs were not provided, and therefore, the temporal association with the adverse event could not be confirmed. In one other case, two of the above concomitant drugs were used for “years” prior to the onset of symptoms, and therefore, their association with the liver failure seemed unlikely. In the remaining seven cases, therapy dates were known and a temporal association was noted for leflunomide and for concomitant use of hepatotoxins. In two of these cases, the temporal association for use of ciprofloxacin and phenprocoumon, respectively, was stronger than for leflunomide.

Four patients had possible underlying hepatic impairment (*e.g. chronic hepatitis (2), cirrhosis, and elevated transaminases*). One patient with underlying cirrhosis had normal LFTs prior to the administration of leflunomide, and it was unknown whether cirrhosis could have contributed to the acute liver injury. Baseline LFTs could not be confirmed in three other cases. Severe septicemia was identified in two of 13 cases, but in one case, clinical details of the sepsis in relation to the development of liver failure were not discussed. The other patient died from overwhelming sepsis, which suggested that a drug-induced effect may not have been the sole cause of the liver failure. This patient also had underlying liver impairment as well. Another patient had pulmonary vasculitis, but its relationship to the development of liver failure could not be determined.

Positive dechallenge was reported in one case (not stated in 12 cases). Cholestyramine washout was performed in six of 13 cases (seven unknown), which suggests that drug toxicity was suspected by the healthcare practitioner. Nine patients died, two cases did not provide outcomes, and in the remaining two cases, the recovery was uncertain at the time of the report. Liver failure was the cause of death in four cases, and in five other cases, the cause of death was pulmonary embolism, necrotic pancreatitis, sepsis, pulmonary insufficiency, and unknown, respectively. However, pulmonary embolism was not related to the development of liver failure. The relationship between liver failure and three other causes of death (*e.g. necrotic pancreatitis, sepsis, and pulmonary insufficiency*) were unknown.

Reported Outcome	Cases
Death/ Death from liver failure	9/4
Hospitalization/ Life-threatening	2
Hospitalization	1
Other	1
Total	13

Summary: In this case series, one report concluded that the hepatic injury was drug-induced (*via a biopsy*). Four other reports were confounded by underlying hepatic impairment, six lacked clinical details, and two had closer temporal relationship to other drugs that have been associated with liver failure or fatal hepatic necrosis, respectively. Despite these confounding factors, a possible association between the use of leflunomide and the development of liver failure could not be excluded in these cases.

The two most compelling cases are as follows:

AERS ISR# 3961172-6 (2002):

A physician reported that a 19-year old female with a history of rheumatoid arthritis discontinued leflunomide after one year of therapy. She presented with icteric skin and mucous membranes, progressive asthenia, anorexia, and episodes of post-prandial vomiting. Her concomitant medications were methylprednisolone, omeprazole, and naproxen. She was hospitalized, and her liver function tests were markedly elevated [AST 2032 (U/L), ALT 1554 (U/L), T bili 12.2 (mg/dL), Alk Phos 481 (U/L)]. The viral serology was negative for CMV and hepatitis A, B, and C. The hepatic echography showed a normal sized liver. Cholestyramine, plasmapheresis and antibiotics (*name unknown*) were started, but despite treatment, encephalopathy was identified, requiring intubation. Subsequently, the patient underwent a liver transplant. Postoperatively, she was in good condition. However, the day after surgery, her general condition began to worsen with the appearance of respiratory insufficiency. Her liver function was normal at this time. She was placed on mechanical ventilation and died about a month later due to respiratory insufficiency. A follow-up report stated that the respiratory insufficiency was secondary to pulmonary vasculitis of immunological nature, which was linked to the underlying rheumatoid arthritis. Acute rejection of the transplanted liver was also noted. The biopsies of two livers and the autopsy findings are pending. Further-follow up is expected to determine if there was a relationship between the initial liver failure and vasculitis in this patient.

AERS ISR# 3857646-9 (2001):

A 68 year old female with a 30-year history of rheumatoid arthritis started leflunomide in January 2001 (LD-100mg x3d, MD-10 mg/d). Other past medical history included recurrent urinary tract infections, diabetes, hypertension, recurrent phlebitis, hypogammaglobulinemia, anemia, and osteitis. Approximately five months after starting leflunomide, she was hospitalized with fungal osteitis and received itraconazole 300 mg/d. LFTs were normal at this time. One month later, leflunomide dose was increased to 20 mg daily. On 7/23/01, Cefixime was prescribed for pseudomonas in the urine culture. Other concomitant medications included furosemide, methylprednisolone, omeprazole, calcium, domperidone, nadroparin, aluminum/magnesium hydroxides, Cetoran, Movicol, and Umuline. On 7/28/01, she was hospitalized with abdominal pain, vomiting, weakness, anemia, fatigue, pallor, dyspnea, and lower limb edema. She had a BP of 95/42 mmHg, HR of 109, and RR of 19. According to the reporter, her LFTs revealed cytolytic hepatitis [AST 577 (ref: 6-25 U/L), ALT 1111 (ref: 5-35 U/L), Alk Phos 62 (ref: 45-145 U/L), PT 43%]. Creatinine clearance was 35 ml/min, and amylase and lipase were elevated. Severe hemorrhage due to hypocoagulation occurred leading to hypovolemic shock. All concomitant medications were stopped. On 7/30/01, cholestyramine was started, but despite this effort, fulminant hepatic failure occurred [AST 5940, ALT 6950, ammonia 163 umol/L (ref 14-38 umol/L), PT 11%]. Post-mortem liver biopsy showed necrosis (*mainly pericentrilobular*), microvesicular steatosis with canalicular cholestasis and very mild portal and lobular inflammation. Findings were compatible with acute toxic cytolytic hepatitis of drug origin.

V. EPIDEMIOLOGY ASSESSMENT (by David J. Graham, M.D., M.P.H.):

AUSTRALIAN DATA

VI. OVERALL CONCLUSION:

Leflunomide has been associated with hepatotoxicity (*per labeling*), and thus, the progression to liver failure is a possible risk with its use. This case series of 13 liver failures provides plausible evidence of such risk. In one case, a liver biopsy concluded that the hepatic injury was drug-induced. Four other cases were confounded by underlying hepatic impairment, six lacked clinical details, and two had closer temporal relationship to other drugs that have been associated with liver failure or fatal hepatic necrosis, respectively. Despite these confounding factors, a possible association between the use of leflunomide and the development of liver failure could not be excluded in these cases. The above data are consistent with the findings in 16 US liver failure cases that addressed the possible risk of liver failure with leflunomide use.

VII. REFERENCES:

1. Product information: Arava (R), leflunomide. Aventis Pharmaceuticals Inc., Kansas City, MO, 2000.
2. Legras A, et al. Fatal hepatitis with leflunomide and itraconazole. *Am J Med.* 2002;113:352-3.
3. Hinrichsen H, et al. Idiosyncratic drug allergic phenprocoumon-induced hepatitis with subacute liver failure initially misdiagnosed as autoimmune hepatitis. *Scan J Gastroenterol* 2001;7:780-783.
4. Therapeutic Goods Administration (TGA), Australia. Dr. Richard Hill, personal communication. August 15, 2002.

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Concur:

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Appendix 4: Foreign Hepatic Failure Cases Associated with Leflunomide

ISRH# (mfr)	Year	Location	Age /Sex	Dx	PMH	Concomitant Medications	Outcome
1 3857646-9 (20011499 81-R)	2001	France	68F	Fulminant hepatic failure, encephalopathy	RA, DM, UTI, osteitis, HTN, hypogammaglobulinemia, anemia, thrombophlebitis	Itraconazole (5/19/01-7/28/01, 10 weeks), methylprednisolone, omeprazole, furosemide, nadroparin, calcium, domperidone, aluminum/magnesium hydroxide, ornithine, osmotic laxative, umuline, sodium bicarbonate, KCL, movicol	Death
Course of Illness:							
<ul style="list-style-type: none"> 1/01: Arava started (LD 100 mg/d x 3d, then 10 mg/d); cyclosporine and methotrexate discontinued due to lack of efficacy 5/01: Hospitalized for fungal osteitis and received surgery and treatment with itraconazole 300 mg/d. During hospitalization, hypogammaglobulinemia at 4.2 g/L (nl: >9.8 g/L) discovered. LFTs normal. 6/01: Arava dose increased to 20 mg/d 7/23/01: Cefixime given for pseudomonas in urine culture. 7/28/01: Hospitalized for abdominal pain, vomiting, weakness, anemia, and lower limb edema. Vitals- BP 95/42 mmHg, HR 109, RR 19, temp 36.6° C. LFTs revealed cytolytic hepatitis (AST 577 (ref:6-25 U/L), ALT 1111 (ref: 5-35 U/L), Alk Phos 62 (ref: 45-145 U/L), and PT 43%). Severe hemorrhage due to hypocoagulation occurred leading to hypovolemic shock. All concomitant meds discontinued. CrCl 35 ml/min, amylase and lipase elevated 7/30/01: Washout started, but despite this effort, fulminant hepatic failure occurred (AST 5940, ALT 6950, ammonia 163 umol/L (ref 14-38 umol/L), PT 11%). Serology: negative for hep A, B, and C, CMV, EBV, and HIV. 8/2/01: Patient died. Liver biopsy: necrosis (mainly pericentriolobular), microvesicular steatosis with canalicular cholestasis and very mild portal and lobular inflammation. Findings were compatible with acute toxic cytolytic hepatitis of drug origin. 							
2 3961172-6 (20021244 71-U)	2002	Italy	19F	Hepatic encephalopathy	RA	Methylprednisolone, omeprazole, naproxen	Transplant, Life-threatening
Course of Illness:							
<ul style="list-style-type: none"> 7/10/02: Arava (5mg/d) discontinued after 1 year of therapy. 7/11/02: Presented with icteric skin and mucous membranes, progressive asthenia, anorexia, and episodes of post-prandial vomiting. 7/15/02: Hospitalized with jaundice. 7/16/02: AST 2032 (U/L), ALT 1554 (U/L), T bili 12.2 (mg/dL), Alk Phos 481 (U/L), PT 48% Serology: HAV, HBV, HCV, CMV negative Hepatic echography- liver size normal. Cholestyramine, plasmapheresis, and antibiotics started. 7/20/02: Despite treatment, encephalopathy grade III identified 7/23/02: Hepatic encephalopathy worsened to grade IV, requiring intubation. 7/24/02: Liver transplantation performed. Post-operatively, she was in good condition. The day after surgery, her condition began to worsen with the appearance of respiratory insufficiency. Liver function normal at this time. She was placed on mechanical ventilation. 9/02: Died due to respiratory insufficiency. A follow-up report stated that the respiratory insufficiency was secondary to pulmonary vasculitis of immunological nature, which was linked to the underlying rheumatoid arthritis. Acute rejection of the transplanted liver was also noted. The biopsies of two livers and the autopsy findings are pending. Further follow up is expected to determine if there was a relationship between the initial liver failure and vasculitis in this patient. 							
3 3539251-7 (20002000 31-E)	2000	Germany	59 F	Acute hepatic failure	RA, DVT, PE (98), amputation of left lower leg and right thigh (99), peripheral arterial occlusive disease, osteoporosis, allergy to prednisolone	phenprocoumon, tilidine (3/99-5/10/00), omeprazole (6/98-5/10/00), methotrexate (9/98-5/10/00), diclofenac (10/99-5/8/00), etidronate (6/98-5/00), ergocalciferol, calcium (3/00-5/00)	Death

Course of Illness:

- 12/16/99: Baseline LFTs normal [ALAT 0.36 (ref: 0.1-0.52), ASAT 0.41 (ref: 0.1-0.52), Alk Phos 4.82 (ref: 1.63-4.65)]
- 1/20/00: Arava added (10 mg/d, unknown if I.D given)
- 4/6/00: DVT detected and phenprocoumon initiated
- 4/17/00: Complained of nausea, vomiting, loss of appetite, and upper abdominal pain.
- 4/27/00: LFTs increased [ALAT 1.37, ASAT 1.11, Alk Phos 7.12]
- 5/2/00: Anticoagulant changed to heparin due to worsening of LFTs [ALAT 8.31, ASAT 5.69, Alk Phos 9.54]. Upper abdominal sonography was normal. INR was 2.48
- 5/8/00: Discontinued Arava. Anticoagulant discontinued despite DVT because LFTs remained unchanged. INR was 3.25. Hepatitis serology negative.
- 5/11-5/12/00: Suffered a massive PE and hospitalized.
- 5/13/00: Died due to PE. Autopsy not performed.
- Reporting physician: Arava and phenprocoumon could have caused the acute hepatic failure that required discontinuation of anticoagulant therapy, thus facilitated the occurrence of PE.

4	3803300-9 (20011165 3F11)	2000	Netherlands	73 F	Hepatic failure	RA, hypercholesterolemia, DM, HTN, pain, dyspepsia, sleep disorder	Naproxen, tramadol, prednisone, insulin, triamterene, HCTZ, amlodipine, pantoprazole, temazepam, sulfasalazine (12/98-3/99), methotrexate (3/99-5/99), lisinopril	Death
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Course of Illness:

- 5/23/00: Arava started (20 mg/d, unknown if I.D given). Liver enzymes normal [SGOT 38, SGPT 70, Alk Phos 86]
- 7/11/00: Developed icterus, nausea, and vomiting. SGOT 119, SGPT 150, Alk Phos 242. T bili 55, conjugated bili 45
- 7/13/00: Discontinued Arava. Washout performed. Liver enzyme levels remained high for more than 2 months after the discontinuation of Arava, consistent with cholestatic hepatic injury.
- 7/28/00: SGOT 106, SGPT 113, Alk Phos 326, GGT 1102, T bili 60, conjugated bili 45
- 8/00: Liver echography was inconclusive
- 8/15/00: SGOT 90, SGPT 79, Alk Phos 487, GGT 1058, T bili 165, conjugated bili 169
- 9/00: Diagnosed as having biliary fibrotic liver with severe cholestasis.
- 9/5/00: SGOT 51, SGPT 37, Alk Phos 522, GGT 916, T bili 202, conjugated bili 165
- 9/14/00: Liver biopsy: steatosis, micronodular cirrhosis appeared to be present in combination with a picture seen in particular with alcohol abuse. (alcohol abuse hx not reported)
- 11/20/00: SGOT 24, SGPT 19, Alk Phos 284, GGT 294, T bili 26, conjugated bili 18
- Biliary tract obstruction excluded. Patient found to have ascites in relation with cirrhosis.
- Viral infections (Hep A, B, C, CMV) ruled out as autoimmune disorders or toxic abnormalities.
- 11/23/00: The patient died probably of terminal liver failure. No other organ failure noted.

Course of Illness:

- 3934203-7
(20021054
90C11)
- 2001
- Switzerland
- 69 F
- Hepatic failure, encephalopathy
- RA, Sjogren's syndrome, mild renal insufficiency
- Prednisone, celecoxib, methotrexate (date of use unk), salazopyrine
- Death

Course of Illness:

- 7/1/00: Arava started (20 mg/d, unknown if I.D given)
- 10/01: LFTs normal
- 12/10/01: Developed corneal ulcer, hepatic cholestasis, and changes in liver enzymes. Discontinued Arava. Continued with celecoxib and prednisone.
- Sonography and CT scan:** No obstruction, compression of bile duct, stone, cancer (general condition worsened. Patient hospitalized with fever and vomiting)
- 3/6/02: Gastrointestinal hemorrhage, cholestatic icterus, and liver failure diagnosed.
- 3/20/02: The patient died in hepatic failure with signs of encephalopathy and hepatorenal syndrome. Pancreatitis considered as cause of death.
- Serology:** Hepatitis A, B, C, CMV, and EBV negative
- Autopsy:** Acute necrotic pancreatitis with hemorrhage, ascites, and peripancreatic steatonecrosis was identified. Whether the pancreatitis was already existing was unknown. Chronic hepatitis and mostly cholestasis could be associated with autoimmune reaction, but a drug toxicity could not be excluded. Chronic gastritis noted with little activity. No major toxic hepatitis from methotrexate as only a slight port fibrosis was found at autopsy.

6	3709313-X (20002038 21E)	2000	Germany	69 F	Fulminant hepatic failure; hepatic coma	Chronic polyarthritis, chronic active hep B with high infectivity, "liver function disturbance", osteoporosis, s/p extirpation of benign mammary gland tumor, splitting of perianal abscess, and distal fracture of radius	rofecoxib (6/00-7/00), methotrexate, prednisolone, metamizole (few mos), sodium aurothiomalate (7/97-6/00), morphine	Death
Course of illness:								
<ul style="list-style-type: none"> 6/8/00: Hospitalized due to high fever and left base pleuropneumonia. Treated with cefotiam and cefuroxime. Anti-rheumatic therapy changed from methotrexate to rofecoxib and Arava (LD 60 mg/d x 3d, then 20 mg/d x 2d). A similar increase of liver enzymes (as under treatment with methotrexate) diagnosed, and Arava and rofecoxib discontinued. No decrease in liver enzymes occurred. 7/13/00: GOT 108 (U/L), GGT 54 (U/L) – uncertain if these values were taken prior to Arava therapy. Hospitalized again with decompensated liver cirrhosis, hepatic coma, and drug-induced hemostatic hepatopathy. 7/28/00: Serology: HCV and HDV antibodies negative, hepatitis E-IgM negative, hepatitis B positive 8/10/00: GOT 565, GPT 244, Bili 5.8 --> 23.8 8/26/00: Died due to fulminant liver failure. No post-mortem done. 								
7	3546587-2 (20002001 4(D)DC)	2000	Australia	23 F	Fulminant hepatic failure	Severe juvenile RA w/ secondary osteoarthritis, attempted suicide by methotrexate overdose (95), depression, osteoporosis, pancreatitis, ulcer, s/p left hip surgery	Methotrexate (92- 4/00, 6/00), celecoxib (unk-4/00, 6/00), morphine, venlafaxine, folic acid, prednisone, paracetamol, dextropropoxyphene, calcitrol, indomethacin, omeprazole, hydroxychloroquine, doxepin	Death
Course of illness:								
<ul style="list-style-type: none"> 97-98: LFTs essentially normal with mildly elevated GGT 102. One episode of abnormal LFTs. Liver biopsy planned but not performed due to stress fracture, pancreatitis and abdominal pain. 97: laparoscopy revealed fatty liver 10/8/99: LFTs normal (AST 19, ALP 20, Alk Phos 129, T bili 9, conjugated bili 5) 2/00: Arava started (10 mg/d, unknown if LD given). Celecoxib and venlafaxine started at the same time. 4/3/00: AST 55, ALP 28, Alk Phos 126, T bili 10 4/6/00: Arava, methotrexate, celecoxib, and morphine discontinued. Dosage of venlafaxine reduced to 75 mg BID due to an episode of "unknown sickness" and diarrhea. 6/1/00: Restarted Arava 10 mg/d, methotrexate, and celecoxib. 6/11/00: Discontinued Arava, methotrexate, and celecoxib. Ceftriaxone started for possible upper respiratory tract infection. 6/21/00: Elevated liver enzymes (AST 105, ALP 39, Alk Phos 260, T bili 86, conjugated bili 65) 6/26/00: Liver tests worsened and patient found to be in liver failure. Unclear if washout performed. Prior to sudden liver failure, LFTs not abnormally high. Reporter: This case was suggestive of fulminant hepatic failure superimposed on an underlying liver impairment. The patient died from overwhelming sepsis. 								
8	3626794-0 (20002380 2(G)DC)	2000	Brazil	34 F	Multi- organ failure	RA	chloroquine, meloxicam	Death
Course of illness:								
<ul style="list-style-type: none"> 7/27/00: Arava started (20 mg/d, unknown if LD given) 9/29/00: Arava discontinued (cause unknown) 11/7/00: Experienced skin rash on palms, face, ears, and neck, toxic hepatitis, dehydration, and multi-organ failure. 11/22/00: Patient died 								

9	3833868-8 (20011449 71D)	2001	Germany	25 F	Acute hepatic failure	chronic polyarthritis, DM, sarcoidosis. Morbus Boeck's, allergy with azulfidine	ciprofloxacin, sulfasalazine, methotrexate, insulin	Not recovered, life-threatening, hospitalization
<p>Course of Illness:</p> <ul style="list-style-type: none"> 7/13/01: Arava started (dose unk) /azulfidine allergy. methotrexate not tolerated/ 7/20/01: Presented with fever and rash. Arava discontinued. No washout performed. 8/6/01: Presented again with fever up to 39°C. and the physician suspected cholecystitis. Ciprofloxacin prescribed. 8/7/01: massive increases of transaminases were detected (SGOT 960 (U/L), SGPT 978 (U/L), Bili 1.9). Previous liver values within normal range. 8/13/01: Patient suffered from acute liver failure (SGOT 1200, SGPT 1200, Bili 19.8). Ciprofloxacin discontinued. The reporting physician suspected leflunomide and ciprofloxacin to have caused the event. Plasma level after washout was 0.022 mg/L. 8/16/01: SGOT 600, SGPT 800, Bili 22.8 Patient not completely recovered as of the report date (11/23/01). 								
10	158984	2000	Australia	49 F	Hepatic failure	severe RA, intolerance to methotrexate, rash with gold	salazopyrine (97-9/13/00), ibuprofen (95-9/13/00), prednisone, alendronate, ranitidine	Not recovered, life-threatening, hospitalization
<p>Course of Illness:</p> <ul style="list-style-type: none"> 6/19/00: Started Arava. 9/13/00: Developed severe E. coli septicemia (urinary source). Experienced profound diarrhea, mouth ulceration, desquamating skin rash, hearing loss. Discontinued Arava. Eleven days of oral cholestyramine and charcoal given. Developed pancytopenia, coagulopathy, weight-loss, and multi-organ failure (liver, kidney). Not recovered as of the report date (10/31/00) 								
11	3879529-0 (20021144 5GDDC)	2001	Great Britain	76 F	Hepatic failure	RA	Prednisolone, gliclazide, furosemide, enalapril, ranitidine, bisoprolol, pravastatin, folic acid, co-dydramol, etidronate, calcium, prochlorperazine, naldidrofuryl	Death
<p>Course of Illness:</p> <ul style="list-style-type: none"> 8/01: Started Arava (20 mg/d, unknown if LID given) 10/28/01: Arava discontinued. 11/20/01: Experienced liver failure. Cholestyramine not administered until after admission (date unknown). 12/9/01: Died of liver failure 								
12	3574549-8 (20002058 0GB)	2000	Great Britain	M	Hepatic failure	RA, lyme disease, allergy to Vioxx and gold	diclofenac, omeprazole (for prevention of NSAID GI disorder), co-dydramol	Hospitalization
<p>Course of Illness:</p> <ul style="list-style-type: none"> Patient (age unknown) who was treated with Arava developed liver failure. 								
13	3894160-9 (20021240 4GDDC)	2002	Australia	---	Hepatic failure	---	---	Unknown
<p>Course of Illness:</p> <ul style="list-style-type: none"> Physician reported that a patient on therapy with Arava developed liver failure. No further information provided. 								