CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-206

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 11, 2008
To:	Scott Monroe, M.D, Division Director Division of Reproductive and Urologic Products
Thru:	Ann McMahon, MD, MS Acting Director Division of Pharmacovigilance II
From:	Melissa M. Truffa, RPh, Safety Evaluator Team Leader Paula Gish, RPh, Safety Evaluator Division of Pharmacovigilance II
Subject:	Hepatic events
Drug Name(s):	Silodosin (Rapaflo)
NDA Numbers:	NDA 22-206
Applicant/sponsor:	Watson
OSE RCM #:	2008-1212

1 INTRODUCTION

Silodosin is an alpha-adrenergic receptor blocker currently under review as a Pilot NDA by the Division of Reproductive and Urologic Products (DRUP) for the treatment of benign prostatic hyperplasia (BPH). Per DRUP, there has been no signal of liver toxicity in silodosin clinical trials. However, most drugs that cause Drug Induced Liver Injury (DILI) do so infrequently; typical drug development databases with up to a few thousand subjects exposed to a new drug will not show any cases. Alfuzosin, another alpha-adrenergic blocker, has been associated with rare reports of DILI in postmarketing.

Silodosin has been marketed in Japan since January 2006 and there have been approximately [redacted] patients exposed to date. In July 2008 DRUP requested the Division of Pharmacovigilance II (DPV II) review and comment on six Japanese cases of hepatic events in association with silodosin. b(4)

2 MATERIALS REVIEWED

Six Japanese cases of hepatic events (fulminant hepatitis-1, hepatic malignancy/jaundice-1, jaundice-3, and liver disorder-1) were forwarded to DPV II on July 28, 2008 by DRUP. All six cases are described in Table 1 in the appendix.

3 DISCUSSION/CONCLUSIONS

The six cases of serious hepatic events with silodosin were discussed with DRUP on August 4, 2008.

Two cases of jaundice (cases #1, #2) were possibly due to gallstones. Both reported a rapid improvement of liver function tests (less than 2 weeks) after silodosin discontinuation, a timeline not usually associated with DILI. Case #3 (jaundice) appeared to be related to the patient's diagnosis of hepatic cancer. The events improved after the patients hepatic cancer was resected. Case #4 (ALT, AST around "3000") in a "hard drinker" reported too little information to make any causality assessment.

The two remaining cases (cases #5, #6) were possibly related to the use of silodosin. Case #5 reported fulminant hepatitis with hepatic encephalopathy and coagulopathy in an 84-year-old male with gastric cancer. The hepatic events occurred 16 days after restarting silodosin post-gastric resection surgery. Silodosin was discontinued and the transaminases and bilirubin improved. Case #6 reported jaundice in a 78-year-old male with chronic hepatitis C 2.5 months after beginning silodosin therapy. Silodosin was discontinued and transaminases and bilirubin improved. Although both cases are confounded by underlying medical conditions (gastric surgery-1, chronic hepatitis C-1) both cases reported the events began within 90 days of initiating therapy and gradually improved after dechallenge. Based on the reported timelines a contributory effect from silodosin to the events could not be ruled out.

Therefore, DPV II suggests the following be specified in the product Approval Letter:

1. The adverse event terms *jaundice* and [redacted] should be included in the postmarketing adverse events section of the silodosin label. b(4) b(4)
2. To ensure timely evaluation of serious [redacted] hepatic events (e.g. jaundice, hepatitis) the sponsor should submit all serious [redacted] hepatic events as expedited 15-day Alert Reports. b(4)

3. The sponsor should obtain comprehensive follow-up of all expedited reports of serious hepatic adverse events.

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APPENDIX

TABLE 1 – HEPATIC EVENT CASES: SILODOSIN (N=6)

#	Mfr #	Age/sex location	Event Terms Reported	Concomitant medications	Medical history	Latency/action taken/outcome	Maximum reported liver function tests Comments
1	2006-05221	74M Japan	Hepatic function abnormal Jaundice Abdominal pain	Trimebutine (duration unk) Eviprostat (duration unk)	large intestine carcinoma BPH impaired urination gallstones	3 days after restarting silodosin post-surgery Dc'd silodosin Recovered	ALT 202 IU/L AST 341 IU/L ALP 706 IU/L GGTP 603 IU/L LDH 448 IU/L T Bili 1.8mg/dL LFTs improved rapidly just 4 day after silodosin dc'd
In August 2006 a 74-year-old male patient began treatment with silodosin 4mg bid for bladder outlet obstruction associated with BPH. On ⟶ endoscopy of large bowel was performed because the stool occult blood was positive. As a result the patient was diagnosed with large intestine carcinoma. On ⟶ he patient underwent surgery for large intestine carcinoma. Silodosin was temporarily held during this period. On 9/5/06 silodosin was restarted (labs: AST 30, ALT 28, ALP 184, GGTP 45, Total bili 1.3mg/dL). On 9/19/06 patient developed a hepatic function disorder (labs AST 29, ALT 88). On 9/21/06 the patient developed jaundice and abdominal pain (AST 341, ALT 202, ALP 706, GGTP 603, Total bili 1.8). Although there was a gallstone, the thickening of the wall of gallbladder was not observed. Silodosin was discontinued on 9/21/06. A drug induced lymphocyte stimulation test was negative. The patient recovered. 9/25/06 labs showed: AST 30, ALT 106, ALP 706, GGTP 284, T bili-0.5mg/dL. 9/28/06 labs showed AST 24, ALT 66, ALP 322, GGTP 194, T bili 0.6mg/dL.							
2	2006-04503	68M Japan	Hepatic function abnormal Jaundice Cholangitis acute Pyonephrosis Hepatic steatosis Renal abscess Infective spondylitis Pyrexia Diarrhoea Vomiting	Cefmetazone (7/25/06 to 7/31/06) Panipenem/betamipron (8/1/06 to 8/4/06)	Impaired urination, bladder obstruction associated with BPH, large intestinal polyp	10 days Dc'd silodosin Recovered	ALT 158 IU/L AST 79 IU/L ALP 575 IU/L GGTP 278 IU/L LDH 148 IU/L T Bili 2.97mg/dL LFTs improved 2 weeks after silodosin dc'd
On 7/14/06 a 68-year-old male patient began treatment with silodosin 4mg bid for bladder outlet obstruction associated with BPH. On ⟶ the patient revealed diarrhea, nausea, vomiting and fever. The patient was seen in the hospital. Vital signs and labs showed body temperature of 39.4 C, WBC 14,000/mm3, CRP 24 mg/dL, AST 79, ALT 158, Total bili 2.97mg/dL, ALP 239, GGTP 278 and amylase 30. The patient was admitted for suspected acute cholangitis and hepatic function disorder. Jaundice developed. Cefmetazole 2 grams IV bid, sanactase 1 capsule tid and maintenance medium with acetic acid 500mL daily were started. Silodosin							

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#	Mfr #	Age/sex location	Event Terms Reported	Co...mitant medications	Medical history	Latency/action taken/outcome	Maximu...ported liver func...n tests Comments

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was discontinued. On —— abdominal CT scan revealed fatty liver. Obstructive jaundice was denied from this result. On 7/31/06 Cefmetazole was dc'd. On 8/1/06 Panipenem/betamipron 0.5g IV tid was started. On 8/2/06 AST and ALT increased again to 64 and 148 respectively. Or —— Panipenem/betamipron and sanactase were dc'd. The patient was transferred to another hospital where he was diagnosed with bilateral pyonephrosis. A few days later the patient's appetite had improved. Labs showed WBC 9900, AST 31, ALT 99, Total bili 1, ALP 575, GGTP 122, CRP 5.2, . Jaundice improved. 8/8/06 labs showed WBC 7100, AST 23, ALT 49, Total bili 0.7, ALP 450, GGTP 87, CRP 1.9. Physician comments: "biliary tract infection was suspected from abnormal hepatic function tests, increased WBC and increased CRP. Viral marker tests were negative for Hepatitis A, B, C. Later the patient was found to have bilateral renal abscess."

3	2007-05415	89M Japan	Hepatic neoplasm malignant Bilirubinuria Hepatic function abnormal Dizziness Anorexia Weight decreased Jaundice Biliary dilatation Urine colour abnormal Oedema	NR	Impaired urination associated with BPH Hepatic cancer	1 year Dc'd silodosin, hepatic cancer diagnosed, resected Recovered	ALT 110 AST 86 ALP 508 GGTP 700 T Bili 3.4 Long time to onset, improved after hepatic cancer resection

On 11/25/06 an 89-year-old male patient began treatment with silodosin for bladder outlet obstruction associated with BPH (Prior to silodosin treatment 6/5/06 lab tests showed AST 21, ALT 24 and GGTP 21). On 12/6/06 lab test showed AST 23, ALT 24, GGTP 31. On 6/6/07 lab test showed AST 33, ALT 30 GGTP 185. On 11/13/07 the patient developed abnormal urine color and jaundice. Lab tests showed AST 86, ALT 110, ALP 508, LDH 251, GGTP 700, T bili 3.4. Silodosin was discontinued. On —— a CT revealed a shadow in the liver. Ursodesoxycholic acid 9 was administered. Gastrocamera revealed choledochal dilation. Physician comment "the secretion of bile was blocked by choledochal swelling". The patient was diagnosed with bilirubinuria and liver carcinoma. On —— the patient underwent a hepatectomy including three quarters of his liver and remaining liver and jejunum were connected. The carcinoma was observed only in his liver without metastasis. Liver carcinoma and bile duct obstruction improved. A pathological examination revealed a grade 3 hepatocellular carcinoma of multiple patterns measuring 4.3x2.7x2cm in size. The patient was discharged from the hospital or ——

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4	2008-03848	65M Japan	Liver disorder	Hachimi-jio-gan (May 08 to unk)	Alcoholic liver disorder "excessive drinking"	2-6 weeks Dc'd silodosin Outcome unknown	AST, ALT "around 3000" Concomitant Chinese medicine , "excessive drinking", very limited information.

In May 2008 a 65-year-old male began treatment with silodosin 8mg QD and Chinese medicine (Hachimi-jio-gan) for bladder outlet obstruction associated with BPH. On 6/13/08 labs revealed AST and ALT values around 3000. Silodosin was discontinued. The patient was reported to have an alcoholic liver disorder "due to his hard drinking". No other information was provided.

#	Mfr #	Age/sex location	Event Terms Reported	Co[illegible]nitant medications	Medical history b(6)	Latency/action taken/outcome	Maximum repor[illegible] liver fun[illegible] tests Comments
5	2007-02194	84M Japan	Hepatitis fulminant Hepatic cirrhosis Hepatic encephalopathy Prothrombin time prolonged Hypoglycaemia Oedema peripheral Ascites Pleural effusion Hepatic atrophy Altered state of consciousness	Cernilton (1966 to unk) Domperidone (11/07/06 to unk) Levercol (11/22/06 to unk)	Gastric cancer Total gastric resection — Impaired urination associated with BPH "Drinker"	16 days after restarting silodosin post surgery Dc'd all medications, Began steroid infusion, plasma exchange, stronger Neo minophagen C, MAP, platelets Recovered "with cirrhosis as sequela"	ALT 1820 IU/L AST 1880 IU/L GGTP 337 IU/L LDH 897 IU/L T Bili 1.7mg/dL

In June 2006 an 84-year-old male patient began treatment with silodosin 8mg daily for bladder outlet obstruction associated with BPH. On —— Silodosin was temporarily discontinued due to surgery. On —— the patient underwent a total gastrectomy due to gastric cancer. Approximately 11/22/06 Silodosin was resumed. On 12/8/06 a blood test was performed and it showed an increase in hepatic enzymes (AST 63, ALT 71). On 1/12/07 hepatic enzymes increased more (AST 1400, ALT 1100). On —— the patient was admitted and all medications were discontinued. On an unspecified date edema of both lower limbs and CK increased were observed. On —— the hepatic function worsened with PT prolongation, hypoglycemia, hepatic encephalopathy with hepatic atrophy without brain edema and hepatic coma (AST 938, ALT 1240). Steroid therapy was started. The patient was transferred to another hospital due to the diagnosis of severe hepatitis. On 1/31/07 hepatic intra-arterial steroid infusion, plasma exchange and Stronger Neo minophagen C injection were started. Mannitol-adenosine-phosphate and platelets were administered. A drug induced lymphocyte stimulation test was negative. Physician comments: "Viruses and autoimmune disease were negative judging from the results of the blood tests." On 2/14/07 the patient recovered, however he was diagnosed as having hepatic cirrhosis as sequela. 2/15/07 labs revealed AST 26, ALT50, GGTP 92, T Bili 1.7mg/dL LDH 427.

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6	2008-00648	78M Japan	Jaundice Liver disorder	Ursodeoxycholic acid Proheparum Norvasc Senna leaf Halcion Mexitil	Chronic Hepatitis C Hypertension Insomnia Spinal column stenosis Arrhythmia Surgery (date unk)	2.5 months Dc'd silodosin, administered Neo-minophagen C. Pt recovered	ALT 635 AST 662 ALP 346 GGTP 361 LDH 412 T Bili 4.45 mg/dL D Bili 2.74 mg/dL Chronic hep C, LFTs improved after silodosin dc'd

In 2006 a 78-year-old male patient began treatment with tamsulosin for BPH. The patient had chronic hepatitis C (unk when diagnosed). In August 2007 labs showed AST 33, ALT 22, ALP 208, LDH 237, GGTP 17, T Bili 1.03mg/dL and D Bili 0.1 mg/dL. On 10/4/07 the patient as switched from tamsulosin to silodosin 4 mg bid. On 10/23/07 labs revealed AST 38, ALT 20, ALP 263, LDH 247, GGTP 19, T Bili 0.68 mg/dL and D bili 0.05mg/dL. On 12/18/07 the patient was found to have aggravated hepatic function. "The possibility of obliterative liver disorder was deselected by an echography." Lab data showed AST 662, ALT 635, ALP 346, GGTP

#	Mfr #	Age/sex location	Event Terms Reported	Co nitant medications	Medical history	Latency/action taken/outcome	Maximum epot. liver fun tests Comments
361, LDH 412, T Bili 4.45 mg/dL and D bili 2.74 mg/dL. Silodosin was discontinued. Neo-minophagen C was started. On 12/25/07 labs revealed AST 99, ALT 156, ALP 283, LDH 228, GGTP 276, T-bili 3.33 mg/dL and D bili 2.10mg/dL. On — the patient was discharged. On 1/22/08 lab data showed AST 79, ALT 73, ALP 329, LDH 347, GGTP 170, T-bili 1.63mg/dl and D Bili 0.47mg/dL.							

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