

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-187

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE

DATE: 17 January 2008

FROM: John R. Senior, M.D., Associate Director for Science, Office of Surveillance and Epidemiology (OSE)

TO: Debra Birnkrant, M.D., Director, Division of Antiviral Products (DAVP)
Charu Mullick, M.D., Medical Officer, DAVP

VIA: Mark Avigan, M.D., Director, Division of Drug Risk Evaluation (DDRE)
Gerald Dal Pan, M.D., Director, OSE

SUBJECT: Case of possible liver injury in patients treated with etravirine (TMC125) under IND 63,646 and NDA 22-187; OSE consultation request 2007-2460.

Documents reviewed:

- 1) Consultation request via e-mail from Dr. Charu Mullick (medical reviewer) dated 29 November and formal written request dated 28 November from Dr. Anne Marie Russell (regulatory project manager) of DAVP, with description of a case of liver injury, with requested date of response by 27 December 2007.
- 2) MedWatch report from Tibotec GB-JNJFOC-20070704917 dated 16 November 2007 concerning a serious (life-threatening, hospitalized) adverse event of hepatotoxicity on or about _____, received by manufacturer from a "private" source in the United Kingdom on 23 July 2007.
- 3) Medical report from the _____ concerning patient _____ sent by fax to USA _____ on 27 November 2007, including many more details and report of liver biopsy done on _____.
- 4) I had started to work on this consultation in early December but was interrupted by a series of urgent other requests that came in then, followed by my being away on leave 19 December to 7 January. With apologies for the delay in getting to assess this case, I now return to its consideration.

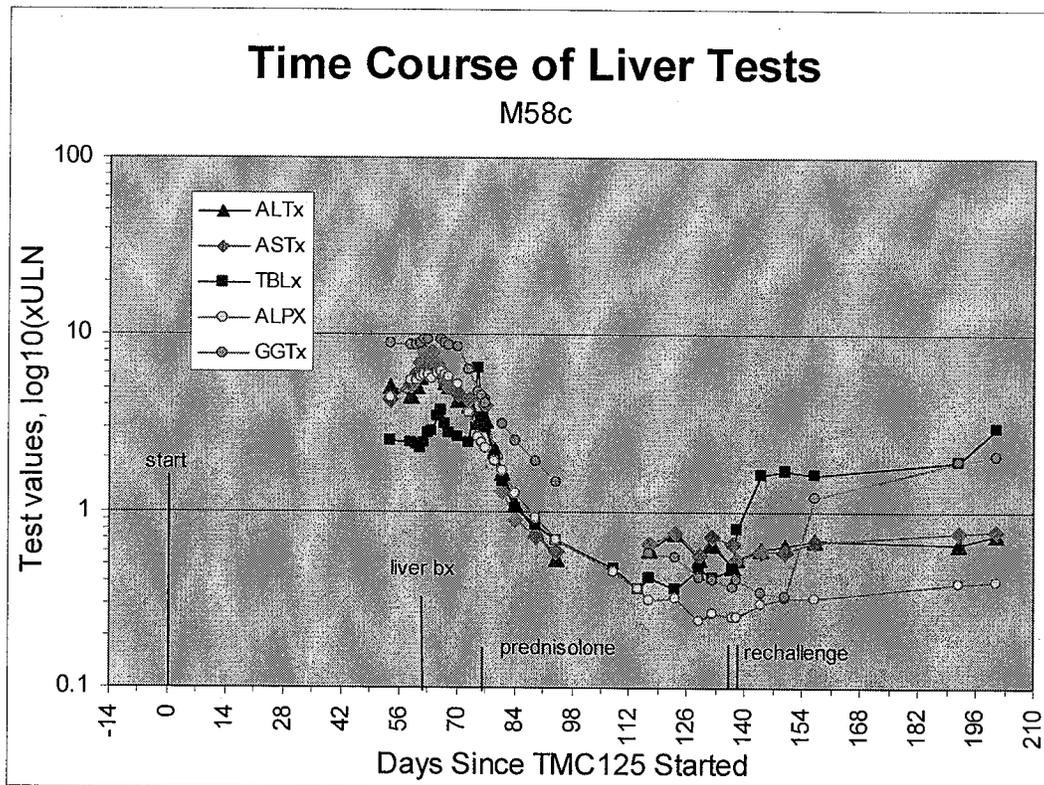
As initially reported to MedWatch, patient — a 58-year-old male (born _____), was on treatment for human immunodeficiency virus type 1 (HIV-1). He was started on a combination of oral darunavir (Prezista) 600 mg b.i.d. on 12 April 2007 and oral etravirine (TMC125) 200 mg b.i.d. on 14 April 2007, in addition to emtracitabine-tenofovir (Truvada), raltegravir (MK-0518, Isentress, Merck), ritonavir, lamivudine (all for HIV treatment), cotrimoxazole for Pneumocystis carinii pneumonia, lansoprazole and folic acid. He had been diagnosed as positive for HIV in 1991, had esophageal candidiasis in 1994, and had been on a great variety of medications over the years. He was said to have a history of rash when taking co-trimoxazole (sulfamethoxazole-trimethoprim). He was said to be "extensively antiretroviral experienced," with triple class resistance. Use of the darunavir-etravirine (TMC114-TMC125) combination was an attempt to optimize his anti-HIV treatment.

About the end of May 2007, he developed nausea, fatigue, abdominal discomfort, a maculopapular skin rash, and "low mood." On examination he was jaundiced, had hepatomegaly of 2 finger-breadths below the right costal margin, and a palpable spleen tip. He claimed to be a non-smoker, used minimal alcohol and no herbal or alternative medications, had a single sexual partner, worked as a _____, and had not traveled. Laboratory test results on _____ were reported "elevated" for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and total bilirubin (TBL). His co-trimoxazole (also called Septrin [probably what is called Septra in the United States]: sulfamethoxazole-trimethoprim) was stopped on 3 June, but the MedWatch details are incomplete, and the _____ report that was received later was much clearer.

According to the supplementary hospital report, the patient was American, under care at the _____ since 2001. His nadir for CD4 count was said to have been 48, but it was a little higher at 151 (8%) when the new regimen was started. He had a history of Septra-induced rash in the USA in 1997, and had become resistant to triple-class antiretroviral therapy. In April 2007 when he was started on the darunavir-etravirine program, he had a HIV viral load of >67,000; at that time his liver tests were said to be normal. Onset of liver problems was detected by non-specific symptoms of fatigue, nausea, abdominal discomfort, but no fever, in late May, about 6 weeks after starting darunavir-etravirine, along with a maculopapular skin rash, for which the sulfamethoxazole-trimethoprim was stopped on 3 June. He was jaundiced, with elevations of serum aminotransferases but even higher of the more cholestatic indicators ALP, GGT, and TBL. Workup was negative for viral hepatitis A, B, C, and E, cytomegalovirus and Epstein-Barr virus. Ultrasound of the liver did not show fatty liver; there was no evidence of autoimmune or alcoholic hepatitis. Liver biopsy on _____ showed acute diffuse portal and parenchymal hepatitis with focal bridging necrosis, no increase in fat or lymphoid aggregates, and few eosinophils. The histologic picture was consistent with the clinical diagnosis of probable acute drug-induced liver injury. The darunavir and etravirine were stopped on 14 and 16 June, respectively, and it was initially thought that darunavir was the likely cause of the acute hepatitis.

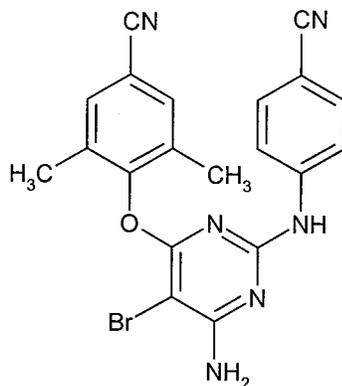
Although blood count data were not provided, it was stated that his blood hemoglobin (Hgb) had been declining since early June, with very dark urine and Hgb 8.6 g/dL, despite a decline in the serum bilirubin by _____. He was admitted for transfusion, but had an acute hemolytic reaction and a further drop in Hgb to 6.5 g/dL or _____ at which time prednisolone was started on advice of a hematology consultant for treatment of drug-induced hemolytic anemia, although it was not clear which drug might have been responsible. His HIV viral load, which had fallen from >67,000 in April to <50 in early June, rebounded to 307,000 on _____ but his Hgb had improved to 11.3 g/dL. Foscarnet was introduced, to bring down the HIV load. It was decided not to restart the darunavir, considered the more likely cause of the hepatitis. The prednisolone was reduced from 1 mg/kg (about 70 mg/day) to 50 mg/day on 16 July, by which time all of the liver tests had returned to the normal range except the GGT which was declining. On 28 August, etravirine was restarted, but within 24 hours an itchy, generalized, erythematous rash developed. The etravirine was stopped, and was replaced by atazanavir, which was followed by a recurrent rise in TBL but not in the serum ALT, AST, or ALP.

The _____ team continued to struggle with the task of controlling his resistant HIV infection without inducing drug reactions of hepatitis, hemolytic anemia, and skin rash.



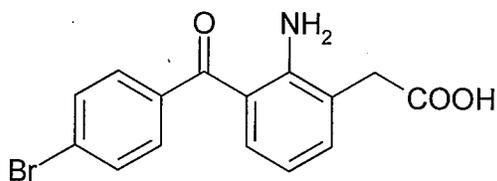
Comment: It may be seen from the graphic plot of the liver test values over time that the onset of the hepatic abnormalities was not detected until the patient was already jaundiced and the enzyme activities were quite high; it seems likely that the first test abnormalities had begun some time before occurrence of symptoms led to testing for serum chemistries. The markers of cholestatic injury (ALP, GGT, TBL) were prominent at the time of detection, and it seems likely that this was not a purely or predominantly hepatocellular injury even initially, although the liver biopsy was reported not to show cholestasis. This is a most complex case in which multiple adverse effects occurred in a patient on a large number of drugs, and it is not clear that a single drug caused all the problems. The acute hepatic reaction probably started at least a couple of weeks before it was detected, and it was fairly far advanced by the time of detection, with a mixed picture of hepatocellular and cholestatic injury, probably drug-induced. The two most likely candidates were darunavir and etravirine, which had been started in mid-April. The attending staff felt that darunavir was the more likely cause, and I do not find evidence against that conclusion. The rash, attributed to the sulfamethoxazole-trimethoprim combination because of the patient's history, may have been wrongly so, because on the rechallenge by etravirine in late August the rash appeared again very promptly. The rechallenge with etravirine was not long enough to show whether or not it might also have caused the hepatic reaction. The cause of the acute hemolytic anemia was never determined, and prednisolone suppression of the reaction did nothing to establish its cause. Finally, substituting atazanavir for etravirine in late August appears to have been responsible for the rise in serum bilirubin without increase in ALT, AST, or ALP, probably through its effect on inhibition of glucuronidation (via uridine-diphospho pyridine glucuronisyl transferase), a well known benign effect and not a recurrence of the hepatitis.

Etravirine, the subject of this consultation request, is a relatively new non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1 developed to be effective against HIV-1 variants that have become resistant by the Tibotec-Virco group now a subsidiary of Johnson and Johnson. The compound was originally developed by Tibotec in collaboration with the Janssen Research Foundation, but the latter is no longer involved in the development of etravirine. The compound is a diarylpyrimidine chosen from a series of that class in search for potency against resistant and wild-type HIV strains carrying mutations (Andries et al., 2004; Das et al., 2004).

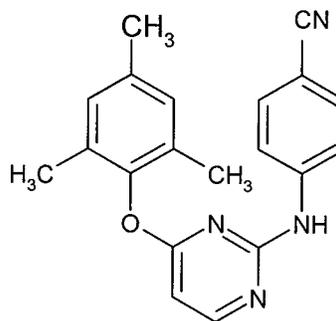


etravirine (TMC125)

Comment: The story of how this compound was developed and selected is well described (Das et al. 2004), and follows the earlier description of the diarylpyrimidine (DAPY) compounds, which were selected for their ability to be effective in cell culture against HIV-1 mutants resistant to the earlier NNRTIs efavirenz and nevirapine that had been selected for antagonism to the wild-type HIV-1 (Ludovici et al., 2001) It may be of interest that Das et al. (2004) reported that another of the DAPY compound, TMC120-R147681, also appeared to be a good candidate. That compound differed from TMC125 in lacking the pyrimidinyl bromide moiety, which could potentially be of interest as a toxic structure, reminiscent of bromfenac. TMC120 does not have an aryl bromide, but the DAPY series appears to have been explored for efficacy and not for toxicity.



bromfenac



(TMC120)

It is difficult to draw firm conclusions from this interesting and extremely challenging case, in which so many adverse effects were seen in a patient on so many drugs. Speculation on whether TMC120 might be less likely than TMC125 to cause idiosyncratic hepatotoxicity does not lead to any firmer conclusions. The clinical staff felt the darunavir was perhaps the more likely of the two drugs to have been responsible for the hepatic injury, but they provided no reasons for that choice. The very brief, one-day rechallenge with etravirine, stopped because of the recurrent skin rash very promptly, cannot be taken as evidence against its possible causal relation for the liver reaction. Postive rechallenges, if adequate in dose and duration, are very strong evidence for causality, if a single drug is changed, but negative reactions are much less useful because of the very common adaptation by the liver to new drugs or other xenobiotic substances to which it is exposed.

Therefore, since the consultation request is centered on etravirine, we can only conclude that maybe it may have had a role in causing the hepatic injury, but the data do not permit any more convincing conclusion, and certainly not enough to affect a regulatory decision.

Recommendations:

I do not find clear evidence that etravirine was likely to have caused the fairly severe mixed hepatic injury in this patient, although its role cannot be ignored. I am suspicious of the pyrimidinyl bromide moiety of TMC125, but only further clinical experience with the drug will tell the tale. If it is effective in treating drug resistant AIDS, it might do more good than harm, but we shall also need to be alert for any more suggestions of its possible causation of skin rashes or other hypersensitivity manifestations.

No regulatory modification is recommended, but we should be watching this drug carefully.

John R. Senior, M.D.

cc: OSE 2007-2460
G. DalPan, OSE
M. Avigan, OSE/DDRE
D. Birnkrant, DAVP
C. Mullick, DAVP
A. Crandall, DAVP

REFERENCES

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Ludovici DW, DeCorte BL, Kukla MJ, Ye H, Ho CY, Lichtenstein MA, et al. Evolution of anti-HIV drug candidates. Part 3: diarylpyrimidine (DAPY) analogues. *Bioorg Med Chem Lett*. 2002; 11(17):2235-9.

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/s/

John Senior
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MEDICAL OFFICER
Submitted to DFS 18 January 2008



**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: November 30, 2007

To: Debra B. Birkant, M.D., Director
Division of Antiviral Products

Thru: Toni Piazza-Hepp, Pharm.D., Deputy Director
Division of Surveillance, Research and Communication Support

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
Division of Surveillance, Research and Communication Support

Subject: DSRCS review of patient labeling

Drug Name(s): Etravirine Tablets

Application Type/Number: NDA 22-187

Applicant/sponsor: Tibotec, Incorporated

OSE RCM #: 2007-2247

INTRODUCTION

Tibotec, Incorporated submitted a New Drug Application, NDA 22-187 for etravirine Tablets to the Agency in 2 parts. The first part was submitted on June 4, 2007 and partially resubmitted on July 6, 2007. The second part of the application was submitted on July 17, 2007. The July 17, 2007 submission contains revised labeling, which includes patient labeling in the form of a Patient Package Insert (PPI). This application was granted a priority review and Fast Track designation by the Agency. A trade name has not yet been determined for etravirine.

The proposed indication for etravirine Tablets is "for the treatment of HIV-1 infection in antiretroviral treatment-experienced adult patients."

DSRCS has been requested to review the patient labeling submitted for this NDA.

MATERIAL REVIEWED

Professional labeling and Patient Package Insert (PPI) dated July 17, 2007.

DISCUSSION

See the attached document for our suggested changes to the PPI. The purpose of patient information is to enhance appropriate use and to provide important risk information about medications. We have simplified wording where possible, made the PPI consistent with the PI, and removed unnecessary information. We have also moved certain pieces of information to more appropriate sections of the PPI. Our changes are consistent with current research to improve risk communication to a wide variety of audiences including those with lower levels of literacy.

Comments to the review division are ***bolded, underlined and italicized***.

CONCLUSIONS AND RECOMMENDATIONS

- A PPI for etravirine Tablets is voluntary. Etravirine Tablets is packaged in bottles of 120. It is likely that a single PPI will be attached to a bottle of etravirine Tablets, which will then be used to fill multiple prescriptions. Unless etravirine Tablets is dispensed in unit-of-use packaging with the PPI enclosed, patients are highly unlikely to receive the PPI. The sponsor should clarify how they intend to distribute the PPI to patients.
- We recommend not including the lengthy list of medications. Patients may feel safe when their medication does not appear on a list. If you feel that this information should be kept in the PPI, ^{If} keeping the table, add St. John's Wort to the appropriate section; we removed it from the statement to tell your doctor about all the medicines you take.]
- The side effects section of the PPI has been re-ordered so that _____
- All relevant future changes to the PI should also be reflected in the PPI.
- We are providing the review division with marked up and clean copies of our revisions to the PPI in Word. We recommend that you use the clean copy as the working document.

Please let us know if you have any questions.

15 Page(s) Withheld

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✓ Draft Labeling

 Deliberative Process

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/s/

Sharon Mills
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DRUG SAFETY OFFICE REVIEWER

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DRUG SAFETY OFFICE REVIEWER