

# Exploration of Four Outcomes: Outcomes and labeling information, in conjunction with other evidence (FNIH grant # OVERHA09OMOP0)

## Final Report

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## Introduction

The goal of this project was to establish a set of gold standard drug-outcome pairs for use in evaluating signal detection methodologies using the OMOP dataset. We sought to identify drugs known to cause one or more of the following outcomes: acute myocardial infarction, gastrointestinal bleeding, acute renal failure, and acute liver injury.

Our proposed identification strategy was a combination of label review (via automated and manual methods), clinician assessment, and limited review of the literature.

## Methods

### Drug and Outcome Identification

#### *Drug Selection*

A list of drugs (n=28092 OMOP concept IDs) was provided by the OMOP team and comprised all non-combination drugs taken by at least one patient in the OMOP dataset. Using the OMOP concept table, we determined the RxNorm identifiers (RxCUIs) for the provided drug list. We then mapped these RxCUIs to Structured Product Label (SPL) set identifiers (n=5333).

#### *Health Outcome Selection*

For the four conditions of interest, we used the MedDRA hierarchy to determine appropriate search terms. Our initial queries were as follows:

#### GI Bleed

```
SELECT * FROM MedDRA_ref where  
HLGT_CONCEPT_NAME='Gastrointestinal ulceration and  
perforation' and PT_CONCEPT_NAME like '%haem%' order by  
PT_CONCEPT_NAME
```

```
SELECT * FROM MedDRA_ref where  
HLT_CONCEPT_NAME='Gastrointestinal haemorrhages' order by  
PT_CONCEPT_NAME
```

```
SELECT * FROM MedDRA_ref where  
HLGT_CONCEPT_NAME='Gastrointestinal haemorrhages NEC' order by  
PT_CONCEPT_NAME
```

#### Hepatic Injury

```
SELECT * FROM MedDRA_ref where  
HLT_CONCEPT_NAME='Hepatocellular damage and hepatitis NEC'  
order by PT_CONCEPT_NAME
```

```
SELECT * FROM MedDRA_ref where HLT_CONCEPT_NAME='Hepatic  
failure and associated disorders' order by PT_CONCEPT_NAME
```

```
SELECT * FROM MedDRA_ref where HLT_CONCEPT_NAME='Hepatic and  
hepatobiliary disorders NEC' order by PT_CONCEPT_NAME
```

### **Renal Failure**

```
SELECT * FROM MedDRA_ref where HLT_CONCEPT_NAME='Renal  
disorders (excl nephropathies)' order by PT_CONCEPT_NAME
```

### **Myocardial Infarction**

```
SELECT * FROM MedDRA_ref where PT_CONCEPT_NAME like  
'%myocardial infarction%'
```

We manually reviewed the resulting terms and removed those that were not consistent with the four primary outcomes. We reviewed our list with the OMOP board, made some recommended changes, then settled on a final list of 177 MedDRA lower level terms (see Appendix A).

### **Label Review**

We previously developed a natural language processing tool known as the Structured Product Label Information Coder and Extractor (SPLICER). SPLICER uses a series of algorithms to identify adverse reactions in drug labels and map them to the Medical Dictionary of Regulatory Activities (MedDRA). For this analysis, we used a database of ADR information for all SPLs present on the DailyMed website as of 1/22/2011.

We looked at SPLICER data for the 5333 product labels, seeking the presence of any of the 177 MedDRA terms meeting one of the following criteria:

- 1) Term present in a black box warning
- 2) Term present in the 'Warnings and Precautions' section and a term within the same MedDRA High-Level Group present in the 'Adverse Reactions' section

Note: The cross referencing with the Adverse Reactions section in the latter criterion was necessary to greatly reduce false positive ADRs.

This process identified 484 potential DOI-HOI pairs.

SPLICER may produce false positives in settings where the term is a patient condition (e.g., patients with diabetes) rather than a true adverse reaction. In order to remove these and other false positives, we manually reviewed the 484 candidate pairs. Of these, 162 were removed, some due to SPLICER error but others due to more subtle findings such as causation of an HOI only when taken with another drug. The final list of 312 pairs is found in Appendix B.

### **Clinician Review**

For the 312 pairs, we conducted a review by the investigators—both practicing clinicians—to assess whether these adverse reactions were likely true positives. The authors independently marked each pair as either Yes, No, or Don't Know. Where appropriate, the authors indicated the source of their judgment—personal clinical experience or based on literature evidence. The results were as follows:

	R1	Y	N	DK
R2				
Y		57	0	41
N		0	0	0
DK		42	5	167

- 57 pairs were marked true positives by both reviewers
- 83 pairs were suggestive, with one reviewer marking true while the other stating 'don't know'
- 5 pairs were unlikely, marked as No by one reviewer and DK by the other
- The majority of pairs, 167, were marked as Don't Know by both reviewers
- In no case did the reviewers disagree with one marking Yes and the other marking No

Full results found in Appendix C.

### **Literature Review**

For a subset of medications, we performed literature review. The goal of this review was to demonstrate an approach to gathering and interpreting the evidence for labeled HOI-DOI pairs. Our review covered 8 medications and was based on PubMed search.

#### *Pairs Reviewed*

#### **Avandia (Rosiglitazone) and myocardial infarction**

The Avandia label states that patients are at a statistically significant increased risk of acute MI in the Black Box section of the label. In fact, directly in the Black Box

section, the label cites a reference to a meta-analysis study of 52 clinical trials (consisting of over 16,000 patients) conducted by the FDA in 2010 which provided statistically significant evidence of this increased risk.

A PubMed search for 'rosiglitazone' and 'myocardial' revealed 190 papers, including several describing long-term, prospective randomized controlled clinical trials.

Apart from the studies included in the meta-analysis described above, there were other significant studies noted upon review of these 190 papers. In 2006 in Lancet, Gerstein et al (PMID: 16997664) published results of a study involving 5,269 subjects who took rosiglitazone 8 mg for 3 years. They found that the incidence of MI was higher in patients who took rosiglitazone and ramipril compared to patients taking ramipril alone. They also found that in patients taking rosiglitazone alone, there was no statistically significant increase in MI compared to the placebo group.

In another meta-analysis conducted in 2007 by Singh et al (PMID: 17848653) and published in JAMA, they examined 42 clinical trials. They found that in the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06). Their conclusions were that rosiglitazone was associated with a significant increase in the risk of myocardial infarction.

Several papers (PMID: 18706281) were also noted that offer criticisms of the meta-analysis and claim several limitations. They generally conclude that the data showing the increased risk for myocardial infarction and death from cardiovascular disease for diabetic patients taking rosiglitazone are inconclusive.

*Conclusion: Supported by multiple long-term, prospective randomized controlled clinical trials. Despite possible limitations of the meta-analysis, there is preponderance of evidence to suggest rosiglitazone increases risk of MI. Would use as a gold standard DOI-HOI pair.*

### **Altace(ramipril) and hepatic failure**

In the Warnings section, the Altace label states 'Rarely, ACE inhibitors, including Altace, have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death'

A PubMed search for 'ramipril' and 'hepatic failure' revealed 11 papers, and a search for 'ramipril' and 'hepatic necrosis' revealed 1 paper.

Yeung et al in 2003 (PMID:14567716) report in the Archives of Pathology & Laboratory Medicine results of a study investigating ramipril-associated hepatotoxicity. The study consists of case reports from three patients who

developed hepatitis with and without jaundice after receiving ramipril. The onset of symptoms after initiating ramipril therapy ranged from 3-8 weeks. In two of the patients hepatitis resolved after stopping the drug, while the third patient went on to develop biliary cirrhosis.

None of the other papers reviewed described studies investigating ramipril and hepatic failure. Another PUBMED search for 'ACE inhibitors' and 'hepatotoxicity' returned a paper by Hagley et al (PMID: 8292107) published in 1993 in The Annals of Pharmacotherapy. They reviewed published reports of hepatotoxicity associated with ACE inhibitors (not ramipril) and explored possible mechanisms of injury. Nineteen cases of ACE-inhibitor-associated hepatotoxicity were presented. They concluded that hepatotoxicity, usually cholestatic in nature, has been reported with captopril, enalapril, and lisinopril use and that potential mechanisms of injury include idiopathic hypersensitivity and modulation of eicosanoid metabolism by inhibition of kininase II and subsequent increased hepatic bradykinin activity. They also concluded that hepatotoxicity resolves if ACE inhibitors are stopped but may progress to liver failure if treatment is continued.

*Conclusion: Supported in the literature by case reports only and is exceedingly rare. Because of lack of definitive evidence, would not use as a gold standard DOI-HOI pair.*

### **Rifampin and renal failure**

In the Precautions section, the rifampin label states 'Doses of rifampin greater than 600 mg given once or twice weekly have resulted in a higher incidence of adverse reactions, including the "flu syndrome" (fever, chills and malaise), hematopoietic reactions (leukopenia, thrombocytopenia, or acute hemolytic anemia), cutaneous, gastrointestinal and hepatic reactions, shortness of breath, shock, anaphylaxis and renal failure.'

A PubMed search for 'rifampin' and 'renal failure' revealed 313 papers. There were no long-term, prospective randomized controlled clinical trials investigating the association of rifampin and renal failure. The vast majority of the studies were case reports, dating back as far as 1970. The most recent case study was from 2011. The more significant case studies are outlined below.

In 1998, Covic et al (PMID:9568851) published in the Journal of Nephrology Dialysis Transplantation the results of a retrospective case study report involving 60 who were admitted to a Romanian dialysis centre from 1987 to 1995 for acute renal failure (ARF) following re-treatment with rifampicin. They concluded that ARF after treatment with rifampin is not an uncommon condition, especially when tuberculosis prevalence is high, but renal prognosis is usually favourable.

Covic et al (PMID:15195854) again in 2004 published the results of another case study involving 170 ARF patients treated at Romanian dialysis centers between

1974-2001 and 1988-2001. The most frequent clinical features of rifampicin-induced ARF were: Anuria, gastro-intestinal (abdominal pain, nausea, vomiting and diarrhoea) and "flu-like" symptoms. The outcome of rifampicin-induced ARF was generally favourable, with complete recovery of the renal function within 30 days in 52% of the cases and within 90 days in 92% of the cases.

In the most recent published study investigating rifampin and ARF, Schubert et al (PMID:20497752) in 2010 reported a retrospective case study of 41 adult patients with a biopsy-proven diagnosis of acute tubulointerstitial nephritis (ATIN) on rifampin for tuberculosis. The average duration of antituberculosis therapy was 19 days before presentation and the duration of the acute illness averaged 5 days. Rifampin was discontinued in 37 (90%) cases. Nine (22%) patients required dialysis. One patient failed to recover renal function and 4 (10%) patients died. Mortality was related to overwhelming tuberculosis infection. The main factor predicting the need for dialysis was duration of oliguria. Their conclusion was that ATIN is a rare, but serious complication of repeat antituberculous therapy mainly due to re-exposure to rifampin. Although the renal prognosis is generally good the disease does carry significant morbidity and mortality risks.

Due to the volume of the published case reports over the past 40 years, the evidence is convincing that likely a true association exists between rifampin and renal failure. But since there have been no prospective, randomized controlled clinical trials documenting this association, it perhaps should not be considered for evaluation of OMOP methodologies.

*Conclusion: Likely true relationship but additional data required to define as gold standard for OMOP methodology testing.*

### **Rivastigmine (Exelon) and Gastrointestinal bleeding**

In the Warnings section, the rivastigmine label states 'Because of their pharmacological action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal antiinflammatory drugs (NSAIDs). Clinical studies of Exelon have shown no significant increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.'

PubMed search for 'rivastigmine and 'bleed', 'rivastigmine' and 'hemorrhage', 'rivastigmine' and 'gastrointestinal', 'rivastigmine' and 'ulcer' revealed no relevant results.

Our findings support the claim in the label that there are no published clinical studies (including case reports) that provide evidence that rivastigmine increases the incidence of gastrointestinal bleeding. The mention of gastrointestinal bleeding in the label is in reference to a **class effect** of cholinesterase inhibitors in general causing an increase of gastric acid secretion which can lead to gastrointestinal bleeding.

The literature does not contain sufficient data to support this relationship.

*Conclusion: Not supported by the literature.*

### **Ciprofloxacin and Hepatic Injury**

The label states that ciprofloxacin may cause hepatic necrosis.

PubMed search for 'ciprofloxacin' and 'hepatic necrosis' returns 9 results, including a review from 2004 entitled "Ciprofloxacin-induced acute liver injury: case report and review of literature." This paper notes the presence of 14 case reports of cipro-induced hepatic necrosis, and presents the clinical-pathological characteristics of this reaction. According to the study's conclusions, it appears likely that the reaction is predominantly dose-independent idiosyncratic, and, more rarely, dose-dependent toxic.

Another study in 2008 entitled "Ciprofloxacin-induced acute cholestatic liver injury and associated renal failure. Case report and review" provides a similar case report and review of the literature. Here, too, a dose-independent idiosyncratic reaction is suspected.

A search for 'ciprofloxacin' and 'liver injury' revealed additional results. The most rigorous evaluation is a 2011 study entitled "Clinical and Histopathologic Features of Fluoroquinolone-Induced Liver Injury." This study looked at 6 years worth of data from the Drug-induced Liver Injury Network (DLIN). Of the 679 registrants, 12 had fluoroquinolone induced injuries, 6 of which were caused by ciprofloxacin. Both hepatocellular and cholestatic injury were seen equally. Overall it was felt to be most often a hypersensitivity reaction, with clear immunoallergic factors present.

The relationship between cipro and liver injury does appear to be true, but is very very rare. No prospective studies or large observational studies have been performed. So while I believe it meets the criteria for true association, it is not recommended for evaluation of OMOP methodologies.

*Conclusion: Supported by the literature but exceedingly rare. Would not use as a gold standard DOI-HOI pair.*

## **Frovatriptan and Myocardial Infarction**

Frova lists acute MI in the Warnings section of the label. This is often attributed to coronary vasospasm.

A PubMed search for 'triptan' and 'myocardial' revealed 13 papers, including several observational studies. A 2004 study published in *Neurology* entitled "Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice" looked at 63,575 migraine patients, 13,664 of whom received a triptan. There was no increased risk of MI in this population.

A retrospective cohort 2004 study in *Headache* looked at 130,411 patients with migraine and 130,411 matched controls using the Ingenix UnitedHealthcare database. MI rates were identical (1.4%) in the two groups, and there was no increase in MI with triptan use.

A second 2004 study in *Headache* was a RCT involving 75 patients with known CAD and migraine history. The group Frovatriptan (2.5mg, low dose), showed no increase in EKG abnormalities and no MI's were recorded.

While the case reports have been noted, the risk is felt to be very low, on the order of 1 MI per 100,000 triptan treatments.

*Conclusion: Supported by pathophysiology and case reports, but previous observational studies have shown no increased risk. Would not use as a gold standard DOI-HOI pair.*

## **Exenatide (Byetta) and Renal Failure**

Byetta's label states that it has been known to cause "altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation."

A PubMed search of 'exenatide' and 'renal failure' reveals 10 results, including multiple case reports noting ischemic renal failure in patients taking Byetta in conjunction with an ACE/ARB and a diuretic. These reports were consistent and the condition was attributed to Byetta by the authors. No observational studies or RCT's are available. However, a review of Swiss pharmacovigilance signals from 2009 appears, stating a signal implicating exenatide in acute renal failure.

Overall the evidence is limited but convincing. This may require further observational data and of course controlling for baseline renal failure in patients with diabetes, but I believe it is a true relationship.



*Conclusion: Likely true relationship but additional data required to define as gold standard for OMOP methodology testing.*

## **Carbidopa and GI Bleed**

The label states upper gastrointestinal hemorrhage is a risk in patients with existing peptic ulcer disease.

PubMed search for 'carbidopa and 'bleed', 'carbidopa' and 'hemorrhage', 'carbidopa' and 'gastrointestinal', 'carbidopa' and 'ulcer' revealed no relevant results.

The literature does not contain sufficient data to support this relationship.

*Conclusion: Not supported by the literature.*

## **Discussion and Conclusions**

In this analysis, we used a combination of product labeling, clinician perspective, and literature review to explore potential gold standard drug-outcome pairs for use in evaluating OMOP statistical methods. We hope this report and the data produced herein will be of value to the OMOP team in identifying appropriate pairs for further review and analysis. Having gone through this process, we would like to offer some lessons learned.

### *HOIs in Labeling*

Technically, we learned a great deal about how to use natural language processing to better extract data from the Boxed Warnings and Warnings and Precautions sections of a drug label. In terms of content (and this will come as no surprise) we found inconsistencies in how and where manufacturers describe adverse reactions within labels. Presumably the placement of adverse reaction information is based on the extent of underlying evidence, but such rules were not immediately discernible on label review. Some outcomes were very robustly supported by the literature while others seemed to have little to no documentation available.

One frequently encountered challenge was dealing with cascading adverse events. For example, if a drug can cause hypotension, which in turn can cause renal failure, should this drug really be considered a causative agent of renal failure? A related issue was dealing with hypersensitivity reactions. If a drug causes an allergic response, are its downstream consequences relevant for our purposes? Another issue was complication related to co-administration or co-morbidity. This might include drugs that exacerbate GI bleeding when taken with a corticosteroid or drugs that can induce renal failure due to Tumor Lysis Syndrome (an expected result in

cancer chemotherapy). We addressed these issues in an *ad hoc* fashion during this analysis, but would recommend a more systematic consideration of such complex scenarios prior to future analyses.

### *Clinical Perspective*

It would be reasonable to assume that the authors have an above average knowledge of adverse drug reactions due to our research in drug safety. Nonetheless, the majority of the candidate drug-outcome pairs were clinically unknown to these reviewers. The fact that in no case did the reviewers directly disagree (i.e., one saying Yes and the other saying No) was reassuring. However, it was quite rare for a reviewer to say 'No' at all, given the breadth of knowledge necessary to claim that something is *not* caused by a particular drug. Of the 57 agreed upon drug-outcome pairs, the majority were 'classics' of medical training, from NSAIDs and GI Bleeding to Isoniazid and Liver Injury. These also tended to be more associated with actual clinical experience than just familiarity through the literature.

For future clinical review, we would recommend a question related to how frequently physicians use the medication in question. Perhaps a simple scale of 0-2 (never, rarely, frequently) would be sufficient.

### *Literature Review*

The strength of evidence varied widely for our DOI-HOI pairs. We took a fairly rudimentary approach—searching key terms on Medline, looking at study design and number of patients, judging size of effect—and did not dig into the clinical pharmacology literature. But this reflects the type of evidence that would persuade a clinician of causality. The greater challenge (and one that we happily return to the OMOP team for deeper consideration) is how to reconcile the notion of causality with detectability in a large observational database. In other words, while we have no doubt that ciprofloxacin can cause hepatic necrosis and is properly labeled as such, we would be hesitant to use it as a gold-standard DOI-HOI pair due to its rarity in the real-world setting.

It is our hope that the triangulation of different sources of evidence as currently suggested by the OMOP team will lead to successful identification of a set of high confidence DOI-HOI pairs.

## **Appendix A**

### *Health Outcomes of Interest (as defined by MedDRA lower level terms)*

MedDra Term	HOI
acute myocardial infarction	Myocardial Infarction
st segment elevation myocardial infarction	Myocardial Infarction
infarct myocardial	Myocardial Infarction
inferior myocardial infarction	Myocardial Infarction
myocardial infarct	Myocardial Infarction
myocardial infarction	Myocardial Infarction
myocardial reinfarction	Myocardial Infarction
Gastric bleeding	GI Bleed
Gastric hemorrhage	GI Bleed
Esophageal hemorrhage	GI Bleed
Bleeding esophageal varices	GI Bleed
Bleeding oesophageal varices	GI Bleed
Hemorrhage of colon	GI Bleed
Large intestinal hemorrhage	GI Bleed
Hemorrhage rectal	GI Bleed
Hemorrhage rectum	GI Bleed
Rectal bleeding	GI Bleed
Rectal haemorrhage	GI Bleed
Rectal hemorrhage	GI Bleed
Rectorrhagia	GI Bleed
Duodenal hemorrhage	GI Bleed
Small intestinal hemorrhage	GI Bleed
Bleeding gastrointestinal	GI Bleed
Gastrointestinal bleed	GI Bleed
Gastrointestinal bleeding	GI Bleed
Gastrointestinal haemorrhage	GI Bleed
Gastrointestinal haemorrhage NOS	GI Bleed
Gastrointestinal hemorrhage	GI Bleed
GI bleed	GI Bleed
GI hemorrhage	GI Bleed
Hemorrhage gastrointestinal	GI Bleed
Haematemesis	GI Bleed
Hematemesis	GI Bleed
Blood in stool	GI Bleed
Bloody stool	GI Bleed
Feces bloodstained	GI Bleed
Haematochezia	GI Bleed
Hematochezia	GI Bleed
Stool bloody	GI Bleed
Melena	GI Bleed
Tarry stools	GI Bleed
Upper gastrointestinal hemorrhage	GI Bleed
Enterocolitis hemorrhagic	GI Bleed
Hemorrhagic colitis	GI Bleed

Hemorrhagic enterocolitis	GI Bleed
Gastritis hemorrhagic	GI Bleed
Hemorrhagic gastritis	GI Bleed
Bloody diarrhea	GI Bleed
Diarrhea hemorrhagic	GI Bleed
Hemorrhagic diarrhea	GI Bleed
Duodenal ulcer hemorrhage	GI Bleed
Duodenal ulcer hemorrhagic	GI Bleed
Gastric ulcer hemorrhage	GI Bleed
Stomach ulcer hemorrhage	GI Bleed
Peptic ulcer hemorrhage	GI Bleed
Disorder hepatic	Liver Injury
Disorder liver	Liver Injury
Hepatic disease	Liver Injury
Hepatic impairment	Liver Injury
Hepatopathy	Liver Injury
Liver disorder	Liver Injury
Damage liver	Liver Injury
Hepatic damage	Liver Injury
Liver damage	Liver Injury
Liver injury	Liver Injury
Acute hepatic failure	Liver Injury
Acute liver failure	Liver Injury
Fulminant hepatic failure	Liver Injury
Hepatic failure	Liver Injury
Hepatic insufficiency	Liver Injury
Liver failure	Liver Injury
Acute cytolytic hepatitis	Liver Injury
Cytolytic hepatitis	Liver Injury
Hepatic cytolysis	Liver Injury
Hepatic necrosis	Liver Injury
Liver necrosis	Liver Injury
Necrosis hepatocellular	Liver Injury
Necrosis liver	Liver Injury
Hepatitis	Liver Injury
Nonspecific hepatitis	Liver Injury
Hepatitis fulminant	Liver Injury
Hepatitis acute toxic	Liver Injury
Hepatitis toxic	Liver Injury
Hepatocellular damage	Liver Injury
Hepatocellular injury	Liver Injury
Hepatotoxicity	Liver Injury
Mixed liver injury	Liver Injury
gamma-glutamyltransferase increased	Liver Injury
ggt increased	Liver Injury
gamma gt increased	Liver Injury
gamma glutamyl transpeptidase increased	Liver Injury
gamma-glutamyltransferase abnormal nos	Liver Injury
gammaglutamyltranspeptidase abnormal	Liver Injury

gamma-gt increased	Liver Injury
hepatic enzyme abnormal	Liver Injury
gamma gt abnormal	Liver Injury
liver enzyme abnormal	Liver Injury
gamma-glutamyltransferase abnormal	Liver Injury
guanase increased	Liver Injury
ggtp increase	Liver Injury
galactose elimination capacity test increased	Liver Injury
galactose elimination capacity test abnormal	Liver Injury
hepatic enzyme increased	Liver Injury
transaminases increased	Liver Injury
transaminase nos increased aggravated	Liver Injury
transaminase value increased	Liver Injury
serum transaminase increased	Liver Injury
transaminases abnormal	Liver Injury
total bile acids increased	Liver Injury
transaminase nos increased	Liver Injury
ggtp abnormal	Liver Injury
liver function tests multiple abnorm	Liver Injury
biliary enzyme increased	Liver Injury
hepatic enzymes increased	Liver Injury
nonspecific abnormal results of function study of liver	Liver Injury
abnormal lfts	Liver Injury
abnormal liver function tests	Liver Injury
liver function test abnormal	Liver Injury
function tests multiple liver abnormal	Liver Injury
liver function tests abnormal	Liver Injury
liver function tests abnormal nos	Liver Injury
liver function tests nos abnormal	Liver Injury
aspartate aminotransferase abnormal	Liver Injury
aspartate aminotransferase abnormal nos	Liver Injury
transaminase glutamic-oxalacetic increased	Liver Injury
got increased transient	Liver Injury
aspartate aminotransferase increase	Liver Injury
aspartate aminotransferase increased	Liver Injury
got increased	Liver Injury
sgot increased	Liver Injury
ast increased	Liver Injury
gpt abnormal	Liver Injury
alanine aminotransferase abnormal nos	Liver Injury
alanine aminotransferase abnormal	Liver Injury
sgpt increased	Liver Injury
alanine aminotransferase increased	Liver Injury
alanine aminotransferase increase	Liver Injury
transaminase glutamic-pyruvic increased	Liver Injury
alt increased	Liver Injury
gpt increased transient	Liver Injury
gpt increased	Liver Injury

blood bilirubin unconjugated increased	Liver Injury
indirect bilirubin increased	Liver Injury
bilirubin indirect increased	Liver Injury
bilirubin unconjugated increased	Liver Injury
bilirubins total increased	Liver Injury
blood bilirubin indirect increased	Liver Injury
direct bilirubin increased	Liver Injury
conjugated bilirubin level increased	Liver Injury
bilirubin conjugated increased	Liver Injury
direct bilirubin abnormal	Liver Injury
bilirubin conjugated abnormal	Liver Injury
bilirubin increased	Liver Injury
bilirubin abnormal	Liver Injury
blood bilirubin increased	Liver Injury
biliverdin increased	Liver Injury
serum bilirubin increased	Liver Injury
bilirubin value increased	Liver Injury
bilirubin total increased	Liver Injury
blood bilirubin abnormal	Liver Injury
Failure kidney	Acute Renal Failure
Kidney failure	Acute Renal Failure
Progressive renal failure	Acute Renal Failure
Renal failure	Acute Renal Failure
Renal failure aggravated	Acute Renal Failure
Renal failure NOS	Acute Renal Failure
Renal insufficiency	Acute Renal Failure
Acute kidney failure	Acute Renal Failure
Acute renal failure	Acute Renal Failure
Acute renal failure, unspecified	Acute Renal Failure
Acute renal insufficiency	Acute Renal Failure
Kidney failure acute	Acute Renal Failure
Renal failure acute	Acute Renal Failure
Shutdown renal	Acute Renal Failure
Azotemia	Acute Renal Failure
Uremia	Acute Renal Failure
Uremic syndrome	Acute Renal Failure

## **Appendix B**

*Drugs with a verified labeled association to the four target HOIs.*

DRUG_CONCEPT_NAME	HOI_CONCEPT_NAME	LABEL_SECTION
6-Aminocaproic Acid	RENAL FAILURE	Warnings/Precautions
6-Mercaptopurine	LIVER INJURY	Warnings/Precautions
abacavir	LIVER INJURY	Warnings/Precautions
abacavir	MI	Warnings/Precautions
Acarbose	LIVER INJURY	Warnings/Precautions
Acetazolamide	LIVER INJURY	Boxed Warning
Acitretin	LIVER INJURY	Boxed Warning
Acyclovir	RENAL FAILURE	Warnings/Precautions
Adenosine	MI	Warnings/Precautions
alatrofloxacin	LIVER INJURY	Boxed Warning
alatrofloxacin	RENAL FAILURE	Warnings/Precautions
Aldesleukin	GI BLEED	Boxed Warning
Aldesleukin	RENAL FAILURE	Boxed Warning
alefacept	LIVER INJURY	Warnings/Precautions
Allopurinol	LIVER INJURY	Warnings/Precautions
Allopurinol	RENAL FAILURE	Warnings/Precautions
almotriptan	MI	Warnings/Precautions
ambrisentan	LIVER INJURY	Warnings/Precautions
Amifostine	RENAL FAILURE	Warnings/Precautions
aminosalicylic acid	LIVER INJURY	Warnings/Precautions
Amiodarone	LIVER INJURY	Boxed Warning
Amiodarone	RENAL FAILURE	Warnings/Precautions
Amlodipine	MI	Warnings/Precautions
Amoxapine	MI	Warnings/Precautions
anidulafungin	LIVER INJURY	Warnings/Precautions
Aprotinin	RENAL FAILURE	Warnings/Precautions
Auranofin	GI BLEED	Warnings/Precautions
Azacitidine	RENAL FAILURE	Warnings/Precautions
Azithromycin	LIVER INJURY	Warnings/Precautions
Bacitracin	RENAL FAILURE	Boxed Warning
bendamustine	RENAL FAILURE	Warnings/Precautions
bevacizumab	GI BLEED	Boxed Warning
bevacizumab	MI	Warnings/Precautions
bicalutamide	LIVER INJURY	Warnings/Precautions
bortezomib	LIVER INJURY	Warnings/Precautions
bosentan	LIVER INJURY	Boxed Warning
Bromocriptine	GI BLEED	Warnings/Precautions
Bromocriptine	MI	Warnings/Precautions
Busulfan	LIVER INJURY	Warnings/Precautions
candesartan	RENAL FAILURE	Warnings/Precautions
capecitabine	GI BLEED	Warnings/Precautions
Capreomycin	RENAL FAILURE	Boxed Warning
Captopril	LIVER INJURY	Warnings/Precautions
Captopril	RENAL FAILURE	Warnings/Precautions
Carbamazepine	LIVER INJURY	Warnings/Precautions

Carbidopa	GI BLEED	Warnings/Precautions
carvedilol	RENAL FAILURE	Warnings/Precautions
Caspofungin	LIVER INJURY	Warnings/Precautions
Cefoxitin	RENAL FAILURE	Warnings/Precautions
celecoxib	GI BLEED	Warnings/Precautions
celecoxib	LIVER INJURY	Warnings/Precautions
celecoxib	MI	Boxed Warning
Chlorothiazide	RENAL FAILURE	Warnings/Precautions
Cidofovir	RENAL FAILURE	Boxed Warning
Ciprofloxacin	LIVER INJURY	Warnings/Precautions
Citalopram	GI BLEED	Warnings/Precautions
Clindamycin	GI BLEED	Warnings/Precautions
clofarabine	LIVER INJURY	Warnings/Precautions
clopidogrel	GI BLEED	Warnings/Precautions
Clozapine	LIVER INJURY	Warnings/Precautions
cyclobenzaprine	MI	Warnings/Precautions
Cyclosporine	LIVER INJURY	Warnings/Precautions
Cyclosporine	RENAL FAILURE	Warnings/Precautions
Cysteamine	RENAL FAILURE	Warnings/Precautions
Cytarabine	LIVER INJURY	Warnings/Precautions
cytotect	RENAL FAILURE	Warnings/Precautions
Dacarbazine	LIVER INJURY	Boxed Warning
darbepoetin alfa	MI	Warnings/Precautions
darunavir	LIVER INJURY	Warnings/Precautions
dasatinib	GI BLEED	Warnings/Precautions
deferasirox	GI BLEED	Boxed Warning
deferasirox	LIVER INJURY	Boxed Warning
deferasirox	RENAL FAILURE	Warnings/Precautions
desflurane	LIVER INJURY	Warnings/Precautions
Desipramine	MI	Warnings/Precautions
Desvenlafaxine	GI BLEED	Warnings/Precautions
Didanosine	LIVER INJURY	Warnings/Precautions
Diflunisal	GI BLEED	Warnings/Precautions
Diflunisal	LIVER INJURY	Warnings/Precautions
Diflunisal	MI	Boxed Warning
Diflunisal	RENAL FAILURE	Warnings/Precautions
Diltiazem	LIVER INJURY	Warnings/Precautions
Dipyridamole	LIVER INJURY	Warnings/Precautions
Dipyridamole	MI	Warnings/Precautions
Disulfiram	LIVER INJURY	Warnings/Precautions
docetaxel	GI BLEED	Warnings/Precautions
docetaxel	LIVER INJURY	Warnings/Precautions
Doxorubicin	LIVER INJURY	Warnings/Precautions
duloxetine	GI BLEED	Warnings/Precautions
efavirenz	LIVER INJURY	Warnings/Precautions
eletriptan	GI BLEED	Warnings/Precautions
eletriptan	MI	Warnings/Precautions
eltrombopag	LIVER INJURY	Boxed Warning
Enalaprilat	LIVER INJURY	Warnings/Precautions



Enalaprilat	MI	Warnings/Precautions
Enalaprilat	RENAL FAILURE	Warnings/Precautions
entecavir	LIVER INJURY	Warnings/Precautions
Epoetin Alfa	MI	Warnings/Precautions
Erythromycin	LIVER INJURY	Warnings/Precautions
Escitalopram	GI BLEED	Warnings/Precautions
Estradiol	MI	Boxed Warning
Estramustine	MI	Warnings/Precautions
Estrogens, Conjugated (USP)	MI	Boxed Warning
estropipate	MI	Boxed Warning
Ethacrynate	GI BLEED	Warnings/Precautions
ethanolamine oleate	RENAL FAILURE	Warnings/Precautions
Etodolac	GI BLEED	Warnings/Precautions
Etodolac	LIVER INJURY	Warnings/Precautions
Etodolac	MI	Warnings/Precautions
Etodolac	RENAL FAILURE	Warnings/Precautions
etravirine	LIVER INJURY	Warnings/Precautions
exenatide	RENAL FAILURE	Warnings/Precautions
ezetimibe	LIVER INJURY	Warnings/Precautions
Factor VIIa	MI	Warnings/Precautions
febuxostat	MI	Warnings/Precautions
felbamate	LIVER INJURY	Boxed Warning
Fenofibrate	RENAL FAILURE	Warnings/Precautions
Fenoprofen	GI BLEED	Warnings/Precautions
Fenoprofen	LIVER INJURY	Warnings/Precautions
Fenoprofen	MI	Boxed Warning
Fenoprofen	RENAL FAILURE	Boxed Warning
Fluconazole	LIVER INJURY	Warnings/Precautions
fludarabine	RENAL FAILURE	Warnings/Precautions
Fluoxetine	GI BLEED	Warnings/Precautions
Fluoxymesterone	LIVER INJURY	Warnings/Precautions
Flurbiprofen	GI BLEED	Warnings/Precautions
Flurbiprofen	LIVER INJURY	Warnings/Precautions
Flurbiprofen	MI	Boxed Warning
Flutamide	LIVER INJURY	Boxed Warning
fluvastatin	RENAL FAILURE	Warnings/Precautions
frovatriptan	MI	Warnings/Precautions
gallium nitrate	RENAL FAILURE	Boxed Warning
gemcitabine	LIVER INJURY	Warnings/Precautions
gemcitabine	RENAL FAILURE	Warnings/Precautions
gemifloxacin	LIVER INJURY	Warnings/Precautions
gemtuzumab	LIVER INJURY	Boxed Warning
gemtuzumab	RENAL FAILURE	Warnings/Precautions
Heparin	MI	Warnings/Precautions
Hydrochlorothiazide	RENAL FAILURE	Warnings/Precautions
hydroxyurea	LIVER INJURY	Warnings/Precautions
Ibuprofen	GI BLEED	Warnings/Precautions
Ibuprofen	LIVER INJURY	Warnings/Precautions
Ibuprofen	MI	Boxed Warning

Ibuprofen	RENAL FAILURE	Warnings/Precautions
imatinib	LIVER INJURY	Warnings/Precautions
Imipramine	MI	Warnings/Precautions
Immunoglobulins, Intravenous	RENAL FAILURE	Warnings/Precautions
Inamrinone	LIVER INJURY	Warnings/Precautions
Indomethacin	GI BLEED	Warnings/Precautions
Indomethacin	LIVER INJURY	Warnings/Precautions
Indomethacin	MI	Boxed Warning
Indomethacin	RENAL FAILURE	Warnings/Precautions
infliximab	LIVER INJURY	Warnings/Precautions
Interferon Alfa-2a	GI BLEED	Warnings/Precautions
Interferon Alfa-2a	MI	Warnings/Precautions
Interferon Alfa-2b	MI	Warnings/Precautions
Interferon beta-1a	LIVER INJURY	Warnings/Precautions
isoniazid	LIVER INJURY	Boxed Warning
Isotretinoin	LIVER INJURY	Warnings/Precautions
Itraconazole	LIVER INJURY	Warnings/Precautions
Ketoprofen	GI BLEED	Warnings/Precautions
Ketoprofen	MI	Boxed Warning
Ketoprofen	RENAL FAILURE	Warnings/Precautions
Ketorolac	GI BLEED	Boxed Warning
Ketorolac	LIVER INJURY	Warnings/Precautions
Ketorolac	MI	Boxed Warning
Ketorolac	RENAL FAILURE	Boxed Warning
lacosamide	LIVER INJURY	Warnings/Precautions
Lamivudine	LIVER INJURY	Boxed Warning
lamotrigine	LIVER INJURY	Warnings/Precautions
lapatinib	LIVER INJURY	Boxed Warning
Levofloxacin	LIVER INJURY	Warnings/Precautions
Levofloxacin	RENAL FAILURE	Warnings/Precautions
Lisinopril	LIVER INJURY	Warnings/Precautions
Lisinopril	RENAL FAILURE	Warnings/Precautions
maraviroc	LIVER INJURY	Boxed Warning
Meclofenamate	LIVER INJURY	Warnings/Precautions
Mefenamate	GI BLEED	Warnings/Precautions
Mefenamate	LIVER INJURY	Warnings/Precautions
Mefenamate	MI	Boxed Warning
Mefenamate	RENAL FAILURE	Warnings/Precautions
meloxicam	GI BLEED	Warnings/Precautions
meloxicam	LIVER INJURY	Warnings/Precautions
meloxicam	MI	Boxed Warning
meloxicam	RENAL FAILURE	Warnings/Precautions
mesalamine	GI BLEED	Warnings/Precautions
mesalamine	LIVER INJURY	Warnings/Precautions
mesalamine	RENAL FAILURE	Warnings/Precautions
Methimazole	LIVER INJURY	Warnings/Precautions
Methotrexate	LIVER INJURY	Boxed Warning
Methotrexate	RENAL FAILURE	Warnings/Precautions
Methyldopa	LIVER INJURY	Warnings/Precautions

milnacipran	LIVER INJURY	Warnings/Precautions
Minocycline	LIVER INJURY	Warnings/Precautions
moexipril	LIVER INJURY	Warnings/Precautions
moexipril	MI	Warnings/Precautions
moexipril	RENAL FAILURE	Warnings/Precautions
Moricizine	MI	Warnings/Precautions
Muromonab-CD3	MI	Warnings/Precautions
mycophenolate mofetil	GI BLEED	Warnings/Precautions
nabumetone	GI BLEED	Warnings/Precautions
nabumetone	LIVER INJURY	Warnings/Precautions
nabumetone	MI	Boxed Warning
Nadolol	MI	Boxed Warning
Naltrexone	LIVER INJURY	Boxed Warning
Naproxen	GI BLEED	Warnings/Precautions
Naproxen	LIVER INJURY	Warnings/Precautions
Naproxen	MI	Boxed Warning
Naproxen	RENAL FAILURE	Warnings/Precautions
naratriptan	MI	Warnings/Precautions
natalizumab	LIVER INJURY	Warnings/Precautions
nefazodone	LIVER INJURY	Boxed Warning
Nelfinavir	LIVER INJURY	Warnings/Precautions
Nevirapine	LIVER INJURY	Boxed Warning
Niacin	LIVER INJURY	Warnings/Precautions
Nifedipine	LIVER INJURY	Warnings/Precautions
Nifedipine	MI	Warnings/Precautions
nitisinone	LIVER INJURY	Warnings/Precautions
Nitrofurantoin	LIVER INJURY	Warnings/Precautions
Nizatidine	LIVER INJURY	Warnings/Precautions
Norfloxacin	LIVER INJURY	Warnings/Precautions
Norfloxacin	RENAL FAILURE	Warnings/Precautions
Nortriptyline	LIVER INJURY	Warnings/Precautions
Nortriptyline	MI	Warnings/Precautions
Ofloxacin	LIVER INJURY	Warnings/Precautions
Ofloxacin	RENAL FAILURE	Warnings/Precautions
Olmesartan medoxomil	RENAL FAILURE	Warnings/Precautions
Oprelvekin	RENAL FAILURE	Warnings/Precautions
orlistat	LIVER INJURY	Warnings/Precautions
oxaliplatin	LIVER INJURY	Warnings/Precautions
Oxandrolone	LIVER INJURY	Boxed Warning
oxaprozin	GI BLEED	Warnings/Precautions
oxaprozin	LIVER INJURY	Warnings/Precautions
oxaprozin	MI	Boxed Warning
oxaprozin	RENAL FAILURE	Warnings/Precautions
Oxymetholone	LIVER INJURY	Boxed Warning
peginterferon alfa-2a	GI BLEED	Warnings/Precautions
peginterferon alfa-2a	LIVER INJURY	Warnings/Precautions
pegvisomant	LIVER INJURY	Warnings/Precautions
Pemoline	LIVER INJURY	Boxed Warning
Penicillamine	LIVER INJURY	Warnings/Precautions

Pentosan Polysulfate	GI BLEED	Warnings/Precautions
Perphenazine	LIVER INJURY	Warnings/Precautions
pioglitazone	LIVER INJURY	Warnings/Precautions
Piperacillin	RENAL FAILURE	Warnings/Precautions
Piroxicam	GI BLEED	Warnings/Precautions
Piroxicam	LIVER INJURY	Warnings/Precautions
Piroxicam	MI	Boxed Warning
Piroxicam	RENAL FAILURE	Warnings/Precautions
Polymyxin B	RENAL FAILURE	Boxed Warning
posaconazole	LIVER INJURY	Warnings/Precautions
Potassium Chloride	GI BLEED	Warnings/Precautions
Progesterone	MI	Boxed Warning
Propylthiouracil	LIVER INJURY	Boxed Warning
quinapril	LIVER INJURY	Warnings/Precautions
Ramipril	LIVER INJURY	Warnings/Precautions
Rho(D) Immune Globulin	RENAL FAILURE	Boxed Warning
Rifampin	LIVER INJURY	Warnings/Precautions
rifapentine	LIVER INJURY	Warnings/Precautions
rituximab	MI	Warnings/Precautions
rituximab	RENAL FAILURE	Boxed Warning
rivastigmine	GI BLEED	Warnings/Precautions
rizatriptan	MI	Warnings/Precautions
rosiglitazone	MI	Boxed Warning
Salsalate	LIVER INJURY	Warnings/Precautions
Salsalate	MI	Boxed Warning
Sertraline	GI BLEED	Warnings/Precautions
Stavudine	LIVER INJURY	Warnings/Precautions
Sulfasalazine	LIVER INJURY	Warnings/Precautions
Sulfisoxazole	LIVER INJURY	Warnings/Precautions
Sulindac	GI BLEED	Warnings/Precautions
Sulindac	LIVER INJURY	Warnings/Precautions
Sulindac	MI	Boxed Warning
Sumatriptan	GI BLEED	Warnings/Precautions
Sumatriptan	MI	Warnings/Precautions
sunitinib	LIVER INJURY	Boxed Warning
sunitinib	RENAL FAILURE	Warnings/Precautions
Tamoxifen	LIVER INJURY	Warnings/Precautions
tegaserod	GI BLEED	Warnings/Precautions
telbivudine	LIVER INJURY	Warnings/Precautions
telmisartan	RENAL FAILURE	Warnings/Precautions
temsirolimus	RENAL FAILURE	Warnings/Precautions
Tenofovir	LIVER INJURY	Boxed Warning
Tenofovir	RENAL FAILURE	Warnings/Precautions
terbinafine	LIVER INJURY	Warnings/Precautions
Thiabendazole	LIVER INJURY	Warnings/Precautions
Thioguanine	LIVER INJURY	Warnings/Precautions
tigecycline	LIVER INJURY	Warnings/Precautions
tipranavir	LIVER INJURY	Boxed Warning
Tolazoline	GI BLEED	Warnings/Precautions

tolcapone	LIVER INJURY	Boxed Warning
Tolmetin	GI BLEED	Warnings/Precautions
Tolmetin	LIVER INJURY	Warnings/Precautions
Tolmetin	MI	Boxed Warning
trandolapril	LIVER INJURY	Warnings/Precautions
Trifluoperazine	LIVER INJURY	Warnings/Precautions
trovafloxacin	LIVER INJURY	Boxed Warning
trovafloxacin	RENAL FAILURE	Warnings/Precautions
valacyclovir	RENAL FAILURE	Warnings/Precautions
valdecoxib	GI BLEED	Warnings/Precautions
valdecoxib	LIVER INJURY	Warnings/Precautions
valganciclovir	RENAL FAILURE	Warnings/Precautions
Valproate	LIVER INJURY	Boxed Warning
voriconazole	LIVER INJURY	Warnings/Precautions
zafirlukast	LIVER INJURY	Warnings/Precautions
Zalcitabine	LIVER INJURY	Boxed Warning
Zidovudine	LIVER INJURY	Warnings/Precautions
zileuton	LIVER INJURY	Warnings/Precautions
zolmitriptan	GI BLEED	Warnings/Precautions
zolmitriptan	MI	Warnings/Precautions
zonisamide	LIVER INJURY	Warnings/Precautions

## **Appendix C**

### *Clinical review of the labeled HOI-DOI pairs*

DRUG_CONCEPT_NAME	HOI_CONCEPT_NAME	Reviewer_1	BASIS	Reviewer_2	BASIS
6-Aminocaproic Acid	RENAL FAILURE	DK		Y	EXP
6-Mercaptopurine	LIVER INJURY	DK		DK	
abacavir	LIVER INJURY	Y	LIT	DK	
abacavir	MI	DK		DK	
Acarbose	LIVER INJURY	DK		DK	
Acetazolamide	LIVER INJURY	DK		DK	
Acitretin	LIVER INJURY	DK		DK	
Acyclovir	RENAL FAILURE	DK		DK	
Adenosine	MI	Y	LIT	DK	
alatrofloxacin	RENAL FAILURE	DK		DK	
alatrofloxacin	LIVER INJURY	Y	LIT	DK	
Aldesleukin	GI BLEED	DK		DK	
Aldesleukin	RENAL FAILURE	DK		DK	
alefacept	LIVER INJURY	DK		DK	
Allopurinol	LIVER INJURY	DK		DK	
Allopurinol	RENAL FAILURE	Y	LIT	Y	EXP
almotriptan	MI	Y	LIT	DK	
ambrisentan	LIVER INJURY	DK		DK	
Amifostine	RENAL FAILURE	DK		DK	
aminosalicylic acid	LIVER INJURY	DK		DK	
Amiodarone	RENAL FAILURE	Y	LIT	Y	EXP
Amiodarone	LIVER INJURY	Y	EXP	Y	EXP
Amlodipine	MI	Y	LIT	DK	
Amoxapine	MI	DK		DK	
anidulafungin	LIVER INJURY	DK		DK	
Aprotinin	RENAL FAILURE	DK		DK	
Auranofin	GI BLEED	DK		DK	
Azacitidine	RENAL FAILURE	DK		DK	
Azithromycin	LIVER INJURY	DK		Y	LIT
Bacitracin	RENAL FAILURE	DK		DK	
bendamustine	RENAL FAILURE	DK		DK	
bevacizumab	GI BLEED	DK		DK	
bevacizumab	MI	DK		DK	
bicalutamide	LIVER INJURY	DK		DK	
bortezomib	LIVER INJURY	DK		DK	
bosentan	LIVER INJURY	DK		DK	
Bromocriptine	MI	DK		DK	
Bromocriptine	GI BLEED	DK		DK	
Busulfan	LIVER INJURY	DK		DK	
candesartan	RENAL FAILURE	Y	LIT	DK	

capecitabine	GI BLEED	DK		DK	
Capreomycin	RENAL FAILURE	DK		DK	
Captopril	LIVER INJURY	DK		Y	EXP
Captopril	RENAL FAILURE	Y	LIT	DK	
Carbamazepine	LIVER INJURY	Y	LIT	DK	
Carbidopa	GI BLEED	DK		DK	
carvedilol	RENAL FAILURE	DK		DK	
Caspofungin	LIVER INJURY	DK		DK	
Cefoxitin	RENAL FAILURE	DK		DK	
celecoxib	GI BLEED	Y	LIT	DK	
celecoxib	LIVER INJURY	DK		Y	LIT
celecoxib	MI	Y	LIT	Y	EXP
Chlorothiazide	RENAL FAILURE	Y	LIT	DK	
Cidofovir	RENAL FAILURE	DK		DK	
Ciprofloxacin	LIVER INJURY	DK		Y	LIT
Citalopram	GI BLEED	DK		DK	
Clindamycin	GI BLEED	Y	EXP	Y	EXP
clofarabine	LIVER INJURY	DK		DK	
clopidogrel	GI BLEED	Y	LIT	Y	EXP
Clozapine	LIVER INJURY	Y	LIT	DK	
cyclobenzaprine	MI	DK		DK	
Cyclosporine	LIVER INJURY	Y	LIT	DK	
Cyclosporine	RENAL FAILURE	Y	LIT	DK	
Cysteamine	RENAL FAILURE	DK		DK	
Cytarabine	LIVER INJURY	DK		DK	
cytotect	RENAL FAILURE	DK		DK	
Dacarbazine	LIVER INJURY	DK		DK	
darbepoetin alfa	MI	DK		DK	
darunavir	LIVER INJURY	DK		DK	
dasatinib	GI BLEED	DK		DK	
deferasirox	RENAL FAILURE	DK		DK	
deferasirox	GI BLEED	DK		DK	
deferasirox	LIVER INJURY	DK		DK	
desflurane	LIVER INJURY	DK		DK	
Desipramine	MI	DK		DK	
Desvenlafaxine	GI BLEED	N		DK	
Didanosine	LIVER INJURY	DK		DK	
Diflunisal	RENAL FAILURE	DK		DK	
Diflunisal	GI BLEED	DK		Y	LIT
Diflunisal	LIVER INJURY	DK		DK	
Diflunisal	MI	DK		Y	LIT
Diltiazem	LIVER INJURY	DK		DK	
Dipyridamole	LIVER INJURY	DK		DK	
Dipyridamole	MI	Y	LIT	DK	

Disulfiram	LIVER INJURY	Y	LIT	Y	EXP
docetaxel	GI BLEED	DK		DK	
docetaxel	LIVER INJURY	DK		DK	
Doxorubicin	LIVER INJURY	Y	LIT	DK	
duloxetine	GI BLEED	N		DK	
efavirenz	LIVER INJURY	DK		DK	
eletriptan	MI	Y	LIT	Y	EXP
eletriptan	GI BLEED	DK		DK	
eltrombopag	LIVER INJURY	DK		DK	
Enalaprilat	LIVER INJURY	DK		DK	
Enalaprilat	MI	DK		Y	EXP
Enalaprilat	RENAL FAILURE	Y	LIT	DK	
entecavir	LIVER INJURY	DK		DK	
Epoetin Alfa	MI	DK		Y	LIT
Erythromycin	LIVER INJURY	DK		DK	
Escitalopram	GI BLEED	N		DK	
Estradiol	MI	Y	LIT	DK	
Estramustine	MI	DK		DK	
Estrogens, Conjugated (USP)	MI	Y	LIT	Y	LIT
estropipate	MI	DK		DK	
Ethacrynate	GI BLEED	DK		DK	
ethanolamine oleate	RENAL FAILURE	DK		DK	
Etodolac	GI BLEED	Y	LIT	Y	EXP
Etodolac	LIVER INJURY	DK		Y	LIT
Etodolac	MI	Y	LIT	Y	EXP
Etodolac	RENAL FAILURE	Y	LIT	Y	LIT
etravirine	LIVER INJURY	DK		DK	
exenatide	RENAL FAILURE	DK		Y	LIT
ezetimibe	LIVER INJURY	DK		Y	LIT
Factor VIIa	MI	DK		DK	
febuxostat	MI	DK		DK	
felbamate	LIVER INJURY	DK		DK	
Fenofibrate	RENAL FAILURE	DK		DK	
Fenoprofen	GI BLEED	Y	LIT	Y	EXP
Fenoprofen	LIVER INJURY	DK		Y	LIT
Fenoprofen	RENAL FAILURE	Y	LIT	Y	EXP
Fenoprofen	MI	Y	LIT	Y	EXP
Fluconazole	LIVER INJURY	DK		Y	LIT
fludarabine	RENAL FAILURE	DK		DK	
Fluoxetine	GI BLEED	N		DK	
Fluoxymesterone	LIVER INJURY	DK		DK	
Flurbiprofen	GI BLEED	Y	LIT	Y	EXP
Flurbiprofen	LIVER INJURY	DK		Y	LIT



Flurbiprofen	MI	Y	LIT	Y	EXP
Flutamide	LIVER INJURY	DK		DK	
fluvastatin	RENAL FAILURE	DK		DK	
frovatriptan	MI	Y	LIT	DK	
gallium nitrate	RENAL FAILURE	DK		DK	
gemcitabine	LIVER INJURY	DK		DK	
gemcitabine	RENAL FAILURE	Y	LIT	Y	LIT
gemifloxacin	LIVER INJURY	DK		DK	
gemtuzumab	LIVER INJURY	DK		DK	
gemtuzumab	RENAL FAILURE	DK		Y	EXP
Heparin	MI	DK		Y	LIT
Hydrochlorothiazide	RENAL FAILURE	Y	LIT	Y	EXP
hydroxyurea	LIVER INJURY	DK		DK	
Ibuprofen	GI BLEED	Y	EXP	Y	EXP
Ibuprofen	LIVER INJURY	DK		DK	
Ibuprofen	MI	Y	LIT	Y	EXP
Ibuprofen	RENAL FAILURE	Y	LIT	Y	LIT
imatinib	LIVER INJURY	DK		DK	
Imipramine	MI	DK		DK	
Immunoglobulins, Intravenous	RENAL FAILURE	DK		DK	
Inamrinone	LIVER INJURY	DK		DK	
Indomethacin	GI BLEED	Y	EXP	Y	EXP
Indomethacin	LIVER INJURY	DK		Y	LIT
Indomethacin	MI	Y	LIT	Y	LIT
Indomethacin	RENAL FAILURE	Y	LIT	Y	LIT
infliximab	LIVER INJURY	DK		Y	LIT
Interferon Alfa-2a	GI BLEED	DK		DK	
Interferon Alfa-2a	MI	DK		DK	
Interferon Alfa-2b	MI	DK		DK	
Interferon beta-1a	LIVER INJURY	Y	LIT	DK	
isoniazid	LIVER INJURY	Y	EXP	Y	EXP
Isotretinoin	LIVER INJURY	Y	LIT	Y	LIT
Itraconazole	LIVER INJURY	Y	LIT	Y	LIT
Ketoprofen	GI BLEED	Y	LIT	Y	EXP
Ketoprofen	MI	Y	LIT	Y	LIT
Ketoprofen	RENAL FAILURE	Y	LIT	Y	EXP
Ketorolac	GI BLEED	Y	LIT	Y	EXP
Ketorolac	LIVER INJURY	DK		Y	EXP
Ketorolac	MI	Y	LIT	Y	EXP
Ketorolac	RENAL FAILURE	Y	LIT	Y	LIT
lacosamide	LIVER INJURY	DK		DK	
Lamivudine	LIVER INJURY	Y	LIT	DK	
lamotrigine	LIVER INJURY	Y	LIT	DK	
lapatinib	LIVER INJURY	DK		DK	

Levofloxacin	LIVER INJURY	DK		Y	LIT
Levofloxacin	RENAL FAILURE	DK		Y	LIT
Lisinopril	LIVER INJURY	DK		DK	
Lisinopril	RENAL FAILURE	Y	EXP	DK	
maraviroc	LIVER INJURY	DK		DK	
Meclofenamate	LIVER INJURY	DK		DK	
Mefenamate	GI BLEED	DK		DK	
Mefenamate	LIVER INJURY	DK		DK	
Mefenamate	MI	DK		DK	
Mefenamate	RENAL FAILURE	DK		DK	
meloxicam	GI BLEED	Y	LIT	Y	EXP
meloxicam	LIVER INJURY	DK		Y	LIT
meloxicam	MI	Y	LIT	Y	EXP
meloxicam	RENAL FAILURE	Y	LIT	Y	LIT
mesalamine	GI BLEED	DK		DK	
mesalamine	LIVER INJURY	DK		DK	
mesalamine	RENAL FAILURE	Y	LIT	Y	LIT
Methimazole	LIVER INJURY	DK		DK	
Methotrexate	RENAL FAILURE	Y	LIT	DK	
Methotrexate	LIVER INJURY	Y	LIT	Y	LIT
Methyldopa	LIVER INJURY	DK		DK	
milnacipran	LIVER INJURY	DK		DK	
Minocycline	LIVER INJURY	DK		DK	
moexipril	LIVER INJURY	DK		DK	
moexipril	MI	DK		DK	
moexipril	RENAL FAILURE	Y	EXP	DK	
Moricizine	MI	DK		DK	
Muromonab-CD3	MI	DK		DK	
mycophenolate mofetil	GI BLEED	DK		DK	
nabumetone	GI BLEED	Y	LIT	Y	EXP
nabumetone	LIVER INJURY	DK		Y	LIT
nabumetone	MI	Y	LIT	Y	EXP
Nadolol	MI	DK		DK	
Naltrexone	LIVER INJURY	DK		Y	EXP
Naproxen	GI BLEED	Y	LIT	Y	EXP
Naproxen	LIVER INJURY	DK		Y	LIT
Naproxen	MI	Y	LIT	Y	EXP
Naproxen	RENAL FAILURE	Y	LIT	Y	LIT
naratriptan	MI	Y	LIT	DK	
natalizumab	LIVER INJURY	DK		DK	
nefazodone	LIVER INJURY	DK		DK	
Nelfinavir	LIVER INJURY	Y	LIT	DK	
Nevirapine	LIVER INJURY	DK		DK	
Niacin	LIVER INJURY	DK		DK	

Nifedipine	MI	Y	LIT	DK	
Nifedipine	LIVER INJURY	DK		DK	
nitisinone	LIVER INJURY	DK		DK	
Nitrofurantoin	LIVER INJURY	DK		DK	
Nizatidine	LIVER INJURY	DK		DK	
Norfloxacin	LIVER INJURY	DK		DK	
Norfloxacin	RENAL FAILURE	DK		Y	EXP
Nortriptyline	LIVER INJURY	DK		DK	
Nortriptyline	MI	DK		DK	
Ofloxacin	RENAL FAILURE	DK		DK	
Ofloxacin	LIVER INJURY	DK		Y	EXP
Olmesartan medoxomil	RENAL FAILURE	Y	LIT	DK	
Oprelvekin	RENAL FAILURE	DK		DK	
orlistat	LIVER INJURY	DK		Y	LIT
oxaliplatin	LIVER INJURY	DK		DK	
Oxandrolone	LIVER INJURY	DK		DK	
oxaprozin	GI BLEED	Y	LIT	Y	EXP
oxaprozin	LIVER INJURY	DK		DK	
oxaprozin	MI	Y	LIT	Y	EXP
oxaprozin	RENAL FAILURE	Y	LIT	DK	
Oxymetholone	LIVER INJURY	DK		DK	
peginterferon alfa-2a	GI BLEED	DK		DK	
peginterferon alfa-2a	LIVER INJURY	DK		DK	
pegvisomant	LIVER INJURY	DK		DK	
Pemoline	LIVER INJURY	DK		DK	
Penicillamine	LIVER INJURY	DK		DK	
Pentosan Polysulfate	GI BLEED	DK		DK	
Perphenazine	LIVER INJURY	DK		DK	
pioglitazone	LIVER INJURY	Y	LIT	DK	
Piperacillin	RENAL FAILURE	DK		Y	LIT
Piroxicam	GI BLEED	Y	LIT	Y	EXP
Piroxicam	LIVER INJURY	DK		Y	LIT
Piroxicam	MI	Y	LIT	Y	EXP
Piroxicam	RENAL FAILURE	Y	LIT	Y	LIT
Polymyxin B	RENAL FAILURE	DK		Y	LIT
posaconazole	LIVER INJURY	DK		DK	
Potassium Chloride	GI BLEED	Y	LIT	Y	EXP
Progesterone	MI	Y	LIT	DK	
Propylthiouracil	LIVER INJURY	DK		Y	LIT
quinapril	LIVER INJURY	DK		DK	
Ramipril	LIVER INJURY	DK		DK	
Rho(D) Immune Globulin	RENAL FAILURE	DK		DK	
Rifampin	LIVER INJURY	Y	LIT	DK	
rifapentine	LIVER INJURY	DK		DK	

rituximab	RENAL FAILURE	DK		DK	
rituximab	MI	DK		DK	
rivastigmine	GI BLEED	DK		DK	
rizatriptan	MI	Y	LIT	DK	
rosiglitazone	MI	Y	LIT	Y	LIT
Salsalate	LIVER INJURY	DK		Y	EXP
Salsalate	MI	DK		DK	
Sertraline	GI BLEED	N		DK	
Stavudine	LIVER INJURY	Y	LIT	DK	
Sulfasalazine	LIVER INJURY	DK		DK	
Sulfisoxazole	LIVER INJURY	DK		DK	
Sulindac	GI BLEED	Y	LIT	Y	EXP
Sulindac	LIVER INJURY	DK		Y	LIT
Sulindac	MI	Y	LIT	Y	EXP
Sumatriptan	MI	Y	LIT	DK	
Sumatriptan	GI BLEED	DK		DK	
sunitinib	LIVER INJURY	DK		DK	
sunitinib	RENAL FAILURE	DK		DK	
Tamoxifen	LIVER INJURY	DK		DK	
tegaserod	GI BLEED	DK		Y	EXP
telbivudine	LIVER INJURY	DK		DK	
telmisartan	RENAL FAILURE	Y	LIT	Y	LIT
temsirolimus	RENAL FAILURE	Y	LIT	DK	
Tenofovir	RENAL FAILURE	DK		DK	
Tenofovir	LIVER INJURY	Y	LIT	DK	
terbinafine	LIVER INJURY	DK		Y	LIT
Thiabendazole	LIVER INJURY	DK		DK	
Thioguanine	LIVER INJURY	Y	LIT	DK	
tigecycline	LIVER INJURY	DK		DK	
tipranavir	LIVER INJURY	DK		DK	
Tolazoline	GI BLEED	DK		DK	
tolcapone	LIVER INJURY	DK		DK	
Tolmetin	GI BLEED	DK		Y	EXP
Tolmetin	LIVER INJURY	DK		Y	EXP
Tolmetin	MI	DK		Y	LIT
trandolapril	LIVER INJURY	DK		DK	
Trifluoperazine	LIVER INJURY	DK		DK	
trovafloxacin	RENAL FAILURE	DK		DK	
trovafloxacin	LIVER INJURY	Y	LIT	DK	
valacyclovir	RENAL FAILURE	DK		DK	
valdecoxib	GI BLEED	Y	LIT	Y	EXP
valdecoxib	LIVER INJURY	DK		Y	LIT
valganciclovir	RENAL FAILURE	DK		DK	
Valproate	LIVER INJURY	Y	LIT	DK	

voriconazole	LIVER INJURY	Y	LIT	DK	
zafirlukast	LIVER INJURY	DK		DK	
Zalcitabine	LIVER INJURY	DK		DK	
Zidovudine	LIVER INJURY	Y	LIT	DK	
zileuton	LIVER INJURY	DK		DK	
zolmitriptan	MI	Y	LIT	Y	LIT
zolmitriptan	GI BLEED	DK		DK	
zonisamide	LIVER INJURY	DK		DK	