

Center for Drug Evaluation and Research (CDER) Drug Safety Oversight Board
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Services for drug-drug interactions (DDI) and DDI research at NLM

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National Library of Medicine (NLM)

- World's largest biomedical library
- Maintains and makes available a vast print collection
- Produces electronic information resources on a wide range of topics that are searched billions of times each year by millions of people around the globe
- Supports and conducts research, development, and training in biomedical informatics and health information technology

<https://www.nlm.nih.gov/about/>

NLM strategic plan (2006-2016)*

- **Goal 1.** Seamless, Uninterrupted Access to Expanding Collections of Biomedical Data, Medical Knowledge, and Health Information
- **Goal 2.** Trusted Information Services that Promote Health Literacy and the Reduction of Health Disparities Worldwide
- **Goal 3.** Integrated Biomedical, Clinical, and Public Health Information Systems that Promote Scientific Discovery and Speed the Translation of Research into Practice
- **Goal 4.** A Strong and Diverse Workforce for Biomedical Informatics Research, Systems Development, and Innovative Service Delivery

<https://www.nlm.nih.gov/pubs/plan/lrpdocs.html>

DDI services at NLM

Drug information services at NLM

- FDA Structured Product Labels
 - DailyMed website
 - DailyMed API
- RxNorm
 - Standard vocabulary for drugs
 - Drug terminology integration
- RxNorm-based applications and services
 - RxNav
 - RxNorm APIs
- ChemIDPlus (part of ToxNet)
- MedlinePlus Drugs and supplements (consumer health information)
- PubMed Health (reviews of clinical effectiveness research)

DailyMed – Access to 94,000 SPLs

The screenshot shows the DailyMed website homepage. At the top, there is a navigation bar with the NIH logo and the text "U.S. NATIONAL LIBRARY OF MEDICINE". To the right of this bar are links for "REPORT ADVERSE EVENTS" and "RECALLS". Below the navigation bar is a large banner image showing a person's hands holding a pill bottle. The "DAILYMED" logo is prominently displayed on the left side of the banner. Below the banner is a search bar with the placeholder text "Enter drug, NDC code, drug class, or Set ID" and a magnifying glass icon. To the left of the search bar are three tabs: "ALL DRUGS", "HUMAN DRUGS", and "ANIMAL DRUGS". Below the search bar is a section titled "MORE WAYS TO SEARCH:" with buttons for "ADVANCED SEARCH" and "VIEW MORE". Below this section is a paragraph of text: "This website contains 94465 drug listings as submitted to the Food and Drug Administration (FDA). At the present time, this Web site does not contain a complete listing of labels for approved prescription drugs." To the right of this text are social media sharing icons for email, Facebook, Twitter, and a plus sign. Below the text are two columns of content. The left column is titled "NEWS" and contains a link for "DailyMed Announcements" with a post date of "October 3, 2016" and a link for "DailyMed/RxNorm Jamboree Workshop 2016 Archive". The right column is titled "FDA GUIDANCES & INFORMATION" and contains a link for "Drug Guidance, Compliance & Regulatory Information" and two links for "View FDA Structured Product Labeling Resources" and "View FDA Drug Labeling Guidances".

<https://dailymed.nlm.nih.gov/>

DDIs in DailyMed

U.S. NATIONAL LIBRARY OF MEDICINE

DAILYMED

Enter drug, NDC code, drug class, or Set ID

ADVANCED SEARCH VIEW MORE

LABEL: LIPITOR- atorvastatin calcium tablet, film coated

LABEL RSS SHARE

VIEW PACKAGE PHOTOS

NDC Code(s): 0071-0155-10, 0071-0155-23, 0071-0155-34, 0071-0155-40, [view more](#)

Packager: Parke-Davis Div of Pfizer Inc

Category: HUMAN PRESCRIPTION DRUG LABEL

DEA Schedule: None

Marketing Status: New Drug Application

DRUG LABEL INFORMATION Updated November 15, 2016

If you are a consumer or patient please visit [this version](#).

White, elliptical, film-coated tablets containing 10, 20, 40, and 80 mg atorvastatin calcium.

RELATED RESOURCES

- Medline Plus
- Clinical Trials
- + PubMed
- Biochemical Data Summary

MORE INFO FOR THIS DRUG

- View Label Archives
- RxNorm
- Get Label RSS Feed

4 CONTRAINDICATIONS

4.1 Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels - 4.2 Hypersensitivity to any ...

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle - Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with LIPITOR and with other drugs in this ...

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label: Rhabdomyolysis and myopathy [see Warnings and Precautions (5.1)] Liver enzyme ...

7 DRUG INTERACTIONS

The risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP 3A4 ...

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy - Pregnancy Category X - LIPITOR is contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides ...

10 OVERDOSAGE

There is no specific treatment for LIPITOR overdose. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to ...

7 DRUG INTERACTIONS

The risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP 3A4 inhibitors (e.g., clarithromycin, itraconazole, voriconazole, posaconazole, isavuconazole, and fluconazole) [see [WARNINGS AND PRECAUTIONS, SKELETAL MUSCLE \(5.1\)](#) and [DOSAGE AND ADMINISTRATION \(2.6\)](#)].

7.1 Strong Inhibitors of CYP 3A4

LIPITOR is metabolized by cytochrome P-glycoprotein (P-gp) and CYP 3A4. Co-administration with strong inhibitors of CYP 3A4 can lead to increased plasma concentrations of atorvastatin. The extent of interaction and the variability of effect on CYP 3A4.

Clarithromycin: Atorvastatin AUC was increased 2.5-fold after administration of LIPITOR 80 mg with clarithromycin compared to that of LIPITOR alone [see [CLINICAL PHARMACOLOGY \(12.3\)](#)]. When taking clarithromycin, caution should be exercised when the LIPITOR dose exceeds 20 mg and should be used with caution [see [WARNINGS AND PRECAUTIONS, SKELETAL MUSCLE \(5.1\)](#) and [DOSAGE AND ADMINISTRATION \(2.6\)](#)].

Combination of Protease Inhibitors: Concomitant administration of LIPITOR with protease inhibitors, as well as with the hepatitis C virus (HCV) protease inhibitor telaprevir, concomitant use of LIPITOR with the HIV protease inhibitor lopinavir or

inhibitor telaprevir, concomitant use of LIPITOR should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing LIPITOR and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the LIPITOR dose should not exceed 20 mg and should be used with caution [see [WARNINGS AND PRECAUTIONS, SKELETAL MUSCLE \(5.1\)](#) and [DOSAGE AND ADMINISTRATION \(2.6\)](#)]. When taking the HIV protease inhibitor nelfinavir, the LIPITOR dose should not exceed 20 mg and should be used with caution [see [WARNINGS AND PRECAUTIONS, SKELETAL MUSCLE \(5.1\)](#) and [DOSAGE AND ADMINISTRATION \(2.6\)](#)].

Itraconazole: Atorvastatin AUC was increased 2.5-fold after administration of LIPITOR 40 mg and itraconazole compared to that of LIPITOR alone [see [CLINICAL PHARMACOLOGY \(12.3\)](#)]. Therefore, itraconazole should be used with caution when the LIPITOR dose exceeds 20 mg and should be used with caution [see [WARNINGS AND PRECAUTIONS, SKELETAL MUSCLE \(5.1\)](#) and [DOSAGE AND ADMINISTRATION \(2.6\)](#)].

7.2 Grapefruit Juice

Contains one or more components that inhibit P-gp and CYP 3A4, resulting in increased concentrations of atorvastatin, especially when consumed in large quantities (>1.2 liters per day).

7.3 Cyclosporine

Atorvastatin and atorvastatin-metabolites are substrates of P-gp and CYP 3A4. Inhibitors of the OATP1B1 (e.g., cyclosporine, gemfibrozil) can increase plasma concentrations of atorvastatin. Atorvastatin AUC was significantly increased after administration of LIPITOR 10 mg and cyclosporine compared to LIPITOR alone [see [CLINICAL PHARMACOLOGY \(12.3\)](#)].

administration of LIPITOR 10 mg and cyclosporine 5.2 mg/kg/day compared to that of LIPITOR alone [see [CLINICAL PHARMACOLOGY \(12.3\)](#)]. The co-administration of LIPITOR with cyclosporine should be avoided [see [WARNINGS AND PRECAUTIONS, SKELETAL MUSCLE \(5.1\)](#)].

7.4 Gemfibrozil

Due to an increased risk of myopathy/rhabdomyolysis, the co-administration of gemfibrozil and statins should be avoided [see [WARNINGS AND PRECAUTIONS, SKELETAL MUSCLE \(5.1\)](#)].

7.5 Other Fibrates

Because it is known that the risk of myopathy/rhabdomyolysis is increased with concurrent administration of statins and fibrates, statins should be administered with caution when used with fibrates [see [WARNINGS AND PRECAUTIONS \(5.1\)](#)].

7.6 Niacin

The risk of skeletal muscle effects may be increased when niacin is administered in combination with statins; a reduction in the dose of niacin may be necessary [see [WARNINGS AND PRECAUTIONS \(5.1\)](#)].

7.7 Rifampin or other Inducers of Cytochrome P-glycoprotein

Concomitant administration of LIPITOR with rifampin (rifampin) or other inducers of cytochrome P-glycoprotein (e.g., efavirenz, rifampin) can lead to variable decreases in plasma concentrations of atorvastatin. Due to the dual interaction of LIPITOR with cytochrome P-glycoprotein and CYP 3A4, the reduction in atorvastatin plasma concentrations after administration of rifampin may be more pronounced [see [CLINICAL PHARMACOLOGY \(12.3\)](#)].

OR LIPITOR after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

7.8 Digoxin

When multiple doses of LIPITOR and digoxin were co-administered, steady state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

7.9 Oral Contraceptives

Co-administration of LIPITOR and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol [see [CLINICAL PHARMACOLOGY \(12.3\)](#)]. These increases should be considered when selecting an oral contraceptive for a woman taking LIPITOR.

7.10 Warfarin

LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

7.11 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

CLOSE

+ 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy - Pregnancy Category X - LIPITOR is contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides ...

+ 10 OVERDOSAGE



Any potential interactions in this meds list?

Bene. ID	NDC	Amount	Date	Dur.	RXCUI	RXN_NAME
49441R0	00071015723	30	84	30	617311	atorvastatin 40 MG Oral Tablet
49441R0	51672125802	30	107	21	562032	Clobetasol 0.5 MG/ML Topical Cream
49441R0	68774012260	28	107	14	197517	Clarithromycin 500 MG Oral Tablet



7.1 Strong Inhibitors of CYP 3A4

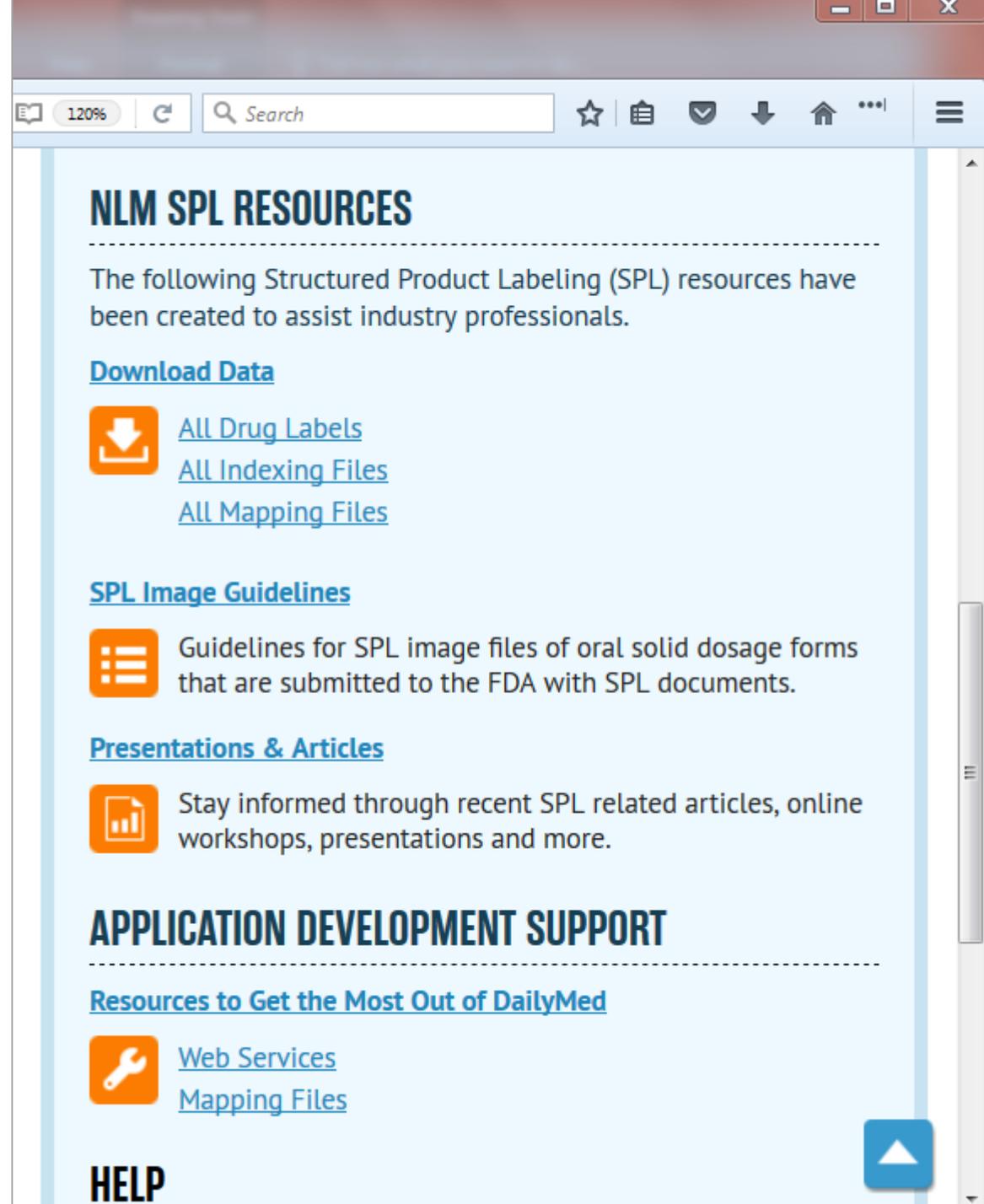
LIPITOR is metabolized by cytochrome P450 3A4. Concomitant administration of LIPITOR with strong inhibitors of CYP 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP 3A4.

Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR 80 mg with clarithromycin (500 mg twice daily) compared to that of LIPITOR alone [see [CLINICAL PHARMACOLOGY \(12.3\)](#)]. Therefore, in patients taking clarithromycin, caution should be used when the LIPITOR dose exceeds 20 mg

Impossible to analyze automatically (human-readable, not machine-readable)

DailyMed API

- Application Programming Interface (API)
 - Retrieve a label by ID
 - List all codes for drugs in any label
 - **No specific support for DDI**
- SPL mapping/indexing files
 - Various structured files relating drugs to classes (EPC, MoA, PE, etc)
 - **No specific support for DDI***



The screenshot shows a web browser window displaying the DailyMed website. The browser's address bar shows a search function and navigation icons. The main content area is titled "NLM SPL RESOURCES" and includes a description of Structured Product Labeling (SPL) resources. Below this, there are three sections: "Download Data" with links for "All Drug Labels", "All Indexing Files", and "All Mapping Files"; "SPL Image Guidelines" with a description of guidelines for oral solid dosage forms; and "Presentations & Articles" with a description of recent SPL related articles and workshops. The bottom section is titled "APPLICATION DEVELOPMENT SUPPORT" and includes a link for "Resources to Get the Most Out of DailyMed" with sub-links for "Web Services" and "Mapping Files". A "HELP" button is visible at the bottom left, and a blue arrow icon is at the bottom right.

NLM SPL RESOURCES

The following Structured Product Labeling (SPL) resources have been created to assist industry professionals.

Download Data

-  [All Drug Labels](#)
- [All Indexing Files](#)
- [All Mapping Files](#)

SPL Image Guidelines

-  Guidelines for SPL image files of oral solid dosage forms that are submitted to the FDA with SPL documents.

Presentations & Articles

-  Stay informed through recent SPL related articles, online workshops, presentations and more.

APPLICATION DEVELOPMENT SUPPORT

Resources to Get the Most Out of DailyMed

-  [Web Services](#)
- [Mapping Files](#)

HELP

RxNorm

- Developed by NLM
- Covers (mostly) prescription drugs
- Terminology scope
 - Standard names and codes for drug entities
 - Standard relations among drug entities (e.g., brand → generic)
 - Integrates names and codes from 15 sources (including all major compendia)
- **No clinical information (indications, drug classes, DDI)**

<https://www.nlm.nih.gov/research/umls/rxnorm/>

RxNav and RxNorm API

- Browser for RxNorm
 - Supported by APIs
- Links RxNorm drugs to other information sources
 - Drug classes (from DailyMed)
 - Pill images
 - DDI information
 - DrugBank
 - ONC “high-priority list”

The screenshot displays the RxNav web application interface. The browser address bar shows the URL <https://mor.nlm.nih.gov/RxNav/search?searchBy=String&searchTerm=clarithromycin>. The page header includes the NIH logo and the text "U.S. National Library of Medicine". The main content area features the RxNav logo and a search bar with "String" selected and "clarithromycin" entered. Below the search bar, the results for "Clarithromycin [RxCUI = 21212]" are displayed. The interface includes several tabs: "RxNorm Graph", "RxNorm Properties", "NDC", "RxTerms", "NDF-RT", "Pill Images", "Class View", and "Interaction View". The "RxNorm Properties" tab is active, showing a grid of property categories and their associated drug products. The categories include IN/MIN (1), PIN (0), BN (1), SCDC (5), SBDC (4), SCD/GPCK (10), SBD/BPCK (8), SCDG (4), DFG (4), and SBDG (3). Each category contains a list of drug products with their respective RxNorm codes and names.

<https://mor.nlm.nih.gov/RxNav/>

DDI information in the drug API

- No curation from NLM

- DDI information simply exposed (machine-readable)

- Sources

- DrugBank



- The DrugBank database is a unique bioinformatics and cheminformatics resource that combines detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information.
- DDI: no notion of severity; short textual description

<https://www.drugbank.ca/>

- ONC high-priority list

- Set of high-severity, clinically significant drug–drug interactions (DDIs) for use in electronic health records (EHRs) developed by D. Bates’ group for ONC

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3422823/>

RxNav
Navigating RxNorm
Drugs

String clarithromycin

Clarithromycin [RxCUI 83367]

Show Interaction with Other Drugs

RxNorm Graph RxNorm Properties NDC RxTerms NDF-RT Pill Images Class View **Interaction View**

Views	Drug	Interaction	Description
• DrugBank	Atazanavir	N/A	The therapeutic efficacy of Clarithromycin can be decreased when used in combination with Atazanavir.
• ONCHigh	Atenolol	N/A	The serum concentration of Atenolol can be increased when it is combined with Clarithromycin.
Download	atomoxetine	N/A	Atomox 83367 may increase the QTc-prolonging activities of Clarithromycin.
	atorvastatin	N/A	The serum concentration of Atorvastatin can be increased when it is combined with Clarithromycin.
	avanafil	N/A	The serum concentration of Avanafil can be increased when it is combined with Clarithromycin.
		N/A	The serum concentration of Axitinib can be increased when it is combined with Clarithromycin.
		N/A	The metabolism of Azelastine can be decreased when combined with Clarithromycin.
	Azithromycin	N/A	Azithromycin may increase the QTc-prolonging activities of Clarithromycin.
	Beclomethasone	N/A	The serum concentration of Beclomethasone dipropionate can be increased when it

Interaction between clarithromycin and atorvastatin in DrugBank

RxNav
Navigating RxNorm
Drugs

String clarithromycin

Clarithromycin [RxCUI = 21212]

RxNorm Graph RxNorm Properties NDC RxTerms NDF-RT Pill Images Class View **Interaction View**

- Views
- DrugBank
 - **ONCHigh**
- Download

58 interacting drugs for Clarithromycin

NAME	SEVERITY	DESCRIPTION
Amiodarone	high	QT prolonging agents - QT prolonging agents
anagrelide	high	QT prolonging agents - QT prolonging agents
arsenic trioxide	high	QT prolonging agents - QT prolonging agents
Astemizole	high	QT prolonging agents - QT prolonging agents
Azithromycin	high	QT prolonging agents - QT prolonging agents
Bepriidil	high	QT prolonging agents - QT prolonging agents
Chloroquine	high	QT prolonging agents - QT prolonging agents
Chlorpromazine	high	QT prolonging agents - QT prolonging agents
cilostazol	high	QT prolonging agents - QT prolonging agents
Ciprofloxacin	high	QT prolonging agents - QT prolonging agents
Cisapride	high	QT prolonging agents - QT prolonging agents

No interaction between clarithromycin and atorvastatin in the ONC high-priority list

DDI research at NLM

2 recent projects

- Extracting drug-drug information from Structured Product Labels
 - Collaboration with FDA
- Comparison of three commercial knowledge bases for detection of drug-drug interactions in clinical decision support
 - Collaboration with drug compendia

Multiple projects with FDA

- Extracting adverse events from MEDLINE indexing
- Using PubMed for pharmacovigilance
- **Extracting drug-drug information from Structured Product Labels**
- Creating a collection of Structured Product Labels annotated for adverse events coded to MedDRA

Extracting drug-drug information from Structured Product Labels

- Inter-agency agreement (ongoing)
 - FDA Office of the Chief Scientist Office of Health Informatics
- To support the FDA Structured Product Labeling indexing initiative
- Natural language processing (NLP) pipeline
 - Extract drug-drug interaction (DDI) information from drug labels
 - Codify them in standard terminologies
- Curation by FDA domain experts
- Expected to result in **structured DDI information**
 - SPL indexing file for DDI
 - Clinical decision support

Comparison of three commercial knowledge bases for DDI information



The screenshot shows the JAMIA website interface. At the top left is the JAMIA logo with the tagline "A SCHOLARLY JOURNAL OF INFORMATICS IN HEALTH AND BIOMEDICINE". At the top right is the AMIA logo with the tagline "INFORMATICS PROFESSIONALS. LEADING THE WAY." Below the logos is a navigation bar with links for "Issues", "More Content", "Publish", "Purchase", "Alerts", and "About". A search bar is located on the right side of the navigation bar, with a magnifying glass icon and the text "Advanced Search".

Article Contents

Comments (0)

Comparison of three commercial knowledge bases for detection of drug-drug interactions in clinical decision support

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J Am Med Inform Assoc ocx010. DOI: <https://doi.org/10.1093/jamia/ocx010>

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Materials and methods

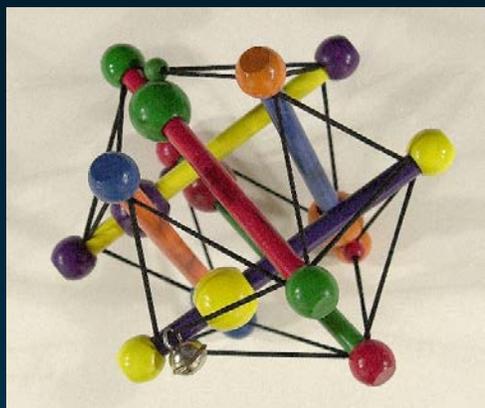
- Materials: DDI tables from
 - First DataBank (FDB)
 - Micromedex
 - Multum
- Methods
 - Mapped drugs to RxNorm
 - Compared at the clinical drug, ingredient, and DDI rule levels
 - Evaluated against the ONC high-priority list of DDIs
 - Applied to a prescription data set to simulate their use in clinical decision support

Results (1/2)

- Wide differences in numbers of DDIs among compendia
 - All sources: 8.6 M unique clinical drug pairs
 - First DataBank: 1.6 M
 - Micromedex: 4.5 M
 - Multum: 4.8 M
- Limited overlap among sources
 - 79% found only in 1 source
 - 5% found in all 3 sources

Results (2/2)

- More agreement than disagreement in the severity rankings
 - Especially for contraindications
- 99.8% of the alerts of the ONC list covered by the 3 sources
- Impact on CDS: number of alerts potentially generated (alerts per 1000 prescriptions)
 - First DataBank: 25
 - Micromedex: 145
 - Multum: 84



Medical Ontology Research

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U.S. National Library of Medicine

