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

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

https://dailymed.nlm.nih.gov/
DDIs in DailyMed

LABEL: LIPICTOR- atorvastatin calcium tablet, film coated

- **NDC Codes:** 0071-0155-10, 0071-0155-23, 0071-0155-34, 0071-0155-40
- **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

**ADVERSE REACTIONS**

4 Conditions mentioned:

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

5 Warnings and Precautions:

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

6 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:

- Pregnancy - Pregnancy Category X - LIPICTOR is contraindicated in women who are or may become pregnant ...
The risk of myopathy during treatment with statins is increased with concurrent administration of fibrin acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP 3A4 inhibitors (e.g., clarithromycin). [see WARNINGS AND PRECAUTIONS, SYMPOMATIC MUSCULAR CRUNCHES (12.3).]

### 7.1 Strong Inhibitors of CYP 3A4

LIPITOR is metabolized by cytochrome CYP 3A4 and concomitant administration of strong inhibitors of CYP 3A4 can lead to increased plasma concentrations of LIPITOR and may result in rhabdomyolysis. The extent of interaction and the magnitude of increased LIPITOR plasma concentrations depend on the activity of the inhibiting compound. Therefore, it is important to know that co-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, SYMPOMATIC MUSCULAR CRUNCHES (12.3)].

Clarithromycin: Atorvastatin AUC was increased by 14% when administered with clarithromycin, together with moderate and severe CYP 3A4 inhibitors. [see WARNINGS AND PRECAUTIONS, SYMPOMATIC MUSCULAR CRUNCHES (12.3)].

Itraconazole: Atorvastatin AUC was increased by 40% when administered with itraconazole, a strong CYP 3A4 inhibitor. [see WARNINGS AND PRECAUTIONS, SYMPOMATIC MUSCULAR CRUNCHES (12.3)].

Combination of Protease Inhibitors: Concomitant administration of LIPITOR with potent inhibitors of the CYP 3A4 isoenzyme results in increased concentrations of LIPITOR and atorvastatin. Therefore, it is important to know that concomitant administration of LIPITOR with any protease inhibitors will result in increased LIPITOR plasma levels. [see WARNINGS AND PRECAUTIONS, SYMPOMATIC MUSCULAR CRUNCHES (12.3)].

Combination of Inhibitors and Inducers: Co-administration of LIPITOR with strong CYP 3A4 inhibitors (e.g., clarithromycin) may result in increased plasma concentrations of LIPITOR and may result in rhabdomyolysis. [see WARNINGS AND PRECAUTIONS, SYMPOMATIC MUSCULAR CRUNCHES (12.3)].

### 7.2 Grapefruit Juice

Contains one or more components that can increase plasma concentrations of atorvastatin, especially in patients taking the HIV protease inhibitor tipranavir or the HIV protease inhibitor telaprevir, concomitant use of grapefruit juice with the HIV protease inhibitor tipranavir should be avoided [see WARNINGS AND PRECAUTIONS, SYMPOMATIC MUSCULAR CRUNCHES (12.3)].

### 7.3 Cyclosporine

Atorvastatin and atorvastatin-metabolites were increased by 27% and 23% when co-administered with cyclosporine, respectively. Atorvastatin AUC was increased by 70% when co-administered with cyclosporine. [see CLINICAL PHARMACOLOGY (12.3)].

### 7.4 Gemfibrozil

Due to an increased risk of myopathy/myalgia, gemfibrozil and strong CYP 3A4 inhibitors are co-administered with gemfibrozil should be avoided [see WARNINGS AND PRECAUTIONS, SYMPOMATIC MUSCULAR CRUNCHES (12.3)].

### 7.5 Other Fibrates

Because it is known that the risk of myopathy/myalgia increases with concurrent administration of fibrates and statins, combined use of fibrates and statins should be avoided [see WARNINGS AND PRECAUTIONS, SYMPOMATIC MUSCULAR CRUNCHES (12.3)].

### 7.6 Niacin

The risk of increased plasma concentrations of atorvastatin may be reduced by using niacin in combination with atorvastatin; a reduction in plasma concentrations of atorvastatin is likely to occur when using niacin in combination with atorvastatin. [see WARNINGS AND PRECAUTIONS, SYMPOMATIC MUSCULAR CRUNCHES (12.3)].

### 7.7 Rifampin or other Inducers of CYP3A4

Concomitant administration of LIPITOR with rifampin (e.g., rifabutin, rifabutin) can lead to variable reduction in atorvastatin plasma concentrations. [see CLINICAL PHARMACOLOGY (12.3)].

### 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.

### 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 ...
Any potential interactions in this meds list?

<table>
<thead>
<tr>
<th>Bene. ID</th>
<th>NDC</th>
<th>Amount</th>
<th>Date</th>
<th>Dur.</th>
<th>RXCUI</th>
<th>RXN_NAME</th>
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<tbody>
<tr>
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<td>00071015723</td>
<td>30</td>
<td>84</td>
<td>30</td>
<td>617311</td>
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<td>51672125802</td>
<td>30</td>
<td>107</td>
<td>21</td>
<td>562032</td>
<td>Clobetasol 0.5 MG/ML Topical Cream</td>
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<tr>
<td>49441R0</td>
<td>68774012260</td>
<td>28</td>
<td>107</td>
<td>14</td>
<td>197517</td>
<td>Clarithromycin 500 MG Oral Tablet</td>
</tr>
</tbody>
</table>

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

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

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
  • 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.drugbank.ca/

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3422823/
Interaction between clarithromycin and atorvastatin in DrugBank

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Type</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>N/A</td>
<td>The therapeutic efficacy of Clarithromycin can be decreased when used in combination with Atazanavir.</td>
</tr>
<tr>
<td>Atenolol</td>
<td>N/A</td>
<td>The serum concentration of Atenolol can be increased when it is combined with Clarithromycin.</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>N/A</td>
<td>Atomoxetine may increase the QTc-prolonging activities of Clarithromycin.</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>N/A</td>
<td>The serum concentration of Atorvastatin can be increased when it is combined with Clarithromycin.</td>
</tr>
<tr>
<td>Avanafil</td>
<td>N/A</td>
<td>The serum concentration of Avanafil can be increased when it is combined with Clarithromycin.</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>N/A</td>
<td>Azithromycin may increase the QTc-prolonging activities of Clarithromycin.</td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>N/A</td>
<td>The serum concentration of Beclomethasone dipropionate can be increased when it is combined with Clarithromycin.</td>
</tr>
</tbody>
</table>
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

Article Contents

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
Published: 22 February 2017 Article history
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