Clinical Organ Impairment DATASET

Transforming scientific data into clinical knowledge

SCHOOL OF PHARMACY
UNIVERSITY OF WASHINGTON
Clinical Organ Impairment Dataset

The Clinical Organ Impairment Dataset contains study results from renal and hepatic impairment studies.

**Detailed study information** regarding design, population, degree of organ impairment, drug dosing, PK, PD, and safety results are extracted from published articles (citations) and NDA reviews. Common metrics (percent changes in AUC, plasma concentrations, oral and renal clearance values) are used across all studies to allow metadata analysis of quantitative results.

**Study results** are organized according to the overall effect and the severity of the disease:
- Users can focus on a specific object drug or disease severity (mild, moderate, or severe)
- Explicit changes in exposure can be searched (Example: “Find all drugs with at least 2-fold change in AUC in patients with a specific degree of impairment”)

**Comprehensive PK parameters** for the object drug and its metabolites are available for each population studied and are compared to a healthy control population.

**Several pre-formulated queries** allow users to retrieve the organ impairment dataset by drug name, changes in exposure, or disease severity.

**Results** can be viewed, customized, and downloaded in multiple formats, allowing users to compile and organize the large body of information available.

[druginteractionsolutions.org](http://druginteractionsolutions.org)
FROM A CITATION OR NDA/BLA REVIEW

The latest, most relevant, peer-reviewed publications and regulatory documents are identified and fully analyzed. Study protocol and results are manually curated to update the knowledgebase on a daily basis.

Most often analyzed files:
- Printed labeling
- Multi-discipline review
- Chemistry review(s)
- Other review(s)
Prior to integration, all data are carefully and critically evaluated. The richness of each citation, including relevant insights, is exploited, generating a highly detailed dataset.

**Tree View of Citation Data**

- **Dosing**
  - Population: females, healthy volunteers, N: 18 postmenopausal control subjects with normal hepatic function, matched for age, weight, and smoking habit with the hepatically impaired cohorts.
  - Population: females, patients, N: 6 postmenopausal subjects with mild HI (Child-Pugh class A).
  - Population: females, patients, N: 6 postmenopausal subjects with moderate HI (Child-Pugh class B).
  - Population: females, patients, N: 6 postmenopausal subjects with severe HI (Child-Pugh class C).
  - Object Administration: Oral.
  - Object Intervals: single dose (8 am).
  - Ethnicity: Caucasian.
  - Associated Pathologies: Severe Hepatic Impairment.
  - Study results: (Means ± SD, Medians (range))
    - PK parameters: bazedoxifene.
    - AUC: 241 ± 202 ng/mL/h.
    - Object plasma concentration: 5.44 ± 5.55 ng/mL (Cmax).
    - Tmax: 49.7 ± 5.7 h.
    - T1/2: 2.0 (1.5-6.0) h.
    - Percent change in AUC vs controls: 327.3% increase.
    - Percent change in Object plasma concentration (Cmax) vs controls: 44.7% increase.

**Pharmacodynamics (PD): not measured**

- Side Effects (SE): reported.
  - SE class: Cardiovascular Disorders.
  - SE class: QT interval prolongation.
  - SE comments: AEs were reported by 1 subject with severe HI. Three women had high QT intervals (defined as >470 milliseconds, using the Bazett correction) after bazedoxifene administration (QTc: Intervals ranged from 436 milliseconds to 518 milliseconds at baseline; 462 milliseconds to 532 milliseconds 4 hours postdose).

**PK results**

**PD and Safety**

**Populations with various degrees of organ impairment**

Bazedoxifene shows an AUC increase of 327.3% in patients with severe hepatic impairment. What other drugs have an AUC change of at least 2-fold in these patients?
POWERFUL TOOL FOR **DATA INTEGRATION**: FROM ONE CITATION TO METADATA ANALYSIS

The data are formatted for immediate use and can be filtered and re-arranged to allow meta-analysis of multiple results.

**Query all drugs exhibiting exposure increases of at least 2-fold in patients with severe hepatic impairment**

---

**Table View of Query Results**

Obtain a complete list of drugs that may need dosing adjustment in patients with severe hepatic impairment.
CLINICAL ORGAN IMPAIRMENT DATASET IN NUMBERS
(as of April 16, 2020)

RENA L IMPAIRMENT

<table>
<thead>
<tr>
<th>859 citations</th>
<th>2,584 entries</th>
</tr>
</thead>
<tbody>
<tr>
<td>183 NDAs/BLAs</td>
<td>573 entries</td>
</tr>
</tbody>
</table>

HEPATIC IMPAIRMENT

<table>
<thead>
<tr>
<th>535 citations</th>
<th>1,235 entries</th>
</tr>
</thead>
<tbody>
<tr>
<td>189 NDAs/BLAs</td>
<td>469 entries</td>
</tr>
</tbody>
</table>

Dedicated organ impairment queries with 123 possible searches

932 drugs evaluated in organ impairment studies

APPLICATIONS OF THE CLINICAL ORGAN IMPAIRMENT DATASET

PROVIDES CONTEXT for RESULTS OBTAINED with candidate compounds

HELPS DEVELOP OVERALL REGULATORY STRATEGY and optimize renal and hepatic impairment trials:
• Guides choice of appropriate study design
• Refines inclusion/exclusion criteria for control population and patients with organ impairment
• Helps select dose regimen of object drug
• Provides PK variability data for power calculations

SUPPORTS PBPK MODELING and SIMULATIONS with drug and disease parameters, changes in exposure validation set

ACCESS REGULATORY ORGAN IMPAIRMENT STUDIES for recently marketed drugs

PROVIDES REFERENCE RESOURCE for ASSESSMENT of DRUG SAFETY in patients with different severity of renal or hepatic function deficiency

CONTACT US

didbase@uw.edu
Isabelle Ragueneau-Majlessi / +1 (206) 543-4669
Jingjing Yu / +1 (206) 221-2856

Follow us

druginteractionsolutions.org