

# Drug Interaction Solutions

Transforming scientific data into clinical knowledge

## Who we are

We are a team of pharmaceutical scientists, pharmacists, and clinicians who together bring over 180 years of cumulative expertise in drug metabolism, transport, pharmacokinetics (PK), drug interactions, and clinical pharmacology.

The Metabolism & Transport Drug Interaction Database program (now Drug Interaction Solutions) was founded at the University of Washington in the late 1990s, after recognizing the advances made in the field of *in vitro* to *in vivo* predictions and the need for more widespread knowledge about the risks of drug interactions. The program was acquired by Certara in June of 2023.

The database subscription program started in 2002. Over the years, the database content was expanded with the addition of pharmacogenetics, food-effect studies, organ impairment data, and additional mechanisms of PK-based drug interactions such as absorption-based interactions.

All curation activities and editorial tasks are performed in-house with a team that is dedicated to the overall platform, identified as the Drug Interaction Database (DIDB®), and user support.

## MEET THE TEAM DRUG INTERACTION SOLUTIONS

**Isabelle Ragueneau-Majlessi**, MD, MS, Co-Founder & Senior Director

**Jingjing Yu**, MD, PhD, Associate Director

**Sophie Argon**, PharmD, MS, Scientist

**Katie Owens**, BPharm, PhD, Scientist

**Ichiko Petrie**, PharmD, Scientist

**Jessica Tay-Sontheimer**, PhD, Scientist

**Yan Wang**, MS, Scientist

**Christy Watson**, MS, Associate Scientist

**Cheryl Wu**, PhD, Scientist

**Marie C. Bodinier**, MS, Marketing & Customer Experience

**Chris Kinsella**, Software Development

### DRUG INTERACTION DATABASE LICENSING:

Contact: DIDBase@Certara.com

## Our Recent Publications

### **SEEING WHAT IS BEHIND THE SMOKESCREEN: A SYSTEMATIC REVIEW OF METHODOLOGICAL ASPECTS OF SMOKING INTERACTION STUDIES OVER THE LAST THREE DECADES AND IMPLICATIONS FOR FUTURE CLINICAL TRIALS**

**Robert Hermann, Amin Rostami-Hodjegan, Ping Zhao, Isabelle Ragueneau-Majlessi**

Clin Transl Sci. 2023 May;16(5):742-758

### **STRONG PHARMACOKINETIC DRUG-DRUG INTERACTIONS WITH DRUGS APPROVED BY THE US FOOD AND DRUG ADMINISTRATION IN 2021: MECHANISMS AND CLINICAL IMPLICATIONS**

**Jingjing Yu, Yan Wang, Isabelle Ragueneau-Majlessi**

Clin Ther. 2022 Nov;44(11):1536-1544

### **EVALUATING THE FEASIBILITY OF PERFORMING PHARMACOGENETIC GUIDED-MEDICATION THERAPY MANAGEMENT IN A RETIREMENT COMMUNITY: A PROSPECTIVE, SINGLE ARM STUDY**

**Lena Chaitesipaseut, Jennifer Wilson Norton, Kristen Trivelli, Sophie M.A. Argon, Ichiko D. Petrie, Isabelle Ragueneau-Majlessi, Tamatha Mikes, Hao Nguyen, Beth Devine**

J Am Coll Clin Pharm. 2022;5(3):291-301

### **PHARMACOKINETIC DRUG-DRUG INTERACTIONS WITH DRUGS APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION IN 2020: MECHANISTIC UNDERSTANDING AND CLINICAL RECOMMENDATIONS**

**Jingjing Yu, Yan Wang, Isabelle Ragueneau-Majlessi**

Drug Metab Dispos. 2022 Jan;50(1):1-7

### **EXPLORING THE RELATIONSHIP OF DRUG BCS CLASSIFICATION, FOOD EFFECT, AND GASTRIC PH-DEPENDENT DRUG INTERACTIONS**

**Katie H. Owens, Sophie M.A. Argon, Jingjing Yu, Xinning Yang, Fang Wu, Sue-Chih Lee, Wei-Jhe Sun, Anuradha Ramamoorthy, Lei Zhang, Isabelle Ragueneau-Majlessi**

AAPS J. 2021 Dec 27;24(1):16

### **ANALYSIS OF DRUG-DRUG INTERACTION LABELING LANGUAGE AND CLINICAL RECOMMENDATIONS FOR NEWLY APPROVED DRUGS EVALUATED WITH DIGOXIN, MIDAZOLAM, AND S-WARFARIN**

**Lindsay M. Henderson, Claire E. Steinbronn, Jingjing Yu, Catherine K. Yeung, Isabelle Ragueneau-Majlessi**

Clin Ther. 2021 Nov;43(11):2032-2039

## What we offer

Drug Interaction Solutions ([www.druginteractionsolutions.org](http://www.druginteractionsolutions.org)) is designed to support research and regulatory scientists in their decision-making when evaluating PK-based drug-drug interactions (DDIs), gene-drug interactions, and drug safety.

- Our main activity is the development of drug interaction content in DIDB®.
- We also provide customized clinical PK datasets to fit specific solutions.

DIDB® has the largest manually curated collection of qualitative and quantitative human *in vitro* and clinical (*in vivo*) information related to various extrinsic and intrinsic factors. These include interacting co-medications, excipients, food products, herbals, tobacco, organ impairment, and genetics, that can affect drug exposure in humans. Its easy-to-use web portal allows users to efficiently retrieve the most relevant and up-to-date information from the large body of publications and regulatory documentation.

### Information on drug disposition available in DIDB® encompasses:

- *In vitro* drug metabolism, transport, and DDIs (involving metabolizing enzymes, transporters, and their variants)
- Clinical DDIs and case reports
- Clinical pharmacogenetics
- Other DDI mechanisms including clinical absorption-based interactions (e.g., food-effect, pH-dependence, etc.)
- Clinical hepatic and renal impairment

### EXAMPLE OF QUERY

**Over 70 queries**

23,627 citations with 159,452 entries  
496 NDA/BLAs with 14,193 entries

[All queries >>](#)

**Resource center**

Watch our video "DIDB - Comprehensive Demonstration"

Lists of substrates, inhibitors and inducers, tutorials, regulatory guidances, and more.

[Resources >>](#)

**Citations recently published**

PubMed 34402068	8 entries	2022 Feb
PubMed 34806331	4 entries	2022 Feb
PubMed 34658072	2 entries	2022 Feb
PubMed 34674222	1 entry	2022 Feb
PubMed 34669023	3 entries	2022 Jan

More recently published citations →

**Monographs**

Our detailed drug monographs contain summaries for DDI, QT, and PK as well as chemical structure depictions, links to external resources, and relationships to other compounds in DIDB.

[Monographs >>](#)

**News**

Data Curation and Entry in DIDB – January Summary  
1/15/2022

New Name and Additional Data for the CYP/P-gp Substrates and Perpetrators Lists: 1/14/2022

Data Curation and Entry in DIDB – December Summary  
1/18/2022

Read more news →

**Basic queries**

- Drug queries
- Search by drug name.

- Therapeutic class queries
- Search by drug or multiple therapeutic classes.

- Enzyme queries
- Search by drug metabolizing enzyme, *in vitro* and/or *in vivo*.

- Transporter queries
- Search by transporter, *in vitro* or *in vivo*.

- In vitro induction queries
- Search by nuclear receptor.

**Advanced queries**

- In vitro* parameter queries
- Search for values of  $K_m$ ,  $V_{max}$ ,  $K_i$ ,  $IC_{50}$ ,  $K_d$  &  $K_{mact}$ , and  $EC_{50}$  of % / fold increase.

- AUC-CL change queries
- Search for AUC and CL changes observed in DDI, impairment, and food-effect studies.

- FDA marker queries
- Search for *in vitro* and clinical data for inhibitors of CYP markers.

**Pharmacokinetics queries**

- Pharmacokinetic queries
- Search for pharmacokinetic measurements of objects and precipitants.

- Hepatic and renal impairment queries
- Search for pharmacokinetic parameters of objects in subjects with hepatic or renal impairment.

- Pharmacogenetics queries
- Search for changes in drug exposure due to genetic variants of enzymes and transporters.

Drug considered as  
**object (victim) or precipitant (perpetrator)**

Monograph
Find all studies
Objects
Precipitants
Object and Precipitant Pair

Find all citations with **Objects** choose one or more compounds (enter at least 2 characters)

Condition
In Vivo or In Vitro
In Vivo
In Vitro

**Submit**

## Our expertise

In practice, we review the latest peer-reviewed publications as well as recent NDA/BLA reviews and drug labels from the FDA and select the content that is most relevant to support drug interaction evaluations at various stages of the drug development process.

We create detailed drug monographs that summarize the main mechanistic and quantitative findings including the drug characteristics, PK profile, DDI summary, QT summary, as well as information regarding the overall DDI risk level and label recommendations for clinical use.

We maintain an up-to-date Resource Center containing:

- A DDI Marker Studies Knowledgebase which includes known sensitive and moderate sensitive substrates, weak/moderate/strong perpetrators, based on available clinical evaluations with marker compounds
- A series of tutorial videos and user guides which describe the content and the functionality of the database, and show how to best retrieve the information of interest
- Regulatory guidances from the FDA, EMA, PMDA, and Health Canada

In addition to data curation, we share the results of our own research by contributing to workshops and conferences, and publishing articles and reviews on an ongoing basis.

We work closely with colleagues from various universities, regulatory agencies, and pharmaceutical companies on the most pressing issues and challenges in the field.

We assist the end-users of DIDB® with highly specific and detailed database searches and outputs, breaking down often complex mechanisms of drug interactions to enable efficient problem solving.

We continuously expand the database content and improve its functionality based on user feedback.

## DRUG MONOGRAPH

**1**

**maribavir**

[General information](#)

[Characteristics](#)

[Pharmacokinetic profile](#)

[DDI summary](#)

[Main routes of elimination](#)

[Main enzymes and associated interactions](#)

[Main transporters and associated interactions](#)

[Inhibition profile](#)

[Induction profile](#)

[Other DDIs](#)

[QT summary](#)

[Relationship to other compounds](#)

[External resources](#)

**maribavir** PubChem

[Print / Save as PDF](#)

How to save a webpage as a PDF

NDA 215596 (43 entries) HI Study Feed Effect Study approval year: 2021

Therapeutic class: Anti-Infective Agents → Antivirals

Brand name: LENTIGENITY (tablets)

Indications and usage: Inhibitor indicated for the treatment of adults and pediatric patients (12 years of age and older and weighing at least 35 kg) with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir, or foscarnet.

Clinical recommended dosage: 400 mg orally twice daily with or without food

Molecular weight: 376.24 g/mol

Bioavailability: Class II: High permeability - Low solubility reference: NDA 215596 Product Quality Review(s)

[All studies containing maribavir »](#)

**3**

**DDI summary** last edited 1/30/2022

Total drug monograph DDI summaries are determined when the drugs are first approved by the FDA and are based on data collected nearly 30k relevant and drug drugs. To review all interactions in monographs, including discontinued drugs, see the All studies page.

NDA 215596 HI Study Feed Effect Study approval date: 2021

Risk level as subject: Risk level as perpetrator:

Drug is rated according to their potential risk of interactions. Please see our documentation on the assignment of DDI Risk Level.

**Key Highlights**

Maribavir (LENTEGENCY) is a cytomegalovirus (CMV) pUL94 kinase inhibitor indicated for the treatment of adult and pediatric patients (12 years of age and older and weighing at least 35 kg) with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir, or foscarnet. The recommended dose is 400 mg orally twice daily with or without food.

In-vivo studies suggest that maribavir is primarily metabolized by CYP3A4. In-vitro, concurrent administration with dexamethasone, a strong CYP3A4 inhibitor, increased median AUC<sub>0-120</sub> (dexamethasone) 1.3-fold. In-vitro, co-administration with ketoconazole, a moderate CYP3A4 inhibitor, was predicted to increase median AUC<sub>0-120</sub> 1.6-fold. However, these changes are not considered to be clinically significant.

**2**

**Characteristics**

**CYP3A49 weak inhibitor**

**CYP3A49 weak inhibitor**

**P-gp critical inhibitor**

In contrast to the DDI summary, which is mostly based on the NDA review at the time of the drug approval, Drug Characteristics are identified based on the most up-to-date information from the literature and/or drug labels, and may change when new information becomes available. Therefore, differences may exist between Drug Characteristics and the DDI summary. For more information on characteristics and to see our full list of characteristics for all drugs see all our characteristics →

**Pharmacokinetic profile**

Accumulation ratio: 1.37-1.47; steady state is reached within 2 days

B<sub>DP</sub>: 1.37 ± 0.13 (0-205-10 µg/mL)

Bioavailability: Class II: High permeability - Low solubility

C<sub>max</sub>: 45.72 µmol/L  
17.2 (38-36) µg/mL  
400 mg orally twice daily in transplant patients with CMV

Clearance: 2.85 L/h (transplant patients with CMV); 0.051 L/h (C10ra)

Clinical recommended dosage: 400 mg orally twice daily with or without food

Dose proportionality: yes - Cmax and AUC increase approximately dose-proportionally at single doses of 60-1600 mg and at multiple doses up to 2400 mg/day; PK is time-independent

Elimination pathway: extensive metabolism

F<sub>o</sub>: 0.90

F<sub>pi</sub>: < 0.02 (oral)

F<sub>TX</sub> in vitro: 0.664 (CYP3A4), 0.338 (CYP1A2) - based on recombinant CYPs

F<sub>TX</sub> in vivo: 0.35 (CYP3A4) - also a substrate of P-gp, this value took calculated from the maximum AUC/R with ketoconazole may overestimate fm as ketoconazole also inhibits P-gp

F<sub>TX</sub> in vitro: 0.73 (fmet)

H<sub>A</sub>: 1.2 h

logP: 2.98 at pH 7.4

Molecular weight: 376.24 g/mol

Permeability: 5.6 × 10<sup>-6</sup> cm/sec (Papp in Caco-2 cells)

pKa: 5.2

Plasma protein binding: 94% (0.05-200 µg/mL)

**QT summary**

Sources: [PharmGKB Clinical Network](#) [DrugBank - Product Labels](#) [Published Literature](#)

**Precinical data**

In-vitro, maribavir had no effect on hERG potassium current (IC50 > 100 µM).

**Clinical data**

In-vivo pre-dose - Through QT (QTc) study

Measurement:	Test	Positive control:	Maribavir:
Conc. Regimen:	100 mg oral 1200 mg/day dose	400 mg single dose	400 mg
Impairment:	Healthy volunteers	Healthy volunteers	
Mean change in QTc (msec):	100 mg: 1.24 ± 0.33, 1,000 mg: 3.1 ± 1.290 mg: 2.97, 400 mg: 3.1	6.10 (9-46), 11.50 (n = 3)	
Significant regression:	(0.008) mg/msec, r <sup>2</sup> = 0.931		

In a randomized, placebo, and positive controlled, four-period crossover through 27 study in healthy volunteers, maribavir (400 mg and 1000 mg) did not prolong the QTc interval in any clinically relevant extent. The 100-mg dose of maribavir (1200 mg, three times higher than the recommended dose) 400 mg was investigated to examine the normal-case extremes of increased cardiac measures due to concentration use of a strong CYP3A4 inhibitor.

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# How we work



## Selection of Citations

We identify the latest, most relevant publications and regulatory documents from NDA/BLA packages for manual curation.



## Data Extraction



Prior to integration, the data is carefully and critically evaluated. When appropriate, and sometimes upon discussion with the study authors, comments are attached to the data. The richness of each citation is exploited, generating a highly detailed dataset. The data is formatted for immediate use and to allow meta-analysis of multiple sources.



## Data Entry and validation

Once entered into the database, the data is validated by a second curator, who thoroughly reviews the studies and citations to make sure all the relevant information has been accurately extracted and represented. Only then, is the data released and accessible to end-users.



## Data release

This process, built over more than 20 years, has been mastered by the team, and is highly-collaborative, allowing the database to be updated with new information daily, and the applications to be enriched with new scientific findings as soon as they become available.



Thorough standard operating procedures support the selection, distribution, data entry, and data validation of citations in DIDB<sup>®</sup>.

**DIDB<sup>®</sup> BY THE NUMBERS**

(as of August 2023)

**PROGRAM ESTABLISHED****20**  
years ago**CITATION COVERAGE****1950**  
to presentOVER 70 queries including  
**450** possible searches**20,000**  
total compounds**900**  
DDI summaries**DRUG-DRUG INTERACTIONS**  
PHARMACOKINETIC DATA FROM OVER**25,000**  
citations  
INCLUDING**180,000**  
entries**550**  
NDAs/BLAs  
INCLUDING**16,000**  
entries

# Who are our users

PHARMACEUTICAL COMPANIES	REGULATORY AGENCIES	ACADEMIC INSTITUTIONS	PUBLISHERS of DRUG INFORMATION
Preclinical and clinical scientists working in drug development and regulatory groups	CONTRACT RESEARCH ORGANIZATIONS	NON-PROFIT ORGANIZATIONS	PROVIDERS of CLINICAL DECISION SUPPORT SYSTEMS

The worldwide userbase includes organizations of **all sizes**

## Benefits

of using DIDB®

**PROVIDE CONTEXT** for the **INTERPRETATION** of results obtained for candidate compounds

**OPTIMIZE and VALIDATE** PBPK MODELS and static predictions

**ASSIST with** PRIORITIZATION and DESIGN of clinical trials

**GAIN INSIGHT** on DDI RISK and possible clinical outcomes

**SUPPORT DRUG LABELING RECOMMENDATIONS** and the safe use of medications in various patient populations

**PROVIDE CUSTOMIZED CLINICAL DATASETS AND EXPERTISE** to support personalized prescription applications

## WHY SUBSCRIBE

The data we select and its presentation are unique reflections of our expertise in drug interactions. As a small and fully independent operation, we are flexible and react rapidly. We are able to continuously incorporate new scientific findings and improve the content and functionality of the database.

DIDB® is internationally recognized as an authoritative, unbiased, and transparent research tool. Our users have trusted our database for over 20 years.

## FUTURE DIRECTIONS

With its mechanistic and quantitative features, and the breadth of its content, DIDB® has the potential to become a standard in supporting various healthcare applications and complex clinical decision algorithms. We believe that its integration into clinical tools for healthcare providers and patients is a next step in the development of Drug Interaction Solutions and will constitute a pivotal milestone in the management of adverse drug interactions in the clinic. We foresee that DIDB® content will help the emergence of new approaches in personalized medicine that aims at selecting the most appropriate drug and dose for each unique patient.

## HONORS and AWARDS

DIDB® and its co-founders: Dr. René Levy and Dr. Isabelle Ragueneau-Majlessi have been selected to receive the 2022 Gary Neil Prize for Innovation in Drug Development.

“

*Your exemplary accomplishments and the superb drug interaction resource that you created" were noted by the ASCPT Awards Committee "as an exceptional achievement to facilitate drug development."*

”

Isabelle Ragueneau-Majlessi was also named a University of Washington CoMotion Presidential Innovation Fellow in 2015 for her work on the DIDB®. The prestigious fellowship program debuted in 2011 to foster entrepreneurial thinking across the University of Washington.

## About Certara

At Certara, we accelerate medicines to patients, partnering with life science innovators. Together we advance modern drug development with biosimulation, regulatory science, and market access solutions.

For more information visit [www.certara.com](http://www.certara.com) or email [DIDBase@Certara.com](mailto:DIDBase@Certara.com)