EPIDEMIOLOGY STUDY REPORT

Drug Utilization Study of Eliglustat in the United States (US) Population Using MarketScan® Database and the International Collaborative Gaucher Group Registry

Eliglustat (Cerdelga)

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Country(-ies) of study	US
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ABBREVIATIONS

CMI:	Concomitant medication of interest
CYP:	Cytochrome P450
DDI:	Drug-Drug Interaction
EMs:	Extensive metabolizers
ERT:	Enzyme replacement therapy
FDA:	Food and Drug Administration
GD:	Gaucher Disease
GD1:	Type 1 Gaucher Disease
HCP:	Health Care Provider
ICGG:	International Collaborative Gaucher Group
IMs:	Intermediate metabolizers
P-gp:	P-glycoprotein
PMs:	Poor metabolizers
RMP:	Risk Management Plan
URM:	Ultra-rapid metabolizers
US:	United States

ABSTRACT

Title: Drug Utilization Study of Eliglustat in the United States (US) Population Using MarketScan® Database and the International Collaborative Gaucher Group (ICGG) Registry

Keywords
Eliglustat, drug utilization, CYP2D6, genotyping, drug-drug interaction

Rationale and background
Eliglustat, a substrate reduction therapy (SRT) for Gaucher disease Type 1 (GD1), is a cytochrome P450 (CYP) 2D6 substrate (CYP2D6). Patients are selected for treatment with eliglustat based on their CYP2D6 predicted phenotype or metabolizer status which is the main determinant of eliglustat exposure. In addition, depending on the patient's metabolizer status, some medications or combination of medications are contraindicated or not recommended for use with eliglustat therapy as they can alter eliglustat metabolism and impact its exposure. Finally, eliglustat is an inhibitor of P-glycoprotein (P-gp) transporter and CYP2D6 and may impact exposure of drugs transported/metabolized using these pathways.

Research question and objectives
The purpose of this drug utilization study is to estimate the proportion of US patients starting eliglustat therapy who have been genotyped for CYP2D6. Another objective is to estimate the proportion of patients taking concomitant medications of interest (CMIs) including strong and moderate CYP2D6 inhibitors and strong and moderate CYP3A inhibitors, strong CYP3A inducers, and P-gp and CYP2D6 substrate medications prior to starting eliglustat and those who continue or start these medications concurrently while on eliglustat treatment.

Study design
Cohort study of US patients from the MarketScan® claims database and the ICGG Gaucher Registry database.

Study population
All patients with at least one prescription of eliglustat in the MarketScan® claims database from 18-SEP-2014 (date of market availability) until 30-SEP-2017 were included for the aims addressing eliglustat drug utilization and CMI use. During the data review it became evident that the MarketScan® claims database does not systematically capture the genotyping status of these patients, as complimentary genotyping services are offered by Sanofi Genzyme, so there was no need for health insurance reimbursement. Thus, to assess the proportion of patients who were genotyped for CYP2D6, data from US patients in the ICGG Gaucher Registry database who initiated eliglustat between 18-SEP-2014 and 30-SEP- 2017 were included.

Subjects and study size
Eighty (80) patients were prescribed eliglustat in the MarketScan® claims database, between 18-SEP-2014 and 30-SEP-2017. In this same time period, 240 US patients initiated eliglustat treatment in the ICGG Gaucher Registry.

Variables and data sources

The Truven MarketScan® medical and prescription claims database was used for this study to measure eliglustat drug utilization and CMI use by type and chronicity in eliglustat patients prior to eliglustat therapy and afterwards. An alternative data source, the ICGG Gaucher Registry was used to estimate the proportion of US patients starting eliglustat therapy who were genotyped for CYP2D6.

Results

Overall, data from the ICGG Gaucher Registry suggested high compliance of CYP2D6 genotype testing in the US patients during the study period. Of patients with information on genotype testing, 99.1% indicated that they were tested and of these patients 95.9% had documentation that the test occurred prior to eliglustat therapy initiation. There was no statistical difference in the prevalence of genotyping over time during the study period.

Seventeen (17) of the 80 patients (21.3%) in the MarketScan® patient population had a record for at least one CMI prescription being filled prior to eliglustat treatment and 20 of the 80 patients (25.0%) had a record of a CMI prescription being filled after the start of eliglustat therapy. However, there were no records of simultaneous prescriptions being filled of strong or moderate CYP2D6 inhibitors and strong or moderate CYP3A inhibitors (contraindicated with eliglustat) after initiating eliglustat therapy, nor was there any record of strong CYP3A inducers or strong CYP3A inhibitors prescribed, either before or after eliglustat therapy began. The specific type of CMIs and the chronicity of the medications used was similar prior to and after starting eliglustat therapy.

The most common CMI types taken after starting eliglustat therapy were CYP2D6 and P-gp substrates, representing the therapeutic areas of antidepressants, oral contraceptives, and anti-nausea medicines. Short term use of antibiotic/antifungals (moderate CYP3A inhibitors/P-gp substrate) was also present.

Discussion

This final report concludes that based on data from US patients in the ICGG Gaucher Registry, suggested compliance with CYP2D6 genotype testing in the US is high. While data from the MarketScan® database indicate that up to 25% of patients are prescribed some CMIs after they have initiated eliglustat therapy, there was no evidence that patients on eliglustat were prescribed CMIs in contraindicated situations that could have led to significant drug-drug interactions.

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None

MILESTONES

Milestone	Planned date
Start of study (first data collection)	June 2016
Interim report 1	September 2016
Interim report 2	September 2017
End of study (final data collection)	June 2018
Final report of study results	Q4 2018

RATIONALE AND BACKGROUND

Gaucher disease (GD) is a rare, autosomal recessive inherited trait, yet one of the most common lysosomal storage diseases. It is caused by mutations in the glucocerebrosidase gene which result in decreased enzymatic activity of glucocerebrosidase, located in the lysosomes (1). If the glucocerebrosidase enzyme does not function properly to degrade glucosylceramide, this substrate will accumulate within the lysosomes. GD is rare, occurring in approximately 1 in 40,000 in the general population, although it is much more common in the Ashkenazi Jewish population (1 in 1000). GD is comprised of three types, each with different ages of onset and progression of symptoms (1). GD1 is the most common form and while the average age of diagnosis is <20 years old, GD1 may not be diagnosed in some patients until later in adulthood. Patients with Gaucher disease type 2 and type 3, are much rarer (1:100,000) and develop severe symptoms during infancy or young childhood and may include neurodegenerative complications. These patients have shortened life expectancy which rarely extends into adulthood (2)(3).

The primary treatment for GD1 has been recombinant enzyme replacement therapy (ERT) via intravenous (IV) infusion which assists the body in the degradation of the glucosylceramide substrate and has a good safety profile. A small proportion (15%) of patients develops IgG antibodies to the enzyme given and a few patients have developed IgE antibodies and anaphylaxis (2). Few adverse events have necessitated discontinuation of treatment (2).

A newer type of therapy for GD has been oral glucosylceramide substrate reduction therapy (SRT), which are agents which inhibit glucosylceramide synthase, the enzyme that synthetizes glucosylceramide. The first approved SRT, miglustat (Zavesca®), is a second line treatment for GD, indicated for adult patients with mild/moderate GD1 for whom ERT is not a therapeutic option. The reported side effects included diarrhea (85-90%), paraesthesias and fine tremor (10%) (2).

Another approved inhibitor of glucosylceramide synthase is eliglustat. As eliglustat is a CYP2D6 substrate, patients have to be dosed based on their CYP2D6 metabolizer status which is the main determinant of eliglustat metabolism. In the US, eliglustat is indicated for the long-term treatment of adult patients with GD1 who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs) or poor metabolizers (PMs) as detected by an FDA-

cleared test. Its limitations of use are as follows: CYP2D6 ultra-rapid metabolizers (URM) may not achieve adequate concentrations of eliglustat to achieve a therapeutic effect, and a specific dosage cannot be recommended for indeterminate metabolizers (4).

Contraindications for prescribing eliglustat therapy in the US are the concomitant use of a strong or moderate CYP2D6 inhibitor together with a strong or moderate CYP3A inhibitor in EM and IM patients, or use of a strong CYP3A inhibitor in IM and PM patients. Additional potential drug interactions could occur if there is co-administration of strong CYP3A inducers, P-gp substrate, and/or CYP2D6 substrate medications while taking eliglustat.

Based on data from Phase 1 drug-drug interaction studies, co-administration of eliglustat with strong CYP3A inducers (e.g., rifampin, carbamazepine) is not recommended due to significant decreases in eliglustat concentrations, which may reduce its therapeutic effectiveness. Moreover, eliglustat treatment with the concomitant use of strong or moderate CYP2D6 and/or CYP3A inhibitors that does not follow the posology of the label with respect to patients' CYP2D6 metabolizer status may lead to increased eliglustat exposure. The concomitant use of those drugs may raise eliglustat plasma concentrations significantly, which may lead to prolongation of the PR, QTc, and/or QRS intervals that could result in cardiac arrhythmias. Use of eliglustat with P-gp or CYP2D6 substrates may result in increased plasma exposure of these substrate drugs, which may require reduced doses of these drugs, especially for drugs with a narrow therapeutic index (e.g., digoxin, phenytoin).

Currently, data on the frequency on patient genotyping prior to eliglustat treatment initiation and CMI use is very limited in literature and eliglustat has only been commercially available since September 2014 in the US. As part of additional pharmacovigilance activities of the eliglustat EU Risk Management Plan (RMP), this drug utilization study will obtain data to allow for an evaluation of physicians' prescribing pattern of eliglustat as compared to US labeling recommendations.

RESEARCH QUESTIONS AND STUDY OBJECTIVES

The goal of the study is to assess the compliance/adherence of HCP to the US labeling recommendations for eliglustat with regard to genotyping for CYP2D6 and the prevention and management of potential drug interactions. The following CMI were examined:

- Strong or moderate CYP2D6 inhibitors
- Strong or moderate CYP3A inhibitors
- Strong CYP3A inducers
- P-gp substrates
- CYP2D6 substrates

Objectives:

1) To estimate the proportion of patients in the US who have been genotyped for CYP2D6 prior to the initiation of eliglustat therapy,
2) To estimate the dose and duration of eliglustat therapy, as well as the prevalence, duration and type of past and concomitant medication use of strong or moderate

CYP2D6 inhibitors, strong or moderate CYP3A inhibitors, strong CYP3A inducers, P-gp, and CYP2D6 substrates, in US patients treated with eliglustat.

AMENDMENTS AND UPDATES

Not applicable.

RESEARCH METHODS

1.1 STUDY DESIGN AND SETTING

Two cohorts of US patients were used for this study.

1. US patients in the MarketScan® claims database with at least one prescription of eliglustat between 18-SEP-2014 and 30-SEP- 2017.
2. US patients from the ICGG Gaucher Registry database who initiated eliglustat between 18-SEP-2014 and 30-SEP-2017.

1.2 SUBJECTS

Inclusion criteria:

1) MarketScan® claims database: US patients who filled a prescription for eliglustat between 18-SEP- 2014 and 30-SEP-2017. The index date was the first drug claim date for eliglustat for each patient within the study period.

2) ICGG Gaucher Registry: US patients who initiated eliglustat therapy between 18-SEP-2014 and 30-SEP-2017.

Exclusion criteria:

None.

1.3 VARIABLES

1.3.1 Exposure measurement

Exposure variables from the MarketScan® claims database.
The National Drug Code (NDC) was used to identify eliglustat prescription claims from the MarketScan® database. Maintained by the Food and Drug Administration (FDA), NDC is a code set that serves as a universal product identifier for human drugs and biologics. The directory consists of prescriptions that are in commercial distribution in the United States. The products have been listed in accordance with the Drug Listing Act and applicable Code of Federal Regulations for submitting drug product information to the FDA (http://www.fda.gov/cder/ndc/).

A patient who had at least one drug claim record for eliglustat (NDC: 58468-0220) was considered to be exposed. The first drug claim dispense date was considered the exposure start date (index date). The eliglustat exposure time window was defined as the period between the exposure start date (fill date of first eliglustat prescription) and the exposure end date (date of the last eliglustat prescription plus the duration of the prescription, i.e., days of

supply). The eliglustat exposure period was also used as the time period to assess for concomitant medication use of CMIs while a patient is receiving eliglustat therapy. Dose and duration of eliglustat therapy was measured for each patient on eliglustat therapy.

Variables collected from the ICGG Gaucher Registry.
The ICGG Gaucher Registry collects data on patient demographics (e.g., date of birth, gender) and GD type in electronic case report forms (eCRFs). The eCRFs also collect the patient's primary GD therapy (e.g., ERT or oral therapies) status including: dates of therapy; if a change has occurred, the type of change; drug; dose; dose unit; dose frequency. The collection of CYP2D6 genotype testing status and the predicted metabolizer phenotype was added to the ICGG Gaucher Registry eCRFs in October 2015. Data entry is voluntary, and may occur retrospectively or prospectively with respect to the date of treatment initiation. CYP2D6 questions on the eCRFs include the following:

1. Has the patient's CYP2D6 genotype been tested? [Yes, No, Unknown];
2. If the answer is Yes, the collection date for the CYP2D6 genotype assay is recorded; and
3. CYP2D6 predicted phenotype [PM, EM, IM, URM, indeterminate, unknown, and missing].

The ICGG Gaucher Registry does not collect data on the genotyping source (e.g., clinical trials program or MAH genotyping service, etc.) or exposure source; nor, does the ICGG Gaucher Registry collect data on past and concomitant medications of interest (CMI) usage (i.e., strong or moderate CYP2D6 inhibitors; strong or moderate CYP3A inhibitors; strong CYP3A inducers; P-gp substrates; CYP2D6 substrates).

1.3.2 Outcome(s) of interest

- CYP2D6 genotyping (CPT codes, see Appendix 1) conducted prior to initiation of eliglustat prescription start date[1] and counts of self-reported CYP2D6 genotype testing from the U. S. participants in the ICGG Gaucher Registry.
- Concomitant medications of interest (CMI, see Appendix 2)
    - CMI prescriptions were identified from the MarketScan® prescription database using NDC codes.
    - CMI included: moderate or strong CYP2D6 inhibitors, moderate or strong CYP3A inhibitors, strong CYP3A inducers, P-gp or CYP2D6 substrates
    - Any use of a concomitant medication was defined as any prescription for a CMI, regardless of the duration

[1] Note that the vast majority of patients did not require reimbursement through health insurance due to free genotype testing availability; thus genotyping was assessed through an alternative data source, the ICGG Gaucher Registry (see Section 8.1)

  - Chronic use of a CMI was defined as total duration of consecutive prescriptions of at least 15 days or more.
  - Dose and duration of eliglustat therapy with concomitant medication

- Other patient demographic characteristics (e.g., age, gender, region etc.)

If a patient has at least one prescription claim to any of the CMIs within the year prior to or after the first prescription of eliglustat, they were counted as exposed to a CMI (a CMI user) at that time point and the duration of prescription (i.e., day supply) of that CMI prescription was measured to assess chronicity of CMI. The chronicity (≥15 days duration is chronic use) of a concomitant medication was defined based on the duration of use. Duration of each concomitant medication use for each patient was defined by the treatment period covering consecutive prescriptions. Prescriptions were considered consecutive when less than 30 days elapse between end date (the last fill date plus day supply) and the subsequent fill date.

1.4 DATA SOURCES AND MEASUREMENT

Two data sources were used for this study.

1.4.1 ICGG Gaucher Registry

The ICGG Gaucher Registry is a multi-center, international, longitudinal, observational program for patients with GD that is designed to track the natural history and outcomes of these patients. The primary objectives are to understand the natural history and progression of GD, provide monitoring of patient outcomes for medical community and optimize patient care, and to evaluate the long-term effectiveness of enzyme replacement therapy and substrate reduction therapy. All patients with a confirmed diagnosis of GD who provide informed consent are eligible. There are no exclusion criteria. Only US patients who initiated eliglustat during the study period were included in this analysis.

1.4.2 Truven MarketScan® health claims database

The MarketScan® health claims database is a large comprehensive US medical and drug insurance claims database, with part of Medicare and Medicaid data, provided from Truven Health Analytics (formerly Thomson Reuters). It contains inpatient admission records, outpatient services and prescription drug claims and enrolment information on over 40 million US lives from 2000 to present. The MarketScan® database is de-identified and compliant with the Health Insurance Privacy and Portability Act of 1996 and was used under Institutional Review Board approval. This database was selected because it is one of the largest databases available and likely to have the largest number of GD patients available for this study.

1.5 BIAS

Not applicable.

1.6 STUDY SIZE

All patients meeting inclusion criteria from each data source were included in the analysis. The final report includes 80 US patients who filed a prescription claim for eliglustat in the

MarketScan® database between 18-SEP-2014 and 30-SEP-2017 and 240 US patients from ICGG Gaucher Registry who initiated eliglustat therapy during the same time period.

1.7 DATA MANAGEMENT AND TRANSFORMATION

1.7.1 ICGG Gaucher Registry data management

The purpose of the ICGG Gaucher Registry is to collect uniform and meaningful clinical data on patients with GD. Data collection includes clinical assessments that are evaluated for patients with GD. Participating physicians are encouraged to collect both retrospective and prospective data on a standard set of eCRFs.

Data collected by physicians or their designees are submitted to the ICGG Gaucher Registry for central processing by Sanofi Genzyme. Secure online technology and other electronic advancements are utilized to enhance data collection, education, and reporting capabilities. Regular data quality-related activities include manual review of data by the Data Management staff, as well as electronic edit checks designed to identify missing, inaccurate, or invalid data. Additional tools available to the Data Management staff to process the data and facilitate the identification of data discrepancies include a data management plan, data review guidelines, data listings and reports, and monthly SAS data checks.

Data Management staff at Sanofi Genzyme perform reviews of the data for missing data points, incomplete information, and discrepancies with previously submitted data. Efforts are made by Sanofi Genzyme Data Management staff to work with monitoring teams to resolve queried and data entry issues with the study sites. In addition, designated “cut-off” values are used to identify any reported dosing or laboratory data that are clearly erroneous (i.e., incompatible with attainable ranges), and these data are queried by Data Management, but not included in the summaries of dosing and laboratory parameters until the data is updated by the study site. All data management and analysis occur in a validated computing environment at the MAH. Analyses for this study were conducted using SAS v.9 statistical software (Cary, NC).

1.7.2 MarketScan® data management

The prescription and medical claims records was extracted from the licensed US administrative health claims MarketScan® database which is stored on an internal server at the MAH. Data processing and cleaning was done by an experienced data analyst within the Epidemiology and Benefit Risk team to prepare data for statistical analysis. All data management and statistical analyses was conducted with SAS v.9 statistical software (Cary, NC).

1.8 STATISTICAL METHODS

1.8.1 Main summary measures

The measures used in this study are descriptive statistics including the frequency and proportion of individuals who fill a prescription for eliglustat and who have had CYP2D6 genotyping procedure, along with the mean, standard deviation, median, minimum and maximum for continuous variables such as dose and duration of concomitant medication use.

1.8.2 ICGG Gaucher Registry analysis

Prevalence of CYP2D6 genotype testing was assessed in US patients who initiated eliglustat treatment during the overall study period. The collection date of the genotype assay was used to assess whether testing occurred prior to treatment initiation. Analyses were performed for each study period separately as well as for the entire period. A Fisher's exact test comparing the prevalence of testing between the periods was used to determine if the percentage of patients genotyped differed over time for the defined study periods (18-SEP-2014 to 30-SEP-2015, 1-OCT-2015 to 30-SEP-2016, and 1-OCT-2016 to 30-SEP-2017).

1.8.3 MarketScan® database analysis

- Descriptive analysis of patient's dose and duration on eliglustat therapy within the study period. Each patient's length of enrollment in prescription plan, both prior and post index date was taken into account when measuring proportion of patients on a CMI.
- Descriptive analyses of the prior medication use of CMIs (proportion, type, and duration) in the year prior to treatment initiation of eliglustat therapy.
    - Prevalence and duration of prior use of any of the CMIs (strong or moderate CYP2D6 and strong or moderate CYP3A inhibitors, strong CYP3A inducers, P-gp substrates and CYP2D6 substrates)
    - Prevalence and duration of patients who have prescriptions for a strong or moderate CYP2D6 inhibitor AND a strong or moderate CYP3A inhibitor, simultaneously
    - Results are displayed for all CMIs, overall, by drug type, and then listed for each specific drug used prior to eliglustat therapy initiation, separately for any use, chronic use, and short term use
- Descriptive analyses of the concomitant medication use of CMIs (proportion, type, and duration) in patients while receiving eliglustat therapy.
    - Prevalence and duration of concomitant medication use of any of the CMIs (strong and moderate CYP2D6 and CYP3A inhibitors, strong CYP3A inducers, P-gp and CYP2D6 substrates)
    - Prevalence and duration of patients who have prescriptions for a strong or moderate CYP3A inhibitor AND a strong or moderate CYP2D6 inhibitor, simultaneously
    - Results are displayed for all CMIs, overall, by drug type, and then listed for each specific drug used concomitantly with eliglustat therapy, separately for any use chronic use, and short-term use

1.8.4 Missing values

Missing values are reported as observed.

1.8.5 Sensitivity analyses

Not applicable.

1.8.6 Amendments to the statistical analysis plan

An alternative data source (the ICGG Gaucher Registry) was identified to estimate the prevalence of CYP2D6 genotype testing prior to eliglustat treatment initiation (Section 8.1).

1.9 QUALITY CONTROL

Data extraction for analysis was performed by programmers/analysts at Sanofi who have extensive programming and analysis experience with the claims data or the registry data. All programs and result tables, programmed by the programmer/analyst, were thoroughly and independently reviewed by a second programmer/analyst at each step of the analysis to validate coding rules and order of operations as well as statistical methodology, as appropriate. The guidelines and standard procedures detailed in Sanofi Quality Documents was followed to ensure the quality, accuracy, validation, and storage of analysis programs, results, as well as key documents (protocol and reports) of the study.

RESULTS

1.10 PARTICIPANTS

ICGG Gaucher Registry
A total of 240 US patients initiated eliglustat therapy between 18-SEP-2014 and 30-SEP-2017. Of the 240 patients, 224 (93.3%) patients had information on whether they had a record of CYP2D6 genotype testing and 16 (6.7%) patients had unknown/missing information with respect to CYP2D6 genotype testing.

MarketScan® database
A total of 80 US patients had at least one prescription claim filled for eliglustat from 18-SEP-2014 and 30-SEP-2017.

1.11 DEMOGRAPHIC CHARACTERISTICS

Demographic characteristics of the ICGG Gaucher patients who underwent CYP2D6 genotype testing (n=222) are presented in Table 1. Of the 222 patients 55% were female and the mean age was approximately 45 years.

Table 1 - Demographic characteristics of ICGG Gaucher patients who underwent CYP2D6 genotype testing (N=222*)

Characteristic	Measure	Value
Age (years) at date of genotype testing	N	222
	Mean (SD)	45.3 (15.8)
	Median	46.1
	Min, Max	18, 80.4
Gender		
Female	N (%)	123 (55.4%)
Male	N (%)	99 (44.6%)

*2 patients of the 224 total patients with information on CYP2D6 genotype testing had information indicating that they were not tested and therefore they were excluded from this analysis.

The demographic characteristics of the eliglustat users from the MarketScan® database are listed in Table 2. A total of 80 patients had at least one prescription claim for eliglustat during the study period. The age and sex distributions of the patients in the MarketScan® database were comparable to those patients included from the ICGG Gaucher Registry. The mean age of patients from the MarketScan® database was approximately 44 years and the distribution of males (51%) and females (49%) was similar. Approximately two-thirds of patients were enrolled at least 3 months prior to their first prescription of eliglustat and the mean duration of follow-up after their first eliglustat prescription was 464 days.

Table 2 - Demographic characteristics of MarketScan® database patients (N=80)

Characteristic	Measure	Value
	N	80 (100%)
Age (years)	Mean (SD)	43. 9 (14. 4)
	Median	43
	Min, Max	18, 77
Gender	Female	39 (48.8%)
	Male	41 (51.3%)
US Region	Midwest	9 (11.3%)
	Northeast	27 (33.8%)
	South	27 (33.8%)
	West	17 (21.3%)
Continuous enrollment in health plan for 3 months prior to index date (patients)	N (%)	54 (67.5%)
Continuous enrollment in health plan for 6 months prior to index date (patients)	N (%)	49 (61.3%)
Length of patient follow-up (days)	Mean (±SD)	464.2 (323.6)
	Median	406
	Min, Max	5, 1082

1.12 MAIN RESULTS

1.12.1 Prevalence of CYP2D6 genotype testing and predicted CYP2D6 phenotype among US patients in the ICGG Gaucher Registry

Table 3 describes the genotyping status of US patients in the ICGG Gaucher Registry who initiated eliglustat during the overall study period and stratified by the following periods (18-SEP-2014 to 30-SEP-2015, 1-OCT-2015 to 30-SEP-2016, and 1-OCT-2016 to 30-SEP-2017). Over the cumulative study period, the prevalence of CYP2D6 genotype testing among the 224 patients who had recorded information on genotyping was 99.1%. The genotype testing prevalence was consistently high over the 3 study periods (93.8-100%), with no patients in period 1, and only one patient each in periods 2 and 3, who were reportedly not tested. A Fisher's exact test comparing the prevalence of non-testing between periods 2 and 1

(p=0.3), and periods 3 and 1 (p=0.1) did not indicate a significant difference in the prevalence of the lack of CYP2D6 genotype testing over the study period. Finally, of the 222 patients who were tested, 213 (95.9%) had documentation that the test occurred prior to the initiation of eliglustat therapy (data not shown).

Table 3 - CYP2D6 Genotyping status of US patients in the ICGG Gaucher Registry initiating eliglustat therapy during the study period (18-SEP-2014 to 30-SEP-2017)

	Period 1	Period 2	Period 3	Cumulative
	18-SEP-2014 to 30-SEP-2015	1-OCT-2015 to 30-SEP-2016	1-OCT-2016 to 30SEP-2017	18-SEP-2014 to 30-SEP-2017
Patients with information on CYP2D6 genotype testing, n	140	68	16	224
Tested, n (% out of people with available information on testing)	140 (100%)	67 (98.5%)	15 (93.8%)	222 (99.1%)
Not tested, n (% out of people with available information on testing)	0 (0%)	1 (1.5%)	1 (6.3%)	2 (0.9%)

*Patients missing information on genotype testing or with unknown result: Period 1 (n=7); Period 2 (n=6); Period 3 (n=4)

Table 4 describes the CYP2D6 predicted phenotype among the ICGG Gaucher Registry patients who were genotyped (n=222). Three (3) patients (1.4%) had a predicted phenotype of URM.

Table 4 - CYP2D6 Predicted Phenotype (N=222)

CYP2D6 Predicted Phenotype	N (%)
Poor Metabolizer	10 (4.5%)
Intermediate Metabolizer	34 (15.3%)
Extensive Metabolizer	174 (78.4%)
Ultra-rapid Metabolizer	3 (1.4%)
Indeterminate	0 (0%)
Unknown*	1 (0.5%)

*1 patient who had information indicating receipt of CYP2D6 genotype testing did not have available data on predicted phenotype

1.12.2 Dose and Duration of eliglustat therapy

The average dose and duration of eliglustat therapy in the patients in the US claims databases is provided in Table 5. The vast majority of patients (90%) had information consistent with a dosing schedule of twice per day (i.e., 168 mg/day total). The average duration a patient was on eliglustat was 438 days, with a median duration of 367 days.

Table 5 - Dose and duration of eliglustat use in US patients (N=80)

Dosing schedule for eliglustat (daily dose)*	N (%)
Once per day (84 mg)	5 (6.3)
Twice per day (168 mg total)	72 (90.0)
Other**	3 (3.8)
Duration of eliglustat (days)	
Mean (SD), days	437.6 (320.7)
Median, days	367
Min, Max	28, 1094

*Definition of dose from claims data: Daily dose was defined as the quantity of the pills dispensed/ number of day supply for each prescription. The values for dose provided in claims database are what is provided in prescription claim and may not be an accurate reflection of patient's actual prescribed dose.
**One patient received a prescription for eliglustat twice per day for >1 year and then was prescribed an increased dosage to 3 times per day; one patient received a prescription for eliglustat twice per day for >1 year and then was prescribed an increased dosage to 4 times per day; and one patient received a prescription for eliglustat 3 times per day for 74 days duration.

1.12.3 Prevalence and duration of overall CMI use

Overall CMI use in eliglustat patients in the before and after initiation of eliglustat therapy is described in Table 6.

Twenty-one (21) percent of patients had a record of at least one CMI prescription prior to starting eliglustat therapy. The most common types of CMI prescriptions observed were P-gp substrates (11%) and moderate CYP3A inhibitors (10%). Additionally, prior to the start of eliglustat therapy, one patient had a concomitant prescription of moderate CYP3A inhibitor and a strong CYP2D6 inhibitor with a duration overlap for up to 1 day. Of note, this patient did not receive this contraindicated combination of CMI after starting eliglustat.

One quarter (25%) of patients had a record of at least one CMI prescription after starting eliglustat. The most common types of CMI prescriptions observed in patients who had started eliglustat therapy were CYP2D6 substrates (15%), P-gp substrates (15%) and moderate CYP3A inhibitors (7.5%). No use of strong CYP3A inhibitors or inducers was observed. There were also no patients prescribed concomitantly CYP2D6 inhibitors and CYP3A inhibitors while on eliglustat therapy.

The specific drug names/therapeutic areas and CMI types can be seen in Section 9.3.6, Table 9.

Table 6 - Prevalence and duration of CMI use stratified by eliglustat start date

	Prior to eliglustat initiation (N=80)				After eliglustat initiation (N=80)			
			Duration (days)				Duration (days)	
	N*	%	Mean (SD)	Median	N*	%	Mean (SD)	Median
Any CMI	17	21.3	192.9 (161.2)	208	20	25.0	259.4 (288.8)	158.5
CYP2D6								
Strong inhibitor	3	3.8	90.0 (52.6)	112	2	2.5	218.5 (171.8)	218.5
Moderate inhibitor	2	2.5	364.0 (2.8)	364	2	2.5	424.0 (333.8)	424
Substrate	5	6.3	241.0 (179.5)	362	12	15.0	232.4 (314.7)	109.5
CYP3A								
Strong inhibitor	0	0.0	0.0	0	0	0.0	0.0	0
Moderate inhibitor	8	10.0	47.5 (111.7)	7	6	7.5	12.3 (9.6)	10
Strong inducer	0	0.0	0.0	0	0	0.0	0.0	0
Strong or moderate CYP2D6 inhibitor AND Concomitant strong or moderate CYP3A inhibitor	1	1.3	1**	1	0	0.0	0.0	0
P-gp substrate	9	11.3	219.8 (145.8)	264	12	15.0	222.5 (243.1)	180

*Note: N is the number of patients who had a claim for a CMI in the year prior to eliglustat therapy. One patient could be on multiple CMIs of the same type and it would only be counted once and if a particular medication functions as two or more types of CMIs (e.g., a CYP2D6 inhibitor and CYP2D6 substrate) then it would count once in each CMI type. Thus, the sum of the CMI subtypes may not total the number of users on any CMI.

**Estimated maximum duration of CMI overlap given dispense date and days of supply of medications.

1.12.4 Prevalence and duration of chronic CMI use

Table 7 **s**hows the prevalence and duration of chronic (≥15 days duration) CMI use before and after eliglustat initiation. Of the patients with a record of any CMI use, the majority were taking a CMI classified as chronic use; 13/17 (76%) of those with a record of CMI use prior to initiation of eliglustat and 15/20 (75%) of those with a record of CMI use following the initiation of eliglustat.

In the year prior to first eliglustat prescription, 16.3% of patients had a prescription of a CMI classified as chronic use. P-gp substrates were the most common chronic CMI type prescribed (10%), followed by CYP2D6 substrates (6.3%). After starting eliglustat, 18.8% of patients had a prescription filled for a CMI classified as chronic use. The most common type of chronic CMI was CYP2D6 substrate (11.3%), followed by P-gp substrate (10%). No patients were prescribed strong CYP3A inhibitors or strong CYP3A inducers for chronic use after the start of eliglustat therapy.

The specific type of CMIs dispensed and CMI treatment for chronic use was similar prior to and after starting eliglustat therapy (the majority were oral contraceptives with ethinyl

estradiol or antidepressants). No patients were observed being prescribed the concomitant use of a CYP2D6 inhibitor and a CYP3A inhibitor for chronic use.

Table 7 - Prevalence and duration of chronic (≥15 days duration) CMI use stratified by eliglustat start date

	Prior to eliglustat initiation (N=80)				Following initiation of eliglustat (N=80)			
			Duration (days)				Duration (days)	
Type of CMI	N*	%	Mean (SD)	Median	N*	%	Mean (SD)	Median
Any CMI	13	16.3	251.5 (137.3)	323	15	18.8	342.8 (287.1)	330
CYP2D6								
Strong inhibitor	3	3.8	90. 0 (52. 6)	112	2	2.5	218.5 (171.8)	218.5
Moderate inhibitor	2	2.5	364. 0 (2. 8)	364	2	2.5	424.0 (333.8)	424
Substrate	5	6.3	241.0 (179.5)	362	9	11.3	307.8 (332.2)	188
CYP3A								
Strong inhibitor	0	0.0	0. 0	0	0	0.0	0. 0	0
Moderate inhibitor	2	2.5	175.5 (208.6)	175.5	1	1.3	30.0 (0.0)	30
Strong inducer	0	0.0	0. 0	0	0	0.0	0.0	0
P-gp Substrate	8	10.0	246.4 (130.5)	293.5	8	10.0	329.8 (228.9)	346

*Note: N is the number of patients who had a claim for a CMI in the year prior to or time period after starting eliglustat therapy. One patient could be on multiple CMIs of the same type and it would only be counted once, and if a particular medication functions as two or more types of CMIs (e.g., a CYP2D6 inhibitor and CYP2D6 substrate) then it would count once in each CMI type. Thus, the sum of the CMI subtypes may not total the number of users on any CMI

1.12.5 Prevalence and duration of short-term CMI use

Table 8 describes the prevalence and duration of short-term (<15 days of duration) use of CMIs before and after patient initiation of eliglustat therapy. Prior to starting eliglustat therapy, 7.5% of patients had short-term use of CMI with a mean duration of 3.8 days. The CMI types prescribed for short-term use in patients before eliglustat therapy initiation were moderate CYP3A inhibitor (7.5%), and P-gp substrate (2.5%).

After starting eliglustat therapy, 10.0% of patients had a record of CMI prescribed for short-term use and the mean duration was 6.4 days. The CMI types included moderate CYP3A inhibitor (6.3%), P-gp substrate (6.3%), and CYP2D6 substrate (5.0%).

The main therapeutic areas for the short-term CMIs were antibiotic/antifungal, and antinausea.

Table 8 - Prevalence and duration of CMIs dispensed to patients for short-term CMI use stratified by eliglustat start date

	Prior to eliglustat initiation (N=80)				Following initiation of eliglustat (N=80)			
			Duration (days)				Duration (days)	
	N*	%	Mean (SD)	Median	N*	%	Mean (SD)	Median
Any CMI	6	7.5	3.8 (3.1)	3.5	8	10.0	6.4 (5.5)	4.5
CYP2D6								
Strong inhibitor	0	0.0	0.0	0	0	0.0	0.0	0
Moderate inhibitor	0	0.0	0.0	0	0	0.0	0.0	0
Substrate	0	0.0	0.0	0	4	5.0	4.8 (3.3)	5
CYP3A								
Strong inhibitor	0	0.0	0.0	0	0	0.0	0.0	0
Moderate inhibitor	6	7.5	3.8 (3.1)	3.5	5	6.3	6.4 (3.5)	6
Strong inducer	0	0.0	0.0	0	0	0.0	0.0	0
P-gp Substrate	2	2.5	7.0 (0.0)	7	5	6.3	4.8 (3.6)	3

*Note: N is the number of patients who had a claim for a CMI in the year prior to eliglustat therapy. One patient could be on multiple CMIs of the same type and it would only be counted once and if a particular medication functions as two or more types of CMIs (e.g. a CYP2D6 inhibitor and CYP2D6 substrate) then it would count once in each CMI type. Thus, the sum of the CMI subtypes may not total the number of users on any CMI

1.12.6 Overall list of CMIs by therapeutic area

Table 9 categorizes the patients exposed to CMIs overall by therapeutic area and CMI type. The major therapeutic areas observed were antidepressants, antibiotic/antifungal, oral contraceptives with ethinyl estradiol, and antinausea agents.

Table 9 - Number of patients by drug name/therapeutic area and CMI type*

	Number of Patients on CMI drugs in relation to eliglustat therapy initiation		
Drug name/Therapeutic area	PRIOR	FOLLOWING	CMI type
Antidepressants (total)	6	9	
Fluoxetine Hydrochloride	1	1	Strong CYP2D6 inhibitor, CYP2D6 substrate
Bupropion Hydrochloride XL	2	1	Strong CYP2D6 inhibitor
Duloxetine Hydrochloride	2	2	Moderate CYP2D6 inhibitor, CYP2D6 substrate
Fluvoxamine Maleate ER	0	1	CYP2D6 substrate
Trazodone Hydrochloride	0	1	CYP2D6 substrate
Trintellix (Vortioxetine)	0	1	CYP2D6 substrate
Venlafaxine Hydrochloride/Effexor XR**	1	2	CYP2D6 substrate

Drug name/Therapeutic area	Number of Patients on CMI drugs in relation to eliglustat therapy initiation PRIOR	FOLLOWING	CMI type
Antibiotic/antifungal (total)***	7	5	
Ciprofloxacin Hydrochloride	2	2	Moderate CYP3A inhibitor, P-gp substrate
Fluconazole	5	4	Moderate CYP3A inhibitor
Oral contraceptives with ethinyl estradiol (total)	7	6	P-gp substrate
Antinausea agents (total)	1	6	
Metoclopramide Hydrochloride	0	1	CYP2D6 substrate
Ondansetron Hydrochloride	1	5	CYP2D6 substrate, P-gp substrate
Other	1	1	
Diltiazem	1	1	Moderate CYP3A inhibitor, P-gp substrate

*Overall total is more than 17 for prior to eliglustat use and 20 for following eliglustat use due to some patients having records for prescriptions in more than one therapeutic area.
** Venlafaxine Hydrochloride/Effexor XR is also considered a CYP2D6 inhibitor, but with no change in AUC of probe substrate available, hence it was not analyzed as a strong or moderate CYP2D6 inhibitor
***Therapeutic area totals may be less than the sum of all specific drugs in a therapeutic area because some patients received more than one type of drug

1.13 OTHER ANALYSES

Not applicable.

1.14 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study was based on the secondary use of data; expedited reporting of AE/ADR is not required.

DISCUSSION

1.15 KEY RESULTS

Overall, the results from the ICGG Gaucher Registry suggest a high compliance of CYP2D6 genotype testing during the study period. Of the 240 patients who initiated eliglustat during the study period, 224 (93.3%) patients had information on whether they had a record of CYP2D6 genotype testing and 16 (6.7%) had unknown or missing information regarding CYP2D6 genotyping. For the 224 patients who had recorded information on whether they were genotyped, the prevalence of genotype testing was 99.1% (222/224) and of these patients 95. 9% had documentation that the test occurred prior to eliglustat therapy initiation. There was no statistical difference in the prevalence of genotype testing over time. Of the 222 patients who had a record of being genotyped, 3 patients (1.4%) had a predicted phenotype of URM.

Seventeen (17) of the 80 patients (21.3%) in the MarketScan® patient population had a record for at least one CMI prescription being filled prior to eliglustat treatment and 20 of the 80 patients (25.0%) had a record of a CMI prescription being filled after the start of eliglustat therapy. However, there were no records of simultaneous prescriptions filled of strong or moderate CYP2D6 inhibitors and strong or moderate CYP3A inhibitors (contraindicated with eliglustat) after initiating eliglustat therapy, nor was there any record of strong CYP3A inducers or strong CYP3A inhibitors prescribed, either before or after eliglustat therapy began. The specific type of CMIs and the chronicity of the medications used was similar prior to and after starting eliglustat therapy.

The most common CMI types taken after starting eliglustat therapy were CYP2D6 substrates and P-gp substrates, representing the therapeutic areas of antidepressants, oral contraceptives, and antinausea medicines. Short term use of antibiotic/antifungals (moderate CYP3A inhibitors/P-gp substrate) was also present.

1.16 LIMITATIONS

The ICGG Gaucher Registry database for information is a voluntary, observational database that has no experimental intervention; thus, a patient receives standard-of-care treatment as determined by the patient's physician. Consequently, the degree of data available for a particular patient may depend on "real world" conditions such as the status of a patient's progression of disease signs and symptoms, along with differences in practice patterns. Because data entry in the ICGG Gaucher Registry is non-compulsory, the absence of reported data, such as a CYP2D6 genotype (e.g., in 16 of the 240 (6.7%) patients), does not confirm that the testing was not performed in those patients; rather, it may be the case that results were not reported to the ICGG Gaucher Registry. Date of collection of the genotype assay is reported and was used to assess whether the testing occurred prior to treatment initiation; however, due to the voluntary reporting, there is a chance that collection date may not completely accurately reflect the actual testing date. Another limitation is that the patients in the ICGG Gaucher Registry database cannot be linked to patients observed in the MarketScan® database so no direct relationship can be inferred between CYP2D6 genotype (collected in the ICGG Gaucher Registry) and the use of concomitant medications of interest (CMI) (collected in the MarketScan™ database).

Furthermore, it is not within the scope of the ICGG Gaucher Registry study to capture specific information about the genotyping source (e.g., clinical trial program, MAH genotyping service, etc.) or exposure source. However, as this study will only include patients who initiated eliglustat on or after 18-SEP-2014, the majority of patients on experimental therapies should be excluded as the major clinical trials for eliglustat had concluded by this point.

Several limitations of observational studies based on any administrative health claims database need to be noted. First, claims data are collected for the purpose of payment and therefore lack the clinical detail of medical charts or prospectively collected data. Second, the databases do not capture medications prescribed in the hospital, as the prescription data available are limited to outpatient pharmacy records only, and the claims database also does not capture all laboratory tests and test results. If a CMI is an injectable medication, it is recorded in the medical claims data however, dose and duration (days of supply) information are not available for these medications (as is available in the prescription claims records). Third, within the prescription claims data, there may be missing or inaccurate information on

the appropriate dose of medication that needs to be considered. Finally, when a medication prescription is filled fora patient, it is not known if the patient actually uses this medication in accordance with how it was prescribed. For example, in some cases, a patient may have stopped and restarted eliglustat therapy or altered the dose of a CMI to avoid a contraindicated use, or a potential drug-drug interaction.

1.17 INTERPRETATION

Almost all (99. 1%; 222 of 224 patients) of patients in the ICGG Gaucher Registry with information on CYP2D6 genotyping indicated that the patient was tested. It is noted that 16 of the 240 patients were missing information on genotype testing, but missing data does not necessarily confirm that testing was not performed on these patients. Of the 222 patients who had a record of being genotyped, only 3 patients (1. 4%) had a predicted phenotype of URM. Prescription of eliglustat is not indicated for URMs as they may not achieve adequate concentrations of eliglustat to achieve a therapeutic effect and a specific dosage cannot be recommended.

One-quarter (20/80) of patients on eliglustat therapy had a record of at least one CMI prescription. Of patients using a CMI while on eliglustat therapy, 75% (15/20) were defined as chronic users and the mean duration of CMI use was 343 days. The most common types of CMIs used in patients on eliglustat therapy were CYP2D6 inhibitors and CYP2D6 substrates (antidepressants and antinausea medications) and P-gp substrates (oral contraceptives). Eliglustat is an inhibitor of P-gp and CYP2D6 *in vitro* and may affect the plasma level of CYP2D6 and/or P-gp substrates. Lower doses of CYP2D6 and/or P-gp substrates may be required. Twelve (12) patients were treated with CYP2D6 substrates and 12 with P-gp substrates, after eliglustat initiation; however, none of the prescribed substrate drugs are known to have a narrow therapeutic index which would require reducing the dosage of the substrate and titrate to clinical effect to avoid increased exposure of the substrates and potential drug-drug interaction.

Because CYP2D6 genotype testing is not systematically captured in the Truven MarketScan® database, it was not possible to link CMI usage with CYP2D6 phenotype. However, none of the patients on eliglustat therapy were prescribed a strong CYP3A inhibitor, and none received concomitantly a strong or moderate CYP3A inhibitor and a strong or moderate CYP2D6 inhibitor. These combinations correspond to contraindicated situations in the US depending on the patient's CYP2D6 phenotype. Additionally, no eliglustat patients received a strong CYP3A inducer to be avoided as per US labeling, whatever the patient CYP2D6 phenotype. Thus, it can be concluded that even without knowing the patients' CYP2D6 metabolizer status, none of the included patients received eliglustat in a contraindicated situation that could have led to significant drug-drug interactions.

In addition, among patients receiving a CMI after eliglustat initiation, situations that might need to be taken into account depending on the patient CYP2D6 phenotype are:

- Strong or moderate CYP2D6 inhibitors in EMs and IMs may increase eliglustat exposure and a reduction of the eliglustat dosage to 84 mg once daily is then recommended. Four (4) patients (5%) had prescription records of concomitant strong or moderate CYP2D6 inhibitors. Two (2) patients were treated with a strong CYP2D6 inhibitor (one with antidepressant fluoxetine hydrochloride and one with

antidepressant bupropion hydrochloride) and two patients were treated with a moderate CYP2D6 inhibitor (antidepressant, duloxetine hydrochloride) after eliglustat initiation. One (1) of the 4 patient's records indicated a prescription for once daily dose of 84 mg of eliglustat. However, the other 3 patients' records indicated prescribed eliglustat dosage of 84 mg twice daily. Three (3) of the 4 patients had been previously taking the same antidepressant prior to eliglustat initiation (1 on fluoxetine and 2 on duloxetine).

- Use of moderate CYP3A inhibitors concomitantly with eliglustat, as it is not recommended in PMs and reduction of the eliglustat dosage to 84 mg once daily should be used in IMs and EMs: Six (6) patients were treated with a moderate CYP3A inhibitor after eliglustat initiation. The majority of this usage was short-term (5 patients with a mean duration of 6.4 days); one patient had usage of 30 days). The predicted CYP2D6 phenotype of these 6 patients is unknown.

1.18 GENERALIZABILITY

The results of this study should be relatively generalizable to the US population of patients prescribed eliglustat as it was based on a large, diverse, US administrative health claims database with national coverage and the most comprehensive GD registry established to date. However, the patients who are part of the ICGG Gaucher Registry may not be entirely representative of all US patients prescribed eliglustat.

OTHER INFORMATION

Not applicable.

CONCLUSION

This final report concludes that based on data from US patients in the ICGG Gaucher Registry, suggested compliance with CYP2D6 genotype testing prior to eliglustat initiation appears to be high. While data from the MarketScan® database indicate that up to one quarter (25%) of patients are prescribed some CMIs after they have initiated eliglustat therapy, there was no evidence that patients on eliglustat were prescribed CMIs in contraindicated situations that could have led to significant drug-drug interactions.

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Appendix 1 - Procedure codes for CYP2D6 Genotyping

Table 1. AMA revised and old CPT claim codes for CYP2D6 genotyping

New CPT Code introduced in 2012	Old CPT codes
81226	83891
	83892
	83900
	83901
	83909
	83912
	83914

Reference: 2012 AMA CPT code changes for molecular testing

APPENDIX 2- CONCOMITANT MEDICATIONS OF INTEREST (CMI)

Table 1. Classification of In Vivo Inhibitors of CYP Enzymes

CYP Enzymes	Strong Inhibitors ≥5-fold increase in AUC	Moderate inhibitors ≥2 but <5-fold increase in AUC
CYP3A	boceprevir clarithromycin conivaptan indinavir * idelalisib itraconazole ketoconazole lopinavir/ritonavir ritonavir mibefradil nefazodone nelfinavir posaconazole saquinavir * telaprevir telithromycin tipranavir/ritonavir cobicistat elvitegravir/ritonavir danopravir/ritonavir troleandomycin voriconazole	amprenavir aprepitant atazanavir * casopitant ciprofloxacin crizotinib darunavir * diltiazem erythromycin faldaprevir fluconazole fosamprenavir imatinib isavuconazole ledipasvir netupitant nilotinib tofisopam verapamil dronedarone cimetidine cyclosporine
CYP2D6	bupropion dacomitinib fluoxetine paroxetine quinidine	cimetidine cinacalcet dronedarone duloxetine terbinafine moclobemide mirabegron rolapitant tipranavir/ritonavir

Adapted from: The Metabolism and Transport Drug Interaction Database™ (DIDB) from University of Washington's Department of Pharmaceutics. April, 2017.

*Alone or in combination with ritonavir

Table 2. Classification of In Vivo Strong Inducers of CYP3A Enzymes

CYP Enzyme	Strong Inducers ≥ 80% decrease in AUC
CYP3A	avasimibe carbamazepine enzalutamide mitotane phenobarbital phenytoin rifabutin rifampin

Adapted from: The Metabolism and Transport Drug Interaction Database™ (DIDB) from University of Washington's Department of Pharmaceutics. April, 2017.

Table 3. List of P-gp Substrates

P-gp Substrates
aldosterone
aliskiren
amiodarone
atorvastatin
boceprevir
celiprolol
Cimetidine
ciprofloxacin
colchicine
cortisol
CPT-11
cyclosporine
dabigatran
daunorubicin
debrisoquine
dexamethasone
DHEA
digoxin
diltiazem
docetaxel
domperidone
doxorubicin
enoxacin
erythromycin
ethinylestradiol
etoposide
everolimus
fexofenadine
fidaxomicin
hydrocortisone
idarubicin
indinavir
itraconazole
ivermectin
lenalidomide
lidocaine
linagliptin
loperamide
lovastatin
methotrexate
methylprednisolone
mibefradil
morphine
nadolol
nelfinavir
nicardipine
ondansetron
paclitaxel
paliperidone
pravastatin
propranolol
quinidine
ranolazine
ranitidine,
rhodamine
rifampin
risperidone

P-gp Substrates
ritonavir
riveroxaban
saquinavir
simvastatin
sparfloxacin
tacrolimus
telapravir
temsirolimus
teniposide
terfenadine
tetracycline
timolol
valinomycin
vecuronium
verapamil
vincristine
vindesine

Adapted from Pharmacology weekly - efflux transporter drug table Accessed October, 14 2015

Table 4. List of CYP2D6 Substrates

CYP2D6 Substrates
amiflamine
amitriptyline
aripiprazole
atomoxetine
brofaromine
bufuralol
bencylcloquidium
brexpiprazole
carvedilol
chlorpromazine
citalopram
clomipramine
(R)-chlorpheniramine
(S)-chlorpheniramine
clozapine
codeine
cyclizine
dacomitinib
debrisoquine
desipramine
dexfenfluramine
dextromethorphan
Dihydrocodeine
Dimemorphan
d-nebivolol
Donepezil
Doxepin
e-trans-doxepin
Duloxetine
Encainide
enclomiphene
Fesoterodine
Flecainide
Fluoxetine
Fluphenazine
Fluvoxamine
Galantamine
Gefitinib
Haloperidol
Hydrocodone
Iloperidone
Imipramine
Lasofoxifene
l-nebivolol
Loratadine
lovastatin lactone
Maprotiline
Methadone
methoxyphenamine
methylphenidate
metoclopramide
Metoprolol
Mexiletine
Mianserin
Mirtazapine
Nebivolol

Nefazodone
Nicergoline
Nortriptyline
Ondansetron
Oxycodone
Pactimibe
Paroxetine
Perhexiline
Perphenazine
Phenformin
pimozide (NTR drug)
Prajmaline
iso-prajmaline
N-prajmaline
Pridopidine
Procainamide
Propafenone
Propranolol
Ranolazine
Repinotan (IV)
Risperidone
Ritonavir
Sabeluzole
Sparteine
Tamsulosin
Tamoxifen
Tetrabenazine
Thioridazine
Timolol
Tolterodine
Tolperisone
Tramadol
Traxoprodil
Trazodone
Trimipramine
Tropisetron
Venlafaxine
Vernakalant
Vortioxetine
Zuclopenthixol

From: The Metabolism and Transport Drug Interaction Database™ (DIDB) from University of Washington's Department of Pharmaceutics. April 2017