1 ABSTRACT

Title: Drug utilisation study of eliglustat for the treatment of Gaucher Disease Type 1 in Europe using electronic healthcare records.

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Rationale and Background: Eliglustat (Cerdelga®) is an oral treatment indicated in Europe for the long-term treatment of adult patients with Gaucher disease type 1 (GD1) who are cytochrome P450 2D6 (CYP2D6) poor metabolisers, intermediate metabolisers or extensive metabolisers. Eliglustat is metabolised primarily by the CYP2D6, and to a lesser extent by the cytochrome P450 family 3, subfamily A (CYP3A4). The ability to metabolise drugs through the CYP2D6 pathway may vary between individuals, leading to intervariable plasma concentrations of eliglustat depending on the individual's CYP2D6 metaboliser phenotype. The concomitant use of drugs inhibiting the CYP2D6 and the CYP3A enzyme activity may lead to substantially elevated eliglustat plasma concentrations. Eliglustat is contraindicated in patients who are CYP2D6 intermediate metabolisers or extensive metabolisers taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor, and patients who are CYP2D6 poor or intermediate metabolisers taking a strong CYP3A inhibitor. Furthermore, use of eliglustat with strong CYP3A inducers substantially decreases the exposure to eliglustat, which may reduce the therapeutic effectiveness, therefore concomitant administration is not recommended. Use of eliglustat with a moderate CYP3A inhibitor in poor metabolisers is also not recommended. A lower dose of eliglustat, 84 mg once daily, should be considered when a strong or moderate CYP2D6 inhibitor is used concomitantly in intermediate metabolisers and extensive metabolisers.

Research Question and Objectives: The primary objective of this Drug Utilisation Study (DUS) was to estimate the dose and duration of eliglustat therapy as well as the proportion, therapeutic class, and duration of past and concomitant medication use in GD1 patients treated with eliglustat. The concomitant medications of interest (CMI) were strong and moderate CYP2D6 inhibitors, strong and moderate CYP3A inhibitors, strong CYP3A inducers, P-gp substrates and CYP2D6 substrates. Simultaneous use of strong or moderate CYP2D6 inhibitors with strong or moderate CYP3A inhibitors concomitantly with eliglustat was also explored. The secondary objective of the DUS was to describe the healthcare service pattern (i.e., prescriber's specialty and types of patient visit) for the prescriptions of concomitant medications in patients treated with eliglustat.

Study Design: This was a drug utilisation study based on the follow-up of a cohort of GD1 patients treated with eliglustat.

Setting: The study period was from one year before the first dispensation of eliglustat in each data source to the study end (i.e., data extraction date) in Q3 2024. The study was based on the secondary use of data of GD1 patients treated with eliglustat that were prospectively and consecutively enrolled in healthcare databases of 3 European countries (France, Germany, and Israel [considered a European country since EU-Israel agreements are in place, including European Medicine Agency agreements]).

Patients and Study Size: The study population included all GD1 patients, of all ages, with at least one recorded prescription of eliglustat over the study period in the selected databases. Since eliglustat is indicated for GD1 only and there are no specific diagnostic/International Classification of Diseases and related health problems, 10th edition codes for this condition, all patients with at least one recorded prescription of eliglustat during the study period were considered to have GD1 diagnosis.

Variables and Data Sources: Data were collected on dose and duration of eliglustat as well as on therapeutic class and duration of drugs used concomitantly with eliglustat that are susceptible to significantly interfere with eliglustat metabolism or whose plasma concentration might be altered by eliglustat intake. These drugs are strong and moderate CYP2D6 inhibitors, strong and moderate CYP3A inhibitors, strong CYP3A inducers, P-gp substrates and CYP2D6 substrates. The primary endpoints were eliglustat dose, duration of eliglustat use, and the use of specific CMIs one year before starting eliglustat and during the period of using eliglustat (independent of each other). Data were also collected on the age, sex and death date of GD1 patients, as well as (whenever feasible) on prescriber's specialty and type of patient visit.

The reported eliglustat dose was calculated as dose and dispensation over duration. from the first eliglustat dispensation until the day before the last eliglustat dispensation. Therefore, although actual dispensations in real-world settings are in either a single or double number of capsules, the average estimated dose over time will include decimal points.

Secondary data from prescription databases in the 3 selected countries were used in this study. Of note, there is generally a time-lag (different for each selected country) between data collection and availability of complete set of data in prescription databases.

Statistical Methods: The statistical analyses were descriptive, and no predictive model was used. All statistical analyses were performed separately in each data source.

Data summaries were presented separately for each data source. Summaries such as average duration of eliglustat were not pooled over the data sources, neither by standard nor meta-analytic approaches.

Results:
Primary endpoints:

France

The median (Q1, Q3) estimated daily dose of eliglustat was 1.93 (1.70, 2.00) capsules, with most patients (83.9%) taking two capsules each day. The median (Q1, Q3) duration of treatment with eliglustat was 1140.0 (331.0, 1679.0) days, with 59.9% of patients being treated for 2 years or longer, 27.7% for less than a year, and 12.4% for 1 to <2 years. Among the 136 patients in France included in the analysis, 49 (36.0%) patients had a dispensation of any CMI one year before starting eliglustat, and 73 (53.7%) patients had a dispensation of any CMI during the period of using eliglustat. The most frequently observed CMIs were CMI6 (P-gp substrates) and CMI7 (CYP2D6 substrates) in both the year prior and during eliglustat use.

Germany

The median (Q1, Q3) estimated daily dose of eliglustat was 1.99 (1.69, 2.05) capsules, with most patients (85.0%) taking two capsules each day. The median (Q1, Q3) duration of treatment with eliglustat was 693.5 (221.5, 1790.0) days, with half of the patients (50.0%) receiving eliglustat for 2 years or more, 30.0% for less than a year, and 20.0% for between 1 and <2 years. Among the 20 patients in Germany, 4 (20.0%) had a dispensation of any CMI one year before starting eliglustat, and 5 (25.0%) patients had a dispensation of any CMI during the period of using eliglustat. The most frequently observed CMIs were CMI6 (P-gp substrates) and CMI7 (CYP2D6 substrates) in both the year prior and during eliglustat use.

Israel

The median (Q1, Q3) estimated daily dose of eliglustat was 1.71 (1.33, 1.87) capsules, with most patients (65.0%) taking two capsules each day. The median (Q1, Q3) duration of treatment with eliglustat was 1509.5 (715.8, 1923.5) days, with most patients (75.0%) being treated for two years or more. A smaller percentage of patients had a shorter treatment duration, with 15.0% treated for 1 to <2 years and 10.0% for less than a year. Among 20 patients in Israel, 7 (35.0%) had a dispensation of any CMI one year before starting eliglustat, and 11 (55.0%) patients had a dispensation of any CMI during the period of using eliglustat. The most frequently observed CMIs were CMI2 (moderate CYP2D6 inhibitors) and CMI4 (moderate CYP3A inhibitors) in the year prior to eliglustat use and CMI4 (moderate CYP3A inhibitors) along with CMI7 (CYP2D6 substrates) during the eliglustat use.

Secondary endpoints:

France

Both in the year prior to starting eliglustat and during the eliglustat use period, the majority of CMI prescriptions were issued by general medicine practitioners, accounting for 87.8% of patients with any CMI before eliglustat and 91.8% of patients with any CMI during the eliglustat use period. The majority of dispensed CMI prescriptions were prescribed by a healthcare professional based in the city with

83.7% of the 49 patients with any CMI one year prior to and 83.6% of the 73 patients with any CMI during eliglustat therapy having had at least one prescription from a city-based prescriber.

Germany

General practitioners prescribed the majority of these CMI prescriptions: for 2 of 4 patients (50.0%) with any CMI before eliglustat and for 4 of the 5 patients (80.0%) who had any CMI during the eliglustat use period. No information on visit type (hospital or outpatient settings) for CMI prescription was available.

Israel

In Israel, CMIs were frequently prescribed by dermatologists/venereologists and specialists in family, medicine and general medicine. Dermatologists/venereologists prescribed 42.9% and family, medicine and general medicine clinicians 28.6% of the CMI prescriptions before eliglustat use, among the 7 patients with any CMI during the period. During the use of eliglustat, dermatologists/venereologists prescribed 9.1% and family, medicine and general medicine clinicians 54.5% of the CMI prescriptions among patients with any CMI during the period. No information on visit type (hospital or outpatient settings) for CMI prescription was available.

Exploratory endpoints:

France

Most patients were prescribed eliglustat by specialists in general medicine (98, 71.5%), followed by internal medicine (41, 29.9%), and paediatrics (11, 8%) [categories were not mutually exclusive]. For those without any recorded specialty, the data were categorised under missing/unknown (13, 9.5%). The majority of the patients (131, 95.6%) received the eliglustat prescription from a prescriber of a public hospital. Of the 137 patients in France, 10 (7.3%) patients had missing or unknown for visit type.

Germany

The most common eliglustat prescribers (categories were not mutually exclusive) were general practitioners, specialists in internal medicine, and haemato-oncologists, each accounting for 25.0% of patients who had an eliglustat prescription from one of the providers. Patients without any recorded specialty for the prescriber of their eliglustat dispensation data were categorised under missing/unknown (8, 40%). No information on visit type for eliglustat prescription was available.

Israel

All patients were prescribed eliglustat by family, medicine and general medicine clinicians (20, 100%). Out of the 20 patients, 4 patients had more than one prescriber. Among these 4 patients, 1 patient was prescribed eliglustat by an otolaryngologist and 3 patients by a paediatrician. No information on visit type for eliglustat prescription was available.

The CMI drugs in two countries (France and Germany) with medication details included:
Antidepressants fluoxetine, paroxetine, and venlafaxine;
Antibiotics ciprofloxacin, clarithromycin and erythromycin;
Antihypertensives metoprolol, propranolol and verapamil;
Lipid-lowering agents simvastatin and atorvastatin.
Data on CMI drugs were not available for Israel.

Discussion: This post-authorisation safety study suggests that based on data from France, Germany and Israel that eliglustat is dispensed according to label. There were CMI dispensations both in the year before eliglustat use and during the eliglustat period. However, the duration of CMI use was shorter during eliglustat use compared to duration of use in the year prior. The most commonly prescribed CMIs during eliglustat were CMI7 (CYP2D6 substrates) for all three countries and CMI6 (P-gp substrates) for France and Germany, which were classes of medication where monitoring and altering the dose of the concomitant medication was advised and these medication classes were not contraindicated or not recommended with eliglustat use. CMIs 1-5 that could alter the plasma concentration of eliglustat and are contraindicated or not recommended for some patients using eliglustat, were less frequent. When observed, moderate CYP2D6 (CMI2) and CYP3A inhibitors (CMI4) were more frequent than strong CYP2D6 (CMI1) or CYP3A (CMI3) inhibitors, and especially strong CYP3A inducers (CMI5). Overall, the results of this PASS were consistent with the findings of a previous similar study in the US, increasing the confidence in the findings presented in this PASS. Moreover, the frequencies of CMIs among patients using eliglustat, observed in this PASS, were of similar magnitude with frequencies reported in other populations.