EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance and Epidemiology Department

Dihydropyrimidine dehydrogenase deficiency related toxicities to fluorouracil and fluorouracil related substances containing medicinal products

Data analysis plan of EudraVigilance and literature review

Procedure number: EMEA/H/A-31/1481

Xeloda EMEA/H/A-31/1481/C/000316/0085

Teysuno EMEA/H/A-31/1481/C/001242/0040

Capecitabine Accord EMEA/H/A-31/1481/C/002386/0032

Capecitabine Medac EMEA/H/A-31/1481/C/002568/0021

Capecitabine Teva EMEA/H/A-31/1481/C/002362/0031

Ecansya EMEA/H/A-31/1481/C/002605/0023

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1. Roles and responsibilities

Role	Responsible
Lead investigator	Luis Pinheiro
Investigator	Julie Durand
Procedure lead	Veronique Le Ber
Data extraction	Luis Pinheiro
Review	Georgy Genov, Peter Arlett
Sign-off	Peter Arlett

2. Milestones

Milestone	Planned	Actual
Data analysis plan	26 March 2019	26 March 2019
Internal report	16 April 2019	
Peer-review	18 April 2019	
Implementation of corrections	19 April 2019	
Submission	22 April 2019	

3. Objectives

The primary objectives of the EudraVigilance analysis are:

- To identify and describe case reports to fluorouracil and fluorouracil related substances and;
- To identify and characterise case reports to these products where dihydropyrimidine dehydrogenase deficiency (DPD) was also reported.

A secondary objective of the EudraVigilance analysis is to estimate the number of case reports of fluorouracil and fluorouracil related substances that might have been due to DPD related toxicity but for which it was not reported as such.

The objective of the literature review is to source any new publications on DPD screening and toxicity published from May 2018 to March 2019.

4. Methodology

4.1. EudraVigilance analysis

4.1.1. Database

The database used will be EudraVigilance. The period of interest is from start of data collection (i.e. 1995) to 15 March 2019.

4.1.2. Ontology

The Medical Dictionary for Drug Regulatory Activities (MedDRA) v.21.1 will be used to code the outcomes of interest and extract the data.

4.1.3. Exposure

The exposure will be defined as use of fluorouracil and fluorouracil related substances, namely capecitabine, fluorouracil, tegafur, flucytosine containing medicinal products.

Considering that DPD related toxicity might be masked, that is, that reporters may not realise that a patient's mutation contributed to the toxicity, it is equally possible that reporters may attribute a causal relationship to a different product unknowingly, thus to define exposure, the characterisation of drug role [ICH E2B(R3) G.k.1] will include suspect, interacting and concomitant.

4.1.4. Case definitions

The toxicity spectrum of DPD related toxicity is extensive. Accumulation of fluorouracil may lead to severe inflammation and ulceration of the gastrointestinal tract, mouth sores, abdominal pain, bleeding, nausea, vomiting, and diarrhoea. Fluoropyrimidine toxicity may also lead to neutropenia and infections. It can also be associated with thrombocytopenia and resulting haemorrhage. Other disorders include hand-foot syndrome, shortness of breath and hair loss.

There is no standardised MedDRA query or published algorithmic diagnostic criteria that can be used to readily classify cases of DPD related toxicity. Only the preferred term "Dihydropyrimidine dehydrogenase deficiency" exists as a MedDRA code under the Congenital, familial and genetic disorders System Organ Class.

This term refers solely to the presence of the mutation and is not fundamentally an adverse drug reaction. Due to its nature, reflecting a genetic mutation, it is, in fact, more likely to be part of the patient history.

4.1.4.1. Dihydropyrimidine dehydrogenase deficiency patient

The MedDRA preferred term "Dihydropyrimidine dehydrogenase deficiency" will be used to identify patients with dihydropyrimidine dehydrogenase deficiency. The term will be queried in three fields: the reaction field [ICH E2B(R3) E.i.2.1b], the test field [ICH E2B(R3) F.r.2.2b] and related fields [ICH E2B(R3) F.r.3.1 to F.r.7] and the medical history field [ICH E2B(R3) D.7.1.r.1b].

4.1.4.2. Dihydropyrimidine dehydrogenase deficiency toxicity spectrum

Whereas the manifestations of toxicity due to DPD are extensive, the terms within the following standardised MedDRA queries will be used as being indicative of DPD related toxicity:

- Gastrointestinal perforation, ulcer, haemorrhage, obstruction non-specific findings/procedures (SMQ),
- Gastrointestinal ulceration (SMQ)
- Gastrointestinal perforation (SMQ)
- Gastrointestinal haemorrhage (SMQ)
- Noninfectious diarrhoea (SMQ)
- Agranulocytosis (SMQ)
- Haematopoietic thrombocytopenia (SMQ)
- Haemorrhages (SMQ)

4.1.5. Covariates

Age, gender, indication for use, route of administration, time-to-onset and origin of report will be defined as relevant covariates.

Time to onset can be calculated at reaction level or at case level. As mentioned above, DPD deficiency can manifest in multiple disorders hence, to ensure comparability between cases, in this analysis it will be assumed that all reactions are a spectrum of the same DPD toxicity hence case level time to onset will be used.

Time to onset will be calculated by subtracting the earliest start date of any reaction reported to the start date of the medicinal product. For instance, if the patient started the drug on 15/01/2000, had diarrhoea on 20/01/2000 and neutropenia on 30/01/2000, the time to onset will be 5 days.

4.1.6. Analytical plan

Descriptive statistics will be performed by substance, age, gender, indication for use, route of administration and origin of reports for all case reports. Cases will be highlighted according to whether they refer to a DPD patient (see 4.1.4.1.) or mention any term within the toxicity spectrum (see 4.1.4.2.).

Where feasible, boxplots of time to onset will be plotted and stratified by product, age, indication for use and route of administration.

To estimate the number of likely DPD related cases, three machine learning models will be run (adaptive boosting, bagged adaptive boosting and bagged classification and regression model). These will identify patterns in the terms reported to DPD patients and detect similar patterns in cases that don't identify the patient as DPD.

Features to be used to model DPD related toxicity cases include age, gender, adverse drug reactions and time to onset. The resulting cases will be profiled.

4.2. Literature review

The literature review's aim is to identify published papers on DPD screening since the last review conducted by the *Institut National du Cancer.* Thus, a methodology similar to the applied by the *Institut National du Cancer* will be used.

There are some differences however. The new literature review will not filter on products or on type of study. This means the search isn't as restrictive and a higher recall will be achieved. The downside is a risk of lower precision however, as the time window is of just one year, and manual review by two investigators will be performed, this seems an acceptable trade-off and ensures all possible publications on DPD are included.

4.2.1. Databases of references and abstracts

The databases of abstracts and references used will be Medline – PubMed and EMBASE. The Cochrane reviews website will also be queried.

4.2.2. Period of publications

The period of publications will be May 2018 to March 2019.

4.2.3. Search algorithm

There will be three distinct search algorithms to be used in the different databases of abstracts and references and the Cochrane reviews website.

Database of abstracts and references	**Search algorithm**
Medline - PubMed	(dihydropyrimidine dehydrogenase OR dpdy OR dihydrouracil dehydrogenase OR dihydropyrimidine dehydrogenase deficiency OR DPYD*2A OR c.2846A>T OR c.1679T>G OR c.1236G>A) AND ((("2018/04/01"[Date - Publication] : "3000"[Date - Publication]))
EMBASE	('dihydropyrimidine dehydrogenase'/exp OR 'dihydrouracil dehydrogenase'/exp OR 'dihydropyrimidine dehydrogenase deficiency'/exp OR DPYD*2A OR c.2846A>T OR c.1679T>G OR c.1236G>A) AND [1-4-2018]/sd
Cochrane	"dihydropyrimidine dehydrogenase" with Cochrane Library publication date Between Apr 2018 and Mar 2019

Database of abstracts and references	Search algorithm
	AND "dihydrouracil dehydrogenase" with Cochrane Library publication date Between Apr 2018 and Mar 2019 AND "dihydropyrimidine dehydrogenase deficiency" with Cochrane Library publication date Between Apr 2018 and Mar 2019

4.2.4. Study classification and selection

Two investigators will perform study classification and selection independently. All combined studies selected by the investigators will be included in a summary table. Papers will be sourced, where possible.

4.2.5. Results

All papers identified will be presented according to their classification in summary table.