EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pharmacogenomics information in SmPC

SmPC training presentation

Note: for full information refer to the European Commission's Guideline on summary of product characteristics (SmPC)

SmPC Advisory Group

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Introduction

Pharmacogenomics (PGx) is defined as the study of variations of DNA and RNA characteristics as related to drug response

- Pharmacogenomics have the potential to improve the discovery, development and use of medicines
- Where possible, the SmPC should inform on important inter-individual variability in drug pharmacokinetics or response, and, on which extent, such variability can have a genetic basis
- Therefore, when relevant, genetic and genomic information should be mentioned in the SmPC

4.1 Therapeutic indication

If the product's indication depends on a particular genotype or the expression of a gene or a particular phenotype, this should be stated in the indication

X is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the CFTR gene

X is indicated for the treatment of patients with HER2 positive metastatic breast cancer

X, in combination with other antiretroviral medicinal products, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable

4.2 Posology and method of administration

Where necessary, dosage adjustments in patients with a particular genotype should be stated (with cross-reference to other relevant sections for further detail as appropriate)

Approximately 7% of Caucasians have a genotype corresponding to a non-functional CYP2D6 enzyme (called CYP2D6 poor metabolisers). Patients with this genotype have a several-fold higher exposure to active substance X when compared to patients with a functional enzyme. Poor metabolisers are therefore at higher risk of adverse events (see Section 4.8 and Section 5.2). For patients with a known poor metaboliser genotype, a lower starting dose and slower up titration of the dose may be considered.

4.3 Contraindications

Situations where the medicinal product must not be given for safety reasons, i.e. contraindications, are the subject of this section. Such circumstances could include … a particular genotype …

G6PD deficiency and other cellular metabolic disorders known to cause haemolytic anaemia.

4.4 Special warnings and precautions for use

Subjects or patients with a specific genotype or phenotype might either not respond to the treatment or be at risk of a pronounced pharmacodynamic effect or adverse reaction. Such situations should be clearly described if known

*HLA-B*1502 allele - in Han Chinese, Thai and other Asian populations*

HLA-B*1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing the severe cutaneous reactions known as Stevens-Johnson syndrome (SJS) when treated with active substance X. The prevalence of HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations. Whenever possible, these individuals should be screened for this allele before starting treatment with active substance X. If these individuals test positive, active substance X should not be started unless there is no other therapeutic option. Tested patients who are found to be negative for HLA-B*1502 have a low risk of SJS, although the reactions may still rarely occur.

4.5 Interaction with other medicinal products and other forms of interaction

If interactions with other medicinal products depend on polymorphisms of metabolising enzymes or certain genotypes, this should be stated

Active substance X should not be used together with potent CYP3A4 inhibitors (see section 4.3) such as protease inhibitors (e.g. ritonavir), ketoconazole and itraconazole. Co-administration of active substance X with the potent CYP3A4 inhibitor ketoconazole 400 mg resulted in a 5-fold increase in steady-state active substance X AUC. In subjects who are poor metabolisers, active substance X exposure increased approximately 10-fold.

4.8 Undesirable effects

This section may include information on any clinically relevant differences specifically observed in patients with a specific genotype

There is increasing evidence regarding the association of genetic markers and the occurrence of cutaneous adverse reactions such as SJS, TEN, DRESS, AGEP and maculopapular rash. In Japanese and European patients, these reactions have been reported to be associated with the use of active substance X and the presence of the HLA-A*3101 allele. Another marker, HLA-B*1502 has been shown to be strongly associated with SJS and TEN among individuals of Han Chinese, Thai and some other Asian ancestry (see sections 4.2 and 4.4 for further information).

5.1 Pharmacodynamic properties

Any relevant pharmacogenetic information from clinical studies may be mentioned here. This should include any data showing a difference in benefit or risk depending on a particular genotype or phenotype

Example 1
Example 2
Example 3

Example of pharmacogenomics information

Related to the mechanism of action

Mechanism of action

Active substance X is a member of a therapeutic class called CCR5 antagonists. Active substance X selectively binds to the human chemokine receptor CCR5, preventing CCR5-tropic HIV-1 from entering cells.

Example of pharmacogenomics information

Related to the main characteristics of the patient population of the main studies supporting the indications

The efficacy of active substance X has been evaluated in two Phase 3 randomised, double-blinded, placebo-controlled, multi-centre studies of clinically stable patients with CF who had the G551D mutation in the CFTR gene on at least 1 allele and had FEV1 ≥40% predicted.

Example of results showing a difference in benefit depending on pharmacogenomics test

This study included 331 patients with unresectable locally advanced or metastatic medullary thyroid cancer.

(...)

Results according to RET* status (positive, unknown and RET M918T mutation negative definition) are presented in the table below.

Summary of efficacy findings in a segment of patients according to RET mutation status

	Patients with documented RET mutation (n=187)	Patients with no M918T mutation and other mutations not tested or Negative (n=79)
Objective response rate (active substance X arm)	52%	35%
Efficacy endpoint PFS HR** (95%) confidence interval	0.45 (0.26, 0.78)	0.57 (0.29, 1.13)

**Rearranged during transfection (RET) **progression-free survival - hazard ratio*

5.2 Pharmacokinetic properties

Variations with respect to polymorphic metabolism should be described, if clinically relevant, in quantitative terms (with cross-reference to 4.2 when applicable)

5.2 Pharmacokinetic properties

General Introduction

Active substance X is metabolised by CYP3A4 and CYP2D6. Due to genetic differences, about 7% of the Caucasians lack the CYP2D6 enzyme and are said to be poor metabolisers. A few percent of the population have increased CYP2D6 enzyme levels (ultrafast metabolisers). The information below applies to subjects who have normal CYP2D6 activity (extensive metabolisers) unless otherwise stated. (…)

CYP2D6 poor metabolisers

The metabolism of active substance X in CYP2D6 poor metabolisers is principally mediated by CYP3A4. In one pharmacokinetic study the steady-state exposure in poor metabolisers was 164% and 99% higher during treatment with 7.5 mg and 15 mg once daily, respectively. However, a population pharmacokinetic analyses of Phase III data indicated that on average steady-state exposure is 66% higher in poor metabolisers than in extensive metabolisers. There was considerable overlap between the ranges of exposures seen in these two populations (see section 4.2).

IV. FAQs

1. Should the SmPC include information on pharmacogenomic testing?

2. Should the SmPC inform on the frequency of a genotype or a phenotype?

1. Should the SmPC include information on pharmacogenomics testing?

- There is currently no specific provision for SmPC information on pharmacogenomics testing in the SmPC guideline, however, the following recommendations of the SmPC guideline may apply if justified:
  - Mandatory conditions of product usage not covered more appropriately in other parts of the SmPC may be included in section 4.1
  - The conditions, in which the use of the medicinal product could be acceptable, provided that special conditions for use are fulfilled, should be described in section 4.4
  - Clinical study data in section 5.1 should present main characteristics of the patient population. Concise information on pharmacogenomics test may be presented as part of inclusion criteria in clinical study

2. Should the SmPC inform on the frequency of a genotype or a phenotype?

- Information on the prevalence (in the overall population or in different ethnic populations) of a genotype or a phenotype which may impact on benefit, risk or pharmacokinetics of a medicinal product may be helpful to estimate the probability for a patient to benefit of the medicinal product or to be exposed to a risk. Information may therefore be presented if well-established

V. More information on pharmacogenomics

- ICH Topic E 15 Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories (CHMP/ICH/437986/06)
- Position paper on terminology in pharmacogenetics (EMEA/CPMP/3070/01)
- Use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products (EMA/CHMP/37646/2009)

For complete and updated guidelines related to Pharmacogenomics, please consult the Agency's website

Thank you for consulting this training presentation

SmPC Advisoy group

Please note the presentation includes examples that may have been modified to best illustrate the related principle