EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Section 5.1: Pharmacodynamic properties

SmPC training presentation

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

SmPC Advisory Group

Index

I. General objectives of section 5.1

This section should provide clear and concise information relevant to healthcare professionals regarding the approved therapeutic indication(s), specific clinical safety data as well as relevant clinical data in special population(s) (e.g. children or elderly)

The section should be regularly updated when new information becomes available, especially in relation to the paediatric information

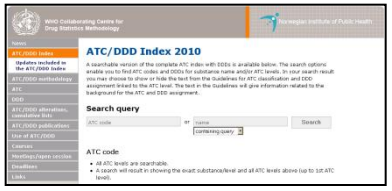
The public assessment reports (EPAR) provide detailed information on medicinal products and are available on the website of the European Medicines Agency

II.1 Pharmacotherapeutic group and ATC code

Pharmacotherapeutic Group + ATC (Anatomical Therapeutic Chemical) code: Include therapeutic subgroup (2nd level) with pharmacological subgroup (3rd level) or chemical subgroup (4th level)

Examples of pharmacotherapeutic group and ATC Code

Medicinal Product		Active substance X 1 mg tablets	Active substance X 75 mg powder and solvent for nebuliser solution	Active substance X
ATC Code		**N04BD02**	**J01DF01**	***Not yet assigned***
Pharmaco-therapeutic Group	**2nd Level**	**ANTI-PARKINSON-DRUGS**	**ANTIBACTERIALS FOR SYSTEMIC USE**	**See FAQ 5**
	WITH 3rd Level		**OTHER BETA-LACTAM ANTIBACTERIALS**	
	OR WITH 4th Level	**Monoamine oxidase B inhibitors**		



In the WHO ATC classification system the drugs are divided into different groups according to the organ and system on which they act and their chemical, pharmacological and therapeutic properties

Click here for presentation of above data in the SmPC

See WHO Collaborating Centre for Drug Statistics Methodology Website

II.1 Pharmacotherapeutic group and ATC code

Active substance X 1mg tablets

Pharmacotherapeutic group: Anti-Parkinson-Drugs, Monoamine oxidase -B inhibitors, ATC code:N04BD02

Active substance X 75 mg powder and solvent for nebuliser solution

Pharmacotherapeutic group: Antibacterials for systemic use, other beta-lactam antibacterials, ATC code: J01DF01

Active substance X 60 mg concentrate and solvent for solution for infusion

Pharmacotherapeutic group: Antineoplastic agents, ATC code: *not yet assigned*

II.2 Mechanism of action and pharmacodynamic effects

Description of mechanism of action
+/- Pharmacological effects, with relevance to:
health-care professionals,
the approved indication(s),
potential adverse reaction(s).

Only conclusions from non-clinical studies that may be of interest should be included

SmPC examples

1 mechanism of action

2 mechanism of action fixed dose combination

3 mechanism of action biological medicinal products

Example 1-mechanism of action

Active substance X 25 mg/ml concentrate for solution for infusion

Mechanism of action

Active substance X binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.

Pharmacodynamic effects

Administration of active substance X or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.

Example 2-mechanism of action fixed dose combination

Active substance X-Y 150 mg/12.5 mg film-coated tablets

Active substance X-Y combines two antihypertensive compounds to control blood pressure in patients with essential hypertension: X belongs to the class of direct renin inhibitors and Y to the class of thiazide diuretics. The combination of these substances with complementary mechanisms of action provides an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Example 3-mechanism of action biological medicinal product

Active substance X, suspension for injection

Active substance X is an adjuvanted non-infectious recombinant quadrivalent vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein of HPV types 6, 11, 16 and 18. The VLPs contain no viral DNA, they cannot infect cells, reproduce or cause disease. HPV only infects humans, but animal studies with analogous papillomaviruses suggest that the efficacy of LI VLP vaccines is mediated by the development of a humoral immune response.

II.3 Clinical efficacy and safety

Provide a concise summary of results regarding pre-specified end-points or clinical outcomes from major trials which support approved indication(s)

4 efficacy & safety
5 efficacy & safety
6 efficacy & safety

Describe the main characteristics of patient population

Results should be statistically compelling & clinically relevant in providing:

- Primary endpoint	Required
- Secondary endpoint	Case by case
- Subgroup or post-hoc analyses	Exceptional

7 sub group analysis
8 sub group analysis

Example 4-clinical efficacy and safety

Provide a concise summary of results from major trials relevant to the prescriber which support approved indication(s)

Magnitude of effects:
Use absolute figures

Active substance X 0.5 mg prolonged-release hard capsules

Results from clinical trials performed with once-daily active substance X

Liver transplantation

The efficacy and safety of Active substance X and Comparator, both in combination with corticosteroids, was compared in 471 de novo liver transplant recipients. The Event Rate Of Biopsy Confirmed Acute Rejection within the first 24 weeks after transplantation was 32.6% in the Active substance X group (N=237) and 29.3% in the Comparator Group (N=234). The treatment difference (Active substance X – Comparator) was 3.3% (95% confidence interval [5.7%, 12.3%]). The 12-month patient survival rates were 89.2% for Active substance X and 90.8% for Comparator.

Example 5-clinical efficacy and safety

Provide a concise summary of results from major trials relevant to the prescriber which support approved indication(s)

Active substance X 400 mg tablets

The efficacy and safety of active substance X has been demonstrated in three phase III double blind placebo-controlled studies in 1,049 adult patients with partial epilepsy refractory to treatment with one to three concomitant anti-epileptic medicinal products. Active substance Y and Z were not allowed as concomitant medicinal products in these studies. Active substance X was tested at doses of 400 mg, 800 mg and 1200 mg, once daily. Active substance X 800 mg once daily and 1200 mg once daily were significantly more effective than placebo in reducing seizure frequency over a 12-week maintenance period. The percentage of subjects with a 50% reduction in seizure frequency over all phase III studies was 19% for placebo, 21% for active substance X 400 mg, 34% for active substance X 800 mg and 36% for active substance X 1200 mg daily.

Example 6-clinical efficacy and safety

Provide a concise summary of results from major trials relevant to the prescriber which support approved indication(s)

Active substance X 1.5 mg/0.3 ml solution for injection, pre-filled syringe

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing hip fracture surgery treated for up to 24 days following an initial prophylaxis of 1 week.

In a randomised double-blind clinical trial, 737 patients were treated with active substance X 2.5 mg once daily for 7 +/- 1 days following hip fracture surgery. At the end of this period, 656 patients were randomised to receive active substance X 2.5 mg once daily or placebo for an additional 21 +/- 2 days. Active substance X provided a significant reduction in the overall rate of VTE compared with placebo [3 patients (1.4%) vs 77 patients (35%), respectively]. The majority (70/80) of the recorded VTE events were venographically detected non-symptomatic cases of DVT. Active substance X also provided a significant reduction in the rate of symptomatic VTE (DVT, and / or PE) [1 (0.3%) vs 9 (2.7%) patients, respectively] including two fatal PE reported in the placebo group. Major bleedings, all at surgical site and none fatal, were observed in 8 patients (2.4%) treated with active substance X 2.5 mg compared to 2 (0.6%) with placebo.

Example 7-subgroup analysis

In EXCEPTIONAL cases when clinically relevant information from subgroup or post-hoc analyses is presented, it should be identified as such in a balanced manner reflecting the limited robustness of both positive and negative secondary observations

Active substance X 75 mg film-coated tablets

The CAPRIE study included 19,185 patients with atherothrombosis as manifested by recent myocardial infarction (<35 days), recent ischaemic stroke (between 7 days and 6 months) or established peripheral arterial disease (PAD). Patients were randomised to active substance X 75 mg/day or active substance Y 325 mg/day, and were followed for 1 to 3 years. In the myocardial infarction subgroup, most of the patients received Y for the first few days following the acute myocardial infarction. X significantly reduced the incidence of new ischaemic events (combined end point of myocardial infarction, ischaemic stroke and vascular death) when compared to Y. In the intention to treat analysis, 939 events were observed in the X group and 1,020 events with Y (relative risk reduction (RRR) 8.7%, [95% CI: 0.2 to 16.4]; p = 0.045), which corresponds, for every 1000 patients treated for 2 years, to 10 [CI: 0 to 20] additional patients being prevented from experiencing a new ischaemic event.
Analysis of total mortality as a secondary endpoint did not show any significant difference between X (5.8%) and Y (6.0%). In a subgroup analysis by qualifying condition (myocardial infarction, ischaemic stroke, and PAD) the benefit appeared to be strongest (achieving statistical significance at p = 0.003) in patients enrolled due to PAD (especially those who also had a history of myocardial infarction) (RRR = 23.7%; CI: 8.9 to 36.2) and weaker (not significantly different from Y) in stroke patients (RRR = 7.3%; CI: 5.7 to 18.7 [p=0.258]). In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, X was numerically inferior, but not statistically different from Y (RRR = - 4.0%; CI: -22.5 to 11.7 [p=0.639]). In addition, a subgroup analysis by age suggested that the benefit of X in patients over 75 years was less than that observed in patients ≤75 years. Since the CAPRIE trial was not powered to evaluate efficacy of individual subgroups, it is not clear whether the differences in relative risk reduction across qualifying conditions are real, or a result of chance.

Example 8-subgroup analysis

In EXCEPTIONAL cases when clinically relevant information from subgroup or post-hoc analyses is presented, it should be identified as such in a balanced manner reflecting the limited robustness of both positive and negative secondary observations

Active substance X 11.5% cream

The safety and efficacy of active substance X was evaluated in two double-blind, randomised, vehicle-controlled clinical trials involving 594 women of skin types I-VI (393 on X, 201 on vehicle) treated for up to 24 weeks. Physicians assessed the change from baseline on a 4-point scale, 48 hours after women had shaved the treated areas of the affected areas of the face and under the chin, considering parameters such as hair length and density, and darkening of the skin associated with the presence of terminal hair. Improvement was seen as early as 8 weeks after initiation of treatment.
Statistically significant ($p \leq 0.001$) improvement for X versus vehicle was seen in each of these studies for women with marked improvement and clear/almost clear responses. These improvements resulted in a corresponding reduction in the darkening appearance of the facial skin associated with the presence of terminal hair. Subgroup analysis revealed a difference in treatment success where 27% of non-white women and 39% of white women showed a marked or better improvement. Subgroup analysis also showed that 29% of obese women (BMI ≥ 30) and 43% of normal weight women (BMI < 30) showed a marked or better improvement. About 12% of women in the clinical trials were postmenopausal. Significant improvement ($p < 0.001$) versus vehicle was seen in postmenopausal women.

II.4 Paediatric population

Results of all pharmacodynamic (clinically relevant) or efficacy studies conducted in children should be presented by age or relevant subset

If DATA are considered INCONCLUSIVE, this should be stated

9 paediatric
10 paediatric

If there is no authorised indication in paediatric population or paediatric subset, this should be made clear (cross reference to 4.2 (and 4.3) if appropriate)

Results of confirmatory studies should supersede and replace those of exploratory studies. Information should be updated when new relevant information becomes available

Information on SPECIFIC CLINICAL SAFETY STUDIES should be given describing objective(s) and main results

Waiver and deferral

If the EMA has waived or deferred a paediatric development in a granted indication, the information should be given as follows:

For waivers applying to all subsets:
"The European Medicines Agency has waived the obligation to submit the results of studies with <name of the product> in all subsets of the paediatric population in <condition as per PIP decision, in the granted indication>. See section 4.2 for information on paediatric use."

For deferrals applying to at least one subset:
"The European Medicines Agency has deferred the obligation to submit the results of studies with <name of the product> in one or more subsets of the paediatric population in <condition, as per PIP decision in the granted indication>. See section 4.2 for information on paediatric use.

<name of the product> has to be:
- Deleted for class waiver
- Replaced with <"the reference medicinal product" containing <name of the active substance>> for generics

Example 9-paediatric

Results of all studies conducted in children should be presented

Active substance X 500 Units powder and solvent for solution for injection

Section 5.1
Paediatric population
Treatment (LEVP 2006-1): The proportion of hereditary angioedema (HAE) attacks achieving unequivocal relief of the defining symptom within 4 hours after active substance X treatment was comparable between the 22 children enrolled (age range: 2-17) and adults, with 89% and 86% of attacks achieving relief, respectively.
Prevention (LEVP 2006-4): Prior to enrollment, 23 children (age range: 3 to 17 years) reported a median monthly HAE attack rate of 3.0 (range: 0.5-28.0). During the study while receiving active substance X prophylaxis, children in the various age subgroups experienced median monthly HAE attack rates of 0.4 (range: 0-3.4), and 87% of children reported an average of ≤1 attack per month; these results were comparable to those observed in adults.
In both studies LEVP 2006-1 and LEVP 2006-4, administration of active substance X resulted in increases in antigenic and functional C1 inhibitor levels post-infusion compared to pre-infusion values, with similar trends observed in children and adults. (see section 4.2)

Section 4.2
Paediatric population
The safety and efficacy of active substance X in children before adolescence has not yet been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on posology can be made.

Example 10-paediatric

Results of all studies conducted in children should be presented

Active substance X 100 micrograms/ml concentrate for solution for infusion

Section 5.1
Paediatric efficacy data from well controlled ICU studies is sparse but active substance X has been used as a sedative in children (see sections 5.2 and 4.4). New-born infants may be particularly sensitive to the bradycardic effects of active substance X in the presence of hypothermia and in conditions of heart rate-dependent cardiac output (see section 4.2).

Section 4.2
Paediatric population:
The safety and efficacy of active substance X in children aged 0 to 18 years has not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

III.1 Biosimilars

In case of medicinal product authorised as similar biological medicinal product, the following statement will be included after information on pharmacotherapeutic group and ATC code:

<< (Invented) Name> is a biosimilar medicinal product. Detailed information is available on the European Medicines Agency website; www.ema.europa.eu>

III.2 "Conditional approval" and "Exceptional circumstances"

For products approved under 'conditional approval' in the centralised procedure, include the following statement:

<This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on the product every year and this SmPC will be updated as necessary.>

For products approved under 'exceptional circumstances', include the following statement:

<This medicinal product has been authorised under 'Exceptional Circumstances'. This means that <due to the rarity of the disease> <for scientific reasons> <for ethical reasons> it has not been possible to obtain complete information on this medicinal product. The {name of Agency} will review any new information which may become available every year and this SmPC will be updated as necessary.>

III.3 Information not to be included in section 5.1

✗ (Non)-clinical pharmacodynamic effects not related to the therapeutic indication with an exception in the paediatric population

✗ Additional information (including study results), which would constitute a new indication

✗ Detailed information from clinical trials that are better placed in the European Public Assessment Report (EPAR)

IV. FAQs

1. When should safety data be included in section 5.1?
2. When could comparative data be included in section 5.1?
3. Should paediatric data in an indication not authorised be presented in section 5.1?
4. How should results of paediatric studies in a non authorised indication be presented?
5. How should the pharmacotherapeutic group be referred to when the ATC code is not yet assigned?

1. When should safety data be included in section 5.1?

- Safety information is presented in other SmPC sections (in particular 4.8)
- Information included in section 5.1 should be limited to relevant information to the prescriber taking into account the approved therapeutic indication(s) and potential adverse drug reactions, for example:
  - A study has been specifically carried out to address a safety concern
  - Pre-specified end-points or clinical outcomes from major trials consist in safety data
  - The safety data in the paediatric population
- Safety data results should be described qualitatively and quantitatively
- Cross-reference e.g. to sections 4.8 or 4.4 should be included as appropriate

2. When could comparative data be included in section 5.1?

- When the major trials supporting the approved indications are well-designed comparative trials, statistically compelling and clinically relevant results of pre-specified end points or clinical outcomes can be given

3. Should paediatric data in an indication not authorised be presented in section 5.1?

- Results of all pharmacodynamic (clinically relevant) or efficacy studies conducted in children should be presented in section 5.1, even if there is no authorised indication in any subset of the population (adult and paediatric populations)
- However, information has to be balanced and has to state uncertainties or conclude on lack of efficacy or safety as appropriate. A cross-reference should always be included to section 4.2
- *See FAQs on paediatrics information in SmPC*

FAQs

4. How should results of paediatric studies in a non authorised indication be presented?

- The results of the main endpoints (using absolute figures), the doses used, and the main characteristics of the patients (age and number of patients) should be given. The results of the study should be provided whether positive or negative and if data are considered inconclusive, this should be stated. In presenting the results, it should be clear why an indication has not been granted, with a cross reference to section 4.2

5. How should the pharmacotherapeutic group be referred to when the ATC code "is not yet assigned"?

- When a product has not yet been assigned an ATC code, the pharmacotherapeutic group should either remain at a high level e.g. 2nd level of WHO classification, if it is certain that the product belongs to that category or presented as "not yet assigned"

Thank you for consulting this training presentation

SmPC Advisory Group

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