



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Section 5.2: Pharmacokinetic properties

Rev. 1

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SmPC training presentation

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

SmPC Advisory Group

An agency of the European Union





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## I. General objectives of section 5.2

This section should provide the pharmacokinetic properties of the active substance(s) relevant for the advised dose, strength and the pharmaceutical formulation marketed

If these are not available, results obtained with other administration routes, other pharmaceutical forms or dosages can be given as alternative

Mean values with a measure of variability should be given for basic primary pharmacokinetic parameters (for instance bioavailability, clearance and half-life)



## II. 1 Pharmacokinetic properties

Pharmacokinetic properties (“ADME” - [Absorption](#), [Distribution](#), [Metabolism](#), [Elimination](#); [linearity/non-linearity](#)) should be presented, following a general introduction addressing as appropriate:

- Whether the medicinal product is a pro-drug
- Whether there are active metabolites
- On chirality, solubility
- On the population in which PK data were obtained, etc.

[1 introduction](#)  
[2 introduction](#)



# Example 1-introduction

Information about whether the medicinal product is a pro-drug or whether there are active metabolites, chirality, solubility, information on the population in which general pharmacokinetic data were obtained etc.

## Active substance X 10 mg film-coated tablets

### **General Introduction**

Active substance X is rapidly converted to the active metabolite, A771726, by first-pass metabolism (ring opening) in gut wall and liver. In a study with radiolabelled <sup>14</sup>C active substance X in three healthy volunteers, no unchanged active substance X was detected in plasma, urine or faeces. In other studies, unchanged active substance X levels in plasma have rarely been detected, however, at ng/ml plasma levels. The only plasma-radiolabelled metabolite detected was A771726. This metabolite is responsible for essentially all the *in vivo* activity of active substance X.



## Example 2-introduction

Information about whether the medicinal product is a pro-drug or whether there are active metabolites, chirality, solubility, information on the population in which general pharmacokinetic data were obtained etc.

### Active substance X 5 mg hard capsules

Active substance X has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). Active substance X is produced as a racemic mixture. Active substance X is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1N HCl buffer.



# Absorption

- Complete or incomplete absorption
- Absolute and/or relative bioavailability
- $T_{\max}$
- Influence of food

*If applicable:*

- First pass effect
- Involvement of transport proteins
- Systemic bioavailability in case of locally applied medicinal product
- Information on site of absorption in the gastro-intestinal tract if available (may be important for administration by enteral feeding tubes)

SmPC examples

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[4 absorption](#)



## Example 3-absorption

Active substance X 15 mg tablets

### **Absorption**

Following oral administration, active substance X is rapidly absorbed, and peak plasma concentrations of unchanged active substance X are usually achieved 2 hours after administration. Proportional increases of the plasma concentration were observed for doses from 2–60 mg. Steady state is achieved after 4–7 days of dosing. Repeated dosing does not result in accumulation of the compound or metabolites. Absorption is not influenced by food intake. Absolute bioavailability is greater than 80%.





## Example 4-absorption

Active substance X 30 mg tablet

### **Absorption**

Following oral administration of a single 30 mg dose, active substance X is rapidly absorbed, with a peak plasma concentration of  $176 \pm 89$  ng/ml occurring approximately 1 hour (0.5-2.0 h) after ingestion, and with an  $AUC_{0-\infty}$  of  $556 \pm 260$  ng.h/ml.

Administration of active substance X together with a high-fat breakfast resulted in approximately 45% lower mean  $C_{max}$ , a delayed  $T_{max}$  (from a median of 0.75 hours to 3 hours) and 25% higher mean  $AUC_{0-\infty}$  compared with administration in the fasted state. Similar results were obtained for the active mono-demethylated metabolite.

The absorption of active substance X is pH-dependent and may be reduced in situations where gastric pH is increased irrespective of cause.



# Distribution

- Plasma protein binding
- Apparent volume of distribution (l/kg)
- Tissue and/or plasma concentrations
- Pronounced multi-compartment behaviour
- Involvement of transport proteins

[5 distribution](#)  
[6 distribution](#)



## Example 5-distribution

Active substance X 200 mg hard capsules

### **Distribution**

In vitro binding of active substance X to human plasma proteins was <4% and independent of concentration over the range of 0.02-200 µg/ml. The mean plasma to blood concentration ratio was approximately 1.0 and the mean semen to plasma concentration ratio was approximately 4.0.

The apparent volume of distribution after intravenous administration of active substance X was  $1.4 \pm 0.3$  l/kg, indicating that active substance X is widely distributed throughout the body to both intracellular and extracellular fluid spaces.



## Example 6-distribution

Active substance X 90 mg/ml powder and solvent for solution for injection

### **Distribution**

The steady state volume of distribution with intravenous administration of a 90 mg dose of active substance X was  $5.5 \pm 1.1$  l. Active substance X is 92% bound to plasma proteins in HIV infected plasma over a plasma concentration range of 2 to 10  $\mu\text{g/ml}$ . It is bound predominantly to albumin and to a lower extent to  $\alpha$ -1 acid glycoprotein. In in vitro studies, active substance X was not displaced from its binding sites by other medicinal products, nor did active substance X displace other medicinal products from their binding sites. In HIV patients, active substance X levels in the cerebrospinal fluid have been reported to be negligible.



# Biotransformation

- Degree of metabolism
- Metabolites
- Activity of metabolites and contribution to effect and toxicity
- Enzymes involved in metabolism
- Site of metabolism

[7 biotransformation](#)

- Results from *in vitro* interaction studies that indicate whether the new compound can induce/inhibit metabolic enzymes

[8 biotransformation](#)



## Example 7-biotransformation

Active substance X 40 mg hard capsules

### **Biotransformation**

Active substance X undergoes extensive metabolism. In healthy young adults, active substance X accounts for approximately 19% of the radioactivity in plasma over 72 hours following a single intravenous administration 100 mg dose of [14C]-fosactive substance X, a prodrug for active substance X, indicating a substantial presence of metabolites in the plasma. Twelve metabolites of active substance X have been identified in human plasma. The metabolism of active substance X occurs largely via oxidation at the morpholine ring and its side chains and the resultant metabolites were only weakly active. *In vitro* studies using human liver microsomes indicate that active substance X is metabolised primarily by CYP 3A4 and potentially with minor contribution by CYP 1A2 and CYP 2C19.



# Example 8-biotransformation

## Active substance X 15 mg tablets

### **Biotransformation**

Active substance X undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. This is predominantly via cytochrome P450 2C8 although other isoforms may be involved to a lesser degree. Three of the six identified metabolites are active (M-II, M-III, and M-IV). When activity, concentrations and protein binding are taken into account, active substance X and metabolite M-III contribute equally to efficacy. On this basis M-IV contribution to efficacy is approximately three-fold that of active substance X, whilst the relative efficacy of M-II is minimal.

*In vitro* studies have shown no evidence that active substance X inhibits any subtype of cytochrome P450. There is no induction of the main inducible P450 isoenzymes 1A, 2C8/9, and 3A4 in man. Interaction studies have shown that active substance X has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon and metformin. Concomitant administration of active substance X with gemfibrozil (an inhibitor of cytochrome P450 2C8) or with rifampicin (an inducer of cytochrome P450 2C8) is reported to increase or decrease, respectively, the plasma concentration of active substance X (see section 4.5)



# Elimination

- Elimination half-lives
- Total clearance
- Inter and/or intra-subject variability in total clearance
- Excretion routes of the unchanged substance and metabolites
  - including the relative portion of the hepatic and renal eliminated fraction
- Involvement of transport proteins

[9 elimination](#)  
[10 elimination](#)





## Example 9-elimination

Active substance X 200 mg hard capsules

### **Elimination**

Active substance X is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and faeces (approximately 14%). Thirteen percent of the active substance X dose was recovered in urine as three metabolites. The systemic clearance of active substance X averaged 307 ml/min (4.03 ml/min/kg). Following oral administration, the elimination half-life of active substance X is approximately 10 hours.



## Example 10-elimination

Active substance X mg/ml powder and solvent for solution for injection

### **Elimination**

Clearance of active substance X after intravenous administration 90 mg was  $1.4 \pm 0.28$  l/h and the elimination half-life was  $3.2 \pm 0.42$  h. Following a 90 mg subcutaneous dose of active substance X the half-life of active substance X is  $3.8 \pm 0.6$  h. Mass balance studies to determine elimination pathway(s) of active substance X have not been performed in humans.



# Linearity/non-linearity

- Linearity/non-linearity of the pharmacokinetics of the active substance with respect to dose and/or time
- The underlying reason for the non-linearity should be presented

[11 linearity](#)  
[12 linearity](#)



## Example 11-linearity/non-linearity

Active substance X 10 mg film-coated tablets

### **Linearity**

Studies in volunteers have demonstrated linear pharmacokinetics in the dose range of 10 to 40 mg.



## Example 12-linearity/non-linearity

Active substance X 150 mg film-coated tablets

### **Linearity/non-linearity**

Exposure to active substance X increased more than in proportion to the increase in dose. After single dose administration in the dose range of 150 to 600 mg, a 2-fold increase in dose results in a ~2.3 and 2.6-fold increase in AUC and C<sub>max</sub>, respectively. At steady state the non-linearity may be more pronounced. Mechanisms responsible for deviation from linearity have not been identified. A possible mechanism is saturation of transporters at the absorption site or at the hepatobiliary clearance route.



## II.2 Characteristics in specific groups

Variations with respect to factors such as:

- Age
- Weight
- Gender
- Smoking status
- Polymorphic metabolism
- Renal impairment
- Hepatic impairment ...

*(including degree of impairment)*

If influence on pharmacokinetics is considered to be clinically relevant, it should be described here in quantitative terms

(cross reference to section 4.2 when applicable)

[13 specific group](#)

[14 specific group](#)

[15 specific group](#)

[16 specific group](#)



## Example 13-specific group

Active substance X 50 mg powder for concentrate for solution for infusion

### *Section 5.2*

Weight was found to influence active substance X pharmacokinetics in the population pharmacokinetic analysis in adult candidiasis patients. The plasma concentrations decrease with increasing weight. The average exposure in an adult patient weighing 80 kg was predicted to be about 23% lower than in an adult patient weighing 60 kg (see section 4.2).

### *Section 4.2*

A single 70 mg loading dose should be administered on Day-1, followed by 50 mg daily thereafter. In patients weighing more than 80 kg, after the initial 70 mg loading dose, active substance X 70 mg daily is recommended (see section 5.2).



## Example 14-specific group

Active substance X 40 mg/ml oral suspension

### *Race*

There was a slight decrease (16 %) in the AUC and C<sub>max</sub> of active substance X in Black subjects relative to Caucasian subjects. However, the safety profile of active substance X between the Black and Caucasian subjects was similar.





## Example 15-specific group

Active substance X 5 micrograms solution for injection, prefilled pen

### *Patients with renal impairment*

In patients with mild (creatinine clearance 50 to 80 ml/min) or moderate renal impairment (creatinine clearance 30 to 50 ml/min), active substance X clearance was mildly reduced compared to clearance in individuals with normal renal function (13% reduction in mild and 36% reduction in moderate renal impairment). Clearance was significantly reduced by 84% in patients with end-stage renal disease receiving dialysis (see section 4.2).



## Example 16-specific group

Active substance X 90 film coated tablets

### *Hepatic impairment*

C<sub>max</sub> and AUC for active substance X were 12% and 23% higher in patients with mild hepatic impairment compared to matched healthy subjects, respectively (see section 4.2). Active substance X has not been studied in patients with moderate or severe hepatic impairment and its use in these patients is contraindicated (see section 4.3 and 4.4).



## II.3 Pharmacokinetic/pharmacodynamic relationships

Relationship between dose/concentration/pharmacodynamic parameter and effect (either true endpoint, validated surrogate endpoint or side effect) with a description of the population studied

[17 pharmacokinetic/pharmacodynamic relationships](#)



## Example 17-PK/PD relationships

Active substance X 40 mg hard capsules

### *Relationship between concentration and effect*

Using a highly specific NK1-receptor tracer, positron emission tomography (PET) studies in healthy young men have shown that active substance X penetrates into the brain and occupies NK1 receptors in a dose- and plasma-concentration-dependent manner. Active substance X plasma concentrations achieved with the 3-day regimen of active substance X are predicted to provide greater than 95% occupancy of brain NK1 receptors.



## II.4 Paediatric population

Results of pharmacokinetic studies in the different paediatric age groups should be summarised with a comparison to adults if available

If appropriate, the dose producing similar product exposure as in adults could be given

The pharmaceutical forms(s) used for pharmacokinetic studies in children should be stated

Uncertainties due to limited experience should be stated

SmPC examples

[18 paediatric](#)

[19 paediatric](#)

[20 paediatric](#)



## Example 18-paediatric population

Active substance X 100 mg powder and solvent for concentrate for solution for infusion

### *Paediatric population*

The pharmacokinetics of active substance X after at least 5 daily doses were investigated in 24 immunocompromised paediatric (2 to 11 years old) and adolescent (12 to 17 years old) patients with neutropenia. Steady state was achieved on the first day after a loading dose (twice the maintenance dose), and steady state C<sub>max</sub> and AUC<sub>ss</sub> increase in a dose-proportional manner. Systemic exposure following daily maintenance dose of 0.75 and 1.5 mg/kg/day in this population were comparable to those observed in adults following 50 and 100 mg/day, respectively. Both regimens were well-tolerated by these patients.



## Example 19-paediatric population

Active substance X 80 mg/ml oral solution

Active substance X steady-state pharmacokinetic parameters were evaluated in HIV infected children above 2 years of age receiving doses ranging from 250 mg/m<sup>2</sup> twice daily to 400 mg/m<sup>2</sup> twice daily. Active substance X concentrations obtained after 350 to 400 mg/m<sup>2</sup> twice daily in paediatric patients were comparable to those obtained in adults receiving 600mg (approximately 330 mg/m<sup>2</sup>) twice daily. Across dose groups, active substance X oral clearance (CL/F/m<sup>2</sup>) was approximately 1.5 to 1.7 times faster in paediatric patients above 2 years of age than in adult subjects.

Active substance X steady-state pharmacokinetic parameters were evaluated in HIV infected children less than 2 years of age receiving doses ranging from 350 to 450 mg/m<sup>2</sup> twice daily. Active substance X concentrations in this study were highly variable and somewhat lower than those obtained in adults receiving 600 mg (approximately 330 mg/m<sup>2</sup>) twice daily. Across dose groups, active substance X oral clearance (CL/F/m<sup>2</sup>) declined with age with median values of 9.0L/h/m<sup>2</sup> in children less than 3 months of age, 7.8 L/h/m<sup>2</sup> in children between 3 and 6 months of age and 4.4 L/h/m<sup>2</sup> in children between 6 and 24 months of age.



## Example 20-paediatric population

Active substance X 1 mg powder for concentrate for solution for infusion

### Paediatrics

The pharmacokinetics of active substance X given as a 30-minute infusion for 5 days were evaluated in two studies. One study included a dose range of 1.4 mg/m<sup>2</sup> to 2.4 mg/m<sup>2</sup> in children (aged 2 up to 12 years, n = 18), adolescents (aged 12 up to 16 years, n = 9), and young adults (aged 16 to 21 years, n = 9) with refractory solid tumours. The second study included a dose range of 2.0 mg/m<sup>2</sup> to 5.2 mg/m<sup>2</sup> in children (n = 8), adolescents (n = 3), and young adults (n = 3) with leukaemia. In these studies, there were no apparent differences in the pharmacokinetics of active substance X among children, adolescents, and young adult patients with solid tumours or leukaemia, but data are too limited to draw definite conclusions.





## III.1 Pharmacokinetic guidelines

Pharmacokinetic Studies in Man (3CC3A, 1987)

Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Renal Function (CPMP/EWP/225/02)

Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function (CPMP/EWP/2339/02)

Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98)

Guideline on reporting the results of population pharmacokinetic analyses (CHMP/EWP/185990/06)

Guideline on Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins (CPMP/EWP/89249/04)

Guideline on the Role of Pharmacokinetics in the development of Medicinal Products in the Paediatric Population (CPMP/EWP/147013/2004)

The Investigation of Drug Interactions (CPMP/EWP/560/95)

*Please refer to the European Medicines Agency's webpage for complete and updated information on scientific guidelines*



## IV. FAQs

1. Can section 5.2 present pharmacokinetic data collected with a different pharmaceutical form?\*
2. When and how should PK differences of a new formulation of an already authorised substance be presented in the SmPC?\*



# 1. Can section 5.2 present pharmacokinetic data collected with a different pharmaceutical form?\*

- Pharmacokinetic (PK) properties described in section 5.2 should be those of the concerned pharmaceutical form. Information on the pharmacokinetic properties of a different pharmaceutical form can be presented in specific cases when e.g:
  - Data is not available with the concerned pharmaceutical form (e.g. due to low absorption with an ocular formulation, other pharmacokinetic characteristics may be described based on oral or IV administration):
  - There is a need to inform healthcare professionals on specific pharmacokinetic differences between different pharmaceutical forms (e.g. information on relative bioavailability could be useful for dose adjustment purpose when switching from one form to another);
  - The SmPC presents data obtained with a different pharmaceutical form in the paediatric population. In this case, a cross reference to section 4.2 should be included to inform on the overall recommendations in the paediatric population.



## 2. When and how should PK differences of a new formulation of an already authorised substance be presented in SmPC?\*

- The SmPC of the new formulation should present the pharmacokinetic (PK) properties of this new formulation in section 5.2. Any PK-related information in the SmPC, in particular the posology recommendations, will correspond to this new formulation.
- No information on other formulation(s) is expected, unless there is a need to inform healthcare professionals on specific differences to prevent medication errors. For example, information on important differences in bioavailability could be useful for dose adjustment when switching from one formulation to another. In such case, warning or precaution to be taken due to the PK differences should be presented in section 4.2 or 4.4 and supportive PK data in section 5.2. There should be cross-references between the sections.



# Thank you for consulting this training presentation

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