



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

## Section 5.3: Preclinical safety data

---

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





# Index

I. [General objectives](#)

II. [Key principles](#)

III. [FAQs](#)



## I. General objectives of section 5.3

This section should provide information on any findings in the non-clinical testing which could be of relevance to the prescriber

If results of non-clinical studies do not add to the information needed by the prescriber, then the results need not be repeated in the SmPC



## II. Key principles

Findings of non-clinical data relevant to prescriber and not already covered in other sections of SmPC should be given

SmPC examples  
[1 safety pharmacology](#)  
[2 toxicology](#)  
[3 genotoxicity](#)  
[4 carcinogenic potential](#)  
[5 reproduction & development](#)

Findings of non-clinical testing should be described in brief with qualitative statements

[example statements](#)

+/- **juvenile animals**: if necessary present findings with discussion on clinical relevance

[6 juvenile animals](#)  
[7 juvenile animals](#)

+/- **<Environmental Risk Assessment>** (include conclusions where relevant; see [Guideline on the environmental risk assessment of medicinal products for human use](#))



# Example 1–safety pharmacology

Findings of non-clinical data relevant to prescriber and not already covered in other sections of SmPC should be given

## Active substance X 60 mg tablets

Non clinical *in vitro* and *in vivo* studies have evidenced the potential of active substance X and its metabolite to prolong cardiac repolarisation and this can be attributed to the blockade of hERG channels.

*In vivo*, high plasma concentrations in monkeys caused a 24 % prolongation in QTc, which is in line with QTc findings in humans.

It is also to be noted that the  $C_{\max}$  observed in the monkeys (1800 ng/ml) is two-fold compared to the mean  $C_{\max}$  observed in humans at a daily dose of 60 mg.

Action potential studies in isolated rabbit heart have shown that active substance X induce cardiac electrophysiological changes which start to develop at concentrations approximately 10 fold compared to the calculated free therapeutic plasma concentration in human.



## Example 2-toxicology

Findings of non-clinical data relevant to prescriber and not already covered in other sections of SmPC should be given

Active substance X 50 mg powder for solution for infusion

In rats, vacuolation of the renal pelvic epithelium as well as vacuolation and thickening (hyperplasia) of the bladder epithelium were observed in 26-week repeat dose studies. In a second 26-week study hyperplasia of transitional cells in the urinary bladder occurred with a much lower incidence. These findings showed reversibility over a follow-up period of 18 months. The duration of active substance X dosing in these rat studies (6 months) exceeds the usual duration of active substance X dosing in patients (see section 5.1).



## Example 3-genotoxicity

Findings of non-clinical data relevant to prescriber and not already covered in other sections of SmPC should be given

Active substance X 250 mg hard capsules

Two genotoxicity assays (*in vitro* mouse lymphoma assay and *in vivo* mouse bone marrow micronucleus test) showed a potential of active substance X to cause chromosomal aberrations.

These effects can be related to the pharmacodynamics mode of action, i.e. inhibition of nucleotide synthesis in sensitive cells. Other *in vitro* tests for detection of gene mutation did not demonstrate genotoxic activity.



## Example 4-carcinogenic potential

Findings of non-clinical data relevant to prescriber and not already covered in other sections of SmPC should be given

Active substance X 1 mg/24 h transdermal patch

In a carcinogenicity study, male rats developed Leydig cell tumours and hyperplasia. Malignant tumours were noted predominantly in the uterus of mid- and high-dose females. These changes are well-known effects of dopamine agonists in rats after life-long therapy and assessed as not relevant to man.



## Example 5-reproduction and development

Findings of non-clinical data relevant to prescriber and not already covered in other sections of SmPC should be given

### Active substance X 0.3 mg solution for injection

Active substance X produced no maternal toxicity and no evidence of teratogenicity or foetal mortality in mice at intravenous doses of 1 to 40 mg/kg/day. Reduced body weight (5%) and minimal delayed ossification in forepaw phalanges were observed, only at exposure levels based on AUC of over 300 fold greater than that expected in humans. These findings are therefore considered to be of limited clinical relevance. In the 40 mg/kg/day group, active substance X concentrations in the amniotic fluid were 0.05% of the maternal plasma levels. There are no reproductive toxicity studies in rabbits.

No data are available to evaluate male or female mating or fertility indices.



# Example statements from SmPC guideline

Findings of non-clinical testing should be described in brief with qualitative statements

## SmPC guideline

- Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development
- Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use
- Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows



## Example 6-juvenile animals

+/- juvenile animals: if necessary present findings with discussion on clinical relevance

Active substance X 250 mg film-coated tablets

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day (x6-17 the MRHD on a mg/m<sup>2</sup> basis)



## Example 7-juvenile animals

+/- juvenile animals: if necessary present findings with discussion on clinical relevance

### Active substance X 100mg hard capsules

In juvenile rats the types of toxicity do not differ qualitatively from those observed in adult rats.

However, juvenile rats are more sensitive. At therapeutic exposures, there was evidence of CNS clinical signs of hyperactivity and bruxism and some changes in growth (transient body weight gain suppression). Effects on the oestrus cycle were observed at 5-fold the human therapeutic exposure.

Reduced acoustic startle response was observed in juvenile rats 1-2 weeks after exposure at >2 times the human therapeutic exposure. Nine weeks after exposure, this effect was no longer observable.



## III. FAQs

1. Should information relevant for use in the paediatric population only be included when there are risks?
2. Which conclusions of environmental risk assessment should be considered relevant for inclusion in section 5.3?



# 1. Should information relevant for use in the paediatric population only be included when there are risks?

- Information in section 5.3 should be limited to relevant data to the prescriber. Therefore, it is recommended to present in a specific paediatric sub-paragraph, the juvenile animals and relevant peri- or postnatal study results when specific toxicity findings relevant for the paediatric population have been observed. The clinical relevance of the findings should be stated, with a cross-reference to related information in other sections of the SmPC, e.g. section 4.2 regarding the indication or not in the various subsets of the paediatric population, or section 4.4/4.8/5.1 regarding related paediatric clinical safety information or lack of data
- When a juvenile animal toxicity study has not revealed any relevant findings suggestive of a specific risk for use in the paediatric population, this can be stated as such (without further details)



## 2. Which conclusions of environmental risk assessment (ERA) should be considered relevant for inclusion in section 5.3?

- When a potential risk to the environment has been identified. See [Guideline on the environmental risk assessment of medicinal products for human use](#)
- If no risk to the environment has been identified or available data do not justify precautionary measures, no statement on the lack of risk or conclusions of the ERA should be included in section 5.3.

In all cases, ERA should be addressed in the public assessment report to which a reference can be made in the SmPC (i.e. “Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>”).



# 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