Annex A

Presentation of pharmacokinetic interaction data in the SPC

These recommendations refer to anti-retroviral drugs with high propensity for pharmacokinetic (PK) interactions. The principles guiding data presentation should take the following into account:

The SPC is a tool to be used by the clinicians. For compounds with complex interaction potential, the most user-friendly way to present data is by therapeutic areas.

- The aim should be to provide clear recommendations as regards use/non-use and, for essential drugs, which dose to be used.
- If major interactions with a specific compound have been identified, there may be alternatives within the same therapeutic area without this interaction propensity. Therefore absence of PK interactions is informative and should be provided for therapeutic areas where (potentially) problematic interactions have been identified.
- For some compounds (e.g. substrates of CYP3A), the number of possible combinations of interacting compounds might be high in clinical practice. For such compounds therapeutic drug monitoring (TDM) might be useful. Information as regards target concentrations may be put forward in sections 5.2 and/or 4.2, depending on the robustness of data and foreseen need for TDM in clinical practice.

The table below may be used as a template to structure information as regards PK interactions in the SPC.

Drugs by Therapeutic Area	**Interaction**	**Recommendations concerning co-administration**
The dose of experimental agent used in interaction study should be stated. If a class of compounds is not affected, this is stated with a general comment. For compounds given with and without ritonavir-boosting, information should be clearly separated. **Example ("HIV Compound Y") :**	Changes in relevant PK-parameters presented with arrows (↑↓) and as mean change and range. Negative findings are of interest – particularly within a therapeutic area where interactions are found for some compounds and not for others. "No interaction" then stated. The mechanism behind the interaction should be stated.	A clinically useful recommendation to be given in this box.
INFECTION *Anti-fungals* **Fluconazole** (HIV compound Y, x mg BID)	Compound Y AUC ↑ 35 % (x-x) Compound Y Cmin ↑ 55 % (x-x) Fluconazole ↔ (CYP3A inhibition)	No dose adjustment necessary. Do not use Fluconazole > 200 mg/d

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
HYPERLIPIDAEMIA *HMG CoA reductase inhibitors* **Simvastatin** **Lovastatin**	Based on theoretical considerations Compound Y is expected to increase simvastatin and lovastatin concentrations.	Combination contra-indicated due to an increased risk of myopathy, including rhabdomyolysis
Atorvastatin (HIV compound Y, x mg BID)	Atorvastatin AUC ↑ 8-10-fold Metabolite AUC ↓ 85% Compound Y ↔ (CYP3A inhibition)	Combination not recommended
Pravastatin **Fluvastatin** **Rosuvastatin**	Interaction not studied, but not expected based on mechanistic consideration	Preferred choice when coadministration with a HMG CoA reductase inhibitor is needed