Annex B

Template section 5.1

The virological data and clinical study data that appear in section 5.1 of the SPC should be limited to the information that is most likely to be useful to the prescriber. Therefore this section should be short, readable and, as far as possible, should display the information in tabulated form.

It is expected that much of the other virological and clinical efficacy data will appear in the EPAR SPC and/or in peer-reviewed publications.

5.1 Pharmacodynamic properties

Mechanism of action: *Brief* description in text.

Antiviral activity *in vitro*: In a brief paragraph it should be described if active vs. HIV-2 as well as HIV-1 and if similar activity seen against all clades tested.

Resistance:

Antiviral activity according to genotypic/phenotypic resistance (new compound in licensed class):

The cut-offs of activity (not affected, decreased, resistance) as measured by change in HIV-RNA from baseline should be justified by the MAH.

Data should be derived from short term functional monotherapy. Alternatively for drugs indicated for the treatment of experienced patients the table could be based on week 4 data, if available, from patients harbouring virus with a sensitivity score of 0.

When applicable, response by an additional international list of mutations (IAS-USA, Stanford etc) should be presented also in cases where the list defined by the MAH correlates somewhat better with the efficacy. As soon as a European Consensus list of mutations is available, this should be used as the additional list.

TABLE 1. Clinical cut off values for reduced activity of MAH compound by baseline genotype/phenotype based on short term functional monotherapy (x weeks)

	Activity not affected	Decreased activity	Resistance
MAH genotypic score[1] (no of mutations)	0-X	X-X	X+
Identified Key mutations [2] (of MAH compound)	0-X	X-X	X+
Additional list (version) [3] (no of mutations)	0-X	X-X	X+
Clinical cut-off Phenotype* (Fold change)	0-X	X-X	X+

1 Codons:
2 Codons:
3 Codons:
* assay:…specified

Clinical results

The data should be presented under separate heading for Treatment Naïve Patients and Treatment Experienced Patients.

The study designs should be *briefly* described.

Examples of tables to be included:

- Primary and most important secondary efficacy parameters. For primary, by subgroups.
- Virological outcomes by number of active compounds in OBT (sensitivity score defined) and by any documented baseline resistance to compound. The sensitivity score of the individual patient should be

based on the drugs actually included in the OBT. (This separate table concerns new compound, existing class).

TABLE 2. Outcome at week X in pivotal studies

Parameter	MAH compound	Control
< 50 cps/mL, %		
All patients		
With Baseline		
HIV-RNA > 100.000 cps/mL		
< 100.000 cps/mL		
CD4-count < 50		
50-100		
101-200		
201-350		
Sensitivity score		
0		
1		
2		
> 1 log_{10} reduction in HIV-RNA, %		

TABLE 3. Proportion (%) of patients with < 50 cps/mL at week X by genotypic sensitivity score in OBT and baseline resistance.

	MAH compound				Control		
	Number of baseline mutations						
Genotypic sensitivity score in OBT *	MAH mutations score[1]				alternative score (if relevant)[2]		
	All	0-X	X-X	X+	0-X	X-X	X+
0							
1							
2 or more							
All patients							

* [Sensitivity score: defined]

[1] Codons:

[2] Codons:

The cut-offs of activity used in TABLE 1 (previous page) should be specifically reflected upon in relation to the table 3.

The section should be updated at relevant intervals. Old studies considered to not to be relevant anymore should be deleted in the updates of the compound.

Template EPAR – pharmacodynamic section

The EPAR (e.g Scientific Discussion) should present pharmacodynamic data in a similar way to that of section 5.1, but in greater detail. Tables are preferred to text format and only relevant information should be included. *In vitro* data (eg activity and resistance) is only briefly mentioned insection 5.1 and should be given in detail in the EPAR, preferably using the formats below.

Antiviral activity *in vitro*:

If a compound is highly protein-bound, a serum-adjusted EC_{90} should be reported. After examining the *in vitro* antiviral activity in the presence of human serum, e.g., at 5, 10, 20 and 40 percent, an EC_{90} value at 100 percent human serum can be estimated.

TABLE. Activity against wild-type virus (cell lines used defined *)

Parameters	**HIV-1 (group M)**		**HIV-1 (group O/N)**	**HIV-2**
EC 50 uM median (range) ng/ml				
EC 90 uM median (range) ng/ml				
Serum adjusted EC90 [if relevant]				
Types of isolates (group M)	N (clin/lab)	EC50 median (range)		
Subtype B				
Non-B				
CRF				

* Cell line:

In vitro resistance:

a) *in vitro* selection of resistance from WT HIV-1 virus:

Assay used for phenotypic resistance testing and type of cell lines used should be specified. Fold change according to accumulating resistance should be presented.

TABLE. Mutations selected *in vitro* in cell line systems [1], in the presence of MAH compound

Parameter	**Mutations at codons**		
	a, b, c	d, e, f	etc
Appearance (number of passages)	X	Y	etc
IC 50 Fold Change [2] versus BL			

1 cell line(s) used specified
2 phenotypic assay: specified

b) cross-resistance *in vitro*:

Detailed analyses of in vitro resistance to clinical isolates resistant (=clinical failure) to other compounds of same drug class.

TABLE. Cross-resistance of clinical isolates resistant (clinical failure) to other drugs (same class)

Parameter	Drug 1	Drug 2	Drug 3	Drug 4
N:o of isolates tested				
Subtypes tested				
Fold Change Drug 1-4 , range vs WT. *				
Fold Change MAH compound, range vs WT*				

* assay:…specified

In vivo resistance:

In addition to the tables presented in section 5.1, the following tables should be constructed as appropriate to the clinical study database and should be updated regularly (e.g. yearly):

TABLE. ***De novo*** **mutations in treatment naive patients failing therapy with (dose regimen)**

Frequency	Codons
>20%	
10-20%	

TABLE. ***De novo*** **mutations in treatment experienced patients failing therapy with (dose regimen)**

Frequency	Codons
>20%	
10-20%	

These tables should be followed by a short description or if possible tabulation of any correlation observed between specific mutations and change in phenotypic sensitivity.