Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for irinotecan (except for liposomal formulations), the scientific conclusions are as follows:

During the 3-years reporting interval covered by this PSUSA procedure, signals of drug-drug interactions with irinotecan have emerged following updates of the French thesaurus on drug interactions.

- Regarding the pharmacodynamics DDI between cytotoxic products, including irinotecan, and olaparib or flucytosine and the risk of increased haematological toxicity, the EU SmPC guideline (September 2009), section 4.5 Interactions with other medicinal products and other forms of interactions, states that: "with regard to pharmacodynamic effects where there is a possibility of a clinically relevant potentiation or a harmful additive effect, this should be stated". Thus Section 4.5 of irinotecan EU SmPC (and PL accordingly) should be revised, an interaction with antineoplastic agents, including flucytosine as a prodrug for 5-fluorouracile, should be added to inform that ADRs of irinotecan, such as myelosuppression, would be expected to be exacerbated by other antineoplastic agents having a similar adverse-effect profile.

- Regarding the DDI with apalutamide and the risk of important decrease in irinotecan concentration and subsequent loss of efficacy due to increased hepatic metabolism caused by apalutamide, a strong inducer of CYP3A4, Irinotecan EU SmpC (sections 4.4 and 4.5) does not recommend concomitant use of strong CYP3A4 inducer with irinotecan. Sections 4.4 and 4.5 of irinotecan containing products EU SmPC (and PL accordingly) should be revised in order to add apalutamide to the list of strong inducer of CYP3A4.

In addition, in the same section of the SmPC (4.5), it is proposed to simplify the wording of the subsection related to concomitant use contraindicated, by mentioning the yellow fever vaccine in the dedicated paragraph of live attenuated vaccines.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for irinotecan (except for liposomal formulations) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing irinotecan (except for liposomal formulations) is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing irinotecan (except for liposomal formulations) are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)>

Summary of Product Characteristics

- Section 4.4

Others

Concomitant administration of irinotecan with a strong inhibitor (e.g. ketoconazole) or inducer (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, **apalutamide**) of CYP3A4 may alter the metabolism of irinotecan and should be avoided (see section 4.5).

- Section 4.5

Concomitant use contraindicated (see section 4.3)

~~Yellow fever vaccine: Risk of fatal generalised reaction to vaccines~~

Saint John's Wort: Decrease in the active metabolite of irinotecan, SN-38, plasma levels. In a small pharmacokinetic study (n=5), in which irinotecan 350 mg/m2 was co-administered with St. John's Wort (Hypericum perforatum) 900 mg, a 42% decrease in the active metabolite of irinotecan, SN-38, plasma concentrations was observed. As a result, St. John's Wort should not be administered with irinotecan.

Live attenuated vaccines **(e.g. yellow fever vaccine)**: Risk of generalised reaction to vaccines, possibly fatal. Concomitant use is contraindicated during treatment with irinotecan and for 6 months following discontinuation of chemotherapy. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Concomitant use not recommended (see section 4.4)

Concurrent administration of irinotecan with a strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) may alter the metabolism of irinotecan and should be avoided (see section 4.4):

Strong CYP3A4 and/or UGT1A1 inducing medicinal products: (e.g. rifampicin, carbamazepine, phenobarbital ~~or~~ phenytoin **or apalutamide**):

Other combination

.../.../...

Antineoplastic agents (including flucytosine as a prodrug for 5-fluorouracil)
Adverse effects of irinotecan, such as myelosuppression, may be exacerbated by other antineoplastic agents having a similar adverse-effect profile.

Package Leaflet

2. What you need to know before you use <Name of the product>

…//…

Other medicines and <Name of the product>

<Name of the product> can interact with a number of medicines and supplements, which may either raise or lower the level of the medicine in your blood. Tell your doctor or pharmacist if you are using, have recently used or might use any of the following:

…//…

- Medicines used to treat cancer (regorafenib, crizotinib**,** ~~and~~ idelalisib **and apalutamide**)

Tell your doctor pharmacist or nurse before being given <Name of the product> if you are already having, or have recently had chemotherapy (and radiotherapy).

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	15 March 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	13 May 2021