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 levonorgestrel / ethinylestradiol, ethinylestradiol (combination pack), the scientific conclusions are as follows:

In view of available data on risk of acquired angioedema associated with COC use from the literature, and in view of a plausible mechanism of action, the Lead Member State considers a causal relationship between levonorgestrel / ethinylestradiol, ethinylestradiol (combination pack) and angioedema acquired is at least a reasonable possibility. The Lead Member State concluded that, in line with the PRAC recommendation for ethinylestradiol / levonorgestrel (PSUSA/00001309/201904), the product information of products containing levonorgestrel / ethinylestradiol, ethinylestradiol (combination pack) should be amended as stated below.

In view of available data on risk of concomitant use of Ethinylestradiol with HCV antiviral **glecaprevir/pibrentasvir** from clinical trial(s), and in view of a plausible mechanism of action, the Lead Member State considers a causal relationship between concomitant use of Ethinylestradiol with HCV antiviral **glecaprevir/pibrentasvir** and transaminsase elevation is at least a reasonable possibility. The Lead Member State concluded that, in line with the PRAC recommendation for ethinylestradiol / levonorgestrel (PSUSA/00001309/201904), the product information of products containing levonorgestrel / ethinylestradiol, ethinylestradiol (combination pack) should be amended as stated below.

Update of section 4.4 and 4.8 of the SmPC to add a warning on angioedema. The Package leaflet is updated accordingly.

Update of section 4.3, 4.4 and 4.5 of the SmPC to add/revise a contraindication regarding direct-acting antivirals. The Package leaflet is updated accordingly.

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 levonorgestrel / ethinylestradiol, ethinylestradiol (combination pack), the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing levonorgestrel / ethinylestradiol, ethinylestradiol (combination pack), 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 levonorgestrel / ethinylestradiol, ethinylestradiol (combination pack), 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 4.3

A contraindication should be added/revised as follows:

<trade name> is contraindicated for concomitant use with ~~the~~ medicinal products containing ombitasvir/paritaprevir/ritonavir, ~~and~~ dasabuvir, **glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir** (see sections 4.4 and section 4.5).

- Section 4.4

A warning should be added/revised as follows:

ALT elevations

During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). **ALT elevations have also been observed with HCV anti-viral medicinal products containing glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir** (see sections 4.3 and 4.5).

A warning should be added/revised as follows:

Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

- Section 4.5

The text should be added/revised as follows:

Pharmacodynamic interactions

Concomitant use with ~~the~~ medicinal products containing ombitasvir/paritaprevir/ritonavir, dasabuvir with or without ribavirin, **glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir**, may increase the risk of ALT elevations (see sections 4.3 and 4.4).

Therefore, <trade name>-users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with ~~this combination~~ **these** drug regimens. <trade name> can be restarted 2 weeks following completion of treatment with **these** ~~this combination~~ drug regimens.

- Section 4.8

The text should be added/revised as follows:

Text under the tabulated list of adverse reactions:

Exogenous estrogens may induce or exacerbate symptoms of hereditary and aquired angioedema.

Package Leaflet

2. What you need to know before you use [brand name]

Do not <take> <use> X<:>

Do not use <trade name> if you have hepatitis C and are taking ~~the~~ medicinal products containing ombitasvir/paritaprevir/ritonavir, dasabuvir, **glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir** (see also in section Other medicines and <trade name>).

Tell your doctor if any of the following conditions apply to you.

If the condition develops or gets worse while you use [trade name], you should also tell your doctor.

- **If you experience symptoms of angioedema such as swollen face, tongue and/or throat and/or difficulty swallowing or hives potentially with difficulty breathing contact a doctor immediately. Products containing estrogens may cause or worsen the symptoms of hereditary and aquired angioedema.**

Other medicines and [trade name]
<Tell your <doctor> <or> <pharmacist> if you are <taking> <using>, have recently <taken> <used> or might <take> <use> any other medicines.>

Do not use <trade name> if you have Hepatitis C and are taking ~~the~~ medicinal products containing ombitasvir/paritaprevir/ritonavir, dasabuvir, **glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir**, as ~~this~~ **these products** may cause increases in liver function blood test results (increase in ALT liver enzyme).

Your doctor will prescribe another type of contraceptive prior to start of the treatment with these medicinal products.
<trade name> can be restarted approximately 2 weeks after completion of this treatment. See section "Do not use <trade name>".

4. Possible side effects

Serious side effects

Contact a doctor immediately if you experience any of the following symptoms of angioedema: swollen face, tongue and/or throat and/or difficulty swallowing or hives potentially with difficulty breathing (see also section "Warnings and precautions").

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	01/11/2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	31/12/2020