Type II variation (via Worksharing)

Public Assessment Report

Yasmin
Yira
Yasmin 28
Yasminelle
Aliane
Liofora
Yasminelle 28
Aliane 28
YAZ
Ethinylestradiol/ Drospirenone 24 + 4
Flexyess
Palandra

(Ethinylestradiol/Drospirenone)

NL/H/xxxx/WS/063

<table>
<thead>
<tr>
<th>Reference Member State:</th>
<th>The Netherlands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finalisation procedure:</td>
<td>19 December 2014</td>
</tr>
<tr>
<td>Date of finalisation of PAR:</td>
<td>27 March 2015</td>
</tr>
<tr>
<td>Date of correction PAR:</td>
<td>7 March 2016</td>
</tr>
</tbody>
</table>
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## ADMINISTRATIVE INFORMATION

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Invented name of the medicinal product(s):</td>
<td>Yasmin and associated trade names, see section V</td>
</tr>
<tr>
<td>INN (or common name) of the active substance(s):</td>
<td>Ethinylestradiol and drospirenone</td>
</tr>
<tr>
<td>MAH(s):</td>
<td>Bayer</td>
</tr>
<tr>
<td>Pharmaco-therapeutic group (ATC code):</td>
<td>G03AA12</td>
</tr>
</tbody>
</table>
| Pharmaceutical form(s) and strength(s) | Film-coated tablets 0.03 mg/3 mg  
Film-coated tablets 0.02 mg/3 mg |
I. RECOMMENDATION

Based on the review of the data on clinical pharmacology the Member States consider that the variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008 for Yasmin and related products containing ethinylestradiol/drospirenone, indicated for oral contraception is approvable.

II. EXECUTIVE SUMMARY

II.1 Introduction and scope of the variation

This application concerns the following changes to the product information in section 4.5 of the SmPC:

1. The deletion of interaction with antibiotics (penicillins and tetracyclines)
2. Update on interactions with HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors

Furthermore, the product information has been updated according to the CMDh QRD template for MR/DC products (Version 3, 04/2013).

The MAH submitted an updated clinical overview to justify the changes of the SmPC for the ethinylestradiol/drospirenone tablets.

III. SCIENTIFIC DISCUSSION

III.1 Clinical aspects

Clinical pharmacology

MAH’s justification for deletion interaction with antibiotics
In the updated overview the MAH gave an historical overview in which the available information on the drug interaction between antibiotics and combined oral contraceptives (COCs) is summarised. The company distinguishes between antibiotics that induce the cytochrome P450 enzymes (mainly CYP3A4) and antibiotics which are non-enzyme inducers.

The enzyme inducing antibiotics can reduce serum concentrations of estrogens and progestins metabolized via CYP3A4 and can reduce the efficacy of oral contraceptives.

For non-enzyme inducing antibiotics the evidence is based on isolated cases of pregnancies that were reported following concomitant use of COC and a wide range of antimicrobial agents. The main hypothesis that was proposed to explain contraceptive failure in antibiotic users is that non-enzyme inducing broad-spectrum antibiotics temporarily reduce colonic bacteria and therefore interfere with the enterohepatic recycling of ethinylestradiol or the progestin. However no clinical studies could confirm this hypothesis and no prospective trials are available demonstrating an association between use of non-enzyme inducing antibiotics and contraceptive failure.

Also several professional health care organizations see no concerns in short term concomitant use of COC and non-enzyme inducing antibiotics and revised their recommendations:

- American College of Obstetricians and Gynecologists (ACOG)
- British National Formulary (BNF)
- Dutch College of General Practitioners (NHG)
- Faculty of Sexual &Reproductive Healthcare (FSRH) Clinical Effectiveness Unit UK
- Society of Obstetricians and Gynaecologists of Canada (SOGC)
The MAH concludes that based on the currently existing evidence the efficacy of combined oral contraceptives is not affected by coadministration of short courses of non-enzyme inducing antibiotics.

The deletion of the interaction between non-enzyme inducing antibiotics has been discussed in the CMD(h) and it was agreed that the evidence for the interaction was questionable. Although no final conclusions have been drawn, it is considered acceptable to delete the interaction.

**MAH’s justification for changes with regard to HIV/HCV inhibitors**

In the justification document the MAH gave an overview in which the available information on the drug interaction between HIV inhibitors, HCV inhibitors and COCs is summarized.

Pharmacokinetic interactions between hormonal contraceptives and HIV inhibitors need to be taken into account, as alterations in the systemic exposure of the steroids may alter their effectiveness and safety. HIV inhibitors have varying effects on the metabolic enzymes and the drug transporter P-glycoprotein (P-gp) that are involved with the glucuronidation, sulphate conjugation and transport of oestrogens and progestagens. Furthermore it should be taken into account that HIV patients are treated with multiple drug regiments.

The effects of anti-retroviral therapies on hormonal contraceptives have been recently reviewed and summarized in the literature (see Table 1).
Drug interactions between HCV inhibitors and combined contraceptives have also been evaluated. (see Table 2).

### Table 1: Drug interaction between HIV therapies and hormonal contraceptives (effect on hormonal contraceptives, AUC changes in %)

<table>
<thead>
<tr>
<th>Antiretroviral therapies, Protease inhibitors and ritonavir-boosted protease inhibitors</th>
<th>Estrogen</th>
<th>Progestin</th>
<th>N</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir</td>
<td>↓ EE (41%)</td>
<td>n.d.</td>
<td>23</td>
<td>Deuellet 1998 (5)</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>↑ EE (48%)</td>
<td>↑ NET (110%)</td>
<td>19</td>
<td>Robinson 2012 (1)</td>
</tr>
<tr>
<td>Atazanavir/ritonavir</td>
<td>↔ EE (19%)</td>
<td>↑ NGMN (95%)</td>
<td>14</td>
<td>Zhang 2011 (13)</td>
</tr>
<tr>
<td>Darunavir/ritonavir</td>
<td>↓ EE (44%)</td>
<td>↔ NET (14%)</td>
<td>13</td>
<td>Sekar 2008 (17)</td>
</tr>
<tr>
<td>Amprenavir*</td>
<td>↔ EE (2%)</td>
<td>↔ NET (18%)</td>
<td>10</td>
<td>Agenerase, product label US</td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir</td>
<td>↓ EE (37%)</td>
<td>↓ NET (34%)</td>
<td>25</td>
<td>Lexiva, product label US</td>
</tr>
<tr>
<td>Indinavir</td>
<td>↑ EE (22%)</td>
<td>↑ NET (26%)</td>
<td>18</td>
<td>Crixivan, product label US</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>↓ EE (59% oral)</td>
<td>↑ NGMN (33% patch)</td>
<td>24/8</td>
<td>Vogler 2010 (12)</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>↓ EE (47%)</td>
<td>↔ NET (18%)</td>
<td>12</td>
<td>Viracept, product label US</td>
</tr>
<tr>
<td>Tipranavir/ritonavir</td>
<td>↓ EE (43%)</td>
<td>↑ NET (27%)</td>
<td>13</td>
<td>Aptivus, product label US</td>
</tr>
</tbody>
</table>

**Non-nucleoside reverse transcriptase inhibitors**

| Efavirenz | ↔ EE (12%) | ↓ NGMN (54%) | ↓ LNG (53%) | 28  | Sevinsky 2011 (15) |
| Nevirapine | ↓ EE (22%) | ↔ NET (18%) | 10  | Milchman 2002 (14) |
| Etravirine | ↑ EE (22%) | ↔ NET (5%) | 24  | Schöller-Gyure 2009 (16) |

- AUC: area under the concentration time curve
- EE: ethinyl estradiol
- NET: norethindrone
- NGMN: norethisterone (metabolite of administered norethisterone)
- LNG: levonorgestrel (metabolite of administered levonorgestrel)
- N: number of subjects
- ‡: not applicable
- ↑: increase (changes > 20%)
- ↓: decrease (changes > 20%)
- ↔: no change (changes < 20%)
- N.d.: not determined
- *: no longer authorized in EU

In general, it needs to be taken into account that the available data on drug-drug interactions between HIV/HCV therapeutics and hormonal contraceptives derive from small, often only in product
information mentioned studies, and that the multi-drug treatment regimens used in clinical practice make it very difficult to predict interactions for an individual patient. Furthermore, the lack of data regarding clinical outcomes such as escape ovulation or unintended pregnancy makes interpretation of findings and determination of their clinical significance and recommendations difficult. Therefore the MAH proposes to introduce the following text to reflect the varying data: ‘Human immunodeficiency virus (HIV)/Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of estrogen and progestin have been noted in some cases of coadministration with HIV/HCV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.’

The Member States consider that the MAH provided an adequate overview of the most recent literature regarding the interaction between COCs and HIV and between COCs and HCV medication. Examples of HIV medication are already discussed in section 4.5 in the paragraph on liver enzyme inducers. Currently, HCV medication, i.e. boceprevir and telaprevir are not mentioned in section 4.5. The new data on concomitant use of COCs and HCV inhibitors do not suggest that a clinically relevant effect on efficacy of COCs can be expected.

As patients are treated with combinations of different HIV/HCV medications it is difficult to predict the net effect on the hormone concentrations and which combination of HIV/HCV medication may reduce the efficacy of COCs. Therefore no concrete advices on the net effect of this combination therapy when used concomitantly with a COC can be given based on the presented literature. The addition of a separate paragraph on HIV/HCV combination therapy was not considered appropriate. Furthermore it was not agreed that the HIV medication ritonavir and nevirapine should be removed from the paragraph on enzyme induction as in most combinations these drugs will lead to decreased EE and progestagen levels.

General recommendation for use of a barrier method for 28 days
The MAH proposed changes with respect to a general advice to use using a barrier method for 28 days when this product is combined with drugs increasing its clearance. This proposed change required further justification, as discussed below.

III.2 Discussion on the clinical aspects

Drug-drug interactions between HIV/HCV inhibitors and COCs
Questions were raised with regard to combined use of HIV/HCV medication and possible interactions which could lead to decreased hormone levels, and possibly to decreased efficacy of combined oral contraceptives. The comments were adequately addressed and led to the following changes:

- The MAH has reintroduced ritonavir and nevirapine in the paragraph on substances increasing the clearance of COCs as requested. Although the exact mechanism is not known, concomitant use is shown to decrease levels of sex hormones.
- The effects of concomitant use with efavirenz were also evaluated, taking into account published guidance (http://www.fsrh.org/pdfs/CEUguidancedruginteractionshormonal.pdf) and the SmPC of efavirenz. It was concluded that also this drug belongs to those HIV medications with proven increased clearance of COCs (significant decrease of levonorgestrel, and norelgestromin (active metabolite of norgestimate). Therefore efavirenz should also be added in the paragraph on increased clearance of COCs.
- In HIV treatment many different drug combinations are used and knowledge is still quickly evolving. It is difficult to predict the net effect of a cocktail of HIV medication on the COCs hormone concentrations. For several combinations of HIV drugs possibly clinically relevant pharmacokinetic interactions have been detected. However, as it is not possible to provide a complete list of every possible relevant combination it is considered acceptable to include a statement on HIV medication. For concrete advices with regard to the interaction with COC should be referred to the SmPC of the individual HIV medication and the HIV treatment guidelines, as is already proposed by the MAH.
• The HCV medications boceprevir and telaprevir, are both strong CYP3A4-5 inhibitors. Concomitant treatment of boceprevir and a COC was evaluated in clinical PK studies. The combination with drospirenone/ethinylestradiol resulted in an increase of drospirenone AUC by 99%, and a decrease of the ethinylestradiol concentration by 24%. The combination with northindrone/ethinylestradiol did not lead to changes in progesterone exposure and resulted in minor changes of the ethinylestradiol exposure (a decrease by 26%) (SmPC Victrelis ®). Concomitant treatment of telaprevir and a COC (containing northindrone and ethinylestradiol) did not lead to changes in the progesterone exposure and resulted in minor changes of the ethinylestradiol exposure (a decrease by 28%) (SmPC Incivo®). These results indicate that the efficacy of concomitant use of these HCV drugs with a COC is unlikely to alter contraceptive effectiveness, which is also stated in the SmPCs of these products. Therefore, it is not supported to indicate that HCV drugs have similar effects compared to HIV drugs. However, as HCV drugs are used in many different drug combinations (including HIV drugs) it can be agreed to additionally mention the HCV drugs within the paragraph of combinations of HIV medications.

The interaction with non-enzyme inducing antibiotics
Based on the initially provided variation dossier, further clarification was required on the strength of the data to support the removal of the interaction warning with penicillins and tetracyclines. Many SmPCs for oral contraceptives state that contraceptive failures have been reported with antibiotics such as ampicillin and tetracyclines, the mechanism of which has not been elucidated. As part of the previous “class label” for COCs, Bayer and other pharmaceutical companies had included the potential drug interaction with antibiotics in their COC product information. The MAH argued that according to a more recent re-assessment of the existing data base by the WHO and other professional health care organisations, these organisations changed their previous recommendation regarding the concomitant use of non-enzyme inducing antibiotics together with COCs. Bayer also reviewed the accessible data and came to the same conclusion. Apart from a few anecdotal case reports, - which could just represent the background COC failure rate -., there are no reliable data on non-enzyme inducing antibiotics (incl. penicillins and tetracycline) available that would justify the warning and precautions currently included in the SmPC’s of COCs. Furthermore, there is a lack of plausible mechanism which could explain such an interaction. E.g., the interference of antibiotics with the enterohepatic circulation of ethinylestradiol often assumed in the literature could not be demonstrated as outlined in the clinical overview addendum submitted with this variation application. The MAH concluded that, based on current evidence, the contraceptive effectiveness of COCs is not affected by co-administration of the usually short courses of non-enzyme inducing antibiotics.

Bayer took up the recommendation by WHO and other organisations in a company-wide initiative to update the product information of all its COCs respectively. It is expected that the product information of generic products will be updated accordingly. This topic has been discussed at CMD(h) level, where it was agreed that the evidence for the interaction is questionable, and that the interaction can be removed from section 4.5 of the SmPC.

Based on the available data, the Member States came to the following conclusions:
• Although several case studies have described COC contraceptive failures in women taking antibiotics, these anecdotal reports are not evidence of a causal relationship. Both antibiotics and COCs are used frequently by reproductive-age women, and often at the same time. These reports are also compromised by lack of knowledge of when in the cycle antibiotics were begun, recall bias, potential confounders, and lack of a control group. The same limitations affect many of the cross-sectional surveys of women presenting for abortion. Additionally, it is possible that the women could have used their antibiotic history as a justification for abortion. When pregnancy rates of women taking COCs and antibiotics are compared to those on COCs alone they are similar, and well within the range of reported typical-use pregnancy rates.
• For many years, it has been assumed that broad spectrum antibiotic may interfere with the enterohepatic cycle of ethinylestradiol or progestagens, however the available evidence does not support this hypothesis. In a drug interaction study with the Nuvaring (containing etonogestrel and ethinylestradiol) and amoxicilline or doxycycline no pharmacokinetic interaction was observed. And in another interaction study with Evra transdermal patches (containing norelgestromin and ethinylestradiol) and tetracycline, no pharmacokinetic interaction was observed. The results obtained for the vaginal ring and transdermal patch can be extrapolated to orally combined oral contraceptives, as the route of administration is not of importance in the mechanism of enterohepatic circulation. The available pharmacokinetic data indicate that there is no change in the exposure of ethinylestradiol or progestin pharmacokinetics with concurrent COC and use of penicillins and tetracycline.

• In section 4.2 of the SmPC is already mentioned that additional contraceptive measures are required during periods of vomiting/diarrhoea. Vomiting and diarrhoea may be caused by illness or as an adverse drug reaction. Gastrointestinal disorders may occur during the use of many different drugs, including antibiotics.

In conclusion, the proposed deletion of the interaction with non-enzyme inducing antibiotics from section 4.5 of the SmPC is considered acceptable. Sufficient justification has been provided.

Usage of barrier methods for 28 days
Questions were asked regarding the proposal for a general advice to use using a barrier method for 28 days when ethinylestradiol/drospirenone is combined with drugs increasing its clearance. The MAH provided additional justification. With the deletion of the warnings and precautions for the non-enzyme inducing antibiotics, the management recommendations have to be fitted to the class of enzyme inducers. It is recommended to use a barrier method or another method of contraception in addition to the COC during and after cessation of the treatment, as enzyme induction may then be sustained for several weeks after the drug therapy has been stopped. The advice to use a barrier method during a period of 28 days after discontinuation is common practice, and included in the SmPC for Zoely. Furthermore, no distinction between rifampicin and other inducers or different advices regarding short and long term treatment with inducing medicinal products is given in the SmPC of Zoely, which is one of the most recently CP approved combined hormonal contraceptives (EU/1/11/690/001-004).

The MAH proposed to add in the SmPC the information that enzyme induction can be observed already after a few days. The current statement “Maximal enzyme induction is generally seen in about 10 days …” [DRSP/EE containing product] or “… not seen for 2-3 weeks” (SmPC for Qlaira) might imply that additional methods of contraception are not required during the first treatment days. The CYP enzyme turnover half-life for synthesis and degradation seems to be on average in the range of 3 days. Applying this estimate new steady state levels will be achieved within 15 days. Allowing a safety factor of 2 (e.g. t1/2 = 6 days), baseline enzyme levels will be achieved 30 days following cessation of drug therapy with an enzyme inducer.

Based on the provided response, the Member States consider the proposed text with regard to the management of drug interactions sufficiently justified. Subheadings should be included to stipulate that recommendations are for short-term and long-term treatment:

Management
Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Short-term treatment
Women on treatment with enzyme-inducing drugs should temporarily use a barrier method or another method of contraception in addition to the COC. The barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation. If the drug therapy runs beyond the end of the tablets in the COC pack, the
next COC pack should be started right after the previous one without the usual tablet-free interval.

*Long-term treatment*
In women on long-term treatment with hepatic enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.

**Laboratory parameters**
The SmPC paragraph regarding laboratory parameters was discussed. The Member States considered whether it should be placed under section 4.4 ‘Special warnings and precautions for use’ or section 4.5 ‘Interaction with other medicinal products and other forms of interaction’. The argumentation of the MAH that keeping the paragraph on laboratory tests in section 4.5 of the SmPC is in line with current guidelines, was accepted. The interactions with laboratory parameters described for combined hormonal contraceptives (CHCs) are not deemed to be of a major clinical importance which could justify presenting them in section 4.4; the wording in section 4.5 states that “changes generally remain within the normal laboratory range.” Moreover, presenting the interactions with laboratory parameters in section 4.5 is consistent with the approved SmPCs for a large number of CHCs reviewed under decentralized and mutual recognition procedures or centralized procedures (e.g., EVRA, Zoely, IOA) over the past years. The provided argumentation was considered acceptable; the paragraph on laboratory parameters is included in section 4.5 of the SmPC.

**III.3 Product information**
The approved changes to the product information are presented in section VI.

**IV. MEMBER STATES OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**
In response to the updated assessment, the MAH has adapted the product information as requested. Therefore, the overall conclusion is that the variation is approvable, based on the following:

- The clinical evidence for the interaction between non-enzyme inducing antibiotics is questionable, evidence shows that antibiotics do not affect the pharmacokinetics of combined oral contraceptive pills. Therefore the interaction can be removed from section 4.5 of the SmPC.
- The MAH’s proposal to reintroduce ritonavir and nevirapine in the paragraph on substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction) is supported.
- The new paragraph on HIV medication, in which also the combination with HCV medication can be mentioned, is accepted.
- The proposed text on management in case of combined treatment with enzyme inducing drugs can be accepted.
- The argumentation of the MAH to keep the text on laboratory parameters in section 4.5 is acceptable.
- The adaptations in the Package Leaflet are acceptable.
- The proposed change to the labelling text is acceptable.

The approved changes to the product information are indicated in section VI below.
V. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Marketing Authorisation holder involved:
Bayer

Products involved:
Yasmin NL/H/0215/MR
Yira NL/H/0218/MR
Yasmin 28 NL/H/0217/MR
Yasminelle NL/H/0701/MR
Aliane NL/H/0702/MR
Liofora NL/H/0703/MR
Yasminelle 28 NL/H/0704/MR
Allane 28 NL/H/0705/MR
YAZ NL/H/1269/MR
Ethinylestradiol/Drospirenone 24 + 4 NL/H/1270/MR
Flexyess NL/H/2041/DC
Palandra PT/H/0322/DC
Yasmin National license
Palandra National license
YAZ National license
Ethinylestradiol/ Drospirenone 24 + 4 National license

VI. CHANGES IN PRODUCT INFORMATION

Changes are indicated “underlined” for additions and “strikethrough” for deletions.

SmPC

4.5 Interaction with other medicinal products and other forms of interaction

Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

Effects influence of other medicinal products on <Product name>

Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones and which between oral contraceptives and other medicinal products may lead to breakthrough bleeding and/or contraceptive failure.

Management
Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Short-term treatment
Women on treatment with enzyme inducing drugs should temporarily use a barrier method or another method of contraception in addition to the COC. The barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation.

(For products without placebo tablets.)
If the drug therapy runs beyond the end of the tablets in the COC pack, the next COC pack should be started right after the previous one without the usual tablet-free interval.
(For products without placebo tablets;)

If the drug therapy runs beyond the end of the active tablets in the COC pack, the placebo tablets must be discarded and the next COC pack should be started right away.

**Long-term treatment**

In women on long-term treatment with enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.

The following interactions have been reported in the literature.

**Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction), e.g.: Hepatic metabolism**

Interactions can occur with drugs that induce hepatic enzymes which can result in increased clearance of sex hormones (e.g. pPhenytoin, barbiturates, primidone, carbamazepine, rifampicin, bosentan and HIV-medication (e.g. ritonavir, nevirapine) and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing the herbal remedy St. John's Wort (Hypericum perforatum). Maximal enzyme induction is generally seen in about 10 days but may then be sustained for at least 4 weeks after the cessation of drug therapy.

Barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin, and HIV medication ritonavir, nevirapine and efavirenz and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (Hypericum perforatum).

Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure (see Management).

**Substances with variable effects on the clearance of COCs, e.g.: Interference with Enterohepatic Circulation**

Ritonavir, nevirapine.

When co-administered with COCs, many combinations of HIV-protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors can increase or decrease plasma concentrations of estrogen or progestins. The net effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations. In case of any doubt, an additional barrier contraceptive method should be used by women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

Contraceptive failures have also been reported with antibiotics, such as penicillins and tetracyclines. The mechanism of this effect has not been elucidated.

**Management**

Women on short-term treatment with any of the above-mentioned classes of medicinal products or individual active substances (hepatic enzyme-inducing medicine) besides rifampicin should temporarily use a barrier method in addition to the COC, i.e. during the time of concomitant medicinal product administration and for 7 days after their discontinuation.

For women on rifampicin a barrier method should be used in addition to the COC during the time of rifampicin administration and for 28 days after its discontinuation.
In women on long-term treatment with hepatic enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.

Women on treatment with antibiotics (besides rifampicin, see above) should use the barrier method until 7 days after discontinuation.
If concomitant medicinal product administration runs beyond the end of the tablets in the COC blister pack, the next COC pack should be started without the usual tablet-free interval.

The main metabolites of drospirenone in human plasma are generated without involvement of the cytochrome P450 system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of drospirenone.

- **Effects Influence of <Product name> on other medicinal products**

Oral contraceptives may affect the metabolism of certain other active substances. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine).

Based on in vitro inhibition studies and in vivo interaction studies in female volunteers using omeprazole, simvastatin and midazolam as marker substrate, an interaction of drospirenone at doses of 3 mg with the metabolism of other active substances is unlikely.

- **Other forms of interactions**

In patients without renal insufficiency, the concomitant use of drospirenone and ACE-inhibitors or NSAIDs did not show a significant effect on serum potassium. Nevertheless, concomitant use of <Product name> with aldosterone antagonists or potassium-sparing diuretics has not been studied. In this case, serum potassium should be tested during the first treatment cycle. See also section 4.4.

- **Laboratory tests**

The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. corticosteroid-binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range. Drospirenone causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity.

4.8 Undesirable effects

(…….)

*Interactions*

Breakthrough bleeding and/or contraceptive failure may result from interactions of other drugs (enzyme inducers) with oral contraceptives (see section 4.5).

**PACKAGE LEAFLET**

Section 2 – Other medicines and <Product name>

(…….)
Some medicines can make <Product name> have an influence on the blood levels of <Product name> and can make it less effective in preventing pregnancy, or can cause unexpected bleeding. These include medicines used for the treatment of:

- HIV and Hepatitis C Virus infections (so-called protease inhibitors and non-nucleoside reverse transcriptase inhibitors such as ritonavir, nevirapine, efavirenz) or other infections (antibiotics such as griseofulvin, penicillin, tetracycline)

LABELLING SECTION - ADDITIONAL INFORMATION PRINTED ON THE WALLET (FROM THE PL)

If you are taking [Product name] and have been using other medicines, for example an antibiotic

Please see the information in the package leaflet under "Other medicines and [Product name]". 

(...