28 March 2019
EMA/256624/2019

Assessment report

Procedure No. EMEA/H/C/WS1544

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Prezista	darunavir	EMEA/H/C/000707/WS1544/0101
Rezolsta	darunavir / cobicistat	EMEA/H/C/002819/WS1544/0030
Symtuza	darunavir / cobicistat / emtricitabine / tenofovir alafenamide	EMEA/H/C/004391/WS1544/0016

Worksharing applicant (WSA): Janssen-Cilag International NV

This application is in the area of: Clinical

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure:	28 Jan 2019	28 Jan 2019	☐
☐	CHMP Rapporteur Assessment Report	04 Mar 2019	04 Mar 2019	☐
☐	CHMP members comments	18 Mar 2019	07 Mar 2019	☐
☐	Updated CHMP Rapporteur Assessment Report	21 Mar 2019	21 Mar 2019	☐
☒	Opinion	28 Mar 2019	28 Mar 2019	☐

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International NV submitted to the European Medicines Agency on 7 January 2019 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB

Update of section 4.3 of the SmPC of Prezista, Rezolsta and Symtuza to contra-indicate the concomitant use with dapoxetine , domperidone, ivabradine and naloxegol , as well as to update section 4.5 of the SmPC of Prezista, Rezolsta and Symtuza on the interaction with dapoxetine, domperidone, fesoterodine, irinotecan, ivabradine, naloxegol and solifenacin based on approved product information. The Package Leaflets are updated accordingly.

In addition, the Worksharing applicant (WSA) took the opportunity to update of section 3 of the SmPC of Symtuza to correct the tablet dimensions (22 mm x 11 mm). Furthermore, the Package Leaflet and Labelling have been updated to reflect information on the in-use shelf-life in line with the approved Symtuza SmPC.

Moreover, as per the revised Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use', the Package Leaflet of Prezista and Rezolsta have been updated to include information on the sodium excipient.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

This variation proposes updates of the Product Information for darunavir (DRV), for darunavir/cobicistat (DRV/COBI) fixed-dose combination (FDC), and for darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) FDC, to provide further guidance for use in combination with other medicinal products:

- Anti-anginals/Antiarrhythmics: ivabradine
- Opioid Antagonist: naloxegol
- Treatment of premature ejaculation: dapoxetine
- Anticancer Agents: irinotecan
- Urinary Antispasmodics: fesoterodine and solifenacin
- Antiemetics: domperidone

No in vivo drug-drug interaction studies have been carried out to support the changes.

Darunavir used in combination with either ritonavir or cobicistat is an inhibitor of CYP3A, CYP2D6, and P-glycoprotein (P-gp). Co-administration of boosted darunavir with medicinal products primarily metabolized by CYP3A and/or transported by P-gp may result in increased systemic exposure to the co- administered medicinal product. Therefore, concomitant treatment with such medicinal products for which elevated plasma concentrations are associated with serious and/or life threatening events is contraindicated (applies to darunavir boosted with either ritonavir or cobicistat).

Based on these sections 4.3 and 4.5 of the SmPC of the Product Information for darunavir, darunavir/cobicistat fixed-dose combination, and darunavir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose combination have been updated to provide further guidance for use in combination specific with ivabradine, naloxegol, dapoxetine, irinotecan, fesoterodine, solifenacin, and domperidone, each of which are metabolized by CYP3A4 and/or CYP2D6, and/or transported by P-gp. This guidance is aligned with the recommendations in the Product Information of those respective products considering the mechanistic basis of these interactions.

The benefit-risk balance of Prezista, Rezolsta,Symtuza, remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB

Update of section 4.3 of the SmPC of Prezista, Rezolsta and Symtuza to contra-indicate the concomitant use with dapoxetine , domperidone, ivabradine and naloxegol , as well as to update section 4.5 of the SmPC of Prezista, Rezolsta and Symtuza on the interaction with dapoxetine, domperidone, fesoterodine, irinotecan, ivabradine, naloxegol and solifenacin based on approved product information. The Package Leaflets are updated accordingly.

In addition, the Worksharing applicant (WSA) took the opportunity to update of section 3 of the SmPC of Symtuza to correct the tablet dimensions (22 mm x 11 mm). Furthermore, the Package Leaflet and Labelling have been updated to reflect information on the in-use shelf-life in line with the approved Symtuza SmPC.

Moreover, as per the revised Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use', the Package Leaflets of Prezista, Rezolsta and Symtuza have been updated to include information on the sodium excipient. Furthermore, the WSA took the opportunity to update the list of local representatives in the Package Leaflets of Prezista and Rezolsta in line with the latest QRD template version 10.0.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to annexes I and IIIB are recommended for Prezista and Rezolsta. In addition, amendments to annexes I, IIIA and IIIB are recommended for Symtuza.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Darunavir used in combination with either ritonavir or cobicistat is an inhibitor of CYP3A, CYP2D6, and P-glycoprotein (P-gp). Co-administration of boosted darunavir with medicinal products primarily metabolized by CYP3A and/or transported by P-gp may result in increased systemic exposure to the co-administered medicinal product. Therefore, concomitant treatment with such medicinal products for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated.

Based on these sections 4.3 and 4.5 of the SmPC of the Product Information for darunavir, darunavir/cobicistat fixed-dose combination, and darunavir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose combination have been updated to provide further guidance for use in combination with ivabradine, naloxegol, dapoxetine, irinotecan, fesoterodine, solifenacin, and domperidone, each of which are metabolized by CYP3A4 and/or CYP2D6, and/or transported by P-gp. This guidance is aligned with the recommendations in the Product Information of those respective products considering the mechanistic basis of these interactions.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

The MAH proposes updates of the Product Information for darunavir (DRV), for darunavir/cobicistat (DRV/COBI) fixed-dose combination (FDC), and for darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) FDC, to provide further guidance for use in combination with other medicinal products:

- Anti-anginals/Antiarrhythmics: ivabradine
- Opioid Antagonist: naloxegol
- Treatment of premature ejaculation: dapoxetine
- Anticancer Agents: irinotecan
- Urinary Antispasmodics: fesoterodine and solifenacin
- Antiemetics: domperidone

No in vivo drug-drug interaction studies have been carried out to support the changes.

DRV when used in combination with low-dose ritonavir (rtv) or COBI is an inhibitor of cytochrome P450 (CYP) 3A, CYP2D6, and P-glycoprotein (P-gp). Co-administration of boosted DRV with medicinal products primarily metabolized by CYP3A and/or transported by P-gp may result in increased systemic exposure to such medicinal products. DRV, DRV/COBI FDC, and D/C/F/TAF FDC must not be combined with medicinal products that are highly dependent on CYP3A for clearance and for which increased plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index).

In the sections below, guidance is provided for co-administration of boosted DRV (as DRV [in combination with rtv or COBI], DRV/COBI FDC, or D/C/F/TAF FDC) specific with ivabradine, naloxegol, dapoxetine, irinotecan, fesoterodine, solifenacin, and domperidone, each of which are metabolized by CYP3A4 and/or CYP2D6, and/or transported by P-gp. This guidance is aligned with the recommendations in the Product Information of those respective products.

6. Clinical Safety aspects

6.1. Ivabradine

Ivabradine is metabolized by CYP3A4. Increased plasma concentrations of ivabradine may be associated with the risk of excessive bradycardia. The Product Information of ivabradine contraindicates co-administration of potent CYP3A4 inhibitors such as human immunodeficiency virus (HIV) protease inhibitors:

SPC Procoralan (ivabradine):

"Section 4.3. Contraindications

….

Combination with strong cytochrome P450 3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin per os, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone (see sections 4.5 and 5.2)

….".

Therefore, co-administration of boosted DRV (in combination with rtv or COBI), DRV/COBI FDC, or D/C/F/TAF FDC with ivabradine is added as a contraindication in the respective updated Product Informations of DRV (Prezista), DRV/COBI FDC (Rezolsta), and D/C/F/TAF FDC (Symtuza) (see below).

Prezista:

SmPC 4.3 Contraindications

….

Darunavir boosted with either ritonavir or cobicistat inhibits the elimination of active substances that are highly dependent on CYP3A for clearance, which results in increased exposure to the co administered medicinal product. Therefore, concomitant treatment with such medicinal products for which elevated plasma concentrations are associated with serious and/or life threatening events is contraindicated (applies to darunavir boosted with either ritonavir or cobicistat). These active substances include e.g.:

- alfuzosin
- amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine
- astemizole, terfenadine

…….

SmPC 4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**
…..		
ANTIANGINA/ANTIARRHYTHMIC		
Disopyramide Flecainide Lidocaine (systemic) Mexiletine Propafenone Amiodarone Bepridil Dronedarone Ivabradine Quinidine Ranolazine	Not studied. Boosted PREZISTA is expected to increase these antiarrhythmic plasma concentrations. (CYP3A and/or CYP2D6 inhibition)	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for these antiarrhythmics when co-administered with boosted PREZISTA. Co-administration of b~~B~~oosted PREZISTA and amiodarone, bepridil, dronedarone, ivabradine, quinidine, or ranolazine is contraindicated (see section 4.3).
……		

Rezolsta:

SmPC 4.3 Contraindications

….

Co administration with the following medicinal products due to the potential for serious and/or life threatening adverse reactions (see section 4.5):

- alfuzosin
- amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine

…

SmPC 4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
…		
ANTIANGINA/ANTIARRHYTHMIC		
Disopyramide Flecainide Lidocaine (systemic) Mexiletine Propafenone Amiodarone Bepridil Dronedarone Ivabradine Quinidine Ranolazine	Based on theoretical considerations REZOLSTA is expected to increase these antiarrhythmic plasma concentrations. (CYP3A and/or CYP2D6 inhibition)	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for these antiarrhythmics when co-administered with REZOLSTA. Co-administration of amiodarone, bepridil, dronedarone, ivabradine, quinidine, or ranolazine and REZOLSTA is contraindicated (see section 4.3).
….		

Symtuza:

SmPC 4.3 Contraindications

…

Co administration with the following medicinal products due to the potential for serious and/or life threatening adverse reactions (see section 4.5):

- alfuzosin
- amiodarone, dronedarone, ivabradine, quinidine, ranolazine

….

SmPC 4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
…		
ANTIANGINA/ANTIARRHYTHMIC		
Disopyramide Flecainide Mexiletine Propafenone Lidocaine (systemic) Amiodarone Dronedarone Ivabradine Quinidine Ranolazine	Based on theoretical considerations DRV/COBI is expected to increase these antiarrhythmic plasma concentrations. (CYP3A inhibition)	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for these antiarrhythmics when co-administered with Symtuza. Co-administration of amiodarone, dronedarone, ivabradine, quinidine, or ranolazine and Symtuza is contraindicated (see section 4.3).
….		

Prezista / Rezolsta / Symtuza PL section 2:

Do not combine PREZISTA/REZOLSTA/Symtuza with any of the following medicines

…

Amiodarone, bepridil, dronedarone, ivabradine, quinidine, ranolazine	to treat certain heart disorders e.g. abnormal heart beat

Assessor's conclusion:

Considering the mechanistic basis of this interaction with ivabradine, the update of the SmPCs and PLs of Prezista, Rezolsta and Symtuza is acceptable.

6.2. Naloxegol

Naloxegol is metabolized primarily by the CYP3A enzyme system and is a substrate of the P-gp transporter. Co-administration of naloxegol with medicinal products that inhibit CYP3A4 and P-gp may increase the concentration of naloxegol. The Product Information of naloxegol contraindicates co-administration of potent CYP3A4 inhibitors:

SPC Moventig (naloxegol):

Section 4.3. Contraindications

….

Strong CYP3A4 inhibitors

Concomitant use with strong CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole, itraconazole or telithromycin; protease inhibitors such as ritonavir, indinavir or saquinavir; grapefruit juice when consumed in large quantities), see section 4.5…..

Therefore, co-administration of boosted DRV (in combination with rtv or COBI), DRV/COBI FDC, or D/C/F/TAF FDC with naloxegol is added as a contraindication in the respective updated Product Informations of DRV (Prezista), DRV/COBI FDC (Rezolsta), and D/C/F/TAF FDC (Symtuza) (see below).

Prezista:

SmPC 4.3 Contraindications

….

Darunavir boosted with either ritonavir or cobicistat inhibits the elimination of active substances that are highly dependent on CYP3A for clearance, which results in increased exposure to the co administered medicinal product. Therefore, concomitant treatment with such medicinal products for which elevated plasma concentrations are associated with serious and/or life threatening events is contraindicated (applies to darunavir boosted with either ritonavir or cobicistat). These active substances include e.g.:

….

- cisapride
- dapoxetine
- domperidone
- naloxegol
- lurasidone, pimozide, quetiapine, sertindole (see section 4.5)…….

SmPC 4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**
…..		
OPIOID ANTAGONIST		
Naloxegol	Not studied.	Co-administration of boosted PREZISTA and naloxegol is contraindicated.
….		

Rezolsta:

SmPC 4.3 Contraindications

….

Co administration with the following medicinal products due to the potential for serious and/or life threatening adverse reactions (see section 4.5):

…..

- cisapride
- dapoxetine
- domperidone
- naloxegol
- lurasidone, pimozide, quetiapine, sertindole (see section 4.5)…

SmPC 4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
…		
OPIOID ANTAGONIST		
Naloxegol	Not studied.	Co administration of REZOLSTA and naloxegol is contraindicated.
….		

Symtuza:

SmPC 4.3 Contraindications

…

Co administration with the following medicinal products due to the potential for serious and/or life threatening adverse reactions (see section 4.5):

……

- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- dapoxetine
- domperidone
- naloxegol
- pimozide, quetiapine, sertindole, lurasidone (see section 4.5)….

SmPC 4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
…		
OPIOID ANTAGONIST		
Naloxegol	Not studied.	Co administration of Symtuza and naloxegol is contraindicated.
….		

Prezista / Rezolsta / Symtuza PL section 2:

Do not combine PREZISTA/REZOLSTA/Symtuza with any of the following medicines

…

Naloxegol	to treat opioid induced constipation

Assessor's conclusion:

Considering the mechanistic basis of this interaction with naloxegol, the update of the SmPCs and PLs of Prezista, Rezolsta and Symtuza is acceptable.

6.3. Dapoxetine

Dapoxetine is metabolized primarily by CYP2D6, CYP3A4, and flavin monooxygenase 1 (FMO1). Co-administration of dapoxetine with strong CYP3A4 inhibitors may lead to an increased dapoxetine plasma concentration, especially in a part of the population which lack a functional CYP2D6 enzyme, ie, CYP2D6 poor metabolizers, or in combination with potent inhibitors of CYP2D6. The Product Information of dapoxetine contraindicates co-administration of potent CYP3A4 inhibitors:

SPC Priligy (dapozetine):

"Section 4.3. Contraindications

….

Concomitant treatment of potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, saquinavir, telithromycin, nefazadone, nelfinavir, atazanavir, etc. (see section 4.5). ….".

Therefore, co-administration of boosted DRV (in combination with rtv or COBI), DRV/COBI FDC, or D/C/F/TAF FDC with dapoxetine is added as a contraindication in the respective updated Product Informations of DRV (Prezista), DRV/COBI FDC (Rezolsta), and D/C/F/TAF FDC (Symtuza) (see below).

Prezista:

SmPC 4.3 Contraindications

….

Darunavir boosted with either ritonavir or cobicistat inhibits the elimination of active substances that are highly dependent on CYP3A for clearance, which results in increased exposure to the co administered medicinal product. Therefore, concomitant treatment with such medicinal products for which elevated plasma concentrations are associated with serious and/or life threatening events is contraindicated (applies to darunavir boosted with either ritonavir or cobicistat). These active substances include e.g.:

…….

- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- dapoxetine
- domperidone

……

SmPC 4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**
…..		
TREATMENT FOR PREMATURE EJACULATION		
Dapoxetine	Not studied.	Co-administration of boosted PREZISTA with dapoxetine is contraindicated.

……		

Rezolsta:

SmPC 4.3 Contraindications

….

Co administration with the following medicinal products due to the potential for serious and/or life threatening adverse reactions (see section 4.5):

…..

- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- dapoxetine
- domperidone

…..

SmPC 4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
…		
TREATMENT FOR PREMATURE EJACULATION		
Dapoxetine	Not studied.	Co-administration of Rezolsta with dapoxetine is contraindicated.
….		

Symtuza:

SmPC 4.3 Contraindications

…

Co administration with the following medicinal products due to the potential for serious and/or life threatening adverse reactions (see section 4.5):

…..

- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- dapoxetine
- domperidone

….

SmPC 4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
…		
ANTIANGINA/ANTIARRHYTHMIC		
Dapoxetine	Not studied.	Co-administration of Symtuza with dapoxetine is contraindicated.
….		

Prezista / Rezolsta / Symtuza PL section 2:

Do not combine PREZISTA/REZOLSTA/Symtuza with any of the following medicines

…

Dapoxetine	to treat premature ejaculation

Assessor's conclusion:

Considering the mechanistic basis of this interaction with dapoxetine, the update of the SmPCs and PLs of Prezista, Rezolsta and Symtuza is acceptable.

6.4. Irinotecan

Irinotecan and its active metabolite SN-38 are metabolized by CYP3A4 and uridine diphosphateglucuronosyl transferase 1A1 (UGT1A1), respectively. Co-administration of irinotecan with medicinal products that inhibit CYP3A4 may increase the systemic exposure to irinotecan and its active metabolite SN-38.3. The Product Information of irinotecan recommends not to co-administer potent CYP3A4 inhibitors unless there are no therapeutic alternatives:

SPC Onivyde (irinotecan sucrosofate salt in a pegylated liposomal formulation):

"Section 4.4. Special warnings and precautions for use

…..

Interactions with strong CYP3A4 inhibitors or strong UGT1A1 inhibitors:

ONIVYDE should not be administered with strong CYP3A4-enzyme inhibitors (e.g. grapefruit juice, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole). Strong CYP3A4 inhibitors should be discontinued at least 1 week prior to starting ONIVYDE therapy.

…..

Section 4.5. Interaction with other medicinal products and other forms of interaction

….

Strong CYP3A4 inhibitors and UGT1A1 inhibitors:

Patients receiving concomitant non-liposomal irinotecan and ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased SN-38 exposure by 109%. Therefore, co-administration of ONIVYDE with other inhibitors of CYP3A4 (e.g. grapefruit juice, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) may increase systemic exposure of ONIVYDE.

…."

Therefore, co-administration of boosted DRV (in combination with rtv or COBI), DRV/COBI FDC, or D/C/F/TAF FDC with irinotecan is not recommended in the respective updated Product Informations of DRV (Prezista), DRV/COBI FDC (Rezolsta), and D/C/F/TAF FDC (Symtuza) (see below).

Prezista:

SmPC 4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**
…..		
ANTINEOPLASTICS		
Dasatinib Nilotinib Vinblastine Vincristine Everolimus Irinotecan	Not studied. Boosted PREZISTA is expected to increase these antineoplastic plasma concentrations. (CYP3A inhibition)	Concentrations of these medicinal products may be increased when co administered with boosted PREZISTA resulting in the potential for increased adverse events usually associated with these agents. Caution should be exercised when combining one of these antineoplastic agents with boosted PREZISTA. Concominant use of everolimus or irinotecan and boosted PREZISTA is not recommended.
……		
IMMUNOSUPPRESSANTS		
Ciclosporin Sirolimus Tacrolimus Everolimus ~~Irinotecan~~	Not studied. Exposure to these immunosuppressants will be increased when co-administered with boosted PREZISTA. (CYP3A inhibition)	Therapeutic drug monitoring of the immunosuppressive agent must be done when co-administration occurs. Concomitant use of everolimus ~~or irinotecan~~ and boosted PREZISTA is not recommended.
….		

Rezolsta:

SmPC 4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
...		
ANTI NEOPLASTICS		
Dasatinib Nilotinib Vinblastine Vincristine Everolimus Irinotecan	Based on theoretical considerations Rezolsta is expected to increase these anti neoplastic plasma concentrations. (CYP3A inhibition)	Concentrations of these medicinal products may be increased when co administered with REZOLSTA resulting in the potential for increased adverse events usually associated with these medicinal products. Caution should be exercised when combining one of these anti neoplastic agents with Rezolsta. Concomitant use of everolimus or irinotecan and Rezolsta is not recommended
.....		
IMMUNOSUPPRESSANTS		
Ciclosporin Sirolimus Tacrolimus Everolimus ~~Irinotecan~~	Not studied. Exposure to these immunosuppressants will be increased when co-administered with boosted PREZISTA. (CYP3A inhibition)	Therapeutic drug monitoring of the immunosuppressive agent must be done when co-administration occurs. Concomitant use of everolimus ~~or irinotecan~~ and boosted PREZISTA is not recommended.
....		

Symtuza:

4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
…		
ANTI NEOPLASTICS		
Dasatinib Nilotinib Vinblastine Vincristine Everolimus Irinotecan	Based on theoretical considerations DRV/COBI is expected to increase these anti neoplastic plasma concentrations. (CYP3A inhibition)	Concentrations of these medicinal products may be increased when co administered with Symtuza resulting in the potential for increased adverse events usually associated with these medicinal products. Caution should be exercised when combining one of these anti neoplastic agents with Symtuza. Concomitant use of everolimus or irinotecan and Symtuza is not recommended.
….		
IMMUNOSUPPRESSANTS		
Ciclosporin Sirolimus Tacrolimus Everolimus ~~Irinotecan~~	Based on theoretical considerations DRV/COBI is expected to increase these immunosuppressant plasma concentrations. (CYP3A inhibition) Co administration of ciclosporin is expected to increase plasma concentrations of tenofovir alafenamide. (P gp inhibition)	Therapeutic drug monitoring of the immunosuppressive agent must be done when co administration with Symtuza occurs. Concomitant use of everolimus ~~or irinotecan~~ and Symtuza is not recommended.

Prezista / Rezolsta / Symtuza PL section 2:

Other medicines and PREZISTA/REZOLSTA/Symtuza

…

The effects of other medicines might be influenced if you take PREZISTA/REZOLSTA/Symtuza. Tell your doctor if you take:

…

- *Dasatinib, everolimus, irinotecan, nilotinib, vinblastine, vincristine* (to treat cancer)

Assessor's conclusion:

Considering the mechanistic basis of this interaction, the update of the SmPCs regarding irinotecan being an anti-neoplastic is acceptable. However, the indication as immunosuppressant is not understood. The MAH should support/clarify this.

MAH response (13 March 2019):

The Applicant agrees that in EU, irinotecan (ONIVYDE) is indicated only as antineoplastic. No supporting data for the indication as immunosuppressant can be provided. The product information of PREZISTA, REZOLSTA and Symtuza have been updated to remove the DDI information for irinotecan as immunosuppressant.

Assessor's conclusion:

DDI information for irinotecan as immunosuppressant has been removed in the SmPCs (section 4.5) of PREZISTA, REZOLSTA and Symtuza. Agreed.

6.5. Fesoterodine and solifenacin

Fesoterodine:

Co-administration of a potent CYP3A4 inhibitor such as ketoconazole with fesoterodine led to a more than 2-fold increase of the plasma concentration of the active metabolite of fesoterodine. The Product Information of fesoterodine indicates that the dose of fesoterodine should be restricted to 4 mg when co-administrated with a potent CYP3A4 or CYP2D6 inhibitor:

SPC Toviaz (fesoterodine):

" 4.4 Special warnings and precautions for use

….

Caution should be exercised when prescribing or uptitrating fesoterodine to patients in whom an increased exposure to the active metabolite (see section 5.1) is expected:

- Hepatic impairment (see sections 4.2, 4.3 and 5.2)
- Renal impairment (see sections 4.2, 4.3 and 5.2)
- Concomitant administration of potent or moderate CYP3A4 inhibitors (see sections 4.2 and 4.5)
- Concomitant administration of a potent CYP2D6 inhibitor (see sections 4.5 and 5.2).

…..

4.5 Interaction with other medicinal products and other forms of interaction

Potent CYP3A4 inhibitors

Following inhibition of CYP3A4 by co-administration of ketoconazole 200 mg twice daily, Cmax and AUC of the active metabolite of fesoterodine increased 2.0 and 2.3-fold in CYP2D6 extensive metabolisers and 2.1 and 2.5-fold in CYP2D6 poor metabolisers, respectively. Therefore, the maximum dose of fesoterodine should be restricted to 4 mg when used concomitantly with potent CYP3A4 inhibitors (e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir (and all ritonavir boosted PI-regimens), saquinavir and telithromycin (see sections 4.2 and 4.4)).

…."

Therefore, caution and clinical monitoring for fesoterodine adverse reactions and a potential dose reduction of fesoterodine is recommended for co-administration of boosted DRV (in combination with rtv or COBI), DRV/COBI FDC, or D/C/F/TAF FDC with fesoterodine in the respective updated Product Informations of DRV (Prezista), DRV/COBI FDC (Rezolsta), and D/C/F/TAF FDC (Symtuza) (see below).

Solifenacin:

Solifenacin is metabolized primarily by CYP3A4. Co-administration of solifenacin with medicinal products that inhibit CYP3A4 may increase the concentration of solifenacin. The Product Information of solifenacin indicates that the dose of solifenacin should be restricted to 5 mg when co-administrated with a potent CYP3A4 inhibitor:

SPC Vesicare (solifenacin):

"4.4 Special warnings and precautions for use

…
- concomitant use of a potent CYP3A4 inhibitor, e.g. ketoconazole (see 4.2 and 4.5).
….

4.5 Interaction with other medicinal products and other forms of interaction

….

Effect of other medicinal products on the pharmacokinetics of solifenacin:

…

Solifenacin is metabolised by CYP3A4. Simultaneous administration of ketoconazole (200 mg/day), a potent CYP3A4 inhibitor, resulted in a two-fold increase of the AUC of solifenacin, while ketoconazole at a dose of 400 mg/day resulted in a three-fold increase of the AUC of solifenacin. Therefore, the maximum dose of Vesicare should be restricted to 5 mg, when used simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4 inhibitors (e.g. ritonavir, nelfinavir, itraconazole) (see Section 4.2).

……"

Therefore, caution and clinical monitoring for solifenacin adverse reactions and a potential dose reduction of solifenacin is recommended for co-administration of boosted DRV (in combination with rtv or COBI), DRV/COBI FDC, or D/C/F/TAF FDC with solifenacin in the respective updated Product Informations of DRV (Prezista), DRV/COBI FDC (Rezolsta), and D/C/F/TAF FDC (Symtuza) (see below).

Prezista:

SmPC 4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**
…..		
UROLOGICAL DRUGS		
Fesoterodine Solifenacin	Not studied.	Use with caution. Monitor for fesoterodine or solifenacin adverse reactions, dose reduction of fesoterodine or solifenacin may be necessary.
……		

Rezolsta:

SmPC 4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
…		
UROLOGICAL DRUGS		
Fesoterodine Solifenacin	Not studied.	Use with caution. Monitor for fesoterodine or solifenacin adverse reactions, dose reduction of fesoterodine or solifenacin may be necessary.
….		

Symtuza:

SmPC 4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
…		
UROLOGICAL DRUGS		
Fesoterodine Solifenacin	Not studied.	Use with caution. Monitor for fesoterodine or solifenacin adverse reactions, dose reduction of fesoterodine or solifenacin may be necessary.
….		

Prezista / Rezolsta / Symtuza PL section 2:

Other medicines and PREZISTA/REZOLSTA/Symtuza

…

The effects of other medicines might be influenced if you take PREZISTA/REZOLSTA/Symtuza. Tell your doctor if you take:

…

- *Fesoterodine, solifenacin* (to treat urologic disorders).

Assessor's conclusion:

Considering the mechanistic basis of this interaction with fesoterodine and solifenacin, the update of the SmPCs and PLs is acceptable.

6.6. Domperidone

The main metabolic pathway of domperidone is through CYP3A4. Co-administration of domperidone with medicinal products that inhibit CYP3A4 may increase the systemic exposure to domperidone. Preclinical data show that inhibition of the CYP3A4 pathway can result in a 3-fold increase in free plasma concentrations of domperidone. The Product Information of domperidone contraindicates co-administration of potent CYP3A4 inhibitors:

SPC Motilium (domperidone):

" 4.4 Contraindications

….

co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects) (see section 4.5)

….".

4.5 Interaction with other medicinal products and other forms of interaction

The main metabolic pathway of domperidone is through CYP3A4. In vitro data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone.

Increased risk of occurrence of QT-interval prolongation, due to pharmacodynamic and/or pharmacokinetic interactions.

Concomitant use of the following substances is contraindicated

….

Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e.:

• protease inhibitors

• systemic azole antifungals

• some macrolides (erythromycin, clarithromycin, telithromycin)

(see section 4.3).

……".

Therefore, co-administration of boosted DRV (in combination with rtv or COBI), DRV/COBI FDC, or D/C/F/TAF FDC with domperidone is added as a contraindication in the respective updated Product Informations of DRV (Prezista), DRV/COBI FDC (Rezolsta), and D/C/F/TAF FDC (Symtuza) (see below).

Prezista:

SmPC 4.3 Contraindications

….

Darunavir boosted with either ritonavir or cobicistat inhibits the elimination of active substances that are highly dependent on CYP3A for clearance, which results in increased exposure to the co administered medicinal product. Therefore, concomitant treatment with such medicinal products for which elevated plasma concentrations are associated with serious and/or life threatening events is contraindicated (applies to darunavir boosted with either ritonavir or cobicistat). These active substances include e.g.:

…….

- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- dapoxetine
- domperidone

……

SmPC 4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**
…..		
ANTIEMETICS		
Domperidone	Not studied.	Co-administration of domperidone with boosted Prezista is contraindicated.
……		

Rezolsta:

SmPC 4.3 Contraindications

….

Co administration with the following medicinal products due to the potential for serious and/or life threatening adverse reactions (see section 4.5):

…..

- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- dapoxetine
- domperidone

…..

SmPC 4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
…		
ANTIEMETICS		
Domperidone	Not studied.	Co-administration of Rezolsta with domperidone is contraindicated.
….		

Symtuza:

SmPC 4.3 Contraindications

…

Co administration with the following medicinal products due to the potential for serious and/or life threatening adverse reactions (see section 4.5):

…..

- ergot derivatives (e.g. dihydroergotamine, ergometrine, ergotamine, methylergonovine)
- dapoxetine
- domperidone

….

SmPC 4.5 Interaction with other medicinal products and other forms of interaction

INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
…		
ANTIEMETICS		
Domperidone	Not studied.	Co-administration of Symtuza with domperidone is contraindicated.
….		

Prezista / Rezolsta / Symtuza PL section 2:

Do not combine PREZISTA/REZOLSTA/Symtuza with any of the following medicines

…

Domperidone	to treat nausea and vomiting

Assessor's conclusion:

Considering the mechanistic basis of this interaction with domperidone, the update of the SmPCs and PLs of Prezista, Rezolsta and Symtuza is acceptable.

7. Changes to the Product Information

As a result of this variation, sections 4.3 and 4.5 of the SmPC of Prezista, Rezolsta and Symtuza are being updated (see section 6 of this assessment report). The Package Leaflet (PL) is updated accordingly.

Next to these updated the following general updates have been applied:

Prezista:

"4.5 Interaction with other medicinal products and other forms of interaction

……

Interaction table

……

Interactions between darunavir/ritonavir and antiretroviral and non antiretroviral medicinal products are listed in the table below ~~(not determined as "ND")~~. The direction of the arrow for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within (↔), below (↓) or above (↑) the 80 125% range (not determined as "ND").

In the table below the specific pharmacokinetic enhancer is specified when recommendations differ. When the recommendation is the same for PREZISTA when co administered with a low dose ritonavir or cobicistat, the term "boosted PREZISTA" is used.

The below list of examples of drug drug interactions is not comprehensive and therefore the label of each drug that is co-administered with PREZISTA should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co administration.

…."

Rezolsta:

"4.5 Interaction with other medicinal products and other forms of interaction

……

Interaction table

……

The below list of examples of drug drug interactions is not comprehensive and therefore the label of each drug that is co-administered with REZOLSTA should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co administration.

…."

Symtuza:

"4.5 Interaction with other medicinal products and other forms of interaction

……

Interaction table

……

The below list of examples of drug drug interactions is not comprehensive and therefore the label of each drug that is co-administered with REZOLSTA should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co administration.

…."

These general updates are agreed.

In addition, the Worksharing applicant (WSA) took the opportunity to update of section 3 of the SmPC of Symtuza to correct the tablet dimensions (22 mm x 11 mm). Furthermore, the Package Leaflet and Labelling have been updated to reflect information on the in-use shelf-life in line with the approved Symtuza SmPC.

Moreover, as per the revised Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use', the Package Leaflet of Prezista, Rezolsta and Symtuza have been updated to include information on the sodium excipient.

Finally, in the Package Leaflet of Prezista and Rezolsta the Local Representative Addresses have been removed, in line with current EU guidelines and QRD. Local Representative names, telephone numbers and email addresses, where applicable, are still retained.

The proposed changes are agreed.

8. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 28th March 2019.

Reminders to the MAH

1. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the *Harmonised Technical Guidance for eCTD Submissions in the EU*.

2. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.