# PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

## Summary of Risk Management Plan for REZOLSTA

This is a summary of the risk management plan (RMP) for REZOLSTA. The RMP details important risks of REZOLSTA, how these risks can be minimised, and how more information will be obtained about REZOLSTA's risks and uncertainties (missing information).

REZOLSTA's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how REZOLSTA should be used.

This summary of the RMP for REZOLSTA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report.

Important new concerns or changes to the current ones will be included in updates of REZOLSTA's RMP.

## I. The Medicine and What it is Used For

REZOLSTA is authorised in combination with other antiretroviral (ARV) medicinal products for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults aged 18 years or older (see SmPC for the full indication). REZOLSTA contains darunavir/cobicistat (DRV/COBI) as the active substance and is given as an oral tablet (DRV 800 mg, COBI 150 mg).

Further information about the evaluation of REZOLSTA's benefits can be found in REZOLSTA's European Public Assessment Report, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002819/human_med_001817.jsp&mid=WC0b01ac058001d124

## II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of REZOLSTA, together with measures to minimise such risks and the proposed studies for learning more about REZOLSTA's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Benefit-Risk Evaluation Report (PBRER)/Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of REZOLSTA is not yet available, it is listed under 'missing information' below.

## II.A. List of Important Risks and Missing Information

Important risks of REZOLSTA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of REZOLSTA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

| **List of Important Risks and Missing Information** | |
|---|---|
| Important identified risks | Severe skin reactions<br>Hepatotoxicity<br>Hyperglycaemia<br>Lipid abnormalities<br>Immune reconstitution inflammatory syndrome<br>Development of drug resistance<br>Drug-drug interactions |
| Important potential risks | Coronary artery events<br>Off-label use in the paediatric population and in ARV treatment-experienced patients with >100,000 copies/mL HIV-1 RNA |
| Missing information | Elderly (65 years and above)<br>Children <18 years of age<br>Long-term safety of DRV/COBI in adults<br>Subjects with severe hepatic impairment (Child-Pugh C)<br>Subjects with renal impairment.<br>Subjects coinfected with HIV and HBV and/or HCV<br>Safety in patients with cardiac conduction disorders |

## II.B. Summary of Important Risks

| **Important Identified Risk: Severe skin reactions** | |
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| Evidence for linking the risk to the medicine | Severe skin reactions and rash in association with DRV boosted with ritonavir (rtv) or COBI have been reported in previously completed clinical trials. Additionally, no cases of erythema multiforme, Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms, acute generalised exanthamatous pustulosis or toxic epidermal necrolysis were seen in clinical trials with DRV/COBI 800/150 mg and 1 and 2 case(s) of SJS were seen in clinical trials with DRV/rtv 800/100 mg once daily, and DRV/rtv 600/100 mg twice daily, respectively. These events are described in the current prescribing information for DRV/COBI. |
| Risk factors and risk groups | • Rash occurred more commonly in treatment-experienced patients receiving regimens containing DRV/rtv + raltegravir compared to patients receiving DRV/rtv without raltegravir or raltegravir without DRV/rtv.<br>• DRV contains a sulphonamide moiety. There may be an increased incidence of rash in patients with prior sulphonamide allergy.<br>• Trial GS-US-216-0130 showed no apparent relationship between the DRV exposure and the occurrence of rash-related adverse events. |
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC Section 4.4<br>• SmPC Section 4.8<br>• PL Section 2<br>• PL Section 4<br>• Advice on the use of REZOLSTA in patients developing severe skin reactions is provided in SmPC Section 4.4<br>• Warning on the use of REZOLSTA in patients with a known sulphonamide allergy is provided in SmPC Section 4.4 and PL Section 2<br>• Advice for patients who develop rash is provided in PL Section 4<br>• Legal status: restricted medical prescription<br>Additional risk minimisation measures:<br>• None |

| **Important Identified Risk: Hepatotoxicity** | |
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| Evidence for linking the risk to the medicine | Adverse reactions related to the liver (such as abnormal liver tests) and hepatitis in association with DRV boosted with rtv or COBI have been reported in previously completed clinical trials. These adverse reactions occurred more often in patients with both HIV-1 infection and hepatitis B virus (HBV) or hepatitis C virus (HCV) than in patients with only HIV-1 infection. These events are described in the current prescribing information for DRV/COBI. |
| Risk factors and risk groups | Liver toxicity has been associated with antiretroviral therapy (ART), including the protease inhibitor (PI) class and has been seen to be more common in subjects coinfected with HBV or HCV. Didanosine, stavudine, nevirapine, efavirenz and tenofovir have been described to be hepatotoxic. |
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC Section 4.2<br>• SmPC Section 4.3<br>• SmPC Section 4.4<br>• SmPC Section 4.8<br>• SmPC Section 5.2<br>• PL Section 2<br>• PL Section 4<br>• Recommendation for liver function monitoring is provided in SmPC Section 4.4<br>• Advice on the use of REZOLSTA in patients with evidence of new or worsening of liver dysfunction is provided in SmPC Section 4.4<br>• Warning for patients with liver problems is provided in PL Section 2<br>• Instructions on how to detect signs and symptoms of liver problems are provided in PL Section 4<br>• Legal status: restricted medical prescription<br>Additional risk minimisation measures:<br>• None |

| **Important Identified Risk: Hyperglycaemia** | |
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| Evidence for linking the risk to the medicine | Hyperglycaemia has been reported in patients receiving ART, including PIs. Hyperglycaemia in association with DRV boosted with rtv or COBI has also been reported in previously completed clinical trials and is described in the current prescribing information for DRV/COBI. |
| Risk factors and risk groups | Hyperglycaemia has been reported in patients receiving ART, including PIs. |
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC Section 4.4<br>• SmPC Section 4.8<br>• PL Section 2<br>• PL Section 4<br>• Recommendation for glucose monitoring is provided in SmPC Section 4.4<br>• Warning for patients with diabetes is provided in PL Section 2<br>• Legal status: restricted medical prescription<br>Additional risk minimisation measures:<br>• None |

| **Important Identified Risk: Lipid abnormalities** | |
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| Evidence for linking the risk to the medicine | Blood lipid-related adverse reactions including hypertriglyceridaemia, hypercholesterolaemia, and hyperlipidaemia in association with DRV boosted with rtv or COBI have been reported in previously completed clinical trials and are described in the current prescribing information for DRV/COBI. |
| Risk factors and risk groups | None have been specifically studied in the clinical trial population. |
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC Section 4.4<br>• SmPC Section 4.8<br>• PL Section 4<br>• Recommendation for blood lipid monitoring is provided in SmPC Section 4.4<br>• Legal status: restricted medical prescription<br>Additional risk minimisation measures:<br>• None |

| **Important Identified Risk: Immune reconstitution inflammatory syndrome** | |
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| Evidence for linking the risk to the medicine | Immune reconstitution inflammatory syndrome (IRIS) in association with DRV boosted with rtv or COBI has been reported in previously completed clinical trials and is described in the current prescribing information for DRV/COBI. |
| Risk factors and risk groups | None have been specifically studied in the clinical trial population. According to a review, the most common causes of IRIS are mostly mycobacterial, including tuberculosis. Very low CD4+ T-cell counts have been cited as risk factors for IRIS. |
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC Section 4.4<br>• SmPC Section 4.8<br>• PL Section 2<br>• PL Section 4<br>• Recommendation on evaluation and treatment in case of inflammatory symptoms is provided in SmPC Section 4.4<br>• Warning for patients with symptoms of infection or other symptoms of autoimmune disorders is provided in PL Section 2<br>• Legal status: restricted medical prescription<br>Additional risk minimisation measures:<br>• None |

| **Important Identified Risk: Development of drug resistance** | |
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| Evidence for linking the risk to the medicine | Development of DRV drug resistance has been reported in previously completed clinical trials investigating DRV/rtv 600/100 mg twice daily in ART-experienced patients and was therefore included as an important identified risk for REZOLSTA as well.<br>Very low rates of developing resistant HIV-1 have been observed in clinical trials investigating ART-naïve patients and ART-experienced patients without DRV resistance-associated mutations and who were treated with REZOLSTA (no DRV phenotypic resistance observed in any subject). |
| Risk factors and risk groups | Patients who have been maintained on a failing PI-containing regimen for a long period of time are less likely to respond to a therapy with REZOLSTA. |
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC Section 4.1<br>• SmPC Section 4.4 |

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| | • Recommendation to use genotypic testing to guide the use of REZOLSTA is provided in SmPC Section 4.1<br>• Recommendation to perform HIV genotypic testing for ART-experienced patients is provided in SmPC Section 4.2<br>• Recommendation to assess virologic response and perform resistance testing is provided in SmPC Section 4.4<br>• Legal status: restricted medical prescription<br>Additional risk minimisation measures:<br>• None |

| **Important Identified Risk: Drug-drug interactions** | |
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| Evidence for linking the risk to the medicine | Interactions between REZOLSTA and other drugs may occur. Current evidence is based on (Phase 1) clinical trials investigating drug-drug interactions and on theoretical considerations.<br>Coadministration of REZOLSTA, together with medicines which are broken down by the same mechanisms (enzymes), may result in increased blood levels of such medicines. This could increase or prolong their therapeutic effect and side effects, which may be serious and potentially life-threatening. Some products may increase the breakdown of REZOLSTA, resulting in loss of efficacy.<br>Clear recommendations on drugs that are contraindicated or that may interact, and the actions to be taken such as dose adjustment based upon drug monitoring trials are described in the current prescribing information for DRV/COBI. |
| Risk factors and risk groups | HIV patients often receive multiple medications, increasing the risk for drug interactions. |
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC Section 4.3<br>• SmPC Section 4.4<br>• SmPC Section 4.5<br>• PL Section 2<br>• Recommendation regarding the concomitant use of REZOLSTA and other medicinal products is provided in SmPC Sections 4.4 and 4.5, and in PL Section 2<br>• Legal status: restricted medical prescription<br>Additional risk minimisation measures:<br>• None |

| **Important Potential Risk: Coronary artery events** | |
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| Evidence for linking the risk to the medicine | Hyperglycaemia and increase in blood lipids such as cholesterol, which are considered identified risks, are risk factors for developing coronary artery events. Coronary artery events in association with DRV boosted with rtv or COBI have been reported in previously completed clinical trials. |
| Risk factors and risk groups | Hyperglycaemia and lipid abnormalities are known risk factors for coronary artery disease. Additional factors that could contribute to developing coronary artery disease in patients with HIV include inflammatory and immunologic factors. The impact of HIV on cardiovascular disease risk is comparable to the traditional risk factors that include hypertension, diabetes, and hyperlipidaemia. |
| Risk minimisation measures | Routine risk minimisation measures:<br>• Legal status: restricted medical prescription<br>Additional risk minimisation measures:<br>• None |

| **Important Potential Risk: Off-label use in the paediatric population and in ARV treatment-experienced patients with >100,000 copies/mL HIV-1 RNA** | |
|---|---|
| Evidence for linking the risk to the medicine | Use of REZOLSTA in HIV-infected patients for whom the drug is not approved may occur, including use in children and adolescents, and in adults who have received anti-HIV drugs before but who have high levels of the virus in their blood at the start of treatment. Use of REZOLSTA in these patients would not necessarily lead to side effects or lack of efficacy.<br>The safety and efficacy of REZOLSTA in the paediatric population and in ARV treatment-experienced patients with HIV-1 RNA >100,000 copies/mL has not been established in the clinical trial programme. |
| Risk factors and risk groups | Antiretroviral treatment-experienced patients with baseline viral load >100,000 HIV-1 RNA copies/mL and the paediatric population, could be treated off-label with REZOLSTA.<br>*Off-label use in the paediatric population*<br>Factors that influence prescription of ARV drugs in off-label situations in the HIV paediatric population could include limited treatment options, especially for heavily treated children and adolescents with high levels of resistance, and improved tolerability and ease of adherence with less frequent dosing of newer agents.<br>*Off-label use in ARV treatment-experienced patients with >100,000 copies/mL HIV-1 RNA*<br>The risk factors for ARV off-label use in HIV-infected adult patients have not been described. |

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| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC Section 4.1<br>• SmPC Section 4.2<br>• SmPC Section 4.4<br>• Legal status: restricted medical prescription<br>Additional risk minimisation measures:<br>• None |

| **Missing Information: Elderly (65 years and above)** | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC Section 4.2<br>• SmPC Section 4.4<br>• SmPC Section 5.2<br>• PL Section 2<br>• Recommendation regarding the use of REZOLSTA in elderly patients is provided in SmPC Section 4.4 and PL Section 2<br>• Legal status: restricted medical prescription<br>Additional risk minimisation measures:<br>• None |

| **Missing Information: Children <18 years of age** | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC Section 4.2<br>• PL Section 2<br>• PL Section 3<br>• PL Section 5<br>• Warning to keep the product out of the sight and reach of children<br>• Legal status: restricted medical prescription<br>Additional risk minimisation measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• One study in children and adolescents (GS-US-216-0128)<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

| **Missing Information: Long-term safety of DRV/COBI in adults** | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC Section 4.4<br>• SmPC Section 4.8<br>• Legal status: restricted medical prescription<br>Additional risk minimisation measures:<br>• None |

| **Missing Information: Subjects with severe hepatic impairment (Child-Pugh C)** | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC Section 4.2<br>• SmPC Section 4.3<br>• SmPC Section 4.4<br>• SmPC Section 5.2<br>• PL Section 2<br>• PL Section 4<br>• Warning for patients with liver problems is provided in PL Section 2<br>• Instructions on how to detect signs and symptoms of liver problems are provided in PL Section 4<br>• Legal status: restricted medical prescription<br>Additional risk minimisation measures:<br>• None |

| **Missing Information: Subjects with renal impairment** | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC Section 4.2<br>• SmPC Section 4.4<br>• PL Section 2<br>• Recommendation on dose adjustments in patients with renal impairment is provided in SmPC Section 4.2<br>• Advice on the use of REZOLSTA in patients taking coadministered medicinal products with effect on the estimated creatinine clearance in SmPC Section 4.4<br>• Legal status: restricted medical prescription<br>Additional risk minimisation measures:<br>• None |

| **Missing Information: Subjects coinfected with HIV and HBV and/or HCV** | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC Section 4.4<br>• SmPC Section 4.5<br>• SmPC Section 4.8<br>• SmPC Section 5.2<br>• PL Section 2<br>• PL Section 4<br>• Recommendation for monitoring of liver function is provided in SmPC Section 4.4<br>• Advice for patients experiencing signs and symptoms of liver problems is provided in PL Section 4<br>• Legal status: restricted medical prescription<br>Additional risk minimisation measures:<br>• None |

| **Missing Information: Safety in patients with cardiac conduction disorders** | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>• Legal status: restricted medical prescription<br>Additional risk minimisation measures:<br>• None |

## II.C. Post-authorisation Development Plan

### II.C.1. Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of REZOLSTA.

### II.C.2. Other Studies in Post-authorisation Development Plan

**GS-US-216-0128 -** A Phase 2/3, multicenter, open-label, multicohort, two-part study evaluating pharmacokinetics (PK), safety, and efficacy of cobicistat-boosted atazanavir (ATV/COBI) or cobicistat-boosted darunavir (DRV/COBI), administered with a background regimen (BR) in HIV-1 infected, treatment-experienced, virologically suppressed pediatric subjects.

Purpose of the study: To evaluate PK, safety, and efficacy of ATV/COBI and DRV/COBI in children and adolescents.