# 5 Part VI: Summary of activities in the risk management plan by product

## 5.1 Part VI.1 Elements for summary tables in the EPAR

**Table 5-1 Part VI.1.1 Summary table of safety concerns**

| Summary of safety concerns | |
|---|---|
| Important identified risks | Severe skin reactions |
| | Hepatotoxicity |
| | Hyperglycemia |
| | Lipid abnormalities |
| | Pancreatitis |
| | Immune Reconstitution Inflammatory Syndrome |
| | Development of Drug resistance |
| | Overdose due to Medication Error |
| | Drug-Drug Interactions |
| Important potential risks | Coronary Artery Events |
| | Cardiac Conduction Abnormalities |
| | Convulsions |
| | Growth Abnormalities in the Paediatric Population |
| Important potential risks<br>Darunavir (DRV)/cobicistat (COBI) | Off –Label Use of DRV/COBI in the Paediatric Population and in ARV treatment-experienced patients with HIV-I RNA > 100,000 copies/mL |
| | Renal toxicity of DRV/COBI |
| Missing information | Older People (65 years and above) |
| | Pregnant and breast-feeding women |
| | Subjects with severe hepatic impairment (Child-Pugh C) |
| | Subjects with renal impairment |
| Missing information<br>Darunavir (DRV)/ritonavir (rtv) | Long-term safety data in children from 3 to 17 years of age |
| Missing information<br>Darunavir (DRV)/cobicistat (COBI) | Long-term safety in adults |
| | Children < 18 years of age |
| | Subjects coinfected with HIV and HBV and/or HCV |

**Table 5-2 Part VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan**

None

**Table 5-3 Part VI.1.3 Summary of Post authorization efficacy development plan**

None

**Table 5-4 Part VI.1.4 Summary table of risk minimization measures**

| Safety concern | Routine risk minimization measures | Additional risk minimization measures |
|---|---|---|
| Severe skin reactions | Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC. | None |
| Hepatotoxicity | Guidance is provided in section 4.2 Posology and method of administration, section 4.3 Contraindications, section 4.4 Special warnings and precautions for use, section 4.5 Interaction with other medicinal products and other forms of interaction, section 4.8 Undesirable effects and section 5.3 Preclinical safety data of the SmPC. | None |
| Hyperglycemia | Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC. | None |
| Lipid abnormalities | Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC. | None |
| Pancreatitis | Guidance is provided in section 4.8 Undesirable effects of the SmPC. | None |
| Immune reconstitution inflammatory syndrome | Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of the SmPC. | None |
| Development of drug resistance | Guidance is provided in section 4.3 Contraindications, section 4.4 Special warnings and precautions for use, section 4.5 Interaction with other medicinal products and other forms of interaction, and section 5.1 Pharmacodynamic properties of the SmPC. | None |
| Overdose due to medication error | Guidance is provided in section 4.9 Overdose of the SmPC. | None |
| Drug-drug interactions | Guidance is provided in section 4.4 Special warnings and precautions for use and section 4.5 Interaction with other medicinal products and other forms of interaction of the SmPC. | None |
| Coronary Artery Events | Guidance is provided in section 4.8 Undesirable effects of the SmPC. | None |
| Cardiac conduction abnormalities | Guidance is provided in section 4.5 Interaction with other medicinal products and other forms of interaction and section 4.8 Undesirable effects of the SmPC. | None |
| Convulsions | Guidance is provided in section 4.8 Undesirable effects of the SmPC. | None |

| **Safety concern** | **Routine risk minimization measures** | **Additional risk minimization measures** |
|---|---|---|
| Growth Abnormalities in the paediatric population | Currently available data do not support the need for risk minimization. | None |
| Off-Label use of DRV/COBI in the paediatric population and in ARV treatment-experienced patients with HIV-I RNA > 100,000 copies/mL | Guidance is provided in section 4.1 Indications of the SmPC. | None |
| Renal toxicity of DRV/COBI | Guidance is provided in section 4.4 Special warnings and precautions for use of the SmPC. | None |
| Older people (65 years and above) | Guidance is provided in section 4.2 Posology and method of administration, section 4.4 Special warnings and precautions for use and section 5.2 Pharmacokinetic properties of the SmPC. | None |
| Pregnant and breast feeding women | Guidance is provided in section 4.6 Fertility, pregnancy and lactation of the SmPC. | None |
| Subjects with severe hepatic impairment (Child-Pugh C) | Guidance is provided in section 4.2 Posology and method of administration, section 4.3 Contraindications, section 4.4 Special warnings and precautions for use, section 4.5 Interaction with other medicinal products and other forms of interaction, section 4.8 Undesirable effects and section 5.2 Pharmacokinetic properties of the SmPC. | None |
| Subjects with renal impairment | Guidance is provided in section 4.2 Posology and method of administration, section 4.4 Special warnings and precautions for use and 4.5 Interaction with other medicinal products of the SmPC. | None |
| Darunavir/ritonavir:<br>Long-term safety data in children from 3 to 17 years of age | Guidance is provided in section 4.2 Posology and method of administration of the SmPC. | None |
| Darunavir/cobicistat:<br>Long-term safety in adults | Currently available data do not support the need for risk minimization. | None |
| Darunavir/cobicistat:<br>Children < 18 years of age | Guidance is provided in section 4.2 Posology and method of administration of the SmPC. | None |
| Darunavir/cobicistat:<br>Subjects coinfected with HIV and HBV and/or HCV | Currently available data do not support the need for risk minimization. | None |

## 5.2 Part VI.2 Elements for a Public Summary

### 5.2.1 Part VI.2.1 Overview of Disease Epidemiology

**HIV infections in Adults:**

HIV, the virus that causes AIDS, "acquired immunodeficiency syndrome," has become one of the world's most serious health and development challenges. There are approximately 36.9 million people currently living with HIV. The global occurrence rate (ages 15-49) is 0.8%. While new cases have been reported in all regions of the world, approximately 70% are in sub-Saharan Africa [Henry J. Kaiser Family Foundation (HJKF Foundation), 2015]. Over 90% of people living with HIV/AIDS do not know they are infected and even if they did, anti-retroviral therapies (medicines for AIDS) are not at present an option for them [Morison L, 2001]. Women represent approximately half (51%) of all adults living with HIV worldwide. HIV is the leading cause of death among women of reproductive age. Most infections are transmitted heterosexually, although risk factors vary. In some countries, men who have sex with men, injecting drug users, and sex workers are disproportionally affected by HIV [HJKF Foundation, 2015].

**HIV infections in Pediatric patients**

Globally, there were 2.6 million children living with HIV [HJKF Foundation, 2015]. An estimated 5.1 million children world-wide have been infected with HIV [Morison L, 2001]. An approximate of 88% of children with HIV infections live in Sub-Saharan Africa [HJKF Foundation, 2015]. Mother-to-child transmission (MTCT) is believed to be responsible for more than 90% of these infections. Around two-thirds of MTCT occurs in utero and at delivery and one-third occurs during breast feeding [Morison L, 2001]. It is estimated that half of all new episodes of HIV transmission to children occur during the breastfeeding period when the majority of breastfeeding women are not receiving the prophylaxis necessary to prevent HIV transmission [UNAID, 2013]. Globally, 40% of people living with HIV are receiving treatment, which includes 41% of adults and 32% of children living with HIV [HJKF Foundation, 2015].

### 5.2.2 Part VI.2.2 Summary of treatment benefits

Darunavir belongs to the group of medicines called protease inhibitors. It is used together with ritonavir as part of a combined therapy against Human Immunodeficiency Virus (HIV) infection in patients who were or were not treated with HIV medication in the past. In patients having been treated before with HIV medication, the efficacy of darunavir boosted with ritonavir was not inferior to that of lopinavir boosted with ritonavir after 48 weeks or was significantly better than boosted lopinavir after 48 and 96 weeks in 2 clinical trials, respectively. This was determined by a significant reduction in the number of viruses in the darunavir treated group [McKeage K, 2009]. Darunavir became the first medicine of the group of protease inhibitors to be approved by the health agencies at two different daily dosages. The main advantages of darunavir combined with ritonavir once daily are a lower pill burden, better tolerability, lower metabolic impact (half ritonavir dose), improvement in maintaining the treatment, and lower pharmaceutical costs due to lower darunavir and ritonavir doses. Darunavir is one of the 12 antiretroviral drugs that have been approved for use in children [Kogawa, 2015]. In clinical trials, ritonavir-boosted darunavir also had

sustained efficacy in children and/or adolescents with HIV infection who were treated with HIV medication in the past [Keating GM, 2015]. Darunavir, when studied in pregnant HIV-infected women in the third trimester and after birth, was not associated with abnormalities present before birth, and no child was infected with HIV. [Colbers A, 2015].

### 5.2.1 Part VI.2.3 Unknowns relating to treatment benefits

There are no adequate and well controlled studies with darunavir in pregnant women.

Limited information is available on the use of darunavir in patients aged 65 and over.

The safety and efficacy of darunavir have not been established in patients with severe underlying liver disorders.

Cobicistat has not been studied in patients receiving dialysis; therefore, no recommendation can be made for the use of darunavir/cobicistat in these patients.

### 5.2.2 Part VI.2.4 Summary of safety concerns

**Table 5-5 Important identified risks**

| Risk | What is known | Preventability |
|---|---|---|
| Severe skin reactions | Patients taking darunavir may develop a skin rash. Infrequently a rash may become severe or potentially life-threatening.<br><br>The rash is usually mild to moderate. A skin rash might also be a symptom of a rare severe situation.<br><br>One of the rare possible side effects of darunavir is skin lesions.<br><br>Skin reactions by darunavir include:<br>Nettle rash, severe swelling of the skin and other tissues (most often the lips or the eyes), skin lesions, a reaction called DRESS [severe rash, which may be accompanied by fever, fatigue, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells)] | Patient should contact doctor whenever a rash develops.<br><br>The doctor will advise how to deal with symptoms or whether darunavir must be stopped. |
| Injury to the liver caused by the drug<br>(Hepatotoxicity) | Liver problems that may occasionally be severe have been reported.<br><br>Signs and symptoms of liver problems include yellowing of skin or whites of eyes, dark (tea colored) urine, pale colored stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or sensitivity on right side below ribs. | Patients should not take darunavir if they have severe liver problems. The patient should ask the doctor if he/she is unsure about the severity of a liver disorder. Some additional tests might be necessary.<br><br>The doctor should be informed if a patient has had any sign or symptoms of a liver disorder before, including hepatitis B or C. The doctor may evaluate how severe the liver disease is before deciding if the patient can take darunavir.<br><br>The doctor should do blood tests prior to initiating darunavir. If the patient has chronic hepatitis B or C infection, the doctor should check blood tests more often because there can be increased chance of developing liver problems. |
| Raised blood sugar | Diabetes was observed commonly during use of darunavir. | Patients should tell their doctor if having diabetes. Darunavir |

| Risk | What is known | Preventability |
|---|---|---|
| (Hyperglycemia) | Some side effects are typical for anti-HIV medicines in the same family as darunavir. These include raised blood sugar and worsening of diabetes. | might increase sugar levels in the blood.<br><br>The dosage of other medicines might need to be changed since either their own or darunavir's therapeutic effect or side effects may be influenced when combined.<br><br>The doctor should be informed if a patient takes metformin to treat Type 2 diabetes. |
| Abnormalities of blood fat levels<br>(Lipid abnormalities) | Increased blood fat levels were observed commonly with use of darunavir. | Blood fat levels can be seen in the results of blood tests. |
| Inflammation of the pancreas (Pancreatitis) | Inflammation of the pancreas was uncommonly observed during treatment with darunavir. | Patients should inform their doctor about pain in the abdominal region. |
| Inflammatory reaction to symptom-free or residual microorganisms which usually dont cause illness, but cause disease when a person's immune response to infections is impaired<br>(Immune reconstitution inflammatory syndrome) | In HIV infected patients with severe immune deficiency at the time of start of combination antiretroviral therapy (CART), an inflammatory reaction to symptom-free or residual microorganisms which usually dont cause illness, but cause disease when a person's immune response to infections is impaired can occur. This reaction may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are Cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and pneumonia (inflammatory condition of the lung affecting primarily the microscopic air sacs known as alveoli) caused by Pneumocystis jirovecii. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. In addition, reactivation of herpes simplex and herpes zoster has been observed in clinical studies with darunavir co-administered with low dose ritonavir.<br>Autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) have also been reported to occur at the time when immune system begins to recover; however, the reported time of | The patient should inform his/her doctor if there are any symptoms of inflammation. These need to be evaluated and treatment initiated. |

| Risk | What is known | Preventability |
|---|---|---|
| | start is more variable and these events can occur many months after start of treatment. | |
| Ability of the virus to multiply even in the presence of a specific drug treatment and diminishing effect of darunavir against the virus as a result of exposure to similarly acting drugs<br>(Development of drug resistance) | Certain medicines like rifapentine, rifampicin, St John's wort and lopinavir have been shown to cause prominent decreases in concentrations of darunavir in blood, which can result in loss of effect of darunavir and development of resistance.<br>However, viruses resistant to most protease (enzyme) inhibitors remain susceptible to darunavir. | Regular assessment of effect of darunavir is advised. In case of lack or loss of effect, resistance testing should be performed.<br><br>Certain medicines like rifampicin, St John's wort and lopinavir should not be taken in parallel with darunavir. |
| Overdose due to medication error | Experience regarding overdose of darunavir in combination with cobicistat or ritonavir is limted. | The patient should tell his/her doctor in case an overdosage happened. |
| Drug-drug interactions | Patients should not combine darunavir with any of the following medicines:<br>Avanafil (to treat erectile dysfunction), Astemizole or terfenadine (to treat allergy symptoms), Triazolam and oral (taken by mouth) midazolam (to help to sleep and/or relieve anxiety), Cisapride (to treat some stomach conditions), in case of kidney and/or liver problems Colchicine (to treat gout), Pimozide, Quetiapine or Sertindole (to treat psychiatric conditions), Ergot alkaloids like Ergotamine, Dihydroergotamine, Ergometrine and Methylergonovine (to treat migraine and headaches), Amiodarone, Bepridil, Dronedarone, Quinidine, Ranolazine and systemic Lidocaine (to treat certain heart disorders, e.g. abnormal heart beat), Lovastatin and Simvastatin (to lower cholesterol levels), Rifampicin (to treat some infections such as tuberculosis), the combination product Lopinavir/Ritonavir (this anti-HIV medicine belongs to the same class as darunavir ), Alfuzosin (to treat enlarged prostate), Sildenafil (to treat high blood pressure in the pulmonary circulation), Ticagrelor (to help stop the clumping of platelets in the treatment of patients with a history of a heart attack), and products that contain St John's wort (Hypericum perforatum). | The doctor should be informed about all medicines that the patient is taking. |

| Risk | What is known | Preventability |
|---|---|---|
| | The effects of other medicines might be influenced if patients take darunavir. The doctor should be informed if a patient takes Amlodipine, Diltiazem, Disopyramide, Carvedilol, Felodipine, Flecainide, Metoprolol, Mexiletine, Nifedipine, Nicardipine, Propafenone, Timolol, Verapamil (for different heart diseases) as the therapeutic effect or side effects of these medicines may be increased.<br>This is not a complete list of medicines. | |

**Table 5-6 Important potential risks**

| Risk | What is known |
|---|---|
| Effects on the blood vessels nourishing the heart<br>(Coronary Artery Events) | Reports of patients treated with darunavir/ritonavir experiencing myocardial infarction have been received. The frequency is uncommon or rare. |
| Conduction disorders of the heart causing an irregular heart beat<br>(Cardiac Conduction Abnormalities) | Heart attack, slow heart beating, palpitations (noticeably rapid, strong, or irregular heartbeat) are few rare side effects of darunavir.<br>Chest pain, changes in electrocardiogram, rapid heart beating are few uncommon side effects of darunavir. |
| Convulsions | Convulsions have been observed in patients treated with darunavir/ritonavir. |
| Growth abnormalities in the paediatric population | There is no sufficient data available for the assessment of an association of darunavir with growth abnormalities in children. |
| Off-label use of DRV/COBI in the paediatric population and in ARV treatment-experienced patients with HIV-I RNA > 100,000 copies/mL | There is no sufficient data available for the assessment of a possible off-label use in this patient group. Indications are clearly labeled. |
| Renal toxicity of DRV/COBI | It is known that cobicistat reduces the clearance of creatinine in the kidneys. |

**Table 5-7 Missing information**

| Risk | What is known |
|---|---|
| Older people (65 years and above) | Darunavir has only been used in limited numbers of patients 65 years or older. If patients belong to this age group, it should be discussed with the doctor if the patient can use darunavir. |
| Pregnant and breast feeding women | The patient should tell her doctor immediately if she is pregnant or breast-feeding. Pregnant or breast-feeding women must not take darunavir unless specifically directed by the doctor. It is recommended that HIV infected women must not breast-feed their infants because of both the possibility of their baby becoming infected with HIV through breast milk and because of the unknown effects of the medicine on the baby. |

| Risk | What is known |
|---|---|
| Subjects with severe hepatic impairment (liver dysfunction) | Liver problems that may occasionally be severe have been reported.<br>The doctor should do blood tests prior to initiating darunavir. If patient has chronic hepatitis B or C infection, doctor should check blood tests more often because there can be increased chance of developing liver problems.<br><br>Patients should not take darunavir if having severe liver problems. The doctor should be asked if a patient is unsure about the severity of his/her liver disease. Some additional tests might be necessary.<br><br>The doctor should be informed if a patient has had problems with the liver before, including hepatitis B or C. The doctor may evaluate how severe the liver disease is before deciding if the patient can take darunavir.<br><br>The doctor should be informed about the signs and symptoms of liver problems. These may include yellowing of skin or whites of eyes, dark (tea colored) urine, pale colored stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or sensitivity on right side below ribs. |
| Subjects with renal impairment | No special precautions or dose adjustments are required in patients with kidney insufficiency. |
| Darunavir/ritonavir:<br>Long-term safety data in children from 3 to 17 years of age | There is no sufficient data available for the assessment of long-term safety in children from 3 to 17 years of age. |
| Darunavir/cobicistat:<br>Long-term safety in adults | There is no sufficient data available for the assessment of long-term safety in adults. |
| Combined treatment with cobicistat and darunavir in children<br>(Darunavir/cobicistat: children < 18 years of age)<br>) | Cobicistat with darunavir should not be used in children as the dose of cobicistat to be used with darunavir in children less than 18 years of age has not been established. |
| Darunavir/cobicistat: Treatment in patient that also have hepatitis<br>(Darunavir/cobicistat:<br>Subjects coinfected with HIV and HBV and/or HCV) | There is no sufficient data available for the assessment of safety and efficacy in patients with co-infections. |

### 5.2.3 Part VI.2.5 Summary of risk minimization measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists and other HCPs with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

This medicine has no additional risk minimization measures.

### 5.2.1 Part VI.2.6 Planned post authorization development plan

None

### 5.2.2 Part VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable (first submission)