Darunavir STADA 400, 600 and 800 mg film-coated tablets

7.9.2016, Version 1.1

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Human immunodeficiency virus (HIV) attacks the cells of the immune system, the body's natural defense against germs and other substances that cause infection and illness and leads to acquired immunodeficiency syndrome, or AIDS.

Up to the end of 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDs) estimated that approximately 37 million people worldwide were living with HIV infection. The 28,5 million of those people are living in Sub-Saharan Africa and women account for more than half of the total number of HIV infected persons in sub-Saharan Africa. New HIV infections have fallen by 35% since 2000 and AIDS-related deaths have fallen by 42% since the peak in 2004. People with AIDS have an increased risk of developing infections, such as pneumonia, herpes infections, fungal infections and tuberculosis as well as certain conditions such as some cancers, liver, kidney and heart problems and bone disorders (*UNAIDS 2015*).

VI.2.2 Summary of treatment benefits

Anti-HIV drugs are used to treat people who are infected with HIV. These drugs reduce the amount of HIV in the body by slowing or stopping the growth of the virus.

A group of ARV drugs called protease inhibitors (PIs) has become the cornerstone in the treatment of HIV disease. Darunavir (DRV) is such a PI. It blocks an enzyme called protease, which is involved in the reproduction of HIV. When the enzyme is blocked, the virus does not reproduce normally, slowing down the rate of replication. Darunavir should be taken with a 'booster' (ritonavir [rtv] or cobicistat [COBI]) which slows down the rate at which DRV is broken down by the human body, thereby, increasing the levels of DRV in the blood. This allows a lower dose of DRV to be used for the same antiviral effect.

Darunavir, taken in combination with other anti-HIV medicines, reduces the amount of HIV in the blood and keeps it at a low level. Darunavir does not cure HIV infection or AIDS, but it may delay or reverse the damage to the immune system and as a consequence, delay the development of infections and diseases associated with AIDS.

Darunavir coadministered with low-dose rtv is indicated in combination with other ARV medicines for the treatment of patients with HIV-1 infection. These patients include:

- adult patients regardless whether they had prior HIV treatment or not

- paediatric patients from the age of 3 years and ≥15 kg body weight

Other PIs are also available on the European market, including boosted lopinavir (LPV), atazanavir, indinavir, saquinavir, nelfinavir, tipranavir and fosamprenavir.

VI.2.3 Unknowns relating to treatment benefits

Limited information is available on the use of rtv-boosted and COBI-boosted darunavir in patients aged 65 years and above. Experience with rtv-boosted and COBI-boosted darunavir in pregnant women is currently limited to case reports. It is not known whether DRV or COBI passes into human breast milk. It is recommended that mothers with HIV do not breast-feed their infants whilst being treated with darunavir.

Darunavir, rtv and COBI have not been studied in patients with severe hepatic and renal impairment, however no change in the dose of darunavir is required in patients with mildly or moderately decreased liver function and in patients with kidney impairment, including those with severe kidney impairment.

The safety and efficacy of DRV and COBI in children aged <18 years have not yet been established so the use of DRV /COBI in children < 18 years of age is not recommended.

Limited information is available on the use of DRV /COBI in patients co-infected with hepatitis B and/or hepatitis C. Appropriate laboratory testing should be conducted prior to initiating therapy with DRV /COBI and patients should be monitored during treatment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Severe skin reactions	Rash has been observed as a common side effect and severe skin reactions has been observed as a rare side effect. Patients with HIV are 15 times more likely to visit their doctor for common skin conditions than patients not infected with HIV. These skin conditions can sometimes be caused by other viruses. In clinical trials, rash was mostly mild to moderate in severity, often occurring within the first 4 weeks of treatment and resolving with continued dosing.	The rash is usually mild to moderate in severity. However, as a rash might also be a symptom of a rare severe situation, it is important to contact your doctor if you develop a rash. Your doctor will advise you how to deal with your symptoms and whether your treatment with darunavir should be stopped.

Risk	What is known	Preventability
	The incidence of rash was higher in patients with allergy to sulpha medicines compared to those without this allergy. Infrequently, a rash may become severe or potentially life-threatening.	
Liver toxicity due to medication (Hepatotoxicity)	Side effects that involve the liver (e.g., abnormal liver tests) have been observed as common side effects and hepatitis has been observed as an uncommon side effect. In clinical trials, these side effects occurred more often in patients with both HIV-I infection and hepatitis B or hepatitis C infection than in patients with only HIV-I infection.	Appropriate laboratory testing should be conducted before initiating therapy with rtv-boosted darunavir and patients should be monitored during treatment. Increased monitoring of liver tests should be considered in patients with underlying chronic hepatitis, cirrhosis (a chronic disease which interferes with normal liver function), or in patients who have pre-treatment abnormal liver tests, especially during the first months of rtv-boosted darunavir treatment.
High blood sugar (Hyperglycaemia)	Diabetes or an increase in blood sugar has been observed as an uncommon side effect. In several clinical trials with darunavir in adults, the incidence of blood sugar-related side effects was similar for patients treated with rtv-boosted darunavir as compared to patients treated with rtv-boosted lopinavir (LPV). Treatment-related increase in blood sugar occurred frequently in DRV/rtv clinical trials and was also observed during DRV/COBI clinical trials, but serious abnormalities were infrequent.	General prevention according to standard medical practices is applicable. No specific measures can be recommended in the absence of identified specific preventable risk factors.
Abnormal blood values for lipid factors (Lipids are cholesterol and fatty acids)	Blood lipid-related side effects have been observed as common side effects.	General prevention according to standard medical practices is applicable.

Risk	What is known	Preventability
(Lipid Abnormalities)	In clinical trials in adults, the incidence of lipid-related side effects was similar or lower in subjects treated with rtv-boosted darunavir compared to rtv-boosted LPV. In 1 clinical trial, the incidence of lipid-related side effects was lower in the 800 mg rtv-boosted darunavir qd group compared to the 600 mg rtv-boosted darunavir bid group.	No specific measures can be recommended in the absence of identified specific preventable risk factors.
Inflammation of the pancreas (Pancreatitis)	Inflammation of the pancreas has been observed as an uncommon side effect. In 2 clinical trials, no difference in the incidence of pancreas-related side effects was noted between rtv-boosted darunavir- and rtv-boosted LPV-treated subjects.	No specific measures can be recommended in the absence of identified specific preventable risk factors.
The immune system begins to recover, but then responds to a previously acquired infection with an overwhelming inflammatory response that makes the symptoms of infection worse (Immune reconstitution inflammatory syndrome [IRIS])	Immune reconstitution inflammatory syndrome has been observed as an uncommon side effect. In HIV -infected patients with severe immune deficiency at the start of HIV therapy, an inflammatory reaction to non-symptomatic or remaining germs from previous infections (e.g. virus, bacteria, fungus, etc.) may arise and cause serious clinical conditions, or aggravation of pre-existing symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of HIV therapy. It is believed that these reactions are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no	Tell your doctor immediately if you notice any symptoms of infection (for example enlarged lymph nodes and fever). Any inflammatory symptoms should be evaluated by your health care professional and appropriate treatment started when necessary.

Risk	What is known	Preventability
	obvious symptoms.	
Development of drug resistance (The ability of the virus to reproduce during treatment with an anti-HIV drug, making the drug ineffective)	In some patients, the virus becomes resistant to the anti-HIV drug. This may also occur during treatment with a PI such as darunavir. When the virus becomes resistant to one PI, other PIs and anti-HIV drugs may also not be effective, which limits the number of treatment options available to the patient. Overall, the proportion of adults unable to maintain suppression of viral load was lower in patients treated with rtv-boosted darunavir than in the control group and low in patients treated with DRV /COBI, reducing the risk of development of resistance.	In deciding to initiate treatment with darunavir, your doctor should give careful consideration to your history of previous HIV treatments. A blood test should be performed to find out if the drug is likely to work ('resistance testing').
Overdose due to medication error	There are different forms and tablet strengths of darunavir available (75-, 150-, 400-, 600- and 800-mg tablets) and as a result there is a risk for prescribing, dispensing and administration errors that could also result in an overdose. There is a risk that patients on the 2 x 400-mg qd regimen erroneously switch to a 2 x 800-mg qd regimen instead of the 1 x 800-mg qd regimen, resulting in an overdose.	The product information contains clear dosing instructions. The different forms and tablet strengths of darunavir, i.e. 75-, 150-, 400-, 600- and 800-mg tablets, are clearly indicated on the packaging in a colour-differentiated bubble and wave, the dose amount is debossed on each tablet that has a strength-specific colour.
Drug-drug interactions	Interactions between rtv-boosted or COBI-boosted darunavir and other drugs may occur. Coadministration of darunavir and rtv or COBI, 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	The product information contains clear recommendations on drugs that should not be combined with darunavir or actions to be taken by your healthcare professional such as dose adjustment based upon drug monitoring.

Risk	What is known	Preventability
	therapeutic effect and side effects, which may be serious and potentially life-threatening. Some products may increase the breakdown of darunavir, resulting in loss of efficacy.	

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Heart attack (Coronary artery events)	High blood sugar and increase in blood lipids such as cholesterol, which are considered identified risks, are risk factors for developing heart attack. In clinical trials conducted in adults, the heart attack-related events were uncommon and did not increase over time.
ECG abnormalities indicating a risk for heart rate disorders (Cardiac conduction abnormalities)	Although the available data in the clinical trials did not indicate a risk for cardiac conduction abnormalities and/or a risk for potentially life-threatening heart rate disorders, this issue is kept under evaluation because of the potential clinical relevance.
Epileptic incident (Convulsions)	In animal studies, convulsions have been observed in young animals, equivalent to <2 years of age in humans. Therefore, darunavir is not authorised for use in children <3 years of age.
Growth abnormalities in children	No side effects related to growth abnormalities were reported in the clinical trials in children. However, HIV-1-infected children are shorter compared to children not infected with HIV-1.
Drug use in patients for whom darunavir in combination with COBI is not approved (Off-label use of DRV /COBI in the paediatric population and in ARV treatment-experienced patients with HIV-1 RNA > 100,000 copies/mL)	Use of darunavir/COBI in HIV-infected patients for whom the drug is not approved may occur, including use in children. Use of darunavir/COBI in these patients would not necessarily lead to side effects.
Kidney toxicity due to medication (Renal toxicity of DRV /COBI)	Measuring creatinine in the blood is a well-known test to evaluate the function of the kidneys. Cobicistat has been shown to decrease the elimination of creatinine from the blood (creatinine clearance) without any further effect on the function of the kidneys. Darunavir/COBI should therefore not be given in patients with a low rate of creatinine clearance if the dose of another drug (e.g. emtricitabine, lamivudine, tenofovir disoproxil fumarate, or adefovir

Risk	What is known (Including reason why it is considered a potential risk)
	dipivoxil) is to be adjusted based upon the creatinine clearance. There is currently not enough information to determine whether coadministration of DRV/COBI and tenofovir disoproxil fumarate is associated with a greater risk of kidney toxicity. The effects on the kidneys should be monitored when DRV/COBI and tenofovir disoproxil fumarate are being given together.

Missing information

Risk	What is known
DRV when used with rtv and COBI	
Older People (65 years and above)	As limited information is available on the use of rtv-boosted and COBI-boosted darunavir in patients aged 65 years and above, caution should be exercised in the administration of darunavir in older patients, reflecting the greater frequency of decreased liver function and of concomitant disease or other therapy.
Pregnant and breast-feeding women	Experience with rtv-boosted and COBI-boosted darunavir in pregnant women is currently limited to case reports. One clinical trial to assess the pharmacokinetics (what the body does with the drug) of rtv-boosted darunavir is ongoing in this population. This trial will be amended to include also COBI-boosted darunavir. HIV may be carried through the breast milk to the infant during nursing. It is not known whether DRV or COBI passes into human breast milk. It is recommended that mothers with HIV do not breast-feed their infants whilst being treated with darunavir.
Subjects with severely decreased liver function (hepatic impairment)	Darunavir, rtv and COBI have not been studied in patients with severely decreased liver function and therefore should not be used in these patients. No change in the dose of darunavir is required in patients with mildly or moderately decreased liver function.
Subjects with decreased kidney function (renal impairment)	No dose adjustment of darunavir is required for patients with kidney impairment, including those with severe kidney impairment. DRV/COBI has not been studied in patients receiving dialysis, and, therefore, no recommendation can be made for these patients. DRV/COBI should not be started in patients with mild kidney impairment and receiving treatment with certain anti-HIV drugs that require dose adjustment for the kidney impairment. A study is ongoing which will provide additional information relevant to the safety of DRV/COBI in HIV-1 infected adults with mild to moderate kidney impairment.
Darunavir (DRV) when used with ritonavir (rtv)	
Long-term safety data in	One 48 Week clinical trial has been performed with rtv-boosted

Risk	What is known
children from 3 to 17 years of age	darunavir in 21 HIV-1-infected patients aged from 3 to <6 years and weighing between 10 and <20 kg, who had received prior HIV treatment. Two clinical trials have been performed to assess the 48 Week safety of the use of darunavir in children aged from 3 to 17 years of age: one clinical trial in 12 ARV-treated adolescents aged from 12 to 17 years of age and weighing ≥40 kg who did not have prior HIV treatment, and one clinical trial in HIV-1-infected paediatric subjects from 6 to 17 years of age who did have prior HIV treatment. Additional long-term safety data in these subjects is collected through a continued access trial TMC 114-TiDP29-C232. The EPPICC study monitors the use of darunavir in children and adolescents with HIV infection in a "real world" setting within EPPICC and monitors patient safety in the short- to long-term.
Darunavir (DRV) when used with cobicistat (COBI)	
Long-term safety of DRV/COBI in adults	Currently clinical trials which will provide information on the use of DRV /COBI for longer than 24 weeks are ongoing.
Children <18 years of age	The safety and efficacy of DRV and COBI in children aged <18 years have not yet been established so the use of DRV /COBI in children < 18 years of age is not recommended.
Subjects infected with HIV and also with either HBV or HCV	Limited information is available on the use of DRV /COBI in patients co-infected with hepatitis Band/or hepatitis C. Patients with pre-existing liver abnormality or dysfunction, including chronic active hepatitis B or hepatitis C, have an increased risk for liver function abnormalities. In case antiviral therapy for hepatitis B or hepatitis C is given together with DRV/COBI, please refer to the relevant product information for these medicinal products. Appropriate laboratory testing should be conducted prior to initiating therapy with DRV /COBI and patients should be monitored during treatment.

VI.2.5 Summary of additional risk minimisation measures by safety concern

Not applicable

VI.2.6 Planned post authorisation development plan

Not applicable

VI.2.7 Summary of changes to the risk management plan over time

Not applicable