VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Darunavir is an antiviral medicine used to treat adults and children aged three years or over with human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS). HIV is a virus that attacks the immune system (the body's natural defences) and weakens it by destroying certain white blood cells (called CD4 T cells), which are important for protecting the body against various bacteria, viruses and other germs. If left untreated, the HIV virus multiplies and the body becomes increasingly unable to fight infections and disease.
In 2011, 34 million people worldwide were living with HIV, including 900,000 in Western and Central Europe and 1.4 million in Eastern Europe and Central Asia. In 2011, 2.5 million people were newly infected with HIV, down by one-fifth (20%) compared with 2001.
There is no cure for HIV, but early detection and effective treatment with medicines that stop the virus multiplying can reduce the amount of HIV virus in the blood and keep it at a low level, allowing people to stay healthy and live longer lives. The development of resistance to HIV medicines can be a problem among patients receiving long-term treatment. This means that over time the HIV virus is no longer controlled properly by a particular combination of medicines, and treatment may need to be changed; treatment may also be changed because of side effects.

VI.2.2 Summary of treatment benefits

The active substance darunavir, is a protease inhibitor. 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 and its rate of replication slows down. Either ritonavir or cobicistat is used with darunavir as a 'booster'. These booster medicines slow the rate at which darunavir is broken down, increasing the levels of darunavir in the blood. This allows a lower dose of darunavir to be used for the same antiviral effect.
Darunavir, taken in combination with other 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 the development of infections and diseases associated with AIDS.

In adults, darunavir has been studied in six main studies. In all of the studies, the patients also took other HIV medicines. The main measures of effectiveness were based on the change in HIV levels in the blood (viral load).

VI.2.3 Unknowns relating to treatment benefits

There are limited data on the use of darunavir in children 3 to < 6 years of age, no available data on the longterm use of darunavir in children aged 3 to 17 years, and about use in certain subgroups of patients: the elderly (65 years and above) and pregnant and breast-feeding women.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Safety concern in lay language ***(medical term)***	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
Severe skin side effects *(Severe skin reactions)*	Rash is a very common side effect, seen in more than 1 patient in 10; 16% of patients experienced rash in a study where they were given darunavir and cobicistat. Although severe reactions are possible, in clinical trials where darunavir was given with cobicistat or ritonavir, rash was mostly mild to moderate in severity, often occurring within the first 4 weeks of treatment and resolving despite continued dosing.	You should be warned to contact your doctor if rash develops, and healthcare professionals should advise patients on appropriate treatment and whether darunavir needs to be stopped.
Side effects on the liver *(Hepatotoxicity)*	Side effects that involve the liver (e.g., abnormal liver tests) are seen in up to 1 patient in 10. Inflammation of the liver (hepatitis) is uncommon (reported in less than 1 patient in 100). In clinical trials, these side effects occurred more often in patients who were also infected with hepatitis B or hepatitis C virus than in patients with HIV-1 infection alone.	Darunavir is contraindicated in patients with severely reduced liver function. You should inform your doctor if you have severe liver problems. Your doctor should monitor your liver function.
High blood sugar levels *(Hyperglycaemia)*	Diabetes or increase in blood sugar is uncommon side effects (reported in less than 1 patient in 100) and serious problems were infrequent.	You should inform your doctor if you have diabetes as darunavir might increase your sugar levels in the blood. Your doctor may consider blood tests if necessary.
Increased fat in the blood *(Lipid Abnormalities)*	Increases in blood levels of various types of fats (lipids), including cholesterol and triglycerides, are common side effects, occurring in up to 1 patient in 100.	During HIV therapy there may be an increase in levels of blood lipids. Your doctor may consider blood tests if necessary.

Inflammation during recovery of the immune system *(Immune reconstitution inflammatory syndrome)*	IRIS is a condition seen in HIV patients whose immune system is recovering, as a result of treatment with HIV medicines. During recovery, there can be a reaction to an existing infection in the body, causing severe inflammation at the site of the infection, or overactivity of the immune system leading it to attack healthy body tissue (autoimmunity). Such effects may be seen in up to 1 patient in 1,000 treated with darunavir.	You should tell your doctor immediately if you notice any symptoms of infection (for example enlarged lymph nodes and fever) or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity. Your doctor should evaluate any inflammatory symptoms and start appropriate treatment if necessary.
Development of resistance by the virus *(Development of drug resistance)*	In some patients treated with an HIV medicine such as darunavir, the virus may become resistant to it and may be able to continue to reproduce. When the virus becomes resistant to one medicine, some other HIV medicines, particularly those in the same class, may also not be effective, which limits the number of treatment options available to the patient. Studies in patients given darunavir with cobicistat showed that when taken properly the risk of resistance was low.	Before recommending treatment with darunavir, the doctor should consider the patient's history of previous HIV treatments and carry out a blood test to find out if the medicine is likely to work ('resistance testing'). Resistance may develop if patients fail to comply with the prescribed treatment; therefore patients should take darunavir regularly with food as directed by their doctor and should not stop treatment without discussing it with their doctor.
Drug application in quantities greater than those recommended due to incorrect or wrongful administration *(Overdose due to Medication Error)*	Medication errors cause a large number of adverse drug reactions (ADR) with negative patient health outcomes each year and are a major public-health burden. A medication error may lead to unintentional overdose through dispensing, preparing or administering medicinal products in clinical practice. Therapy with darunavir should be initiated by a health care provider experienced in the management of HIV infection.	Always take this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure. After therapy has been initiated, the dose or dosage form must not be changed or therapy must not be stopped without instruction of the doctor.
Taking other medicines with darunavir	Giving darunavir with other medicines that are broken down in the body in the same way may	Read the patient information leaflet carefully before you start taking this medicine. Tell

(Drug-drug Interactions)	interfere with the breakdown of such medicines and increase their blood levels. This can increase the risk of potentially serious side effects. In addition, some other medicines may increase the breakdown of darunavir, resulting in loss of effectiveness.	your doctor or pharmacist if you are taking or have recently taken any other medicines since there are some medicines that you must not combine with darunavir.

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 fats such as cholesterol, which are considered identified risks, are also risk factors for developing hardening and thickening of the walls of the arteries (arteriosclerosis). If this occurs, in the arteries that supply blood to the heart muscle it can cause angina (chest pain) and/or heart attack, which are therefore considered potential risks of darunavir.
Growth abnormalities in children *(Growth Abnormalities in the Paediatric Population)*	The risk of growth abnormalities in the children has been included as an important potential risk. Janssen-Cilag International NV is planning to initiate a study to assess growth abnormalities (height) in children.
Use in patients for whom the combination treatment of Darunavir and Cobicistat is not approved (off-label use)	There is a risk of unapproved or off-label use of combination treatment of Darunavir and Cobicistat, including use in children and adolescents under 18 years old and in adults who have already received treatment with HIV medicines but who have high levels of the virus in their blood (more than 100,000 copies/ml HIV-1 RNA) at the start of treatment. The safety and effectiveness of the combination of darunavir and cobistat in such patients has not been shown.

Missing information

Risk	**What is known**
Older people (65 years and above)	There is limited information from studies with darunavir in patients over 65 years of age. It is therefore not known whether patients above 65 years of age respond differently to younger patients.
Pregnant and breast-feeding women	Darunavir has not been studied in pregnant women. Pregnant women should not take darunavir unless it has been agreed with the doctor that the potential benefits outweigh any risks.

	It is not known whether darunavir passes into human breast milk but in any case it is recommended that mothers with HIV do not breastfeed their infants. Currently, Janssen-Cilag International NV has initiated a study to assess the pharmacokinetics of darunavir in HIV-1-infected pregnant women.
Use in patients with severely decreased liver function (hepatic impairment)	Darunavir and has 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.
Use in patients with decreased renal function (renal impairment)	No dose adjustment of Darunavir is needed in patients with reduced kidney function. Cobicistat has not been studied in patients with decreased renal function, and, therefore, no recommendation can be made for the use of combination of Darunavir and Cobicistat in these patients.
DRV/rtv Long-term safety data in children 3 to < 6 years of age	A study has been initiated to assess the safety of darunavir oral suspension with low dose ritonavir in children 3 to < 6 years of age with HIV-1 infection, who have already received anti-retroviral treatment.
Impact of palatability of the oral suspension of combination of Darunavir and ritonavir on adherence and efficacy in treatment-experienced children >15 kg	A study (DELPHI) has been initiated to assess pharmacokinetics, safety, tolerability, and efficacy of darunavir with low dose ritonavir in paediatric patients with HIV-1 infection, who have already experienced anti-retroviral therapy. In this study, children who could stop therapy due to intolerance of ritonavir oral solution (e.g. taste aversion) were allowed to switch to the capsule formulation.
Use of combination of Darunavir and Cobicistat in children below 18 years of age	The safety and effectiveness of darunavir and cobicistat in patients aged less than 18 years have not yet been established. Therefore, the use of the combination Darunavir and Cobicistat in this age group is not recommended.
Use of combination of Darunavir and Cobicistat in adults	A study has been initiated with aiming to evaluate the safety and tolerability of combination of Darunavir and Cobicistat plus 2 fully active Nucleoside/nucleotide reverse transcriptase inhibitors in adults.
Use of combination Darunavir and Cobicistat in patients who also have hepatitis B or C infection	Only limited information is available on the use of combination Darunavir and Cobicistat in patients who also have hepatitis B and/or hepatitis C infection. Patients with pre-existing liver problems, including chronic active hepatitis B or hepatitis C, have an increased risk for abnormalities of liver function including severe and potentially fatal effects. Patients should have their liver function tested before and during treatment, especially during the first few months of treatment and in patients with inflammation of the liver (hepatitis), scarring (cirrhosis) or raised liver enzyme values in the blood. If antiviral therapy for hepatitis B or

	hepatitis C is given together with combination Darunavir and Cobicistat, the product information for these medicines should also be consulted.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable

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

Version	Date	Safety concerns	Change
1.0	27.09.2016	**Important identified risks** • Severe Skin Reactions • Hepatotoxicity • Hyperglycaemia • Lipid Abnormalities • Pancreatitis • Fat Redistribution • Immune Reconstitution 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 **Missing information** • Elderly (65 years and above) • Pregnant and breast-feeding women • Children 3 to < 6 years of age (limited data are available from Phase 2 trial)	Initial version

		• Long-term safety data in children from 3 to 17 years of age	
1.0	16.5.2017	**Important identified risks** • Severe Skin Reactions • Hepatotoxicity • Hyperglycaemia • 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 • Off-label use of DRV/COBI in the paediatric population and in ARV treatment-experienced patients with HIV-1 RNA > 100,000 copies/mL • Renal toxicity of DRV/COBI **Missing information** • Older (65 years and above) • Pregnant and breast-feeding women • Subjects with severe hepatic impairment (Child-Pugh C) • Subjects with renal impairment DRV/rtv • Long-term safety data in children 3 to < 6 years of age • Impact of palatability of the oral suspension on adherence and efficacy in treatment-experienced children >15 kg DRV/COBI • Children <18 years of age • Long term safety of DRV/COBI in adults • Subjects co-infected with HIV and HBV and/or HCV	Day 70 Preliminary Assessment Report responses
1.0	28.8.2017	**Important Identified Risks** • Severe Skin Reactions	Day 100 and 120 P reliminary Assess ment Report respon

		• Hepatotoxicity • Hyperglycaemia • Lipid Abnormalities • Immune reconstitution inflammatory syndrome • Development of drug resistance • Overdose due to Medication Error • Drug-drug Interactions **Important potential Risks** • Coronary Artery Events • Growth Abnormalities in the Paediatric Population • Off-label use of DRV/COBI in the paediatric population and in ARV treatment-experienced patients with HIV-1 RNA > 100,000 copies/Ml **Missing information** • Older (65 years and above) • Pregnant and breast-feeding women • Subjects with severe hepatic impairment (Child-Pugh C) • Subjects with renal impairment DRV/rtv • Long-term safety data in children 3 to < 6 years of age • Impact of palatability of the oral suspension on adherence and efficacy in treatment-experienced children >15 kg DRV/COBI • Children <18 years of age • Long term safety of DRV/COBI in adults Subjects co-infected with HIV and HBV and/or HCV	ses
1.0	19.09.2017		Day 160 Preliminary Assessment Report responses and SmPC-PIL update
1.0	14.11.2017		Day 210 SmPC-PI

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