VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

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

Darunavir is used together with low-dose ritonavir and other HIV medicines to treat adults and children aged three years or over who are infected with human immunodeficiency virus (HIV-1), a virus that causes acquired immune deficiency syndrome (AIDS).

In adults, darunavir is also used with another medicine, cobicistat, in combination with other HIV medicines to treat HIV-1 infection. The medicine can only be obtained with a prescription. Based on the available data from clinical studies and clinical experience of several years, darunavir represents an effective drug in the treatment of HIV-1 infection.

If administered as indicated in the Summary of Product Characteristics and taking into account the contra-indications, the warnings and precautions, darunavir can be considered effective in the approved indications and generally well tolerated.

VI.2.3 Unknowns relating to treatment benefits

The benefits of darunavir use have not yet been established in the following patient groups:

- Elderly (65 years and above)
- Pregnant and breast-feeding women
- Children from 3 to 17 years of age (when darunavir is co-administrated with ritonavir)
- Children <18 years of age (when darunavir is co-administrated with cobicistat)
- Long- term safety in adults in case darunavir is co-administrated with cobicistat
- Subjects with renal impairment and severe hepatic impairment (when darunavir is co-administrated with cobicistat or with ritonavir)

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Severe skin reactions	People taking darunavir may develop a skin rash. Infrequently a rash may become severe or potentially life-threatening. In patients taking darunavir and raltegravir (for HIV infection), rashes (generally mild or moderate) may occur more frequently than in patients taking either medicine separately.	Patients should be warned to contact their doctor if rash develops, and healthcare professionals should advise patients on appropriate treatment and whether darunavir therapy needs to be stopped.
Liver injury (hepatotoxicity)	Liver problems that may occasionally be severe have been reported. Your doctor should do blood tests prior to initiating darunavir therapy. If you have chronic hepatitis B or C infection, your doctor should check your blood tests more often because you have an increased chance of developing liver problems.	Patients should talk to their doctor about the signs and symptoms of liver problems. These may include yellowing of your skin or whites of your eyes, dark (tea coloured) urine, pale coloured stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching, or sensitivity on your right side below your ribs. Patients should inform their doctor if they have had liver problems before, including hepatitis B or C. Doctor may evaluate how severe liver disease is before deciding to administer darunavir to a patient. Darunavir is contraindicated in patients with severely reduced liver function.
High blood sugar (hyperglycaemia)	Darunavir might increase sugar levels in the blood.	Patients should inform their doctor if they have diabetes. The product information includes warnings to doctors and patients on the risk of increased blood sugar. Doctors may consider blood tests where appropriate.
Increased fat in the blood (lipid abnormalities)	Increases in blood levels of various types of fats (lipids), including cholesterol and	The product information includes warnings to doctors and patients of the risk of increased blood

Risk	What is known	Preventability
	triglycerides, are common side effects.	fats. Doctors may consider blood tests where appropriate.
Inflammation of the pancreas (pancreatitis)	Inflammation of the pancreas may occur in up to 1 patient in 100.	The product information includes warnings to doctors and patients of the possibility of developing acute pancreatitis. Patients should contact their doctor in case of pain in the abdomen since it may be caused by inflammation of the pancreas.
Inflammation during recovery of the immune system (immune reconstitution 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 over activity of the immune system leading it to attack healthy body tissue (autoimmunity).	Patients should tell their doctor immediately if they 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. Any inflammatory symptoms should be evaluated by a healthcare professional and appropriate treatment started if necessary.
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.	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.
Overdose due to medication error	Human experience of acute overdose with Darunavir co-administered with cobicistat or low dose ritonavir is limited. There is no specific antidote for	If indicated, elimination of darunavir is to be achieved by vomiting. Administration of activated charcoal may also be used to aid in removal of

Risk	What is known	Preventability
	overdose with Darunavir. Treatment of overdose with Darunavir consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.	unabsorbed active substance. Since darunavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.
Taking other medicines with darunavir (drug-drug interactions)	Giving darunavir with other medicines that are broken down in the body in the same way may 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.	The product information for darunavir contains clear recommendations on medicines that should not be taken during treatment or actions to be taken by healthcare professionals such as adjusting doses based on levels of the medicine in the body.

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.
Alterations in the electrical activity of the heart (cardiac conduction abnormalities)	Alterations in the electrical activity in the heart can result in potentially serious effects on heart rate and rhythm. Such alterations have not been reported in studies in patients given darunavir with cobicistat. However, because they have been reported in patients given darunavir with an alternative booster medicine, ritonavir, they are considered a potential risk with darunavir.
Seizures (convulsions)	In animal studies with darunavir, convulsions have been observed in young animals, equivalent to less than 2 years of age in humans.
Growth abnormalities in the paediatric population	Children treated with darunavir may be at risk of developing growth abnormalities. The exact mechanism by which darunavir may cause growth abnormalities is not well-understood.
Off-label use of darunavir/cobicistat in the paediatric population in ARV Treatment-experienced Patients	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

Risk	What is known (Including reason why it is considered a potential risk)
with HIV-1 RNA >100,000 copies/mL	side effects.

Missing information

Risk	What is known
Elderly (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.
Long-term safety data in children from 3 to 17 years of age	There is limited information on darunavir long-term safety effect in children from 3 to 17 years of age.
Children <18 years of age	There is limited information from studies with darunavir and cobicistat given at the same time in patients under 18 years of age. It is therefore not known whether patients under 18 years of age respond differently than adult patients.
Long-term safety of DRV/COBI in adults	There is limited information on darunavir and cobicistat long-term safety effect in adults.
Patients with severely damaged liver (subjects with severe hepatic impairment (Child-Pugh C)	No data are available in patients with severe hepatic impairment. Therefore, darunavir must not be used in patients with severe hepatic impairment (Child-Pugh Class C). Patients should ask the doctor if they are unsure about the severity of their liver disease. Some additional tests might be necessary.
Subjects with renal impairment	Darunavir is often combined with cobicistat, another anti-HIV drug that has been shown to decrease estimated creatinine clearance (a test that shows how well kidneys work and dispose drugs). Therefore, cobicistat should not be initiated in patients with creatinine clearance less than 70 ml/min if any other drug (e.g. emtricitabine, lamivudine, tenofovir disoproxil fumarate, or adefovir) requires dose adjustment based on creatinine clearance. When darunavir is combined with ritonavir, there are no special precautions or dose adjustments required in patients with renal impairment.
Use of DRV/COBI in subjects coinfected with HIV and HBV and/or HCV	Limited information is available on the use of DRV/COBI in patients coinfected with hepatitis B and/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

Risk	What is known
	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 risk minimisation measures by safety concern

No additional risk minimisation measures are proposed.

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 (PL). The measures in these documents are known as routine risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Study / activity	Objectives	Safety concerns addressed	Status	Planned date for submission of (interim and) final results
Antiretroviral pregnancy registry (APR)	Objective of the APR is to detect any major teratogenic effect involving any of the Registry drugs when administered to pregnant women	Use in pregnancy	In progress	Regular APR reports. Estimated study completion date- January 2099

Studies which are a condition of the marketing authorisation

None of the above studies are conditions of the marketing authorisation

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

Not applicable.