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Summary of the risk management plan (RMP) for Neofordex (dexamethasone)

This is a summary of the risk management plan (RMP) for Neofordex, which details the measures to be taken in order to ensure that Neofordex is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Neofordex, which can be found on Neofordex's EPAR page.

Overview of disease epidemiology

Neofordex is a medicine used together with cancer medicines to treat multiple myeloma, a cancer of a type of blood cells called plasma cells.

Multiple myeloma affects about 2 to 3 people in 10,000 in the European Union. The exact causes of multiple myeloma are not known. It is more common in men than in women and in black people than among those of white or Asian descent. Most people diagnosed with multiple myeloma are over 65 years of age. The choice of treatment depends on several factors, including how advanced the disease is. With current treatments, about half of all patients with the disease survive for more than 45 to 60 months following diagnosis.

Summary of treatment benefits

Neofordex contains the active substance dexamethasone. It is a 'hybrid medicine'. This means that it is similar to a reference medicine containing the same active substance, but Neofordex is available at a higher strength (40 mg). The reference medicine for Neofordex is Dectancyl.

The effects of high-dose dexamethasone in multiple myeloma are well established. A bioequivalence study in 24 healthy volunteers showed that Neofordex has comparable quality to the reference medicine, Dectancyl.

Unknowns relating to treatment benefits

No detailed information on the use of dexamethasone in patients with liver impairment is available. Since dexamethasone is broken down by the liver, use of dexamethasone in patients with liver disorders requires appropriate supervision. However, no difference in the effectiveness of high-dose dexamethasone is expected in these patients.

Dexamethasone is broken down in the liver by specific enzymes known as cytochromes (especially cytochrome CYP3A4). Due to the genetic variability between individuals, these cytochromes can be slightly different from one person to another and, consequently, dexamethasone can be broken down to different extents in different individuals. No detailed information is currently available on the use of dexamethasone in individuals with variant cytochrome CYP3A4.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Arterio-venous thromboembolism (blood clots in the vein and arteries) [predominantly: • deep vein thrombosis (blood clot in a deep vein); • pulmonary embolism (clot in a blood vessel supplying the lungs)]	Arterio-venous thromboembolic events (predominantly deep vein thrombosis and pulmonary embolism) have been reported commonly (in up to 1 patient in 10) in patients treated with dexamethasone together with other medicines targeting the immune system (e.g. lenalidomide thalidomide or pomalidomide).	Patients with risk factors for thromboembolism should be closely monitored. Medicines that increase the production of red blood cells or other medicines that may increase the risk of thrombosis such as hormone replacement therapy should be used with caution in multiple myeloma patients receiving Neofordex with thalidomide and similar medicines. Preventative antithrombotic treatment should be considered, especially in patients with additional thrombotic risk factors. Patients should be instructed to seek medical care if they develop symptoms of thromboembolism such as shortness of breath, chest pain, and arm or leg swelling. If the patient experiences any thromboembolic events, treatment for multiple myeloma must be stopped and standard anticoagulation therapy started.
Myelosuppression (a condition in which the bone marrow cannot make enough blood cells) [predominantly: thrombocytopenia (low blood platelets counts) and neutropenia (low levels of neutrophils, a type of white blood cell)]	Neutropenia and thrombocytopenia have been reported commonly (in up to 1 patient in 10) in patients treated with dexamethasone alone or together with other medicines. These side effects can be severe.	Patients should be monitored for haematological (blood) side effects. Patients should be advised to promptly report any fever and bleeding. The dose of lenalidomide or pomalidomide may need to be reduced.
Infections	Infections including serious cases occur with dexamethasone	Before starting treatment, any source of infection, especially

Risk	What is known	Preventability
	alone in a majority of patients (57 to 68%; up to 6%-11% serious infections). Their frequency is higher with high-dose dexamethasone than with low-dose dexamethasone.	tuberculosis, should be removed. During treatment, patients should be closely monitored for the appearance of infections, in particular pneumonia (lung infection). Patients should be informed of the signs and symptoms of pneumonia and be advised to seek medical attention in case of their appearance. Patients must avoid contact with people with chickenpox or measles. Exposed patients should be advised to seek medical attention without delay.
Psychiatric disorders	Many different psychiatric disorders have been reported with dexamethasone, such as depression, somnolence, altered mood, euphoria, insomnia, anxiety, irritability and agitation.	Caution is required when considering the use of Neofordex in patients with existing or previous severe psychiatric disorders. Patients/carers should be warned that potentially severe psychiatric disorders may occur with Neofordex. Symptoms typically emerge within a few days or weeks of starting the treatment. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Insomnia may be minimised by administering Neofordex in the morning.
Interaction with live attenuated vaccines	Patients with multiple myeloma are more likely to develop vaccine-related illnesses when	Live attenuated vaccines should not be given to patients under Neofordex treatment.

Risk	What is known	Preventability
	given live vaccines.	
Interaction with high-dose acetylsalicylic acid (aspirin)	The combination of dexamethasone and high-dose acetylsalicylic acid increases the risk of gastrointestinal bleeding, ulceration, and perforation.	Administration of high-dose acetylsalicylic acid should be avoided in patients under Neofordex treatment.

Important potential risks

Risk	What is known
Off-label use (use outside of the current Neofordex authorisation for multiple myeloma)	High-dose dexamethasone in association with other medicines is commonly used in the treatment of certain advanced haematologic (blood) diseases other than multiple myeloma (e.g. B cell lymphoproliferative diseases, other lymphocytic leukaemias, Waldenstrom macroglobulinaemia and idiopathic thrombocytopenia purpura). Neofordex has been used in the treatment of these indications in France under a special authorisation granted by the French medicines regulatory authority (ANSM) (patients had to be enrolled in a compassionate use programme).
Medication error related to administration of a 20 mg dose	Elderly and/or frail patients may have difficulty breaking tablets in order to take the 20 mg dose that they are frequently prescribed. Halved tablets may not be stable under storage conditions encountered in patients' homes and it must be ensured that patients discard tablet halves that are not taken immediately and in agreement with environmental protection precautions.
Interaction with oral contraceptives	No interaction study has been performed with dexamethasone and oral contraceptives. However, dexamethasone may decrease blood levels of oral contraceptives which would lead to an ineffective contraception.
Interaction with substances given by mouth that prevent blood clotting (so-called anticoagulants)	The use of dexamethasone may accelerate the processing in the liver of anticoagulants, leading to a faster elimination from the body, which consequently leads to a lower effectiveness of the anticoagulants.
Interaction with medicines that stimulate red blood cell production (so-called erythropoietic medicines)	Erythropoietic medicines have been identified as a risk factor for developing blood clots (thromboembolic events). The combination of lenalidomide or thalidomide with dexamethasone is associated with an increased risk of venous and arterial blood clots. Consequently, the association of erythropoietic medicines and lenalidomide or thalidomide with dexamethasone further increases the risk of blood clots.

Missing information

Risk	What is known
Use in patients with reduced liver function (so-called hepatic	Dexamethasone is broken down by the liver but no detailed information is available on its use and dose in patients with reduced liver function. Patients with reduced liver function require appropriate supervision.

Risk	What is known
impairment)	
Use in people with genetic differences in some cytochromes (CYP3A4, CYP2D6) and proteins (multidrug resistance proteins - MRP)	Dexamethasone is known to have some effects on certain cytochromes and proteins (CYP3A4, CYP2D6, MRP 1, MRP3 and MRP4). No information is available on the exact effect of dexamethasone in patients with genetic differences in these cytochromes and proteins. Patients known to have some of these genetic differences should be carefully supervised by their physician.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Neofordex can be found on Neofordex's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of activities in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Development of a 20 mg oral dosage form to supplement Neofordex 40 mg tablets.	To reduce the risk of medication errors with Neofordex 40 mg	Medication error related to administration of 20 mg dose	Planned	A marketing authorisation application for a 20 mg oral dosage form should be filed within 12 months of the authorisation of Neofordex 40 mg tablets
Removal of the score line for sub-division of the 40 mg tablet, and consequent deletion of the 20 mg posology	To reduce the risk of medication errors with Neofordex 40 mg	Medication error related to administration of 20 mg dose	Planned	A variation application should be submitted within 12 months of the first approval of the 20 mg oral dosage form

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 02-2016.