ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Neofordex 40 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains dexamethasone acetate, equivalent to 40 mg dexamethasone.

Excipient with known effect: Each tablet contains 98.1 mg lactose (as monohydrate).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White, oblong (11 mm × 5.5 mm) tablet with a score-line on one face.
The tablet can be divided for administration of a 20 mg dose (see section 4.2).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neofordex is indicated in adults for the treatment of symptomatic multiple myeloma in combination with other medicinal products.

4.2 Posology and method of administration

Treatment must be initiated and monitored under the supervision of physicians experienced in the management of multiple myeloma.

Posology

The dose and administration frequency varies with the therapeutic protocol and the associated treatment(s). Neofordex administration should follow instructions for dexamethasone administration when described in the Summary of Product Characteristics of the associated treatment(s). If this is not the case, local or international treatment protocols and guidelines should be followed. Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

The usual posology of dexamethasone is 40 mg once per day of administration.

At the end of dexamethasone treatment, the dose should be tapered in a stepwise fashion until a complete stop.

Elderly
In elderly and/or frail patients, the daily dose may be reduced to 20 mg of dexamethasone, according to the appropriate treatment regimen.

Hepatic impairment or renal insufficiency
Patients with hepatic impairment or renal insufficiency require appropriate monitoring; patients with hepatic impairment should be dosed with caution as there are no data for this patient population (see sections 4.4 and 5.2).

Paediatric population
There is no relevant use of Neofordex in the paediatric population in the indication multiple myeloma.

Method of administration
Oral use.

In order to minimise insomnia, the tablet should preferably be taken in the morning.

Tablets should be kept in the blister package until administration. Individual tablets in intact packaging should be separated from the blister using the perforation, e.g. for use in multi-compartment compliance aids.

Tablets may be broken in two equal halves using the score line to provide the 20 mg dose. **Due to possible stability issues affecting half tablets stored after division, half-tablets that are not taken immediately should be discarded** in agreement with local precautions for environmental protection (see also 6.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active viral disease (especially viral hepatitis, herpes, varicella, shingles).

Uncontrolled psychoses.

When Neofordex is given in combination with other medicinal products, refer to their Summaries of Product Characteristics for additional contraindications.

4.4 Special warnings and precautions for use

Neofordex is a high-dose glucocorticoid. This should be taken into consideration in the surveillance of the patient. The benefit from dexamethasone treatment should be carefully and continuously weighed against actual and potential risks.

Risk of infection
Treatment with high-dose dexamethasone increases the risk of developing serious infections, in particular due to bacteria, yeasts and/or parasites. Such infections can also be caused by microorganisms that rarely cause disease under normal circumstances (opportunistic infections). Signs of a developing infection may be masked by dexamethasone therapy.

Before the start of treatment, any source of infection, especially tuberculosis, should be removed. During treatment, patients should be closely monitored for the appearance of infections. In particular, pneumonia occurs commonly. Patients should be informed of the signs and symptoms of pneumonia and be advised to seek medical attention in case of their appearance. In case of active infectious disease, appropriate anti-infective treatment must be added to the treatment with Neofordex.

In cases of prior tuberculosis with major radiological sequelae or if it is not certain that a full 6-month rifampicin treatment course has been followed, a prophylactic anti-tuberculosis treatment is required.

There is a risk of severe strongyloidiasis. Patients from endemic areas (tropical and sub-tropical regions, southern Europe) should have a stool examination and if required an eradication of the parasite before initiating dexamethasone treatment.

Certain viral diseases (varicella, measles) can be aggravated in patients receiving glucocorticoid treatment or who have received glucocorticoid treatment within the previous 3 months. Patients must avoid contact with subjects with chickenpox or measles. Immunocompromised patients who have not previously had chickenpox or measles are particularly at risk. If such patients have been in contact with people with chickenpox or measles, a preventive treatment with intravenous normal immunoglobulin or passive

immunisation with varicella zoster immunoglobulin (VZIG) must be started as appropriate. Exposed patients should be advised to seek medical attention without delay.

Neofordex should not be used with live attenuated vaccines (see section 4.5). Vaccinations with inactivated vaccines are usually possible. However, the immune response and hence the effect of the vaccination can be diminished by high glucocorticoid doses.

Dexamethasone can suppress skin reaction to allergy testing. It can also affect the nitro blue tetrazolium (NBT) test for bacterial infections and cause false-negative results.

Psychiatric disorders
Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses (see also section 4.5 for pharmacokinetic interactions that can increase the risk of adverse reactions), although dose levels do not allow prediction of the onset, type severity or duration of reactions. 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. Patients/carers should also be alert to possible psychiatric disturbances that may occur either during, or immediately after, dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychoses.

Insomnia may be minimised by administering Neofordex in the morning.

Gastrointestinal disorders
Treatment for active gastric or duodenal ulceration should be commenced prior to initiation of corticosteroids. Appropriate prophylaxis should be considered for patients with a previous history of, or risk factors for, gastric or duodenal ulceration, haemorrhage or perforation. Patients should be monitored clinically, including by endoscopy.

Eye disorders
Systemic treatment with glucocorticoids can induce chorioretinopathy which may result in impaired vision including loss of vision.

Prolonged use of corticosteroids may produce subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses. Particular care is needed when treating patients with glaucoma (or family history of glaucoma) as well as when treating patients with ocular herpes simplex, because of possible corneal perforation.

Tendonitis
Corticosteroids can favour the development of tendonitis and, in exceptional cases, rupture of the affected tendon. This risk is increased by concomitant use of fluoroquinolones and in patients undergoing dialysis with secondary hyperparathyroidism or after renal transplantation.

Elderly
The common adverse reactions to systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

Monitoring
Use of corticosteroids requires appropriate monitoring in patients with ulcerative colitis (due to perforation risk), recent intestinal anastomoses, diverticulitis, recent myocardial infarction (risk of left ventricular free

wall rupture), diabetes mellitus (or family history), renal insufficiency, hepatic impairment, osteoporosis and myasthenia gravis.

Long-term treatment
During treatment, a diet low in simple sugars and high in protein should be followed due to the hyperglycaemic effect of corticosteroids and their stimulation of protein catabolism with a negative nitrogen balance.

Water and sodium retention is common and can lead to hypertension. Sodium intake should be reduced and blood pressure should be monitored. Particular care is needed when treating patients with renal impairment, hypertension or congestive heart failure.

Potassium levels should be monitored during treatment. Potassium supplementation should be given particularly if there is a risk of cardiac arrhythmia or concurrent hypokalaemic medicinal products.

Glucocorticoid therapy may reduce the effect of anti-diabetic and antihypertensive treatment. The dose of insulin, oral anti-diabetics and anti-hypertensive medicinal products may have to be increased.

Depending on the duration of treatment, calcium metabolism may be impaired. Calcium and vitamin D levels should be monitored. In patients not already prescribed bisphosphonates for multiple myeloma related bone disease, bisphosphonates should be considered, particularly if risk factors for osteoporosis are present.

Lactose intolerance
Neofordex contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Use in combination with other multiple myeloma treatment(s)

When Neofordex is given in combination with other medicinal products, the Summary of Product Characteristics of these other medicinal products must be consulted prior to initiation of treatment with Neofordex.

When Neofordex is used in combination with known teratogens (e.g. thalidomide, lenalidomide, pomalidomide, plerixafor), particular attention to pregnancy testing and prevention requirements is needed (see section 4.6).

Venous and arterial thromboembolic events
In patients with multiple myeloma, the combination of dexamethasone with thalidomide and its analogues is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event) (see sections 4.5 and 4.8).

Consequently, patients with known risk factors for thromboembolism (including prior thrombosis) should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic medicinal products may also increase thrombotic risk in these patients. Therefore, erythropoietic medicinal products, or other medicinal products that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving dexamethasone with thalidomide and its analogues. A haemoglobin concentration above 12 g/dl should lead to discontinuation of erythropoietic medicinal products.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Prophylactic antithrombotic treatment should be recommended, especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors.

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the treatment with dexamethasone and thalidomide or its analogues may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of treatment with dexamethasone and thalidomide or its analogues.

Neutropenia and thrombocytopenia
The combination of dexamethasone with lenalidomide in multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients; see section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients; see section 4.8). Neutropenia was the most frequently reported Grade 3 or 4 haematological adverse reaction in patients with relapsed/refractory multiple myeloma treated with the combination of dexamethasone with pomalidomide. Patients should be monitored for haematological adverse reactions, especially neutropenia. Patients should be advised to promptly report febrile episodes. A dose reduction of lenalidomide or pomalidomide may be required. In case of neutropenia, the physician should consider the use of growth factors in patient management.

The combination of dexamethasone with lenalidomide in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients) (see section 4.8). Thrombocytopenia was also reported very commonly by patients with relapsed/refractory multiple myeloma treated with the combination of dexamethasone with pomalidomide. Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in case of concomitant treatment susceptible to induce bleeding. A dose reduction of lenalidomide or pomalidomide may be required.

A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of dexamethasone/lenalidomide treatment and monthly thereafter to monitor for cytopenias.

4.5 Interaction with other medicinal products and other forms of interaction

Prior to the use of Neofordex in combination with any other medicinal product, reference should be made to the Summary of Product Characteristics of that product.

Pharmacodynamic interactions

The following combinations should be avoided due to safety concerns:
- With acetylsalicylic acid, at doses ≥ 1 g per dose or 3 g per day, due to an increased risk of bleeding. At doses ≥ 500 mg per dose or < 3 g per day, precautions are required due to increased risk of haemorrhage, ulcerations and gastro-intestinal perforation. However, antithrombotic prophylaxis with low-dose acetylsalicylic acid is possible.
- With live attenuated vaccines, due to risk of vaccine-related illness with risk of death.

The following combinations require precautions due to safety concerns:
- With hypokalaemic medicinal products: hypokalemic diuretics, single or in combination, laxatives, tetracosactide, intravenous amphotericin B, due to increased risk of hypokalaemia. Potassium levels should be monitored and corrected as necessary. In addition, amphotericin B carries a risk of cardiac enlargement and cardiac failure with concurrent use.
- With digitalis, as hypokalaemia enhances the toxic effects of digitalis. Any hypokalaemia should be corrected and patients should be monitored clinically, for electrolytes and by electrocardiograpy.

- With medicinal products that carry a risk of Torsades de Pointes, due to increased risk of ventricular arrhythmia. Any hypokalaemia should be corrected and patients should be monitored clinically, for electrolytes and by electrocardiography.
- With erythropoietic medicinal products or other medicinal products that may increase the risk of thrombosis, such as hormone replacement therapy, in patients receiving thalidomide or its analogues with Neofordex (see sections 4.4 and 4.8).
- With non-steroidal anti-inflammatory drugs (NSAIDs), due to an increased risk of gastrointestinal ulceration.
- With hypoglycaemic medicinal products, as dexamethasone can raise glycaemic levels and diminish glucose tolerance, with a possibility of ketoacidosis. Patients should be made aware of this risk and self-monitoring of blood and urine should be reinforced, especially during the initiation of treatment. The posology of anti-diabetic medicinal products may have to be adjusted during and after the treatment with dexamethasone.
- With anti-hypertensive medicinal products, due to a reduction of their effect (water and sodium retention). The dose of the anti-hypertensive treatment may have to be adjusted during the treatment with dexamethasone.
- With fluoroquinolones, due to possibly increased risk of tendonitis and, in exceptional cases, rupture of the affected tendon, particularly after long-term treatment.
- With methotrexate, due to an increased risk of haematological toxicity.

Pharmacokinetic interactions

Effects of other medicinal products on dexamethasone
Dexamethasone is metabolized via cytochrome P450 3A4 (CYP3A4), and transported by the P-glycoprotein (P-gp, also known as MDR1). Concomitant administration of dexamethasone with inducers or inhibitors of CYP3A4 or P-gp may lead to decreased or increased plasma concentrations of dexamethasone, respectively.

The following combinations require precautions due to changes in dexamethasone pharmacokinetics:
– Medicinal products that may reduce dexamethasone plasma concentration:
  - Aminogluthetimide, due to a reduction of the efficacy of dexamethasone through an increase of its hepatic metabolism.
  - Anticonvulsants that are hepatic enzyme inducers: carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone, due to the reduction of dexamethasone plasma levels and hence its efficacy.
  - With rifampicin, due to reduction of dexamethasone plasma concentrations and efficacy by an increase of its hepatic metabolism.
  - Topical gastro-intestinal medicinal products, antacids and activated carbon, as well as colestyramine, due to reduction of the intestinal absorption of dexamethasone. The administration of such medicinal products and Neofordex should be separated by at least two hours.
  - Ephedrine, due to a reduction in dexamethasone plasma levels by increased metabolic clearance.
– Medicinal products that may increase dexamethasone plasma concentration:
  - Aprepitant and fosaprepitant, due to an increase of dexamethasone plasma concentrations by a reduction of its hepatic metabolism.
  - Clarithromycin, erythromycin, telithromycin, itraconazole, ketoconazole, posaconazole, voriconazole, nelfinavir, ritonavir: Increased dexamethasone plasma concentration due to reduction of its hepatic metabolism by these enzyme inhibitors.

Effects of dexamethasone on other medicinal products
Dexamethasone is a moderate inducer of CYP3A4 and of P-gp. Concomitant administration of dexamethasone with substances that are metabolised via CYP3A4 or transported by P-gp could lead to increased clearance and decreased plasma concentrations of these substances:

- Oral contraceptives, as it cannot be excluded that the efficacy of oral contraceptives may be reduced during treatment. No interaction study has been performed with oral contraceptives. Effective measures to avoid pregnancy must be taken (see section 4.6). Efficacy of hormone replacement therapy may also be reduced.

- Oral anticoagulants, due to a possible impact of corticosteroids on the metabolism of the oral anticoagulant and on coagulation factors, as well as the haemorrhagic risk (mucosa of the digestive tract, vascular fragility) of dexamethasone therapy itself at high doses or treatment periods above 10 days. It the combination is required, monitoring should be reinforced and coagulation parameters controlled after one week and then every other week of treatment as well as after the end of treatment.
- Docetaxel and cyclophosphamide, due to reduction of their plasma levels by induction of CYP3A and P-gp.
- Lapatinib, due to increased hepatotoxicity of lapatinib likely due to induction of CYP3A4 metabolism.
- Ciclosporin, due to a reduction of ciclosporin bioavailability and plasma levels. Ciclosporin may also increase the intracellular uptake of dexamethasone. In addition, convulsions have been reported with concurrent use of dexamethasone and ciclosporin. Concomitant use of dexamethasone and ciclosporine should be avoided.
- Midazolam, due a reduction in midazolam plasma levels by CYP3A4 induction. The efficacy of midazolam may be reduced.
- Ivermectin, due to a reduction of ivermectin plasma levels. Parasite eradication must be successfully terminated before dexamethasone use (see section 4.4).
- Rifabutin, due to reduced rifabutin plasma levels by induction of intestinal and hepatic CYP3A4.
- Indinavir, due to a strong reduction of indinavir plasma levels by intestinal CYP3A4 induction.
- Erythromycin, due to increased metabolism of erythromycin in non-carriers of the *CYP3A5*1* allele after dexamethasone treatment.
- Isoniazid, as glucocorticoids may decrease isoniazid plasma concentrations, probably due to a stimulation of hepatic metabolism of isoniazid and a reduction of glucocorticoid metabolism.
- Praziquantel, due to the reduction of praziquantel plasma concentrations due to an increase of its hepatic metabolism by dexamethasone, with a risk of failure of treatment. The treatments with the two medicinal products should be separated by at least one week.

Repeated, daily administration of dexamethasone also leads to reduced dexamethasone plasma levels due to the induction of CYP3A4 and P-gp. No dose adjustment is needed in the treatment of multiple myeloma.

Dexamethasone has no clinically significant pharmacokinetic interaction with thalidomide, lenalidomide, pomalidomide, bortezomib, vincristine or doxorubicin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women should avoid pregnancy during Neofordex treatment. Dexamethasone may cause congenital malformations (see section 5.3). Dexamethasone may be used with known teratogens (e.g. thalidomide, lenalidomide, pomalidomide, plerixafor), or with cytotoxic substances which are contraindicated in pregnancy. Patients receiving Neofordex in combination with products containing thalidomide, lenalidomide or pomalidomide should adhere to the pregnancy prevention programmes of those products. Reference should be made to all the relevant Summary of Product Characteristics prior to the commencement of any combination treatment for additional information.

Contraception in males and females
Women of childbearing potential and their male partners should take appropriate contraceptive measures. In particular, the requirements of the pregnancy prevention programme for combination treatment with thalidomide or its analogues must be followed. The efficacy of oral contraceptives may be reduced during dexamethasone treatment (see section 4.5).

Pregnancy
Based on human experience, dexamethasone is suggested to cause congenital malformations, particularly intra-uterine growth retardation and rarely neonatal adrenal insufficiency, when administered during pregnancy.
Studies in animals have shown reproductive toxicity (see section 5.3).

Neofordex should not be used during pregnancy unless the clinical condition of the woman requires treatment with dexamethasone.

Breast-feeding
Glucocorticoids are excreted in human milk and effects have been shown in breastfed newborns/infants of treated women.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Neofordex therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Studies in animals have shown reductions in female fertility (see Section 5.3). No data on male fertility are available.

4.7 Effects on ability to drive and use machines

Neofordex has moderate influence on the ability to drive and use machines.
Dexamethasone may cause confusional state, hallucinations, dizziness, somnolence, fatigue, syncope and blurred vision (see section 4.8). If affected, patients should be instructed not to drive, use machines or perform hazardous tasks while being treated with dexamethasone.

4.8 Undesirable effects

Summary of the safety profile
Adverse reactions to Neofordex correspond to the predictable safety profile of glucocorticoids. Hyperglycaemia, insomnia, muscle pain and weakness, asthenia, fatigue, oedema and weight increase occur very commonly. Less common but serious adverse reactions include: pneumonia and other infections and psychiatric disorders (see section 4.4). In combination with thalidomide or its analogues the most serious adverse reactions were venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism, and myelosuppression, particularly neutropenia and thrombocytopenia (see section 4.4).

The incidence of predictable adverse reactions, including adrenal atrophy, correlates with dose, timing of administration and the duration of treatment (see section 4.4).

Tabulated list of adverse reactions
The adverse reactions observed in patients treated with dexamethasone are listed below by system organ class and frequency. Data are derived from historical experience and clinical studies in multiple myeloma patients in which dexamethasone was used as monotherapy or in combination with placebo. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000 including isolated reports), not known (cannot be estimated from the available data).

System organ class	**Adverse reactions**
Infections and Infestations	*Common*: Pneumonia, herpes zoster, upper respiratory tract infection, lower respiratory tract infection, oral candidiasis, oral fungal infection, urinary tract infection, herpes simplex, candidal infection; *Not known*: Infection, sepsis.
Blood and the lymphatic system disorders	*Common*: Neutropenia, anaemia, thrombocytopenia, lymphopenia, leukopenia, leukocytosis; *Uncommon*: Febrile neutropenia, pancytopenia, coagulopathy.
Endocrine disorders	*Common*: Cushing's syndrome; *Uncommon*: Hypothyroidism; *Not known*: Adrenal atrophy, steroid withdrawal syndrome, adrenal insufficiency, hirsutism, menstrual irregularity.

Metabolism and nutrition disorders	*Very common*: Hyperglycaemia; *Common*: Hypokalaemia, diabetes mellitus, anorexia, increased or decreased appetite, hypoalbuminaemia, fluid retention, hyperuricaemia; *Uncommon*: Dehydration, hypocalcaemia, hypomagnesemia; *Not known*: Glucose tolerance impaired, sodium retention, metabolic alkalosis.
Psychiatric disorders	*Very common*: Insomnia; *Common*: Depression, anxiety, aggression, confusional state, irritability, nervousness, mood alteration, agitation, euphoric mood; *Uncommon*: Mood swings, hallucinations; *Not known*: Mania, psychosis, behavioural disturbance.
Nervous system disorders	*Common*: Peripheral neuropathy, dizziness, psychomotor hyperactivity, disturbance in attention, memory impairment, tremor, paraesthesia, headache, ageusia, dysgeusia, somnolence, lethargy, balance impaired, dysphonia; *Uncommon:* Cerebrovascular accident, transient ischaemic attack, amnesia, coordination abnormal, ataxia, syncope; *Not known:* Convulsions.
Eye disorders	*Common*: Vision blurred, cataract; *Uncommon*: Conjunctivitis, increased lacrimation; *Not known:* Chorioretinopathy, glaucoma.
Ear and labyrinth disorders	*Common:* Vertigo.
Cardiac disorders	*Common:* Atrial fibrillation, supraventricular extrasystoles, tachycardia, palpitations; *Uncommon*: Myocardial ischaemia, bradycardia; *Not known*: Congestive heart failure.
Vascular disorders	*Common*: Venous thromboembolic reactions, predominantly deep vein thrombosis and pulmonary embolism, hypertension, hypotension, flushing, blood pressure increased, diastolic blood pressure decreased; *Not known:* Purpura, bruising.
Respiratory, thoracic, or mediastinal disorders	*Common*: Bronchitis, cough, dyspnoea, pharyngolaryngeal pain, hoarseness, hiccough.
Gastrointestinal disorders	*Very Common*: Constipation; *Common*: Vomiting, diarrhoea, nausea, dyspepsia, stomatitis, gastritis, abdominal pain, dry mouth, abdominal distension, flatulence; *Not known*: Pancreatitis, gastrointestinal perforation, gastrointestinal haemorrhage, gastrointestinal ulcer.
Hepatobiliary disorders	*Common:* Liver function tests abnormal, alanine aminotransferase increased.
Skin and subcutaneous tissue disorders	*Common*: Rash, erythema, hyperhidrosis, pruritus, dry skin, alopecia; *Uncommon*: Urticaria; *Not known:* Skin atrophy, acne.
Musculoskeletal and connective tissue disorders	*Very common*: Muscular weakness, muscle cramps; *Common*: Myopathy, musculoskeletal pain, arthralgia, pain in extremity; *Not known*: Pathological fracture, osteonecrosis, osteoporosis, tendon rupture.
Renal and urinary disorders	*Common*: Pollakiuria; *Uncommon:* Renal failure.
General disorders and administration site conditions	*Very common*: Fatigue, asthenia, oedema (including peripheral and facial oedema); *Common*: Pain, mucosal inflammation, pyrexia, chills, malaise; *Not known*: Impaired healing.

Investigations	*Common:* Weight decreased, weight increased.

Description of selected adverse reactions

Prior to the use of Neofordex in combination with any other medicinal product, reference should be made to the Summary of Product Characteristics of that product.

The incidence rate of certain adverse reactions varies depending on the combination treatment used.

The combination of lenalidomide with dexamethasone in relapsed or refractory multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients). A similar incidence of high-grade neutropenia was reported in newly diagnosed patients treated with the combination of lenalidomide and dexamethasone.

Neutropenia occurred in 45.3% of relapsed and refractory multiple myeloma patients who received low dose dexamethasone plus pomalidomide (Pom + LD-Dex), and in 19.5% of patients who received high dose dexamethasone (HD-Dex). Neutropenia was Grade 3 or 4 in 41.7% of patients who received Pom + LD-Dex, compared with 14.8% who received HD-Dex. In Pom + LD-Dex treated patients neutropenia was infrequently serious (2.0% of patients), did not lead to treatment discontinuation, and was associated with treatment interruption in 21.0% of patients, and with dose reduction in 7.7% of patients. Febrile neutropenia (FN) was experienced in 6.7% of patients who received Pom + LD-Dex, and in no patients who received HD-Dex. All were reported to be Grade 3 or 4. FN was reported to be serious in 4.0% of patients. FN was associated with dose interruption in 3.7% of patients, and with dose reduction in 1.3% of patients, and with no treatment discontinuations.

The combination of lenalidomide with dexamethasone in relapsed or refractory multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients). A similar incidence of high-grade thrombocytopenia was reported in newly diagnosed patients treated with the combination of lenalidomide and dexamethasone. Thrombocytopenia occurred in 27.0% of relapsed and refractory multiple myeloma patients who received Pom + LD-Dex, and 26.8% of patients who received HD-Dex. Thrombocytopenia was Grade 3 or 4 in 20.7% of patients who received Pom + LD-Dex and in 24.2% who received HD-Dex. In Pom + LD-Dex treated patients, thrombocytopenia was serious in 1.7% of patients, led to dose reduction in 6.3% of patients, to dose interruption in 8% of patients and to treatment discontinuation in 0.7% of patients.

The combination of lenalidomide, thalidomide or pomalidomide with dexamethasone is associated with an increased risk of deep vein thrombosis and pulmonary embolism in patients with multiple myeloma (see section 4.5). Concomitant administration of erythropoietic medicinal products or previous history of deep vein thrombosis may also increase thrombotic risk in these patients.

Low-grade peripheral neuropathic reactions, predominantly grade 1 paraesthesia, may be observed with dexamethasone alone in up to 34% of newly diagnosed multiple myeloma patients. However, both incidence and severity of peripheral neuropathy increase with concomitant bortezomib or thalidomide administration. In one study, 10.7% of patients treated with thalidomide and dexamethasone experienced grade 3/4 neuropathic reactions, compared to 0.9% of patients treated with dexamethasone alone.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Acute toxicity of dexamethasone is weak and toxic effects have rarely been observed after an acute overdose. No antidote exists and treatment is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids for systemic use, glucocorticoids, ATC code: H02AB02

Mechanism of action

Dexamethasone is a synthetic glucocorticoid; it combines high anti-inflammatory effects with low mineralocorticoid activity. At high doses (e.g. 40 mg), it reduces the immune response.

Dexamethasone has been shown to induce multiple myeloma cell death (apoptosis) via a down-regulation of Nuclear Factor-κB activity and an activation of caspase-9 through second mitochondria-derived activator of caspase (Smac; an apoptosis promoting factor) release. Prolonged exposure was required to achieve maximum levels of apoptotic markers along with increased caspase-3 activation and DNA fragmentation. Dexamethasone also down-regulated anti apoptotic genes and increased IκB-α protein levels.

Dexamethasone apoptotic activity is enhanced by the combination with thalidomide or its analogues and with proteasome inhibitor (e.g. bortezomib).

Multiple myeloma is a progressive rare haematologic disease. It is characterized by excessive numbers of abnormal plasma cells in the bone marrow and overproduction of intact monoclonal immunoglobulin (IgG, IgA, IgD, or IgE) or Bence-Jones protein only (free immunoglobulin monoclonal κ and λ light chains).

Clinical efficacy and safety
No clinical efficacy and safety studies have been conducted using Neofordex in the treatment of multiple myeloma.

The efficacy and safety of dexamethasone combination treatment in multiple myeloma has been confirmed in numerous clinical studies in newly diagnosed patients and in patients with relapsed or refractory disease. The patient populations studied included a wide range of ages, as well as patients considered eligible or ineligible for autologous stem cell transplantation. High-dose (40 mg or 20 mg) oral dexamethasone has been studied in the therapy of multiple myeloma in combination with chemotherapy in the VAD regimen (vincristine, adriamycin/doxorubicin and dexamethasone) or in association with novel agents, including thalidomide and its analogues as well as proteasome inhibitors. In controlled studies, combination treatment with dexamethasone consistently showed better outcomes in terms of survival and response than single-agent dexamethasone.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Neofordex in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
After oral administration of Neofordex, dexamethasone peak plasma levels are reached at a median of three hours. Bioavailability of dexamethasone is approximately 80%. There is a linear relationship between administered and bioavailable doses.

Dexamethasone is transported by the P-glycoprotein (also known as MDR1). Other MDR transporters may also have a role in dexamethasone transport.

Distribution
Dexamethasone is bound by plasma proteins, principally albumin, up to about 80%, depending on the administered dose. At very high doses the majority of dexamethasone circulates unbound in the blood. The volume of distribution is approximately 1 l/kg. Dexamethasone crosses the blood-brain barrier and the placental barrier and passes into breast milk.

Biotransformation
A minor part of administered dexamethasone is excreted unchanged by the kidney. The major part is hydrogenated or hydroxylated in humans, the major metabolites being hydroxy-6-dexamethasone and dihydro-20-dexamethasone. 30 to 40% are conjugated to glucuronic acid or sulphated in the human liver and excreted in this form in the urine. Dexamethasone is metabolized via cytochrome P450 3A4 (CYP3A4). Other cytochrome P450 isoenzymes may also play a role in dexamethasone biotransformation.

Elimination
The plasma half-life of dexamethasone is approximately 250 minutes.

Specific groups of patients

No data are available on the biotransformation of dexamethasone in hepatically impaired patients.

Smoking has no influence on dexamethasone pharmacokinetics. No differences were found in dexamethasone pharmacokinetics between subjects of European and Asian (Indonesian and Japanese) descent.

5.3 Preclinical safety data

Glucocorticoids have only weak acute toxicity. No chronic toxicity and carcinogenicity data are available. Genotoxicity findings have been shown to be artefactual. In reproductive toxicity studies in mice, rats, hamsters, rabbits and dogs, dexamethasone has led to embryo-fetal malformations such as increase in cleft palate and skeletal defects; decreases in thymus, spleen and adrenal weight; lung, liver, and kidney abnormalities; and inhibition of growth. Post-natal development assessment of animals treated prenatally presented decreased glucose tolerance and insulin sensitivity, behavioural alterations and decrease in brain and body weight. In males, fertility may be decreased through germ cell apoptosis and spermatogenic defects. Data on female fertility are contradictory.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Magnesium stearate
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Tablets should be kept in the blister package until administration. Individual tablets in intact packaging should be separated from the blister using the perforation, e.g. for use in multi-compartment compliance aids. Halved tablets that are not taken immediately should be disposed of (see section 6.6).

6.5 Nature and contents of container

10 x 1 tablets in OPA/Aluminium /PVC-Aluminium perforated unit dose blister. Pack size of 10 tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Advise patients to not dispose of unused tablets through household waste or wastewater.

7. MARKETING AUTHORISATION HOLDER

Laboratoires CTRS
63, rue de l'Est
92100 Boulogne-Billancourt
France
Email: ctrs@ctrs.fr

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1053/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 March 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Amatsi
17, Parc des Vautes
34980 Saint Gély du Fesc
France

Or

Laboratoires CTRS
63, rue de l'Est
92100 Boulogne-Billancourt
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

N/A

- **Obligation to conduct post-authorisation measures**

N/A

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Neofordex 40 mg tablets
dexamethasone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains dexamethasone acetate equivalent to 40 mg dexamethasone.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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63, rue de l'Est
92100 Boulogne-Billancourt
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Email: ctrs@ctrs.fr

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1053/001

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neofordex

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Neofordex 40 mg tablet
dexamethasone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Laboratoires CTRS

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Neofordex 40 mg tablet
Dexamethasone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Neofordex is and what it is used for
2. What you need to know before you take Neofordex
3. How to take Neofordex
4. Possible side effects
5. How to store Neofordex
6. Contents of the pack and other information

1. What Neofordex is and what it is used for

Neofordex is a medicine that contains the active substance dexamethasone. Dexamethasone is a type of hormone called a glucocorticoid, sometimes called a corticoid or corticosteroid, with various actions including effects on white blood cells, which form part of the immune system (the body's natural defences). Dexamethasone is similar to glucocorticoids which are naturally produced in the body.

Neofordex is used to treat adult patients with multiple myeloma, a cancer of the blood affecting the white blood cells that produce antibodies. Neofordex will be given with other medicines for multiple myeloma. They act together by killing cancerous white blood cells.

2. What you need to know before you take Neofordex

Do not take Neofordex
- if you are allergic to dexamethasone or one of the other ingredients of this medicine (listed in section 6),
- if you have a viral infection, especially viral hepatitis, herpes, chickenpox or shingles,
- if you have an untreated psychiatric illness.

Warnings and precautions
Treatment with a high-dose corticosteroid may reduce your body's ability to fight infection. This can sometimes lead to infections caused by germs that rarely cause infection under normal circumstances (called opportunistic infections). If you get an infection of any kind during treatment with this medicine, contact your doctor immediately. This is particularly important if you notice signs of pneumonia: cough, fever, shortness of breath and chest pain. You may also feel confused, particularly if you are elderly. You should also tell your doctor if you have had tuberculosis or if you have stayed in regions where roundworm infections are common.

Note: It is important that while you are taking Neofordex you avoid contact with anyone who is suffering from chickenpox, measles or shingles. If you think you may have had contact with anyone with these conditions, you should inform your doctor immediately.

High-dose corticosteroids, including dexamethasone, can cause psychological problems that may sometimes be serious. Talk to your doctor before taking Neofordex if you or a member of your immediate family have suffered, or currently suffer from severe depression or manic attacks. This is especially important if you feel depressed or might be thinking about suicide.

During treatment with this medicine it is important to maintain a balanced diet. Your doctor will advise on an appropriate diet, and may prescribe potassium, calcium or vitamin D supplements.

If you have had blood clots in the past you should inform your doctor before taking Neofordex. The combination of dexamethasone with thalidomide, lenalidomide or pomalidomide (medicines to treat multiple myeloma) increases the risk of blood clots in the veins and arteries. You must tell your doctor immediately if you experience shortness of breath, chest pain or swelling in the arms or legs.

The combination of dexamethasone with lenalidomide or pomalidomide may cause a decrease in normal white blood cells (blood cells that help fight infection) and/or blood platelets (which help prevent bleeding). Your doctor will arrange appropriate blood tests before and during treatment.

Treatment with this medicine may cause central serous chorioretinopathy, an eye disease that leads to blurred or distorted vision. This happens usually in one of the eyes. If you notice blurring or distorted vision that lasts for several days, please contact your doctor.

Treatment with this medicine may cause tendon inflammation. In extremely rare cases, a tendon may rupture. This risk is increased by treatment with certain antibiotics and by kidney problems. Contact your doctor if you notice painful, stiff or swollen joints or tendons.

Please inform any doctor, dentist or person who may prescribe a treatment for you that you are currently taking or have recently taken dexamethasone.

If you become ill or are involved in an accident, or if you need surgery (even at the dentist) or require a vaccination (particularly “live virus” vaccines) you should inform the doctor treating you that you are taking or have recently taken high-dose corticosteroids.

If you need tests (in particular for infections) you should inform the person performing the tests as dexamethasone may interfere with the results.

Talk to your doctor before taking Neofordex
- if you have liver or kidney disease,
- if you have heart disease or you have recently had a heart attack,
- if you have high blood pressure, high cholesterol or you are a smoker,
- if you have diabetes or if there is a history of diabetes in your family,
- if you have osteoporosis, especially if you are a woman who has been through the menopause,
- if you have glaucoma (increased eye pressure) or if there is a history of glaucoma in your family,
- if you have myasthenia gravis (a disease affecting the muscles),
- if you have a peptic ulcer (ulcer in your stomach or duodenum), or a history of peptic ulcers, stomach bleeding or perforation,
- if you have inflammation of the colon, diverticulitis, or have recently had surgery on the intestine,
- if you have inflammation of a tendon.

You doctor will observe you more closely if you have any of the listed diseases.

If you are elderly, some of the side effects of Neofordex may be more serious, especially thinning of the bones (osteoporosis), high blood pressure, low potassium levels, diabetes, susceptibility to infection and thinning of the skin. Your doctor will monitor you more closely.

Children and adolescents
Children do not develop multiple myeloma. This medicine should not be given to children (i.e. anyone below the age of 18 years).

Other medicines and Neofordex
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You must read the package leaflets of all medicinal products to be taken in combination with Neofordex for information related to these medicines before starting treatment with Neofordex. When thalidomide, lenalidomide or pomalidomide is used, particular attention to pregnancy testing and prevention requirements is needed.

If you are taking any of the following medicines, you should consult your doctor before taking Neofordex:
- Anticoagulant medicines (which thin the blood)
- Acetylsalicylic acid, a substance present in many medicines used to relieve pain and lower fever, and other medicines to treat pain, inflammation and fever: ibuprofen, naproxen, diclofenac, meloxicam and others;
- Medicines for treatment of hypertension or heart disease;
- Medicines for treatment of diabetes;
- Medicines for an upset stomach (for example antacids) and colestyramine (to lower cholesterol);
- Medicines that reduce blood potassium levels: for example some diuretics or laxatives;
- Cortisone or other corticosteroids, tetracosactide (used to test for adrenal function) or aminogluthetimide (used to treat Cushing's syndrome or breast cancer);
- Antibiotics, with active substance names ending in –mycin and in –floxacin; antifungals (to treat fungal infections) with active substance names ending in –conazole or amphotericin B injection; and anti-HIV medicines with active substance names ending in –navir;
- Rifampicin, rifabutin or isoniazid (used to treat tuberculosis);
- Praziquantel or ivermectin (for certain worm infections);
- Oestrogen hormones including the contraceptive pill and hormone replacement therapy (HRT);
- Anticonvulsants (for the treatment of epilepsy) and midazolam (used as sleeping pill and for the treatment of epilepsy);
- Aprepitant or fosaprepitant (for the treatment of nausea and vomiting after surgery or caused by chemotherapy [cancer treatment]);
- Certain medicines to treat cancer: docetaxel, cyclophosphamide, lapatinib or methotrexate. Methotrexate is also used to treat rheumatism or psoriasis;
- Erythropoietin (EPO, to treat anaemia)
- Ciclosporin (for the treatment of psoriasis, atopic dermatitis, rheumatoid arthritis or nephrotic syndrome, and to suppress immune reactions after an organ or bone marrow transplantation)
- Ephedrine (to treat asthma attacks or relieve nasal congestion).

You should also tell your doctor if you have recently received a vaccination or are planning to be vaccinated.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Neofordex should not be taken if you are pregnant unless clearly indicated by your doctor.

You must avoid getting pregnant during treatment with Neofordex. You and your partner must use appropriate contraception. Inform your doctor immediately if you are pregnant or if you become pregnant during treatment.

You must not breast-feed during treatment.

Driving and using machines
Do not drive, use any tools or machines or carry out any hazardous tasks if you experience side effects, such as confusion, hallucinations, dizziness, tiredness, sleepiness, fainting or blurred vision.

Neofordex contains lactose
Neofordex contains lactose, a sugar. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Neofordex

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Your doctor will decide the dose and tell you on which days you should take it. The recommended dose is one tablet each time. If you are over 65 years old and/or frail, your doctor may prescribe a half tablet each time. Do not exceed or take less than the prescribed dose. You must take this medicine on the appropriate days, exactly as your doctor prescribed.

Your doctor may change the dose and frequency of administration based on certain parameters including your blood analyses, your general condition, other medicines prescribed to you and your response to the treatment.

Swallow the prescribed dose of one tablet (40 mg) or half a tablet (20 mg) in the morning with a glass of water.

If your dose is half a tablet (20 mg), the tablet should be divided into two equal halves. Take one half tablet straightaway**. Do not save the spare half tablet to take on another day as this medicine may deteriorate once divided and taken out of its packaging.** Then, keep the spare half tablet in a safe place, out of the sight and reach of children, until you can throw it away properly, as you should not throw away any medicines in wastewater or household waste. Ask your pharmacist how to throw them away. If you have difficulties taking the tablet out of the blister or breaking the tablet, ask somebody for help.

If you take more Neofordex than you should
If you take too much Neofordex contact your doctor or hospital immediately.

If you forget to take Neofordex
If you forget to take Neofordex at the usual time and
- if you are less than 12 hours late: take the tablet immediately.
- if you are more than 12 hours late: do not take the tablet but take the next tablet at the usual time.

Do not take a double dose to make up for a forgotten tablet.

If you stop taking Neofordex
You may experience serious side effects if you stop taking this medicine suddenly. If you stop taking this medicine too quickly, you may have low blood pressure. You may also feel a ‘withdrawal symptom’. This may include headache, problems with your vision (including pain or swelling in the eye), feeling or being sick, fever, pain in your muscles and joints, swelling in the inside of your nose, weight loss, itchy skin and conjunctivitis. If your treatment is to be stopped follow your doctor’s advice.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Your doctor will discuss these with you and will explain the potential risks and benefits of your treatment.

The side effects listed below were seen when dexamethasone was taken for the treatment of multiple myeloma and for the treatment of other diseases. In some cases, the combination of several medicines can increase the side effects of one or the other of these medicines taken separately.

Neofordex may cause serious mental health problems. These are common (may affect up to 1 in 10 people) and may include:

- feeling depressed (including thinking about suicide)
- feeling high (mania), very happy (euphoria) or moods that go up and down,
- feeling anxious, having difficulty in concentrating and memory loss,
- feeling, seeing or hearing things that do not exist or believing in things that are not real, having gloomy thoughts, changing how you act.

If you notice any of these symptoms talk to a doctor straight away.

Other possible side effects may be:

Very common: may affect more than 1 in 10 people

- Increased blood sugar levels, constipation;
- Having trouble sleeping;
- Muscle cramps, muscle weakness;
- Tiredness, weakness, swelling of the body and face.

Common: may affect up to 1 in 10 people

- Bacterial, viral or fungal infections, including pneumonia, shingles, infections of the nose, mouth, tonsils or throat, bronchitis, herpes, bladder infection;
- Reduction in the number of red or white blood cells and/or platelets, or increased number of white blood cells, decreased levels of potassium or of albumin (a protein) in the blood, increased levels of uric acid in the blood, changes in liver function tests;
- Cushing's syndrome, i.e. weight gain of the trunk and face, excessive sweating, stretch marks, visible swollen capillaries (small blood vessels) and dryness of the skin, growth of extra facial hair (especially in women) and thinning of the hair;
- Development of diabetes, loss or increase of appetite, weight gain or weight loss, water retention;
- Aggression, confusion, irritability, nervousness, restlessness, altered mood;
- Sensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands or feet due to nerve damage, dizziness, trembling, headache, loss of or change in the sense of taste;
- Cataract, blurred vision;
- Fast or irregular heart rhythm, too high or too low blood pressure, formation of blood clots that may clog blood vessels (for example in legs or lungs), swelling of arms or legs, reddening of the skin of the face or body;
- Cough, breathing difficulties, difficulties speaking, sore throat or mouth, hoarseness, dry mouth, hiccough, inflammation of the mucous membranes;
- Vomiting, nausea, diarrhoea, indigestion, bloating, swollen and/or painful stomach;
- Rash, itching, reddened skin;
- Muscle wasting, pain of the muscles, joints, bones or limbs;
- Frequent urination;
- Pain, fever, chills, fainting, vertigo, exhaustion, drowsiness, impaired sense of balance.

Uncommon: may affect up to 1 in 100 people

- Fever due to a lack of certain white blood cells, lack of all types of blood cells, diminished blood clotting, decreased magnesium or calcium levels in the blood;
- Failure of the thyroid gland to produce normal amounts of hormones (hypothyroidism);
- Lack of body water (dehydration) with thirst or headache;
- Stroke, difficulties in coordination or movement, fainting;
- Inflammation of the eye and/or eyelids, increased tearing;
- Heart attack, abnormally slow heartbeat;
- Hives;
- Failure of the kidneys.

Not known: frequency cannot be estimated from the available data

- Infection, inflammation of the whole body due to infection (sepsis);
- Inability of the body to respond normally to severe stress such as accidents, surgery or illness due to insufficient function of the adrenal glands, severe unusual headache with visual disturbances linked to the withdrawal of treatment, irregularity of menstrual cycles in women;

- Increased need for diabetes medicine, salt imbalance, potassium loss due to low carbon dioxide levels (a condition called metabolic alkalosis);
- Epileptic fits;
- Increased pressure in the eye including glaucoma, choroid and retinal disorders (chorioretinopathy);
- Inability of the heart to pump enough blood round the body (heart failure);
- Ulcers, perforations and/or bleeding in the oesophagus (gullet), stomach or intestine, inflamed pancreas (which may show as pain in the back and abdomen);
- Slow wound healing, acne, thinning of the skin, bruising, red or purple discolorations on the skin (purpura);
- Thinning of the bones with increased risk of fracture, bone disease, ruptured tendon.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Neofordex

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Do not use this medicine if you notice any defects, or any signs of deterioration of the tablets or packaging.

This medicine does not require any special storage conditions. Keep tablets in the blister packaging until you take them. If you are using a pill organiser box, use the perforation to separate individual tablets from the blister without opening the packaging.

Throw away half tablets that you have not taken. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Neofordex contains
- The active substance is dexamethasone. Each tablet contains dexamethasone acetate equivalent to 40 mg dexamethasone.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, magnesium stearate and colloidal anhydrous silica (see section 2).

What Neofordex looks like and contents of the pack
Each tablet is white, oblong in shape, with a score line on one face. The tablet can be divided into two equal halves.

Each carton contains 10 x 1 tablets in OPA/Aluminium /PVC-Aluminium perforated unit dose blister.

Marketing Authorisation Holder

Laboratoires CTRS
63, rue de l'Est
92100 Boulogne-Billancourt
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Manufacturer

Amatsi
17, Parc des Vautes
34980 Saint Gély du Fesc
France

Or

Laboratoires CTRS
63, rue de l'Est
92100 Boulogne-Billancourt
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.