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Public Assessment Report

Name of the Product:

Dexamethasone Krka

4 mg, 8 mg, 20 mg, 40 mg tablets

(dexamethasone)

Procedure number: HU/H/0399/001--004/DC

Marketing authorisation holder: Krka d.d.

Date: 31 January 2017

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Dexamethasone Krka 4 mg, 8 mg, 20 mg and 40 mg tablets. The holder of the marketing authorisation is Krka d.d.

The active substance of the tablets is dexamethasone.

The other ingredients are lactose monohydrate, starch pregelatinised, colloidal anhydrous silica and magnesium stearate (E572).

The 4 mg tablets are white or almost white, round with bevel edges and scored on one side.

The 8 mg tablets are white or almost white, oval, scored on one side.

The 20 mg tablets are white or almost white, round with bevel edges, scored and engraved with 20 on one side.

The 40 mg tablets are white or almost white, oval, scored on both sides.

The tablets can be divided into equal doses.

The tablets are available in boxes in blisters.

The active substance dexamethasone is a synthetic glucocorticoid. Glucocorticoids are hormones produced by the cortex of adrenal glands. The medicine has anti-inflammatory, analgesic and anti-allergic effects, and suppresses the immune system.

Dexamethasone 4 mg and 8 mg tablets are recommended for the treatment of rheumatic and autoimmune diseases (e.g. systemic lupus erythematosus, rheumatoid artritis, juvenil idiopathic arthritis, polyartheritis nodosa), diseases of respiratory tract (e.g. bronhial asthma, croup), skin (e.g. erythroderma, pemphigus vulgaris), tuberculous meningitis only in conjunction with anti-infective therapy, diseases of blood (e.g. idiopathic thrombocytopenic purpura in adults), cerebral oedema, certain forms of cancer (e.g. treatment of symptomatic multiple myeloma, acute lymphocytic leukaemia, Hodgkin's disease and non-Hodgkin's lymphoma in combination with other medicinal products), palliative treatment of neoplastic diseases, prophylaxis and treatment of nausea and womiting caused by chemotherapy and prevention and treatment of vomiting after operation, within antiemetic treatment.

Dexamethasone 20 mg and 40 mg tablets are recommended for the treatment of rheumatic and autoimmune diseases (e.g. myositis), skin (e.g. pemphigus vulgaris), diseases of blood (e.g. idiopathic thrombocytopenic purpura in adults), treatment of symptomatic multiple myeloma, acute lymphocytic leukemia, acute lymphoblastic leukemia, Hodgkin's disease and non-Hodgkin's lymphoma in combination with other medicinal products, palliative treatment of neoplastic diseases, prophylaxis and treatment of nausea and womiting caused by chemotherapy, within antiemetic treatment.

What patients need to know before taking Dexamethasone Krka tablets?

Those patients who:
- are allergic to dexamethasone or any of the other ingredients of this medicine,
- have an infection that affects the whole body (unless receiving treatment),
- have a stomach or duodenal ulcer,
- are going to have a vaccination by live vaccines

must not take Dexamethasone Krka tablets.

Warnings and precautions

Those patients who:
- have or ever had severe depression or manic depression (bipolar disorder). This includes having had depression before or while taking steroid medicines like dexamethasone,
- have any close family member who has had these illnesses

must talk to their doctor before taking Dexamethasone Krka tablets.

Mental health problems can happen while taking steroids like Dexamethasone Krka tablets.
- These illnesses can be serious.
- Usually they start within a few days or weeks of starting the medicine.
- They are more likely to happen at high doses.
- Most of these problems go away if the dose is lowered or the medicine is stopped. However, if problems do happen, they might need treatment.

The patient must consult a doctor if he/she (or someone taking this medicine), shows any signs of mental health problems. This is particularly important if the patient is depressed, or might be thinking about suicide. In a few cases, mental health problems have happened when doses are being lowered or stopped.

Patients must talk to their doctor before taking this medicine if:
- having kidney or liver problems,
- haveing a tumour of the adrenal gland
- having high blood pressure, heart disease or having recently had a heart attack,
- having diabetes or there is a family history of diabetes,
- having osteoporosis (thinning of the bones), particularly if the patient is are a female who has been through the menopause,
- having been suffered from muscle weakness with this or other steroids in the past,
- having glaucoma (raised eye pressure) or there is a family history of glaucoma, cataract (clouding of the lens in the eye leading to a decrease in vision),
- having myasthenia gravis (a condition causing weak muscles),
- having a bowel disorder or a stomach (peptic) ulcer,
- having psychiatric problems or having had a psychiatric illness which was made worse by this type of medicine,
- having epilepsy (condition where the patient has repeated fits or convulsions),
- having migraine,

- having an underactive thyroid gland,
- having a parasitic infection,
- having tuberculosis, septicaemia or a fungal infection in the eye,
- having cerebral malaria,
- having herpes (cold sores or genital herpes and ocular herpes simplex because of possible corneal perforation),
- having asthma,
- having liver cirrhosis or chronic liver failure,
- are treated for a blockage of blood vessels by blood clots (thromboembolism),
- having corneal ulcerations and corneal injuries.

Treatment with corticosteroid may reduce your body's ability to fight infection. If the patient develops an infection whilst on this medicine, the doctor should be informed.

It is important that whilst the patient is taking this medicine, contact with anybody who has chickenpox, shingles or measles should be avoided. If the patient thinks he/she may have had exposure to any of these diseases, he/she should consult the doctor immediately. Patients should also inform their doctor if they have ever had infectious diseases such as measles or chickenpox and of any vaccinations.

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. The doctor should be contacted if the patient notices blurring or distorted vision that lasts for several days .

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. Patients should contact the doctor if they notice painful, stiff or swollen joints or tendons.

Treatment with Dexamethasone Krka tablets can cause a condition called adrenocortical insufficiency. This can cause change in effectiveness of the medicine following stress and trauma, surgery, childbirth or illness and your body may not be able to respond in the usual way to severe stress such as accidents, surgery, childbirth or illness.

If the patient has an accident, is ill, has other specific physical stress conditions, or requires any surgery (even at the dentists) or requires a vaccination (particularly with 'live virus' vaccines) whilst taking or when just have finished taking Dexamethasone Krka tablets, he/she should inform the treating person that he/she is taking or has taken steroids.

If the patient has suppression tests (test for the amount of hormone in the body), skin test for allergy or test for bacterial infection, the person performing the test should be informed that dexamethasone is taken as it may interfere with the results.

Some of the side effects of this medicine may be more serious in elderly, especially thinning of the bones (osteoporosis), high blood pressure, low potassium levels, diabetes, susceptibility to infection and thinning of the skin.

The doctor will reduce the amount of salt in the patient's diet and give him/her a potassium supplement whilst taking this medicine.

Children

If children are taking this medicine, it is important that the doctor monitors their growth and development at frequent intervals.

Other medicines and Dexamethasone Krka tablets

The patient must inform the doctor if taking, has recently taken or might take any other medicines, particularly:
- anticoagulant medicines that thin the blood (e.g. warfarin),
- acetylsalicylic acid or similar (Non-Steroidal Anti-Inflammatory) drugs e.g. indomethacin,
- medicines used to treat diabetes,
- medicines used to treat high blood pressure,
- medicines used to treat cardiac diseases,
- diuretics (water tablets),
- amphotericin B injection,
- phenytoin, carbamazepine, primidone (epilepsy medication),
- rifabutin, rifampicin (antibiotics used to treat tuberculosis),
- antacids – particularly those containing magnesium trisilicate,
- barbiturates (medication used to aid sleep and relieve anxiety),
- aminoglutethimide (anti-cancer treatment),
- carbenoxolone (used in the treatment of stomach ulcers),
- ephedrine (nasal decongestant),
- acetazolamide (used for glaucoma and epilepsy),
- hydrocortisone, cortisone and other corticosteroids,
- ketoconazole (for fungal infections),
- ritonavir (for HIV),
- antibiotics including erythromycin,
- medicines that help muscle movement in myasthenia gravis (e.g. neostigmine),
- colestyramine (for high cholesterol levels),
- estrogen hormones including the contraceptive pill,
- tetracosactide used in the test for adrenocortical function,
- sultopride used to calm emotions,
- ciclosporin used to prevent rejection after transplants,
- thalidomide used for e.g. multiple myeloma,
- praziquantel given for certain worm infections
- Vaccination with live vaccines
- Chloroquine, hydroxychloroquine and mefloquine (for malaria)
- Somatotropin
- Protirelin.

Some medicines may cause serious side effects if the patient takes dexatmethasone together with them:
- Acetylsalicylic acid or similar (Non-Steroidal Anti-Inflammatory drugs) e.g. indometacin
- Medicines used to treat diabetes

- Medicines used to treat cardiac diseases
- Diuretics (water tablets)
- Amphotericin B injection
- Acetazolamide (used for glaucoma and epilepsy)
- Tetracosactide used in the test for adrenocortical function
- Carbenoxolone (used in the treatment of stomach ulcers)
- Chloroquine, hydroxychloroquine and mefloquine (for malaria)
- Medicines used to treat high blood pressure
- Thalidomide used for e.g. multiple myeloma
- Vaccination with live vaccines
- Medicines that help muscle movement in myasthenia gravis (e.g. neostigmine)
- Antibiotics including fluoroquinolones

Before starting treatment with Dexamethasone Krka tablets patent should read the package leaflets of all medicinal products to be taken in combination with Dexamethason Krka for information related to these medicines. When thalidomide, lenalidomide or pomalidomide is used, particular attention to pregnancy testing and prevention requirements is needed.

Dexamethasone Krka tablets with food, drink and alcohol

Dexamethasone Krka tablets should be taken with or after food to minimise irritation to the gastrointestinal tract. Drinks containing alcohol or caffeine should be avoided. Eating small, frequent meals is recommended, and possibly taking of antacids, if recommended by the doctor.

Pregnancy and breast-feeding

Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby should ask their doctor for advice before taking this medicine.

Dexamethasone Krka tablets should be prescribed during pregnancy and particularly in the first trimester only if the benefit outweighs the risks for the mother and child. If the patient becomes pregnant during the use of the product, she must not stop using Dexamethasone Krka tablets, but the doctor must be informed immediately that she is pregnant.

Dexamethasone is excreted in breast milk. A risk to the newborns/infants cannot be excluded. A decision on whether to continue/discontinue breast feeding or to continue/discontinue therapy with dexamethasone should be made taking into account the benefit of breast feeding to the child and the benefit of dexamethasone therapy to the woman.

Driving and using machines

Dexamethasone Krka tablets can cause side effects such as confusion, hallucinations, dizziness, tiredness, sleepiness, fainting or blurred vision. If the patient experiences such side effects is recommended not to drive, to use any tools or machines or to carry out any hazardous tasks.

Dexamethasone Krka tablets contain lactose

Those who have been told by their doctor that they have an intolerance to some sugars, contact

the doctor before taking this medicine.

How to take Dexamethasone Krka tablets?

Dexamethasone Krka tablets are in the form of tablets 4 mg, 8 mg, 20 mg and 40 mg. The tablets can be divided into equal halves to provide additional 2 mg and 10 mg strengths or to help swallowing.

Dosage depends on the severity of the disease.

In order to minimise side effects, the lowest effective possible dose should be used.

Dexamethasone is given in usual doses of 0.5 to 10 mg daily, depending on the disease being treated. In more severe disease conditions doses above 10 mg per day may be required. The dose should be titrated to the individual patient response and disease severity.
The dose and administration frequency varies with the therapeutic protocol and the associated treatment(s). Dexamethaosne 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.

Long term treatment

For the long-term treatment of several conditions, after initial therapy, glucocorticoid treatment should be switched from dexamethasone to prednisone/prednisolone to reduce suppression on the function of the adrenal cortex.

Use in children

As mentioned earlier, if a child is taking this medicine, it is important that the doctor monitors their growth and development at frequent intervals.

What to do if more Dexamethasone Krka tablets have been taken than it should have been?

Those who take too much medicine should contact a doctor or hospital immediately.

What to do if taking Dexamethasone Krka tablets have been forgotten?
Those who have forgotten to take a dose, should take it as soon as they remember unless it is almost time for the next dose. No double dose to make up for a forgotten tablet may be taken.

May patients stop taking Dexamethasone Krka tables?

If the treatment is to be stopped, the doctor's advice should be followed. He may tell the patient to reduce the amount of medicine gradually until it will be stopped completely. The symptoms

that have been reported when treatment has been stopped too quickly have included low blood pressure and in some cases, relapse of the disease for which the treatment was given.

A 'withdrawal syndrome' may also occur which includes fever, muscle and joint pain, inflammation of the nose lining (rhinitis), weight loss, itchy skin and inflammation of the eye (conjunctivitis). If the patient stops the treatment too soon and some of the mentioned symptoms occur, he/she must talk to the doctor as soon as possible.

Possible side effects

Like all medicines, Dexamethasone Krka tablets can cause side effects, although not everybody experiences them.

Patients must tell a doctor straight away if they experience serious mental health problems. Such problems can affect about 5 in every 100 people taking medicines like dexamethasone. These problems include:
- feeling depressed, including thinking about suicide,
- feeling high (mania) or moods that go up and down,
- feeling anxious, having problems sleeping, difficulty in thinking or being confused and losing the memory,
- feeling, seeing or hearing things that do not exist. Having strange and frightening thoughts, changing how you act or having feelings of being alone.

The patient must tell a doctor straight away if he experiences:
- severe abdominal pains, nausea, vomiting, diarrhoea, profound muscle weakness and fatigue, extremely low blood pressure, weight loss and fever as these may be signs of adrenocortical insufficiency;
- sudden abdominal pain, tenderness, nausea, vomiting, fever and blood in stool as these may be signs of tearing of the bowel particularly if the patient has or has had a bowel disease.

This medicine may worsen patient's existing heart problem. If the patient experiences shortness of breath or ankle swelling, he should consult his doctor straight away.

Other side effects may be:
- Greater chance of picking up infections, including viral and fungal infections e.g. thrush; recurrence of tuberculosis or some other infections, e.g. eye infections if the patient has already had it
- Reduction in the number of white blood cells or increased number of white blood cells, abnormal coagulation
- An allergic reaction to the medicine, including serious, potentially life-threatening allergic reaction (which may show as a rash and swelling of the throat or tongue and in severe cases difficulty in breathing or dizziness)
- Impairment of the body's regulation of hormones, swelling and weight gain of the body, full-moon face (Cushingoid state), change in effectiveness of endocrines following stress and trauma, surgery, childbirth or illness, your body may not be able to respond in the usual way to severe stress such as accidents, surgery, childbirth or illness, stunted growth in children and teenagers, irregular and absence of menstrual cycles (periods) development of excess body

hair (particularly in women)
- Weight gain, loss of protein and calcium balance, increased appetite, salt imbalances, water retention in the body, potassium loss which can cause rhythm disorder, increased requirement for diabetic medication, unknown diabetes becomes evident, high levels of cholesterol and triglycerides in the blood (hypercholesterolemia and hypertriglyceridaemia)
- Extreme mood swings, schizophrenia (mental disorder) may become worse, depression, inability to sleep
- Severe unusual headache with visual disturbances linked with the withdrawal of treatment, fits and worsening of epilepsy, dizziness
- Increased pressure in the eye, papilloedema, thinning of the eye membranes, increased eye viral, fungal and bacterial infections, worsening of symptoms associated with corneal ulcers, worsening of existing eye infections, protrusion of the eyeballs, cataracts
- Congestive heart failure in susceptible people, cardiac muscle rupture after a recent heart attack, cardiac decompensation
- High blood pressure, blood clots: formation of blood clots that may clog blood vessels for example in legs or lungs (thromboembolic complications)
- Hiccups
- Nausea, vomiting, stomach discomfort and swollen abdomen, inflammation and ulcers in the oesophagus, peptic ulcers that may split and bleed, inflamed pancreas (which may show as pain in the back and abdomen), flatulence, oesophageal candidiasis
- Thinned delicate skin, unusual marks on the skin, bruising, redness and inflammation of the skin, stretch marks, visible swollen, capillaries, acne, increased sweating, skin rash, swelling, thinning of the hair, unusual fat deposits, excessive hair growth, water retaining in the body, pigment disorders, weakened capillaries that rupture easily, observed as bleeding under the skin (increased capillary fragility), skin irritation around the mouth (perioral dermatitis)
- Thinning of the bone with an increased risk of fractures (osteoporosis), bone necrosis, tendinitis, ruptured tendons, muscle wasting, myopathy, muscle weakness, early stoppage of bone growth (premature epiphyseal closure)
- Changes to the number and movement of sperm, impotence
- Impaired reaction to vaccination and skin tests, slow wound healing, discomfort, malaise.
- A ‘withdrawal syndrome’ may also occur which includes fever, muscle and joint pain, inflammation of the nose lining (rhinitis), weight loss, painful itchy skin nodules and inflammation of the eye (conjunctivitis).

How to store Dexamethasone Krka tablets?

They do not require any special temperature storage conditions. They should be stored in the original package in order to protect from light and moisture.

This medicine must be kept out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Dexamethasone Krka 4 mg, 8 mg, 20 mg and 40 mg tablets. The procedure was finalised at 18 July 2016. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Bulgaria, Croatia, the Czech Republic, Estonia, Germany, Latvia, Lithuania, Poland, Portugal, Romania, the Slovak Republic, Slovenia, Spain and the United Kingdom) concerned the application of dexamethasone 4 mg, 8 mg, 20 mg and 40 mg tablets (Dexamethasone Krka tablets). The applicant was Krka d.d., Novo mesto, Slovenia.

The application was being made in accordance with Article 10a of Directive 2001/83/EC (bibliographic application, well-established use), and therefore contained no new clinical or preclinical data, other than supporting literature. The active substance of the medicinal product, dexamethasone, has been in well-established medicinal use within the Community for at least 10 years, with recognized efficacy and an acceptable level of safety.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Dexamethasone Krka 4 mg, 8 mg, 20 mg and 40 mg tablets from Krka d.d.

Dexamethasone 4 mg and 8 mg is indicated for the treatment of a wide range of disorders:

Neurology: cerebral oedema (only with symptoms of intracranial pressure evidenced by computerised tomography) caused by a brain tumour, neuro-surgical intervention, cerebral abscess.

Pulmonary and respiratory diseases: acute asthma exacerbations when use of an oral corticosteroid (OCS) is appropriate, croup.

Dermatology: initial treatment of extensive, severe, acute, skin diseases responding to glucocorticoids, e.g. erythroderma, pemphigus vulgaris.

Autoimmune disorders/rheumatology: initial treatment of autoimmune disorders like systemic lupus erythematodes. Active phases of systemic vasculitides like panarteritis nodosa (treatment duration should be limited to two weeks in cases of concomitant positive hepatitis B serology). Severe progressive course of active rheumatoid arthritis, e.g. fast proceeding destructive forms and/or extraarticular manifestations. Severe systemic course of juvenile idiopathic arthritis (Still's disease).

Haematological disorder: idiopathic thrombocytopenic purpura in adults.

Infectology: tuberculous meningitis only in conjunction with anti-infective therapy.

Oncology: palliative treatment of neoplastic diseases. Prophylaxis and treatment of emesis induced by cytostatics, emetogenic chemotherapy within antiemetic treatment. Treatment of symptomatic multiple myeloma, acute lymphocytic leukaemia, acute lymphoblastic leukaemia, Hodgkin's disease and non-Hodgkin's lymphoma in combination with other medicinal products.

Various: prevention and treatment of postoperative vomiting, within antiemetic treatment.

Dexamethasone 20 mg and 40 mg is indicated for:

*Dermatology:*Pemphigus vulgaris.

Autoimmune disorders/rheumatology: Myositis.

Haematological disorder: Idiopathic thrombocytopenic purpura in adults.

Oncology: Metastatic spinal cord compression. Prophylaxis and treatment of emesis induced by cytostatics, emetogenic chemotherapy within antiemetic treatment.
Treatment of symptomatic multiple myeloma, acute lymphocytic leukemia, acute lymphoblastic leukemia, Hodgkin's disease and non-Hodgkin's lymphoma in combination with other medicinal products.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics (SmPC).

II. QUALITY ASPECTS

II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Dexamethasone Krka 4 mg, 8 mg, 20 mg and 40 mg tablets via a decentralized procedure according to Article 10a of consolidated Directive 2001/83/EC (i.e. a well-established use application).

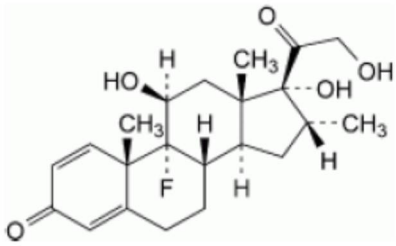
The drug products contain 4 mg, 8 mg, 20 mg and 40 mg dexamethasone, respectively, developed by Krka, d.d., Novo mesto.

The referred products used in the comparative studies were Fortecortin 4 mg and 8 mg tablets manufactured by Merck.

II.2 Drug substance

Data on the quality and manufacture of dexamethasone were provided in the submission using the European Pharmacopoeia (Ph. Eur.) Certificate of Suitability (CEP) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: dexamethasone
Chemical name: 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione
Structure:



The active substance is white or almost white, crystalline powder, practically insoluble in water, sparingly soluble in anhydrous ethanol, slightly soluble in methylene chloride. It shows polymorphism, the manufacturer consistently produces the same polymorphic form.

The substance is specified according to the requirements of the current Ph. Eur. monograph, additional specification has only been set for residual solvent, heavy metals, sulphated ash, particle size distribution and microbial impurities.

The Ph. Eur. specification includes the following tests for dexamethasone: appearance, identification by IR and TLC, specific optical rotation, loss on drying, related substances, and assay.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the International Council on Harmonisation (ICH) Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data a re-test period of 5 years is acceptable in two polyethylene bags closed by a tamper-evident closure system placed into HDPE box or cardboard drum with the storage condition “stored at controlled room temperature (≤25 °C), protected from light”.

Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim was to develop tablets containing dexamethasone as drug substance in 4, 8, 20 and 40 mg doses, respectively

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the products are shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation.

As a result of development studies products with the following appearance, composition and packaging was obtained:

> 4 mg tablets: white or almost white, round tablets with bevelled edges and scored on one side. Diameter: 5.7-6.3 mm. The tablets can be divided into equal doses.

8 mg tablets: white or almost white, oval tablets scored on one side. Length: 8.7-9.3 mm. The tablets can be divided into equal doses.
20 mg tablets: white or almost white, round tablets with bevelled edges scored and engrave with 20 on one side. Diameter: 10.7-11.3 mm. The tablets can be divided into equal doses.

40 mg tablets: white or almost white, oval tablets scored on both side. Length: 18.7-19.3 mm. The tablets can be divided into equal doses.

The excipients used in the finished products were lactose monohydrate, magnesium stearate, colloidal anhydrous silica and pregelatinised (maize) starch. All excipients used comply with their respective Ph. Eur. monographs. Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product's specifications are satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification.

The container closure system of the products is OPA/Al/PVC//Al blisters and box. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 2 years with the storage conditions "This medicine does not require any special temperature storage conditions. Store in the original package in order to protect from light and moisture" is approved.

The SmPC, the Package (Patient Information) Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The products have been shown to meet the current regulatory requirements with regards to their quality and content of the active substances as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the products.

From quality aspects the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of dexamethasone are well known. No further non-clinical studies are required in support of this well-established use application for marketing authorisation and therefore no new non-clinical data was provided in this submission.

The applicant submitted a non-clinical overview based on a literature review of the pre-clinical pharmacology, pharmacokinetic and toxicology characteristics of dexamethasone which is considered adequate. No further studies are required.

III.2 Pharmacology

The active substance in Dexamethasone Krka 4 mg, 8 mg, 20 mg and 40 mg tablets is a synthetic corticosteroid with anti-inflammatory and anti-allergic action.

The active substance is a well-known compound. No further new information was provided regarding the pharmacology of dexamethasone.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant.

III.4 Toxicology

No new toxicity studies were submitted by the applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmental risk assessment

The applicant initially claimed that the absence of a complete Environmental Risk Assessment (ERA) is justified because no significant increase of the environmental exposure is anticipated when granting marketing authorization for Dexamethasone 4 mg, 8 mg, 20 mg, and 40 mg tablets. Due to CMS request, the applicant presented ERA on the basis of sales data and PECsw calculation according to EMA/CHMP/SWP/44609/2010.

The PECsw calculation was above the phase I trigger value if the worst-case scenario and the default values are used, but Fpen refinement was possible with the available sales data in the European countries.

The PECsw concentrations based on the sales data were approximately 10-times below the phase I trigger value for all concerned member states, therefore it could be concluded that dexamethasone does not represent a risk for the environment and the environmental risk assessment could stop in Phase I.

However, CMS pointed out that dexamethasone is a potential endocrine disruptor which triggers the phase II assessment according to the current guideline, therefore the applicant additionally performed ERA phase II assessment based on the published literature. ERA phase II demonstrated that the calculated worst-case risk quotient was less than 1.

The applicant presented experimentally derived Kow value which is available in the literature. Even though the literature data on Kow and Koc demonstrate that dexamethasone has low bioaccumulation potential and has low potential to adsorb to organic matter in sludge, soil or river sediments, the CMS further requested own experimental data to additionally support this statement.

The applicant will therefore perform Kow, Koc and transformation studies and provide the reports to the member states by the end of year 2017.

III.6 Discussion on the non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of dexamethasone are well-known. There was no need for further non-clinical studies.

The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacodynamics, pharmacokinetics, efficacy and safety of the active ingredient in the proposed indications, doses and dosing regimens are well known. Dexamethasone has been widely marketed and used, and is well established in medicinal use. It is broadly acknowledged to be efficacious and to have an acceptable risk/benefit profile.

In a well-established use application results of clinical trials are replaced by detailed references to published scientific literature.

For this application the applicant was requested to perform a bioequivalence study with 20 mg dose in order to support the statement that the 20 mg and 40 mg formulations are sufficiently similar to the formulations used in the bibliographic data referred to, and in order to bridge the literature clinical data of 4 mg and 8 mg dose strength to 20 mg and 40 mg tablets. For safety reason the dose of 20 mg was chosen as it was more suitable for exposure of healthy volunteers since higher number of adverse effects can be expected with the use of higher strengths of dexamethasone, particularly with 40 mg.

The applicant justified the assumed comparability of the *in vivo* pharmacokinetic profiles after using a multiple dose of the lower 4 mg strength or one tablet with the higher 20 mg strength.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Dexamethasone is well absorbed when given by mouth; peak plasma levels are reached between 1 and 2 hours after ingestion and show wide inter-individual variations. The mean plasma half-life is 3.6 ± 0.9 h. Dexamethasone is bound (to about 77%) to plasma proteins, mainly albumins. Percentage protein binding, unlike that of cortisol, remains practically unchanged with increasing steroid concentrations. Corticosteroids are rapidly distributed to all body tissues. They cross the placenta and may be excreted in small amounts in breast milk.

Dexamethasone is metabolised mainly in the liver but also in the kidney.

Dexamethasone and its metabolites are excreted in the urine.

IV.2.2 Bioequivalence study

The applicant demonstrated that one Dexamethasone Krka 20 mg tablet is bioequivalent to five Fortecortin® 4 mg tablets (the chosen reference product, manufactured by Merck KGaA & Co., Austria).

The bioequivalence study has been performed in healthy adult volunteers under fasting conditions according to the bioequivalence guideline in force (*CPMP/EWP/QWP/1401/98/rev 1/Corr** 2010*).

Based on study results criteria used to assess bioequivalence between the test and reference formulations were all fulfilled. The Test to Reference (T/R) ratio of geometric LSmeans and corresponding 90% confidence intervals for the C_{max} and AUC_{0-t} were all within the acceptance range of 80.00 to 125.00%. Therefore, single doses of the Test formulation (one Dexamethasone Krka 20 mg tablet) has been judged to be bioequivalent to the Reference formulation (five Fortecortin® 4 mg tablets, Merck KGaA & Co., administered together) under fasting conditions.

Pharmacokinetic parameter	Ratio (T/R) %	90% Confidence Interval	Intra-subject CV%
C_{max}	108.56	102.65 – 114.81	13.2
AUC_{0-t}	~~98.17~~ 102.15	98.17 – 106.29	9.4

Biowaiver

The biowaiver claim for the 4 mg, 8 mg and 40 mg dose strengths is acceptable on the basis of general biowaiver requirements *(CPMP/EWP/QWP/1401/98 Rev 1 Corr**):*

a) all the strengths i.e. 4, 8, 20 and 40 mg of proposed pharmaceutical products are manufactured by the same manufacturer and using the same manufacturing process;
b) the qualitative composition of the different strengths is the same;
c) the compositions of the claimed four strengths (4, 8, 20 and 40 mg) are proportionally similar;
d) *in vitro* dissolution data confirm the in vivo similarity between the claimed strengths determined in three dissolution media raging from acidic conditions expected in the stomach to neutral pH expected in the intestine;
e) dexamethasone exhibits linear pharmacokinetics in the claimed therapeutic range (4-40 mg).

No death or serious adverse events occurred during the study.

The incidence of adverse events was lower for subjects administered the Test product than for subjects administered the Reference product. Drug related adverse events were also reported with a slightly lower incidence by subjects administered Test product than by subjects administered the Reference product. Most of the adverse events were considered mild or moderate in the study.

IV.3 Pharmacodynamics

The clinical pharmacology of dexamethasone is well known. No novel pharmacodynamic data were supplied or required for this application.

Dexamethasone is a highly potent and long-acting glucocorticoid with negligible sodium retaining properties. It is used principally as an anti-inflammatory or immunosuppressant agent. The mechanism of action is mediated via activation of glucorticoid receptors that leads to increased or decreased transcription of a number of genes involved in the inflammatory process. Particularly, the repression of cytokine gene transcription and the direct interaction between the glucocorticoid receptor and other transcription factors are activated in chronic inflammation. Dexamethasone has a biological half-life of 36 - 54 hours and therefore is suitable in conditions where continuous glucocorticoid action is required.

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required for this type of application. The applicant has provided an adequate literature review to describe the efficacy profile of dexamethasone. The data provided supported the well-established efficacy of the active ingredient in the approved indications.

IV.5 Clinical safety

The safety profile for dexamethasone is well-known and has been extensively described in the literature. No new safety data have been submitted and none are required for this type of application. The Applicant has provided an adequate literature review to describe the safety profile of dexamethasone.

The applicant has also provided safety data from the bioequivalence study performed with the product under assessment which supports that the product has a similar safety profile as already described for other dexamethasone products.

The safety aspects are adequately reflected in the product information.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System version. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns	
Important identified risks	Hypersensitivity including anaphylaxis to dexamethasone or any excipients. Risk of opportunistic infection, aggravation or masking of signs of infection: impaired immune response to vaccines. Reduced glucose tolerance. Adrenal suppression (associated with long-term use in children). Osteoporosis, especially in patients at risk. Gastrointestinal ulcers or bleeding, intestinal perforation. Cataract, glaucoma or corneal ulcer. Exacerbation or recurrence of the underlying disease, acute adrenocortical insufficiency, corticosteroid withdrawal syndrome upon interruption/discontinuation of long-term glucocorticoid administration.
Important potential risks	Cardiovascular complications at high risk patients (such as post-infarct myocardial rupture, congestive heart failure). Congenital abnormalities.
Missing information	None.

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Krka products of dexamethasone 4 mg, 8 mg, 20 mg and 40 mg tablets. No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in SmPC, PL and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to Dexamethasone Krka 4 mg, 8 mg, 20 mg and 40 mg tablets. No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 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.

Currently, no routine PSUR reporting is required for well-established use products containing dexamethasone.

IV.7 Discussion on the clinical aspects

This application concerns a well-established use product under Article 10a of Directive 2001/83/EC as amended.

The indication is the treatment of a wide range of disorders and conditions, where the anti-inflammatory and immunosuppressive effect of dexamethasone is desirable.

Approval is recommended from the clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Dexamethasone Krka 4 mg, 8 mg, 20 mg and 40 mg tablets.

The product is indicated for the treatment of a wide range of disorders and conditions, where the anti-inflammatory and immunosuppressive effect of dexamethasone is desirable.

The application was submitted according to Article 10a of Directive 2001/83/EC (bibliographic or well-established use application).

The active substance dexamethasone has a well-established medicinal use with recognized efficacy and an acceptable level of safety in clinical medicine as outlined in the Clinical Overview. The compound is both effective and safe when used in accordance with recommendations published in the literature.

The application contains an adequate review of published clinical data. Moreover, a bioequivalence study with one Dexamethasone Krka 20 mg tablet and five tablets of the chosen comparator product, the marketed Fortecortin® 4 mg tablets (Merck KGaA & Co., Austria) was successfully performed in order to bridge the literature clinical data of the lower and higher strengths.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the member states have granted marketing authorisation for Dexamethasone Krka 4 mg, 8 mg, 20 mg and 40 mg tablets.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached