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Public Assessment Report

Name of the Product:

Dexeto

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

(dexamethasone)

Procedure number: HU/H/0492/001-004/DC

Marketing authorisation holder: Krka d.d.

Date: 14 May 2020

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Dexeto 4 mg, 8 mg, 20 mg and 40 mg tablets (called Dexamethasone HCS in Austria, Denmark and Iceland). The holder of the marketing authorisation is Krka d.d., Slovenia.

The active substance is dexamethasone. Each tablet contains 4 mg or 8 mg or 20 mg or 40 mg dexamethasone.

The other ingredients are lactose monohydrate, pregelatinised maize starch, colloidal anhydrous silica and magnesium stearate (E470b).

- The 4 mg tablets are white or almost white, round tablets with bevelled edges and scored on one side (thickness: 2.5-3.5 mm; diameter: 5.7-6.3 mm).
- The 8 mg tablets are white or almost white, oval tablets, scored on one side (thickness: 3.5-5.5 mm; length: 8.7-9.3 mm).
- The 20 mg tablets are white or almost white, round tablets with bevelled edges, scored and engraved with 20 on one side (thickness: 4.0-6.0 mm; diameter: 10.7-11.3 mm).
- The 40 mg tablets are white or almost white, oval tablets, scored on both sides (thickness: 6.0-8.0 mm; lenght: 18.7-19.3 mm).

All tablets can be divided into equal doses.

The tablets are available in boxes in blisters.

Dexeto 4 mg, 8 mg, 20 mg, 40 mg tablets (further on: Dexeto) belong to a group of medicines called glucocorticoids. This medicine reduces inflammation, pain and symptoms of allergic reactions, and suppresses the immune system.

Dexeto (4 mg and 8 mg) is used 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), infectious diseases (tuberculous meningitis), diseases of blood (e.g. idiopathic thrombocytopenic purpura in adults), brain oedema, treatment of cancer (e.g. multiple myeloma, acute lymphoblastic leukemia, Hodgkin's disease and non-Hodgkin's lymphoma in combination with other medicinal products), palliative treatment of cancer, prevention and treatment of nausea and vomiting caused by chemotherapy and prevention and treatment of vomiting after operation.

Dexeto (20 mg and 40 mg) is used 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 cancer (e.g. multiple myeloma, acute lymphoblastic leukemia, Hodgkin's disease and non-Hodgkin's lymphoma in combination with

other medicinal products), palliative treatment of cancer, prevention and treatment of nausea and vomiting caused by chemotherapy.

What patients need to know before takeing Dexeto

Patients must not take Dexeto if they
- 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.

Warnings and precautions
Patients must talk to their doctor before taking Dexeto if:
- they have or ever had severe depression or maniac depression (bipolar disorder). This includes having had depression before or while taking steroid medicines like dexamethasone,
- if any of their close family has had these illnesses.

Patients must take special care and talk to their doctor if they:
- have kidney or liver problems (liver cirrhosis or chronic liver failure),
- have a tumour of the adrenal gland (pheochromocytoma),
- have high blood pressure, heart disease or they have recently had a heart attack (myocardial rupture has been reported),
- have diabetes or there is a family history of diabetes,
- have osteoporosis (thinning of the bones), particularly if they are a female who has been through the menopause,
- have suffered from muscle weakness with this or other steroids in the past,
- have eye disease, such as 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), have corneal ulcerations and corneal injuries. They must contact their doctor if experiencing blurred vision or other visual disturbances,
- have myasthenia gravis (a condition causing weak muscles),
- have a bowel disorder or a stomach (peptic) ulcer,
- have psychiatric problems or they have had a psychiatric illness which was made worse by this type of medicine,
- have epilepsy (condition where they have repeated fits or convulsions),
- have migraine,
- have an underactive thyroid gland,
- have an infection or get an infection of any kind and anywhere in the body during treatment with this medicine. They should also tell their doctor if having had tuberculosis,
- have asthma,
- are treated for a blockage of blood vessels by blood clots (thromboembolism),
- notice painful, stiff or swollen joints or tendons,
- have fever, feel stressed, have an accident, childbirth or require any surgery (even at the dentists) since these may require a change of the dose,

- have suppression tests (test for the amount of hormone in the body), skin test for allergy or test for bacterial infection as this medicine may interfere with the results,
- are elderly, because some of the side effects of this medicine 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.

The patients should also avoid contact with anybody who has chickenpox, shingles or measles, and they should also inform their doctor if they have ever had infectious diseases such as measles or chickenpox and of any vaccinations,

Children

If children are taking this medicine, it is important that the doctor monitors their growth and development at frequent intervals. Dexamethasone should not be used routinely in preterm neonates with respiratory problems.

Other medicines and Dexeto

Patients should tell their doctor if they are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Particularly they must inform their doctor if they are taking:
- anticoagulant medicines which 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, isoniazid (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, itraconazole (for fungal infections),
- ritonavir (for HIV),
- antibiotics including erythromycin, fluoroquinolones,
- 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 increase the effects of Dexeto and the doctor may wish to monitor the patient carefully if taking these medicines (including some medicines for HIV: ritonavir, cobicistat).

Patients may be at an increased risk of serious side effects if taking dexatmethasone together with these medicines:
- acetylsalicylic acid or similar (Non-Steroidal Anti-Inflammatory drugs) e.g. indomethacin,
- 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.

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

Dexeto with food, drink and alcohol

Dexamethasone 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 you may be pregnant or are planning to have a baby, ask their doctor for advice before taking this medicine.

Dexeto 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 should not stop using Dexeto, but tell her doctor immediately that she is pregnant.

Corticosteroids may pass into 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

Patients who take Dexeto should not drive, use any tools or machines or carry out any hazardous tasks if experiencing side effects, such as confusion, hallucinations, dizziness, tiredness, sleepiness, fainting or blurred vision.

Dexeto contains 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 Dexeto

Patients should always take this medicine exactly as their doctor has prescribed.

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

> Patients must be aware that Dexeto 20 mg and 40 mg tablets are high dosage medicinal products. Dexeto is recommended to be used at the lowest effective dose, recommended by the doctor!

The dosage will be determined by the doctor.

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

Use in children

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

What to do if more Dexeto has been taken than it should have been?

If taking too much medicine thee patient must contact a doctor or hospital immediately.

What to do if taking Dexeto has been forgotten?

If patients forget to take a dose, take it as soon as they remember unless it is almost time for the next dose. They should not take a double dose to make up for a forgotten tablet.

May patients stop taking Dexeto?

If the treatment is to be stopped, patients should follow their doctor's advice. He may tell them to reduce the amount of medicine they are taking gradually until they stop taking it altogether. 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 patients stop treatment too soon and some of the mentioned symptoms occur, they must talk to their doctor as soon as possible.

Possible side effects

Like all medicines, Dexeto can cause side effects, although not everybody experiences them.

Patients must tell a doctor straight away if they:
- are feeling depressed, including thinking about suicide,
- are feeling high (mania) or moods that go up and down,
- are feeling anxious, having problems sleeping, difficulty in thinking or being confused and losing the memory,
- are feeling, seeing or hearing things that do not exist. Having strange and frightening thoughts, changing how they act or having feelings of being alone,
- experience 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,
- experience sudden abdominal pain, tenderness, nausea, vomiting, fever and blood in stool as these may be signs of tearing of the bowel particularly if they have or have had a bowel disease,
- experience shortness of breath or ankle swelling, as these may be signs of worsening the existing heart problem.

Other side effects may be (frequency not known):
- 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, blurred vision,
- 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).

5. How to store Dexeto

This medicine does not require any special temperature storage conditions, but it should be stored in the original package in order to protect from light and moisture and should 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 Dexeto 4 mg, 8 mg, 20 mg, 40 mg tablets. The procedure was finalised at 25 October 2017. 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:

procedure HU/H/0492/001/DC Austria, Denmark, Iceland, Norway and Sweden,
procedures HU/H/0492/002-004/DC Austria

concerned the Article 10a (well-established use) application of dexamethasone 4 mg, 8 mg, 20 mg and 40 mg tablets (Dexeto tablets, named Dexamethasone HCS in Austria, Denmark and Iceland).

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 Dexeto 4 mg, 8 mg, 20 mg and 40 mg tablets from Krka d.d., Slovenia.

Dexamethasone 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 lymphoblastic leukemia, Hodgkin's disease and non-Hodgkin's lymphoma in combination with other medicinal products.

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

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

II. QUALITY ASPECTS

II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Dexeto 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).

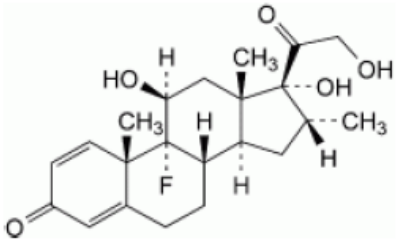
The drug products contain 4 mg, 8 mg, 20 mg and 40 mg dexamethasone, developed by Krka, d.d., Novo Mesto.

The referred product used in the comparative studies was Fortecortin 4 mg and 8 mg tablets manufactured by Merck Serono GmbH.

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.

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



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

Testing methods not described in detail 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.

The drug substance is packed in two polyethylene bags closed by a tamper-evident closure system, in high density polyethylene box (for small quantity) or cardboard drum.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period is acceptable when 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 film-coated tablets containing dexamethasone as drug substance in 4, 8, 20 and 40 mg doses, respectively which are similar to the selected, marketed product Fortecortin tablets produced by Merck Serono GmbH.

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 marketed, referred 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.

- The 4 mg tablets are white or almost white, round tablets with bevelled edges and scored on one side (thickness: 2.5-3.5 mm; diameter: 5.7-6.3 mm).
- The 8 mg tablets are white or almost white, oval tablets, scored on one side (thickness: 3.5-5.5 mm; length: 8.7-9.3 mm).
- The 20 mg tablets are white or almost white, round tablets with bevelled edges, scored and engraved with 20 on one side (thickness: 4.0-6.0 mm; diameter: 10.7-11.3 mm).
- The 40 mg tablets are white or almost white, oval tablets, scored on both sides (thickness:

6.0-8.0 mm; lenght: 18.7-19.3 mm).

The tablets can be divided into two equal doses.

The excipients used in the finished products are lactose monohydrate, magnesium stearate, colloidal anhydrous silica and pregelatinised (maize) starch. All excipients used comply with their respective Ph. Eur. monograph. 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 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 Summary of Product Characteristics, Package Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Dexeto 4 mg, 8 mg, 20 mg and 40 mg tablets 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 chemical-pharmaceutical points of view the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

As 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 marketing authorisation and therefore no new non-clinical data was provided in this application. The applicant submitted a nonclinical 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 Dexeto 4 mg, 8 mg, 20 mg and 40 mg tablets is dexamethasone, 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 demonstrated that the absence of a complete 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.

Nevertheless, a PECsw calculation according to EMA/CHMP/SWP/44609/2010 was additionally performed.

The PECsw calculation is above the phase I trigger value if the worst-case scenario and the default values are used. Fpen refinement was possible because there are sales statistical data available for dexamethasone in the European countries for the period 2013-2016.

The presented calculations demonstrate that the Fpen value based on sales data in the member states is much lower than the default value specified in the guideline. The calculated PECsw is considered to present more realistic environmental concentrations after dexamethasone tablets consumption and clearly demonstrates that there is no risk for the environment. Since dexamethasone is considered to be a potential endocrine disruptor, the applicant further performed a phase II Environmental Risk Assessment, even though the PECsw concentrations for all member states were below the phase I trigger value of 0.01 μg/L.

III.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals.

Pharmacodynamics, pharmacokinetics and toxicology of dexamethasone are well-known. No environmental risk was identified.

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 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 performed 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 profile after using a multiple of tablets with the lower 4 mg dose strengths to the pharmacokinetic profile after using one tablet with the higher 20 mg dose 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 interindividual 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 Bridging bioequivalence study

In a well-established use application, the relevance of the literature data to the claimed product should be justified ("bridging"). In order to do it, essential similarity of the 20

mg strength with the selected marketed product has been proven then the conditions of biowaiver to the other strengths justified.

The application contains an adequate review of published clinical data and a bioequivalence study to bridge the literature clinical data of 4 mg and 8 mg dose strengths to 20 mg and 40 mg strengths.

Essential similarity was demonstrated by means of a bioequivalence study between the Test and Reference products. The study has demonstrated that a single dose of Dexamethasone 20 mg tablets (Krka, Test product) is bioequivalent to the five tablets of Fortecortin® (4 mg dexamethasone each, manufactured by Merck KGaA & Co. Austria, Reference product)) in healthy adult volunteers under fasting conditions according to the bioequivalence guideline in force (*CPMP/EWP/QWP/1401/98/rev 1/Corr** 2010*).

The results are shown in the Table below.

Pharmacokinetic parameter	Ratio T/R	Confidence interval	Intrasubject CV%
C_{max}	108.56	102.65 – 114.81	13.2
AUC_{0-t}	102.15	98.17 – 106.29	9.4

Based on study results criteria used to assess bioequivalence between the test and reference formulations were all fulfilled. The Test to Reference ratio of geometric last squares means and the corresponding 90% confidence intervals for the C_{max} and AUC_{0-t} were within the acceptance range of 80.00 to 125.00%. Therefore, the Test formulation is judged to be bioequivalent to the Reference formulation following a 20 mg dose (single 20 mg dose administered as 5 x 4 mg tablets) administration under fasting conditions.

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**)*:

- 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,
- the qualitative composition of the different strengths is the same,
- the compositions of the claimed four strengths (4, 8, 20 and 40 mg) are proportionally similar,
- *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,
- dexamethasone exhibits linear pharmacokinetics in the claimed therapeutic range (4-40 mg).

Safety results of the bioequivalence study: no death or serious adverse events occurred during the study. Adverse effects in the Test and Reference arm were comparable.

On the basis of the above study clinical literature data are relevant to Dexeto tablets of Krka.

IV.3 Pharmacodynamics

The clinical pharmacology of dexamethasone is well known. No novel pharmacodynamic data are 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 support the well-established efficacy of the active ingredient in the approved indications.

IV.5 Clinical safety

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 safety profile for dexamethasone is well-known and has been extensively described in the literature. 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. 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 Pharmacovigilance Practices 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	Not applicable.

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all safety concerns connected to Krka's products containing dexamethasone. No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in Summary of Peroduct Characteristics, Package Leaflet, and classification as a prescription-only medicine) are considered sufficient to manage all safety concerns connected to Krka's products containing dexamethasone. 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 these medicinal products 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.

IV.7 Discussion on the clinical aspects

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

Well-established use applications avoid the need for repetitive tests on humans. For these applications, the proof for the time-period of medical use and justification of the relevance of the literature data to the submitted product are pivotal.

Both conditions have been fulfilled in the application.

Approval is recommended from the clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Dexeto 4 mg, 8 mg, 20 mg, 40 mg film-coated tablets.

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

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 contains an adequate review of published clinical data and a bioequivalence study to bridge the literature clinical data of 4 mg and 8 mg dose strength to 20 mg and 40 mg strength.

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 Dexeto 4 mg, 8 mg, 20 mg, 40 mg film-coated 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 H/H/0492/	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
IB Change of the invented name of the medicinal product in Denmark and Sweden	001/IB/001	yes	27. 11. 2017	27. 12. 2017	approval	no
IB C.1.z Stand-alone submission of Environmental Risk Assessment studies	(001-004/IB/002	no	08. 01. 2018	13. 04. 2018	approval	no
IB B.II. f. 1.b.1 Extension of the shelf-life of the medicinal product as packaged for sale to 36 months	001-004/IB/003	yes	02. 09. 2019	12. 10. 2019	approval	no