SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dexamethasone Krka 3.3 mg/ml solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of 1 ml contains 3.3 mg dexamethasone (as dexamethasone sodium phosphate).

Excipient(s) with known effect
Each ampoule of 1 ml contains approx. 3 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion (injection/infusion)

The solution for injection/infusion is a clear, colourless to light yellow solution, practically free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Systemic administration:

- cerebral oedema associated with cerebral tumour, neurosurgical procedures, cerebral abscess, bacterial meningitis (e.g. tuberculosis, typhoid, brucellosis)
- polytraumatic shock/prophylaxis of post-traumatic shock-lung syndrome
- severe, acute asthma attack
- initial parenteral treatment of extensive, acute, severe skin diseases like erythroderma, pemphigus vulgaris, acute eczema
- initial parenteral treatment of autoimmune diseases like systemic lupus erythematosus (especially visceral forms)
- active rheumatoid arthritis with a severe, progressive course, e.g. fast proceeding destructive forms and/or with extra-articular manifestations
- palliative therapy of malignant tumours
- prophylaxis and treatment of post-operative or cytostatic-induced vomiting as part of anti-emetic regimens.

Local administration:

- Intraarticular injection: persistent inflammation of one or a few joints after general management of chronic inflammatory joint diseases, activated osteoarthritis, acute forms of periarthropathia humeroscapularis

- Infiltration therapy (when strictly indicated): non-bacterial tendovaginitis and bursitis, periarthropathy, insertional tendinopathy

- Ophthalmology: subconjunctival administration in non-infectious keratoconjunctivitis, scleritis (except necrotising scleritis), uveitis anterior and intermedia.

4.2 Posology and method of administration

Posology

Dosage depends on the nature and severity of the disease and the individual response of the patient to treatment. In general, relatively high initial doses are administered, and they should be significantly higher in acute severe forms than in chronic diseases.

All doses are expressed as mg dexamethasone base.

Unless otherwise prescribed, the following dosage recommendations apply:

Systemic administration:

- Cerebral oedema:
  Adults: depending on the cause and severity, initial dose of 6.6–8.25 mg (up to 66 mg) i.v., followed by 13.2–19.8 mg (up to 39.6 mg)/day i.v., divided into 3–4 (6) individual doses for 4–8 days. A longer-term, lower-dose administration of Dexamethasone Krka may be required during irradiation and in the conservative treatment of inoperable brain tumours.

- Cerebral oedema due to bacterial meningitis: 0.12 mg/kg body weight every 6 hours for 4 days, children 0.33 mg/kg body weight every 12 hours for 2 days; starting before the first administration of the antibiotic. Severe cases, toxic states (e.g. tuberculosis, typhoid; only with concomitant anti infective therapy): 3.3–16.5 mg/day i.v., in single cases (e.g. typhoid) initially up to 165 mg.
  Consideration should be given to official guidance for the resort to corticotherapy for the adequate management of infectious diseases.

- Post-traumatic shock/prophylaxis of post-traumatic shock-lung syndrome: initially 33-82.5 mg (children 33 mg) i.v., a repeated dose after 12 hours or 13.2–33 mg every 6 hours for 2–3 days.

- Severe acute asthma attack: Adults: 6.6–16.5 mg i.v. as early as possible.
Children: 0.12–0.25 mg/kg body weight i.v. Doses should be repeated if necessary, based on the individual response and clinical need.
- Acute skin diseases: Depending on the nature and extent of the disease, daily doses of 6.6–33 mg i.v., in severe cases up to 82.5 mg. Followed by treatment with decreasing doses.

- Active phases of rheumatic systemic diseases: systemic lupus erythematosus 4.95–13.2 mg/day.

- Active rheumatoid arthritis with a severe, progressive course: in rapidly destructive forms 9.9–13.2 mg/day, in extra-articular manifestations 4.95–9.9 mg/day.

- Palliative treatment of malignant tumours: initially 6.6–13.2 mg/day, in prolonged treatment 3.3–9.9 mg/day.

- Prophylaxis and treatment of cytostatic-induced vomiting in anti-emetic regimens: 6.6–16.5 mg i.v. before starting chemotherapy, then 3.3–6.6 mg one to two times daily for 2–3 days as necessary (moderately emetogenic chemotherapy), or up to 3-4 days (highly emetogenic chemotherapy).

- Prophylaxis and treatment of post-operative vomiting: a single dose of 3.3–6.6 mg i.v. before

the start of surgery; in children over 2 years of age: 0.12 mg/kg body weight (max. up to 4.13 mg).

Local administration:

Local infiltration and injection therapy is usually carried out with 3.3–6.6 mg; 1.65 mg of dexamethasone is sufficient if injected into small joints or administered by subconjunctival injection.

Method of administration

Dexamethasone Krka should be administered by slow (over 2-3 minutes) intravenous injection, or by infusion, but may also be administered intramuscularly if problems occur with venous access and blood circulation is adequate. Dexamethasone Krka may also be administered by infiltration and by intra-articular or subconjunctival injection. Treatment duration depends on the indication.

In hypothyroidism or liver cirrhosis, low doses may be sufficient or a dose reduction may be necessary.

Administration by intra-articular injection should be considered open joint procedure and carried out under strict aseptic conditions. A single intra-articular injection is usually sufficient for effective symptom relief. Should a repeated injection be necessary, it should not be administered sooner than after 3–4 weeks. Not more than 3–4 injections should be used on one joint. A medical check of the joint is required, especially after repeated injections.

Infiltration: The region of greatest pain or tendon attachments is infiltrated with Dexamethasone Krka. Caution, do not inject into tendon! Frequent injections should be avoided and strict aseptic precautions should be observed.

In case high doses are required in a single treatment, use of dexamethasone medicinal products with higher strengths/volume should be considered.

Suitability for use

Only clear solutions should be used. The content of the ampoule is intended for single withdrawal. Any remaining solution for injection should be disposed.

See section 6.6 for compatibility information.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
Systemic fungal infection; systemic infection unless specific anti-infective therapy is employed.

Intra-articular injection is contraindicated

- if infection is present in or in the immediate vicinity of the joint to be treated
- in bacterial arthritis
- instability of the joint to be treated
- in tendency to bleeding (spontaneously or due to anticoagulant agents)
- in periarticular calcification
- in avascular bone necrosis
- in tendon rupture
- in Charcot joint

Infiltration without causal additional treatment is contraindicated if infection is present in the administration area, as is subconjunctival administration in viral, bacterial and mycotic eye conditions

or corneal injuries and ulcers.

4.4 Special warnings and precautions for use

Single cases of severe anaphylactic reactions with circulatory collapse, cardiac arrest, arrhythmia, bronchospasm and/or hypotension of hypertension have been observed with the use of Dexamethasone Krka.

Through immunosuppression, treatment with Dexamethasone Krka can lead to an increased risk for bacterial, viral, parasitic, opportunistic and fungal infections. It can mask the symptoms of an existing or developing infection, thereby making a diagnosis more difficult. Latent infections, like tuberculosis or hepatitis B, can be reactivated.

In cases of particular physical stress situations (trauma, surgery, childbirth, etc.) during treatment with Dexamethasone Krka, a temporary increase in dose may be required.

Treatment with Dexamethasone Krka should only be administered in the event of the strictest indications and, if necessary, additional targeted anti-infective treatment if any of the following is present:

- acute viral infections (hepatitis B, herpes zoster, herpes simplex, varicella, herpetic keratitis)
- HBsAG-positive chronic active hepatitis
- approximately 8 weeks prior to 2 weeks after vaccinations with live vaccines
- systemic mycoses and parasitoses (e.g. nematodes)
- in patients with suspected or confirmed strongyloidiasis (infection with threadworms), glucocorticoids can lead to activation and mass proliferation of these parasites
- poliomyelitis
- lymphadenitis after BCG vaccination
- acute and chronic bacterial infections
- in patients with a history of tuberculosis, use only under tuberculostatic protection

In addition, treatment with Dexamethasone Krka should only be administered in strict indications and, if necessary, additional specific treatment must be provided for:

- gastrointestinal ulcers
- osteoporosis
- severe cardiac insufficiency
- high blood pressure that is difficult to control
- diabetes mellitus that is difficult to control
- psychiatric disorders (also in the past), including suicidality: neurological or psychiatric monitoring is recommended
- narrow- and wide-angle glaucoma: ophthalmic monitoring and adjunctive therapy are recommended
- corneal ulcerations and corneal injuries: ophthalmic monitoring and adjunctive therapy are recommended

<u>Visual disturbance</u>

Visual disturbances may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vison or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Because of the risk of an intestinal perforation, Dexamethasone Krka may only be used under urgent indication and under appropriate monitoring for:

- severe ulcerative colitis with threatened perforation, possibly without peritoneal irritation
- diverticulitis
- enteroanastomosis (immediately post-operatively)

Signs of peritoneal irritation after gastrointestinal perforation may be absent in patients receiving high doses of glucocorticoids.

The possibility of a higher need for insulin or oral antidiabetics must be taken into consideration when administering Dexamethasone Krka to diabetics.

Regular blood pressure monitoring is necessary during treatment with Dexamethasone Krka, particularly during administration of higher doses and in patients with high blood pressure that is difficult to control.

Because of the risk of deterioration, patients with severe cardiac insufficiency should be carefully monitored.

With high doses of dexamethasone bradycardia may occur.

Severe anaphylactic reactions may occur.

The risk of tendon disorders, tendinitis and tendon rupture is increased when fluoroquinolones and glucocorticoids are administered together.

A concurrent myasthenia gravis may initially worsen during treatment with Dexamethasone Krka.

Vaccinations with inactivated vaccines are generally possible. However, it should be noted that the immune response and thus the vaccine may be compromised at higher doses of corticosteroids.

At high doses, sufficient potassium intake and sodium restriction should be ensured and serum potassium levels should be monitored.

Abrupt discontinuation of treatment after about 10 days can result in exacerbation or relapse of the underlying disease and acute adrenocortical insufficiency/cortisone withdrawal syndrome; therefore, the dose should be slowly reduced if treatment is to be discontinued.

Certain viral diseases (chickenpox, measles) may be very severe in patients treated with glucocorticoids. Immunocompromised patients without previous chickenpox or measles infection are particularly at risk. If these patients have contact with people infected with measles or chickenpox while undergoing treatment with Dexamethasone Krka, a preventative treatment should be introduced, if necessary.

In post marketing experience tumour lysis syndrome (TLS) has been reported in patients with haematological malignancies following the use of dexamethasone alone or in combination with other chemotherapeutic agents. Patient at high risk of TLS, such as patients with high proliferative rate, high tumour burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.

Intravenous administration should be by slow (over 2–3 minutes) injection, since side effects such as unpleasant prickling or paraesthesia can occur if injected too rapidly.

Dexamethasone Krka is intended for short-term use. If used improperly over a longer period, additional warnings and precautions, as described for long-term administration of glucocorticoid-containing medicinal products, should be considered.

Possible systemic side effects and interactions should be taken into account after local administration.

Intra-articular administration of glucocorticoids increases the risk of joint infections. Long-term administration and repeated injections of glucocorticoids into weight-bearing joints can aggravate wear-related changes of the joints. This is probably due to overburdening of the affected joints after pain or other symptoms have been relieved.

Local ophthalmic use:

Cushing's syndrome and/or adrenal suppression can occur after systemic absorption of ophthalmic dexamethasone during intensive or long-term treatment in predisposed patients, including children and patients treated with CYP3A4 inhibitors (including ritonavir and cobicistat). In these cases, the treatment should be gradually discontinued.

Caution is advised with subconjunctival administration of steroids as this may be associated with a potential risk of scleral thinning or scleral melt.

Children and adolescents
Preterm neonates:
Available evidence suggests long-term neurodevelopmental adverse events after early treatment (< 96 hours after birth) of premature infants with chronic lung disease at starting doses of 0.21mg/kg twice daily.

In the growth phase of children, the benefit-risk balance of treatment with Dexamethasone Krka should be carefully weighed.

Elderly patients

Because elderly patients are at an increased risk of osteoporosis, the benefit-risk balance of treatment with Dexamethasone Krka should be carefully weighed.

The use of Dexamethasone Krka can lead to positive results in doping controls.

Important information about some of the ingredients
Dexamethasone Krka 3.3 mg/ml solution for injection/infusion
This medicinal product contains 3 mg sodium per ampoule, equivalent to 0.15% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Oestrogens (e.g. oral contraceptives): The half-life of glucocorticoids may be prolonged. Therefore, the effect of corticoids may be increased.

Medicines that induce CYP3A4, such as rifampicin, phenytoin, carbamazepine, barbiturates and primidone: The effect of corticoids may be reduced.

CYP3A4 inhibitors (including ketoconazole, itraconazole, ritonavir and cobicistat) can reduce dexamethasone clearance, which can lead to an increase in effect and adrenal suppression/Cushing's syndrome. This combination should be avoided, except in cases where the benefit of treatment outweighs the increased risk for systemic adverse effects of corticosteroids. If this is the case, the patients should be monitored for systemic corticosteroid effects.

Ephedrine: The metabolism of glucocorticoids may be accelerated and thus their effectiveness reduced.

ACE inhibitors: Increased risk of blood count changes.

Cardiac glycosides: The effect of glycosides may be increased by potassium deficiency.

Saluretics/laxatives: Potassium excretion may be increased.

Antidiabetics: The hypoglycaemic effect may be reduced.

Coumarin derivatives: The anticoagulant effect may be reduced or increased. Dosage adjustment of the anticoagulant may be necessary when co-administered.

Nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates and indomethacin: The risk of gastrointestinal ulcers and bleeding is increased.

Non-depolarizing muscle relaxants: The muscle-relaxing effect may last longer.

Atropine, other anticholinergics: Additional intraocular pressure increases are possible during concomitant use.

Praziquantel: Corticosteroids may cause a fall in praziquantel concentration in the blood.

Chloroquine, hydroxychloroquine, mefloquine: There is an increased risk of myopathies, cardiomyopathies.

Protirelin: Reduced increase in TSH may be noted during administration of protirelin.

Immunosuppressive agents: Increased susceptibility to infections and possible aggravation or manifestation of latent infections. Additionally, for cyclosporine: The blood levels of cyclosporine are increased: There is an increased risk of seizures.

Fluoroquinolones may increase the risk of tendon disorders.

Effect on investigation methods:
Skin reactions in allergy tests can be suppressed.

4.6 Fertility, pregnancy and lactation

Pregnancy
Dexamethasone crosses the placenta. During pregnancy, especially in the first trimester, this medicine should only be administered after careful benefit-risk assessment.

In long-term treatment with glucocorticoids during pregnancy, foetal growth disorders cannot be excluded.

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development, including cleft palate, intra-uterine growth retardation and effects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in humans (see section 5.3).

If glucocorticoids are administered towards the end of pregnancy, there is a risk of atrophy of the foetal adrenal cortex, which may necessitate replacement therapy in the newborn, which has to be slowly reduced.

Breast-feeding
Dexamethasone is excreted in breast milk. There have been no known cases of harm to the infant. Nevertheless, the medicine should be used under strict indications during lactation. If the disease requires higher doses, breast-feeding should be discontinued.

4.7 Effects on ability to drive and use machines

There have been no indications that Dexamethasone Krka affects the ability participate actively in road traffic or use machines; the same applies to working without a secure hold.

4.8 Undesirable effects

The risk of undesirable effects is low during short-term treatment with dexamethasone, with the exception of parenteral high-dose therapy where changes in electrolytes, occurrence of oedema, possibly increase in blood pressure, heart arrest, heart rhythm disturbances or convulsions can occur, and clinical manifestations of infections can also be observed during short-term treatment. Attention should be paid to possible gastric and intestinal ulcerations (often stress-induced), because corticoid treatment can reduce their symptoms, and to decrease in glucose tolerance.

The following undesirable effects may occur; they are highly dependent on the dose and duration of treatment, so their frequency cannot be specified:

Infections and infestations:
Masking of infections, manifestation and exacerbation of viral infections, fungal infections, bacterial, parasitic and opportunistic infections, activation of strongyloidiasis (see section 4.4).

Blood and lymphatic system disorders:
Moderate leucocytosis, lymphocytopenia, eosinopenia, polycythaemia.

Immune system disorders:
Hypersensitivity reactions (e.g. medication-induced exanthema), severe anaphylactic reactions, such as arrhythmias, bronchospasm, hypo- or hypertension, circulatory collapse, cardiac arrest, weakening of the immune system.

Endocrine disorders:
Cushing's syndrome (typical symptoms: moon face, central obesity and plethora), adrenal suppression (see section 4.4).

Metabolism and nutrition disorders:
Sodium retention with oedema, increased potassium excretion (risk of arrhythmias), weight gain, reduced glucose tolerance, diabetes mellitus, hypercholesterolemia and hypertriglyceridemia, increased appetite.

Psychiatric disorders:
Depression, irritability, euphoria, increased drive, psychoses, mania, hallucinations, emotional lability, anxiety, sleep disorders, suicidality.

Nervous system disorders:
Pseudotumor cerebri, manifestation of latent epilepsy, increase in seizure susceptibility in manifest epilepsy.

Eye disorders:
Cataract, especially with posterior subcapsular opacity, glaucoma, deterioration of symptoms associated with corneal ulcer, increased occurrence of viral, fungal and bacterial infections of the eye, deterioration of bacterial infections of the cornea, ptosis, mydriasis, chemosis, iatrogenic scleral perforation, chorioretinopathy. Rare cases of reversible exophthalmus, and after subconjunctival administration also herpes simplex keratitis, corneal perforation in cases of existing keratitis, blurred vision (see also section 4.4).

Vascular disorders:

Hypertension, increased risk for atherosclerosis and thrombosis, vasculitis (also as withdrawal syndrome after long-term therapy), increased capillary fragility.

Gastrointestinal disorders:
Gastrointestinal ulcers, gastrointestinal bleeding, pancreatitis, stomach discomfort, hiccup.

Skin and subcutaneous tissue disorders:
Striae rubra, atrophy, telangiectasia, petechiae, ecchymosis, hypertrichosis, steroid-induced acne, rosacea-like (perioral) dermatitis, changes in skin pigmentation.

Musculoskeletal and connective tissue disorders:
Myopathy, muscle atrophy and weakness, osteoporosis (dose-dependent, possible also in short-term administration), aseptic bone necrosis, tendon disorders, tendinitis, tendon rupture, epidural lipomatosis, growth inhibition in children.

Reproductive system and breast disorders:
Disorders of sexual hormone secretion (consequently: irregular menstruation up to amenorrhea, hirsutism, impotence).

General disorders and administration site conditions:
Delayed wound healing.

Local administration: Local irritation and intolerability reactions are possible (sensation of heat, prolonged pain), particularly with ophthalmic use. Skin atrophy and atrophy of subcutaneous tissue at injection site cannot be excluded if corticoids are not carefully injected into the joint cavity.

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
Acute intoxications with dexamethasone are not known. In case of chronic overdosing, an increase in undesirable effects (see section 4.8), in particular endocrine, metabolic and electrolyte-related effects, can be expected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Dexamethasone is a mono-fluorinated glucocorticoid with pronounced anti-allergic, anti-inflammatory and membrane-stabilising properties and effects on carbohydrate, protein and fat metabolism. Dexamethasone has an approximately 7.5 times greater glucocorticoid effect than prednisolone and prednisone, and compared to hydrocortisone it is 30 times more effective, lacking mineralocorticoid effects.
Glucocorticoids, such as dexamethasone, exert their biological effects by activating the transcription of corticosteroid-sensitive genes. The anti-inflammatory, immunosuppressive and anti-proliferative effects are caused by decreased formation, release and activity of inflammatory mediators, by the inhibition of specific functions and the migration of inflammatory cells. In addition, the effect of

sensitised T lymphocytes and macrophages on target cells may be prevented by corticosteroids.

When long-term corticoid treatment is required, the possibility of induction of transient adrenal insufficiency must be considered. The suppression of the hypothalamic-pituitary-adrenal axis also depends on individual factors.

5.2 Pharmacokinetic properties

Dexamethasone binds dose-dependently to plasma albumins. At very high doses, the largest portion circulates freely in the blood. In hypoalbuminaemia the proportion of the unbound (active) corticoid rises. Four hours after intravenous administration of radioactively marked dexamethasone in humans, maximum concentration of dexamethasone in the liquor is about 1/6 of its plasma concentration. With its biological half-life of more than 36 hours, dexamethasone belongs to glucocorticoids with a very long action. Due to its long duration of action, accumulation and overdosing may occur with daily, continuous administration of dexamethasone.
The mean serum elimination half-life of dexamethasone in adults is approximately 250 minutes (+ 80 minutes). It is excreted predominantly through the kidney in form of free dexamethasone alcohol. It is partially metabolised. The metabolites are, as glucoronates or sulphate, also predominantly excreted through the kidneys. Renal dysfunction does not substantially affect the elimination of dexamethasone. The elimination half-life is prolonged in severe liver disease.

5.3 Preclinical safety data

In animal studies, cleft palate was observed in rats, mice, hamsters, rabbits, dogs and primates; not in horses and sheep. In some cases these divergences were combined with defects of the central nervous system and of the heart. In primates, effects in the brain were seen after exposure. Moreover, intrauterine growth can be delayed. All these effects were seen at high dosages.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Creatinine
Sodium citrate, anhydrous
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

24 months

After reconstitution:
Chemical and physical in-use stability has been demonstrated for 48 hours at 15-25°C.
From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Dexamethasone Krka 3.3 mg/ml solution for injection/infusion
Ampoule marked with white point and yellow ring (glass type I, amber glass): 1, 3, 5, 10, 20, 25, 50 and 100 ampoules of 1 ml of solution for injection/infusion, packed into PVC - aluminium blister, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Dexamethasone Krka 3.3 mg/ml solution for injection/infusion and Dexamethasone Krka 6.6 mg/2 ml solution for injection/infusion is preferably administered by direct intravenous injection or injected into the infusion tube. Solution for injection/infusion is compatible with the following infusion solutions (each time 250 and 500 ml) and intended to be used within 48 hours:

- isotonic saline solution
- Ringer's solution
- glucose solution 5%
- glucose solution 10%

When used in combination with solutions for infusion, each supplier's information on their solutions for infusion, including information on compatibility, contraindications, undesirable effects and interactions should be considered.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Krka, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

PL 01656/0279

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

15/01/2020