SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PREDNISOLON F 0.5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains dexamethasone of 0.5 mg as an active substance.

Excipient(s) with known effect: lactose monohydrate of approximately 75 mg in one tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets
White to off-white, round, biconvex tablets with diameter of 6 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prednisolon F is used in the treatment of different diseases, indicated for glucocorticoid therapy, including the complex therapy of brain oedema.

- **Allergic diseases and conditions**

Its use is appropriate in cases, where a rapid therapeutic response is required or in acute episodes of bronchial asthma, atopic and contact dermatitis, allergic drug reactions, annual or seasonal allergic rhinitis or serum disease, refractory to conventional therapeutic regimens.

- **Dermatologic diseases**

Bullous herpetiform dermatitis, exfoliative erythroderma, mycosis fungoides, pemphigus and severe erythema multiforme (Stevens-Johnson syndrome).

- **Endocrine disorders**

Primary and secondary adrenal insufficiency (hydrocortisone or cortisone is the agent of choice). Prednisolon F may be administered concomitantly with synthetic analogues of mineralocorticoids, which are applied, particularly in paediatric population, when their addition is of special importance.

Congenital adrenal hyperplasia, neoplastic-related hypercalcaemia and non-suppurative thyroiditis.

- **Gastrointestinal diseases**

Usually, the medicinal product is administered to patients in the terminal stage of regional enteritis and ulcerative colitis.

- **Haematologic diseases**

Autoimmune haemolytic anaemia, congenital (erythroid) hypoplastic anaemia (Diamond-Blackfan anemia), idiopathic thrombocytitopenic purpura in adults, aplasia of the red blood lines and in certain cases of secondary thrombocytopenia.

- **Neoplastic diseases**

The medicinal product is used as an agent for palliative management in leukaemia and lymphoma.

- **Neurologic diseases**

Acute exacerbation of multiple sclerosis (MS), brain oedema, related with a primary or metastatic tumour, craniotomy or cerebral trauma.

- **Ophthalmologic diseases**

Ophthalmia sympathica, temporal arteritis, uveitis and ocular inflammatory diseases and conditions, refractory to local corticosteroid therapy.

- **Renal diseases**

For the inducement of diuresis or remission of proteinuria in idiopathic nephrotic syndrome or lupus erythematosus.

- **Pulmonary diseases**

Borreliosis, fulminant or disseminated pulmonary tuberculosis on the background of appropriate antituberculosis therapy, idiopathic eosinophylic pneumonia, acute sarcoidosis.

- **Rheumatic diseases and collagenoses**

For short-term use in the complex therapy (acute episode or exacerbation) of acute gout attack, acute rheumatic carditis, ankylosing spondylitis, psoriasic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis (in isolated cases, where low-dose maintenance therapy is required).
For the treatment of dermatomyositis, polymyositis and systemic lupus erythematosus.

- **Other**

In diagnostic tests for adrenocortical hyperfunction, trichinosis with neurological and cardiac symptoms, tuberculous meningitis with a subarachnoid block in the course of appropriate antituberculosis therapy.

4.2 Posology and method of administration

The dosage of glucocorticoids is determined by the severity of disease and the patient's response to the treatment.

In conditions of stress or changes in clinical symptoms or in the course of disease, re-evaluation of therapy and daily dosage may be required.

If the expected therapeutic response is lacking in the course of sufficiently continuous treatment, the therapy with glucocorticoids should be discontinued.

Adults
Usually, a daily dose of 0.5 – 10 mg is sufficient for achieving the therapeutic effect.
In certain cases, a higher daily dose may be required temporarily for managing the disease, which should be reduced subsequently to the appropriate lowest effective daily dose, under continuous supervision and monitoring of the patient.

Short-term suppressive test
1 mg dexamethasone is received at 23:00 hour, and cortisol plasma levels are determined in the morning hours.

In patients, for whom no reduction of plasma cortisol has been observed, more continuous tests may be performed: 500 µg dexamethasone is administered over 6-hour intervals for 48 hours, followed by 2 mg every 6 hours for the next 48 hours.

The 24th hour morning sample is obtained prior to, during and after completion of the test for determining the levels of 17-hydroxycorticosteroids.

Children
The recommended daily dose is 0.01 – 0.1 mg/kg b.w.
The dosage should be individualised and adjusted in accordance with the patient's individual response.

4.3 Contraindications

- Systemic infections, unless corticosteroid preparations are not included in the specific anti-infection therapy;
- Hypersensitivity to the active substance or to any of the excipients.
- The administration of live vaccines should be avoided in patients receiving immunosuppressive doses (the serum antibody response is diminished).

4.4 Special warnings and precautions for use

Psychiatric disorders

Patients and their relatives should be informed that during treatment with systemic corticosteroids, there is a risk of potentially severe psychic disturbances, as adverse reaction manifestations.

Most commonly, these symptoms present within several days or weeks after treatment initiation. The risk is higher after a high-dose treatment or long-term systemic exposure, although there is no definite correlation between the amount of the administered dose and the rate, type, severity or duration of these reactions. Most of them resolve completely after dose reduction or treatment discontinuation, but this does not cancel the necessity of specific treatment administering.

Patients and their relatives should be informed that they should consult a medical specialist if depressive feeling or suicidal thoughts appear. They should also be aware of the presentations of psychic disorders that may be observed in the course of treatment, as well as immediately after the cessation of product administration, although these reactions and manifestations are uncommon.

This is of particular importance for patients with existing or anamnestic severe affective disorders, as well as familial history for such diseases (especially depressive or maniac-depressive disorders or preceding steroid psychosis).

Undesirable effects can be minimised by using the lowest effective dose for the shortest period possible and by administering the required daily dose as a single daily dose in the mornings or a single daily dose received every other morning. Frequent, periodical re-evaluation of the patient's status is required to appropriately titrate the dose against disease activity.

Discontinuation of therapy

Adrenal atrophy develops during prolonged therapy and may persist for years after discontinuation of the treatment.

Withdrawal of corticosteroids after prolonged therapy must therefore always be gradual to avoid acute adrenal insufficiency, being tapered-off over weeks or months according to the dose and duration of treatment.

In patients who have received more than physiological doses of systemic corticosteroids (approximately 1 mg dexamethasone) for more than 3 weeks, withdrawal should not be abrupt.
The reduction of high doses should be done in a way to avoid eventual relapse of the main disease. Periodical clinical assessment of disease activity may be needed during the withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids, but there is uncertainty about HPA suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose of 1 mg dexamethasone is reached, dose reduction should be slower to allow the HPA-system to recover.

Abrupt cessation of systemic corticosteroid therapy with duration of treatment of up to 3 weeks may be considered in cases of lacking clinical evidence of a probable relapse.

Abrupt reduction of daily doses of up to 6 mg dexamethasone, taken for 3 weeks, usually does not lead to clinically significant HPA suppression in most of the patients.

Gradual reduction of the daily dose and cessation of therapy should be considered when the duration of therapy has continued for 3 or less weeks in the following groups of patients:

- patients, who have undergone repeated treatment courses with systemic corticosteroids, especially these with duration > 3 weeks;
- patients, who have undergone short-term treatment courses within one year, following the cessation of continuous therapy (for months or years);
- patients, who present grounds for adrenocortical insufficiency, non-related with exogenic corticosteroid therapy;
- patients receiving systemic corticosteroids at doses > 6 mg dexamethasone daily;
- patients receiving repeated dosing in the evenings.

In the course of continuous treatment, any intercurrent disease, trauma, surgical intervention, requires a temporary increase of the dose; when corticosteroids have been discontinued after a continuous period of administration, the need of their temporary therapeutic re-administration may occur.

Anti-inflammatory/ Immunosuppressive effects and infections

Suppression of the immune response and inflammatory reaction increases the susceptibility to and severity of infections. In many cases, clinical manifestations can be atypical and may progress to advanced forms prior to their verification (septicaemia, tuberculosis). The immunosupressive effect of corticosteroids may lead to activation of latent infections or exacerbation of intercurrent ones.

The administration of appropriate antimicrobial therapy may be required in the course of treatment with systemic glucocorticoids, for example, in tuberculosis or viral or mycotic eye infections.

Varicella/chickenpox may have a fatal course in immunocompromised patients, for which, patients with uncertain anamnestic data for the disease, should avoid close contacts with varicella- or herpes zoster-infected or contact individuals.
Passive immunisation with varicella/zoster immunoglobulin (within 10 days following an exposure or a contact) is recommended in immunocompromised patients receiving systemic corticosteroids or in these having been treated with systemic corticosteroids for the last 3 months. In a case of verified varicella, close, regular monitoring by a specialist and adequate treatment are required. Corticosteroid therapy should not be discontinued and even a dose increase may be required.

Exposure to and contacts with morbilli/measles-diseased individuals should be avoided. Prophylaxis with a common intramuscular immunoglobulin, as well as regular medical supervision by a specialist may be required.

In immunocompromised patients, the administration of live vaccines should be avoided. The antibody-response to other vaccines may be diminished.

Caution and strict control on corticosteroid treatment are required in patients suffering from the following diseases:

- Tuberculosis, history or radiographic evidence of preceding tuberculosis;

The product administration should be limited in active tuberculosis, except for the cases of fulminant or disseminated tuberculosis. In such cases, corticosteroids are included in the complex treatment with suitable anti-tuberculosis therapy.

If corticosteroid therapy is indicated in patients with latent tuberculosis or positive tuberculin test results, strict control is required to prevent re-activation of the disease. During a long-term treatment with corticosteroids, these patients should receive adequate chemoprophylaxis.

- Osteoporosis (there is an increased risk in postmenopausal women);
- Arterial hypertension or congestive heart failure;
- History of severe affective disorders and history of steroid-related psychoses;
- Emotional lability or psychotic tendency may worsen during treatment with corticosteroids;
- Diabetes mellitus (including familial aggravation);
- Glaucoma (including familial history);
- Preceding corticosteroid-induced myopathy;
- Liver insufficiency or cirrhosis;
- Renal insufficiency;
- Hypothyroidism;
- Epilepsy and seizures of different genesis;
- Peptic ulcer;
- Migraine;
- Parasitoses, including amebiasis;
- Incomplete growth in children and adolescents, since glucocorticoids may stimulate the closure of epiphysis upon continuous use;
- Patients with myocardial infarction (myocardial rupture has been reported);
- Predisposition to thrombophlebitis, venous thrombosis, thromboembolism (during treatment with corticosteroids, the risk of haemocoagulation increases);
- Myasthenia gravis.

After administration of glucocorticosteroids, serious anaphylactoid reactions may be observed, such as glottis oedema, urticaria and bronchospasm, particularly in patients with a history of allergy.
In the event of occurred anaphylactoid reactions, the following measures are recommended: immediate slow, intravenous injection of 0.1 - 0.5 ml adrenaline, intravenous administration of aminophylline and artificial respiration.

Adrenal insufficiency

Long-term administration of corticosteroids at pharmacologically active doses may lead to suppression of the hypothalamic-pituitary-adrenal axis, the so-called secondary adrenocortical insufficiency. The rate and duration of adrenocortical insufficiency varies among individual patients, depending on the dose, frequency, time and duration of administration.

Acute adrenal failure resulting in a fatal outcome may be observed when glucocorticoids are ceased abruptly. Drug-induced secondary adrenal failure can be avoided by gradually reducing the dose. This type of relative insufficiency may persist for months following treatment cessation; in a stress-situation during this period, steroid therapy should be resumed.

Due to the possibility of disturbances in mineral-corticoid secretion, sufficient intake of salt and/or mineral-corticoid preparations should be ensured.

Patients receiving systemic corticosteroids should be informed in details, prior to treatment, as well as during its course, about the method of administration, instructions on recommended treatment duration and, particularly, instructions on treatment cessation.

Ophthalmic effects

Long-term administration of corticosteroids may lead to development of posterior subcapsular cataract or nuclear cataract (especially in children), exophthalmos or intraocular pressure elevation resulting in glaucoma with a possible subsequent damage of the optic nerve.

Secondary fungal and viral eye infections may be observed at a higher incidence in patients receiving glucocorticoids.

Corticosteroids should be administered only as an exception in persons with herpes simplex ophthalmicus because of a possible corneal perforation.

Cushing’s disease

Corticosteroids may provoke or worsen Cushing’s syndrome and, therefore, they should be avoided in these cases.

Other

The effect of corticosteroids is intensified in patients with hypothyroidism and in these with cirrhosis.

Psychic disorders and confusion (euphoria, insomnia, unstable mood, changes in personality, severe depressions) may be observed during treatment with corticosteroids.

Use in children

Corticosteroids may induce growth retardation in children and adolescents, irreversible in some cases.

The treatment should be limited to the lowest dose and for the shortest administration period possible.
If a long-term treatment is required with regard to minimising suppression of the hypothalamic-pituitary-adrenal system and growth, the treatment should be performed, where possible, as an intermittent dose regimen.
Growth and development of children receiving corticosteroids should be closely monitored.

Use in the elderly

The common adverse effects of systemic corticosteroids may manifest more seriously in the elderly; this particularly applies to osteoporosis, hypertension, hypokalaemia, diabetes mellitus, predisposition to infections and skin atrophy.

In patients of this age group, intensified clinical control is recommended in order to avoid life-threatening undesirable effects.

Excipients

Because of the presence of lactose in the composition of this medicinal product, it is not suitable for patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

Liver enzyme inducers

Medicines that induce hepatic enzymes associated with the cytochrome P-450 (CYP) isoenzyme 3A4, such as rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin, primidone and aminoglutethimide intensify the metabolism of corticosteroids and may lower their therapeutic effect.

Ephedrine also accelerates the metabolism of dexamethasone.

CYP3A4 inhibitors

Cimetidine, erythromycin, ketoconazole, itraconazole, troleandomycin, diltiazem and mibefradil may lower the rate of liver metabolism and clearance of corticosteroids and, thus, increase their serum concentrations.

Antidiabetics

The desired effects of hypoglycaemic agents (including insulin) may be lowered, since corticosteroids increase the levels of blood glucose. In patients with diabetes mellitus, receiving insulin and/or oral anti-diabetic products, dose adjustment may be required.

NSAIDs and salicylates

Concomitant administration of medicines with a high ulcerogenic potential (e.g. indomethacin) may increase the risk of gastrointestinal ulcerations and haemorrhages.

Salicylates and NSAIDs should be administered with caution to patients with hypoprothrombinaemia.

Serum concentrations of salicylates may decrease when concomitantly received with corticosteroids. The renal clearance of salicylates increases also with corticosteroid discontinuation, which may lead to salicylic intoxication.

Anti-bacterial, anti-fungal and anti-viral agents

Rifampicin intensifies the metabolism of corticosteroids and may lower their therapeutic effect.

Erythromycin inhibits the metabolism of corticosteroids.

The risk of hypokalaemia may increase during co-administration with amphotericin.

Ketoconazole and itraconazole inhibit the metabolism of corticosteroids.

Dexamethasone decreases the plasma concentrations of antiviral agents, such as indinavir and saquinavir.

Anticoagulants

The efficacy of coumarin anticoagulants may undergo changes (a decrease and, more rarely, an increase), when concomitantly administered with corticosteroids, which requires intensified monitoring of the INR and prothrombin time, in order to avoid spontaneous bleeding.

Other

During treatment with cardiac glycosides, their toxicity and the risk of developing hypokalaemia increase.

Corticosteroids may reduce the effects of anticholinesterases in myasthenia gravis.
The desired effects of antihypertensives and diuretics are antagonised by corticosteroids, and the hypokalaemic effects of acetazolamide, loop and thiazide diuretics, carbenoxolone and theophylline are increased.

There are reports of steroid interactions with neuromuscular blockers, such as pancuronium, due to partial reversal of the neuromuscular blockade.

There is an increased risk of haemotoxicity during concomitant administration with methotrexate.

Oral contraceptives (oestrogens and progesterone) may potentiate the effects of glucocorticosteroids, for which dose adjustment is required when the oestrogens are included or excluded from the stable-dose regimen.

Corticosteroids may inhibit the growth-stimulating effect of somatotropic hormone and somatotropin.

There is an increased risk of hypokalaemia during the concomitant administration of high-dose corticosteroids and high-dose bambuterol, fenoterol, formoterol, ritodrine, salbutamol, salmeterol and terbutaline.

Corticosteroid effect may be reduced during co-administration with mifepristone.

4.6 Pregnancy and lactation

Pregnancy

The ability to pass through the placenta varies among the different representatives of the group. Dexamethasone crosses rapidly the placenta.

Administration of corticosteroids to pregnant animals may cause abnormalities in the foetal development, including hard palate clefts, delayed intrauterine development, effects on cerebral growth and development.

There is no evidence that corticosteroids may lead to increased incidences of congenital abnormalities, such as hard palate clefts in humans, but their long-term or repeated administration during pregnancy may increase the risk of foetal development retardation.

Theoretically, the development of hypo-adrenalism cannot be excluded in newborns with prenatal exposure to corticosteroids, but usually, this condition restores spontaneously after birth and is rarely of clinical significance. Cases of cataract have been observed in newborns, whose mothers were continuously treated with prednisolone during pregnancy.

Like other medicines, dexamethasone should be administered during pregnancy only when the benefits for the mother and/or foetus exceed the risks.

When corticosteroids are absolutely required, they may be administered to patients with normal pregnancies in accordance to generally accepted rules.

Patients with preeclampsia and oedemas require close monitoring.

Breast-feeding

Corticosteroids are excreted in small quantities in breast milk. They may suppress the growth of the breast-fed child and affect the endogenic secretion of glucocorticoids.

Corticosteroids should be administered to breast-feeding women only when the potential benefit for the mother overweighs significantly the risk for the breast-fed child, because there are no data of relevant controlled studies.

4.7 Effects on ability to drive and use machines

Not known.

4.8 Undesirable effects

The frequency of expected undesirable effects related with the use of corticosteroids, including hypothalamic-pituitary-adrenal suppression, correlates with the relative potency of the active substance, dosage, method of administration and duration of treatment.

The physician should find the optimal balance between the therapeutic effect and the risk of occurrence of undesirable effects by administering the lowest effective dose possible for the shortest period, and it is recommended to administer the daily dose in the morning hours as an alternative regimen of dosing. The early recognition and appropriate treatment of undesirable effects may minimise the potentially severe complications of glucocorticoid therapy.

A great number of psychic reactions, including affective disorders (irritability, euphoria, depression and mood lability, suicidal thoughts), psychotic reactions (including mania, delusion, hallucinations and schizophrenia worsening), behavioural disorders, excitability, anxiety, sleep disturbances have been reported during the administration of corticosteroids of all groups. The reactions are common and may be observed in both adults and children. In adults, the incidence of severe reactions reaches 5-6%. Psychological effects have been observed with treatment discontinuation, as their frequency remains unknown.

During therapy with dexamethasone, the following undesirable effects are likely to occur with unknown frequency (cannot be estimated from the available data):

Blood and lymphatic system disorders
Leukocytosis

Endocrine system disorders
Hypothalamic-pituitary-adrenal system disorders, adrenal suppression, Cushingoid face.

Eye disorders
Papillary oedema (in children, with symptoms of brain pseudotumour, usually after discontinuation of therapy), glaucoma, posterior subcapsular cataract, thinning of the cornea and sclera

Gastrointestinal disorders
Dyspepsia, vomiting, gastric and duodenal ulceration with haemorrhages and perforation, acute pancreatitis.

General disorders and administration site conditions
Oedemas, impaired healing, thromboembolism, myocardial rupture after recent myocardial infarction.

Immune system disorders
Drug hypersensitivity, anaphylactic reactions.

Infections and infestations
Primary and secondary infections (increased susceptibility and severity, and masking of clinical symptoms), opportunistic infections, activation of tuberculosis, varicella, exacerbation of ocular viral or fungal infections, candidiasis.

Injury, poisoning and procedural complications
Vertebral fractures, tendon rupture, contusions.

Investigations
Weight gain, reduced carbohydrate tolerance, increased intraocular pressure.

Metabolism and nutrition disorders
Increased appetite, impaired control on diabetes mellitus, lipoprotein deficit, calcium deficit, sodium retention, fluid retention, hypokalaemia, hypokalaemic alkalosis.

Musculoskeletal system and connective tissue disorders
Growth retardation in newborns, children and adolescents, premature closure of epiphyses, osteoporosis, osteonecrosis, myopathy.

Nervous system disorders
There are reports of increased intra-cranial pressure with papilloedema in children (*pseudotumour cerebri*), usually, after treatment discontinuation, aggravation of epilepsy.

Psychiatric disorders
Nervousness, euphoric behaviour, drug dependence, depression, insomnia, aggravation of schizophrenia.

Reproductive system and breast disorders
Irregular menstruation, amenorrhoea.

Skin and subcutaneous tissue disorders

Allergic dermatitis, hirsutism, skin atrophy, telangiectases, formation of striae, acne.

Vascular disorders
Hypertension, embolism.

Investigations
Suppression of the reaction in skin tests for demonstrating hypersensitivity.

Withdrawal symptoms
During a long-term treatment, a rapid reduction of the dose may lead to acute adrenal insufficiency, hypotension and death.

Steroidal "withdrawal syndrome", seemingly non-related with adrenocortical insufficiency, may be observed after abrupt discontinuation of the medicine.

The withdrawal syndrome includes the following symptoms: anorexia, nausea, vomiting, lethargy, headache, fever, joint pains, skin desquamation, myalgia, arthralgia, rhinitis, conjunctivitis, painful, itching cutaneous nodules and weight loss and/or hypotension. These effects are probably due to a hidden change in the corticosteroid concentration, lower than the lowest physiological levels.
Fever may also be observed with the withdrawal syndrome.

4.9 Overdose

Acute intoxication and/or fatal outcomes, due to overdose with corticosteroids, have been reported rarely.

There is no known specific syndrome in acute overdose with dexamethasone, and the treatment is supportive and symptomatic. Serum electrolytes should be closely monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemic hormonal preparations, corticosteroids for systemic use, glucocorticosteroids
ATC code: H02AB02

Dexamethasone is a synthetic glucocorticoid with pronounced anti-inflammatory potency, approximately 7 times greater than that of prednisolone.
Like other corticosteroids, dexamethasone also has anti-allergic, antipyretic and immunosuppressive effects.

Dexamethasone has practically no mineralocorticoid effects and does not lead to water and electrolyte retention, and is, therefore, suitable for the use in patients with cardiac failure or hypertension.

Because of its long biological half-life (36-54 hours), dexamethasone is especially suitable in diseases and conditions, where continuous glucocorticoid action is desired.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, dexamethasone is readily absorbed from the gastro-intestinal tract. It is also well absorbed from sites of local application.

Distribution
Dexamethasone is intensively distributed to all body tissues and fluids. It crosses the placenta and may be excreted in small amounts in breast milk.

Most corticosteroids in the circulation are extensively bound to plasma proteins, mainly to globulin and less so to albumin.
The corticosteroid-binding globulin has high affinity but low binding capacity, while the albumin has low affinity but large binding capacity.

The synthetic corticosteroids are less extensively protein bound than hydrocortisone (cortisol). They also tend to have longer half-lives.

Biotransformation
Corticosteroids are metabolised mainly in the liver but also in the kidneys. The slower metabolism of the synthetic corticosteroids with their lower protein-binding affinity may account for their increased potency compared with the natural corticosteroids.

Elimination
Synthetic corticosteroids are excreted in the urine.

5.3 Preclinical safety data

The mean lethal dose of oral dexamethasone, administered in mice, is 6.5 g/kg.

In chronic intoxication, the targeted tissues and organs are the lungs and mucosae of the gastrointestinal tract and respiratory system. Repeated dose administration in experimental animals has resulted in a loss of appetite, negative dynamics of the body mass curve and decrease in the number of leukocytes. Decreases in the weight of thymus, adrenal glands and spleen have been observed, as well as myeloid alterations in the bone marrow.

There are no sufficient data of the embryotoxic and teratogenic potential of dexamethasone. In high-dose treated experimental animals, an increase of the cases with hard palate clefts, as well as a tendency to lowered body weight of the newborns have been observed.

There are no data of a mutagenic potential and carcinogenic activity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate/Maize starch (85:15)
Magnesium stearate

6.2 Incompatibilities

Not known.

6.3 Shelf life

3 (three) years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

10 (ten) tablets are packed in a PVC/AL foil or PVC/PVdC/AL foil blister.
Three blisters are inserted in a carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Antibiotic-Razgrad AD
Office 201, 68 “Aprilsko vastanie” Blvd.
7200 Razgrad, Bulgaria

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

September 2011