SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEKORT 8 mg/2 mL I.M./I.V. Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each 2 mL ampoule contains 8.75 mg of dexamethasone 21-phosphate disodium, equivalent to 8 mg of dexamethasone 21-phosphate.

Excipients with known effect:
Sodium citrate dihydrate 20 mg
Sodium hydroxide (for pH adjustment)
Sodium metabisulphite 2 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

2 mL ampoule solution;
Almost colorless, clear solution with characteristic odor.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DEKORT is used in conditions responsive to corticosteroid therapy due to its anti-inflammatory, antirheumatic and anti-allergic effects.

Primary diseases in which DEKORT is indicated are as follows:

- Allergic diseases: Anaphylactic shock, allergic reactions due to a drug or transfusion, acute asthma, serum sickness, angioneurotic edema, larynx edema, acute dermatoses (If transfusion reactions are suspected, DEKORT should be administered before transfusion).
- Rheumatic diseases: Evaluative chronic polyarthritis, rheumatic fever, rheumatoid arthritis (including juvenile rheumatoid arthritis), psoriatic arthritis, osteoarthritis, spondylitis, synovitis, tenosynovitis, bursitis.
- Endocrine disorders: Shocks which are unresponsive to the known treatment (if adrenal insufficiency is suspected). Addison disease, acute adrenal insufficiencies such as surrenalectomy, congenital adrenal hyperplasia, non-suppurative thyroid, hypercalcemia associated with cancer. In acute adrenocortical insufficiency, DEKORT can be added to serum physiological administered.
- Dermatological diseases: Psoriasis, seborrheic dermatitis, exfoliative dermatitis, pemphigus, dermatomyositis, scleroderma.
- Collagen diseases: Systemic lupus erythematosus, acute rheumatic carditis.
- Respiratory system diseases: Acute, severe and disseminated pulmonary tuberculosis (co-administered with anti-tuberculosis drugs), aspiration pneumonia, emphysema, lung granulomatosis, symptomatic sarcoidosis, Loeffler syndrome, berylliosis.
- Ophthalmic diseases: Conjunctivitis, ceratitis, keratoconjunctivitis, scleritis, episcleritis, uveitis, chorioretinitis, sympathetic ophthalmia, iritis, iridocyclitis, herpes zoster ophthalmic (not herpes simplex), optic neuritis, retrobulbar neuritis.

- Hematological disorders: Idiopathic thrombocytopenic purpura (IM administration is contraindicated), thrombocytopenia, hemolytic anemia, erythroblastopenia, congenital hypoplastic anemia.
- Neoplastic diseases: Leukemia and lymphomas, Hodgkin disease, lymphosarcoma.
- Diseases which cause edema: Idiopathic or nephrotic syndrome induced by lupus erythematosus.
- Gastrointestinal system diseases: Ulcerative colitis, terminal ileitis.
- Brain edema: Brain edema caused by primary or metastatic brain tumors, craniotomy or concussions (provided that it is administered for an operation or other specific treatments).
- Conditions which require intralesional application: Cheloid; localized inflammatory lichen planus, granuloma annulare, lichen simplex chronicus lesions; psoriatic stains, discoid lupus erythematosus, Necrobiosis lipoidica diabeticorum, alopecia areata.
- Other diseases: Trichinosis causing neurologic or myocardial symptoms.
- Tuberculous meningitis which causes or has strong possibility to cause subarachnoid block (when co-administered with anti-tuberculosis drugs), periarteritis nodosa, Chauffard-Still syndrome.

4.2. Posology and method of administration

Posology/frequency and duration of administration:
4 mg dexamethasone 21-phosphate has therapeutic effect equivalent to that of 100 mg hydrocortisone. Although it is usually administered at doses of 4-20 mg, 80 mg daily should never be exceeded.

Dose is usually adjusted according to the type and severity of the disease, and to the reaction of the patient. Intravenous and intramuscular injections are recommended for acute diseases. It should be administered immediately 4-5 hours as soon as the acute period passes.

The following method of administration is recommended for acute allergic diseases.
Day 1 : 1 -2 ml DEKORT 8 mg/2 ml IM/IV Solution for Injection (via IM route)
Day 2 : 2 DEKORT tablets 0.75 mg twice daily
Day 3 : 2 DEKORT tablets 0.75 mg twice daily
Day 4 : 1 DEKORT tablet 0.75 mg twice daily
Day 5 : 1 DEKORT tablet 0.75 mg once daily
Day 6 : 1 DEKORT tablet 0.75 mg once daily
Day 7 : Treatment is discontinued.
Day 8 : The physician is seen.
So that, the risk of overdose is eliminated.

In general, glucocorticoid dose depends on the severity (seriousness) of the condition and response of the patient. Under certain circumstances, for instance in stress, extra dose adjustments may be necessary. If no favorable response is noted within a couple of days, glucocorticoid therapy should be discontinued.

Adults and Elderly
Once the disease is under control, the dose should be reduced or tapered off to the lowest suitable level under continuous monitoring and observation of the patient (see section 4.4).
For acute life-threatening situations (e.g. anaphylaxis, acute severe asthma), substantially higher doses may be needed.

Cerebral edema (adults): The initial dose of 8-16 mg IV followed by 5 mg IV or IM every 6 hours, until a satisfactory result has been obtained. In brain surgery, these doses may be necessary until

several days after the operation. Thereafter, the dose has to be tapered off gradually. Increase of intracranial pressure associated with brain tumors can be counteracted by continuous treatment.

For local treatment, the following doses can be recommended:

intra-articular	1.6-3 mg large joints 0.6-0.8 mg small joints
intrabursal	1.6-3 mg;
in tendon sheath:	0.3-0.8 mg

The frequency of these injections may vary from every 3-5 days to every 2-3 weeks.
For rectal drip in cases of ulcerative colitis: 4 mg diluted in 120 ml saline.

Method of administration:
Anatomic structure should be well-known for injection. Injection should never be administered into intervertebral joints.

The synovial fluid should be drawn before giving injection to ensure whether or not the needle reaches the desired point.

If there is no requirement for local anesthesia, anesthetic agent can be given into the soft tissue before the administration of intra-articular corticosteroid in considerably susceptible patients.

After injection, patient should not move his/her joint much. In gonococcic and tuberculoid origin specific arthritis, intra-articular injection should not be administered.

Additional information on special populations
Renal/Hepatic insufficiency:
There is no special dose adjustment for patients with renal or hepatic insufficiency.

Pediatric population:
Initial dose of dexamethasone may vary according to the severity of the disease in pediatric population. The initial dose range is 0.02-0.3 mg/kg/day and administered as divided into 3 or 4 doses.
Dose requirements are variable and may have to be changed according to individual needs. Usually 0.2 mg/kg to 0.4 mg/kg of body weight daily.

Geriatric population
Clinical studies did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In particular, the increased risk of diabetes mellitus, fluid retention and hypertension in elderly patients treated with corticosteroids should be considered.

4.3. Contraindications

It is contraindicated in patients who are hypersensitive to any components of this product, acute infections, systemic fungal infections, in patients with ulcerative herpes simplex in their eye in herpes zoster as it compromises immunological response and inflammatory reactions. Administration of live

vaccines is contraindicated.

4.4. Special warnings and precautions for use

Undesirable effects may occur at therapeutic doses. Therefore, dose should be increased gradually and slowly. Administration of corticosteroid may mask signs of some diseases which are about to emerge. It may yield (-) result in nitro blue tetrazolium test used for bacterial infections.

Corticosteroids may activate latent amebiasis. Therefore, it is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in patients with unexplained diarrhea.

Prolonged corticosteroid therapy may cause damage to optic nerves and subcapsular cataract and glaucoma may occur as a consequence. Oral corticosteroid is not recommended for use in optic neuritis and may cause increase in new hazardous situations.

Corticosteroids should not be used in active ocular herpes simplex. In some patients, intraocular pressure may increase. If steroid treatment persists for more than 6 weeks, intraocular pressure should be monitored.

Administration of average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, sodium and water retention and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. Since corticosteroid administration may cause potassium loss and water retention as a result of edema, these agents should be used with caution in patients with congestive heart failure, hypertension or renal impairment.

Administration of live virus vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. With the use of corticosteroids at these doses, the expected serum antibody response may not occur after the administration of inactivated bacteria and virus vaccines. Immunization procedures may be undertaken in patients who are receiving corticosteroid replacement therapy, such as Addison's disease.

Chicken pox and measles can have a more serious and even fatal in pediatric and adult patients on corticosteroids. Particular caution is required in pediatric and adult patients with chickenpox and measles. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. Treatment with prophylaxis with immunoglobulin (IG) if measles develops, antiviral agents should be considered if chickenpox develops.

In patients with known and suspected *Strongyloides* infestations, corticosteroids should be used with extreme caution. In such patients, corticosteroid-induced immunesuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

In patients with active tuberculosis, corticosteroid can be used with an appropriate antituberculous regimen. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Withdrawal of corticosteroids should not be abruptly. It should be gradually tapered off over a period

of time to avoid symptoms including fever, myalgia, arthralgia and malacia accompanied by adrenal insufficiency.

Effect of corticosteroids is enhanced in patients with hypothyroid and cirrhosis.

Psychic derangements may appear upon use of corticosteroid. There may also be euphoria, insomnia, character change, severe depression, and frank psychotic manifestations. Emotional instability or psychotic tendencies may be aggravated by corticosteroid use.

In patients with hypoprothrombinemia, aspirin should be used cautiously in conjunction with corticosteroids.

Steroids should be used with caution in cases of non-specific ulcerative colitis, pyogenic inflammations, diverticulitis, new intestinal anastomosis, active or latent peptic ulcer, diabetes mellitus, renal impairment, hypertension, osteoporosis and myasthenia gravis. Peritoneal and gastrointestinal irritation has occurred at large doses. Fat embolism has been reported as a complication of hypercortisolism.

It has been reported that it is more appropriate to take the drug after meals when large dose of corticosteroid is used and even taking antacid between meals will provide protection against peptic ulcer. Steroids may increase or decrease motility and number of spermatozoa in some patients. Corticosteroids may exacerbate systemic fungal infections. However; glucocorticoid treatment can be initiated if specific antifungal treatment is to be applied.

The efficacy and safety of corticosteroids in children depend on the course of action of corticosteroids, which is similar in children and adults. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (patients >2 years of age), and aggressive lymphomas and leukemias (patients >1 month of age).

Other indications for pediatric use of corticosteroids, such as severe asthma and wheezing, are based on adequate and well-controlled trials conducted in adults. Consequently, the disease and its pathophysiological aspect are considered to be the same in both populations.

Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcer, cataract, and osteoporosis. Decreased growth rate may be observed in children using corticosteroids, including corticosteroids that enter the systemic circulation.

The linear growth of children using corticosteroids should be monitored. The potential growth effect of continued therapy should be weighed against the clinical benefit achieved and the availability of treatment alternatives. In children, the least effective dose should be used to minimize the potential growth effect of corticosteroids.

No clinical studies have been conducted in the elderly 65 years of age and older to determine whether there is a difference in response compared to adults. In other reported clinical studies, however, no differences were found between the elderly and adults. Care should be taken in dose selection in the geriatric population, usually starting at the low end of the dosage range, taking into account the extreme frequency of renal, hepatic or cardiac function decline and concomitant disease or other drug therapy. The risk of diabetes, fluid retention and hypertension should be considered, especially in

elderly patients treated with corticosteroids.
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially 'sodium- free'.

4.5. Interaction with other medicinal products and other forms of interaction
Rifampicin, rifabutin, ephedrine, carbamazepine, phenylbutazone, phenobartital, phenytoin, primidone, and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced.

The effects of anticholinesterases are antagonized by corticosteroids in myasthenia gravis.

The desired effects of hypoglycemic agents (including insulin), anti-hypertensives and diuretics are antagonized by corticosteroids, and the hypokalemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced.

The efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication.

There may be interaction with salicylates in patients with hypoprothrombinemia.

Additional information on special populations:
No interaction study has been performed for special populations.

Pediatric population:
No interaction study has been performed for pediatric populations.

4.6 Fertility, pregnancy and lactation
General recommendation
Pregnancy category is C.

Women of child-bearing potential/Contraception
As sufficient data is not available as to use of dexamethasone in pregnant women, women of child-bearing potential are recommended to administer a suitable birth control method.

Pregnancy
There are no adequate and well-controlled studies as to teratogenic effect of corticosteroids used in pregnant women. However; DEKORT should not be used during pregnancy unless it is necessary. Corticosteroids should be administered only under physician's supervision and and if the benefit to the mother outweighs the harm to the fetus.

Signs of hypoadrenalism which may occur when substantial doses of corticosteroids have been received during pregnancy should be carefully monitored.

There is no adequate data as to use of dexamethasone 21-phosphate in pregnant women.

Animal studies are insufficient for effects on pregnancy / and-or / embryonal / fetal development / and-or / birth / and-or / postnatal development. DEKORT should not be used during pregnancy unless

it is necessary. The potential risk for humans is unknown.

Breast-feeding

Corticosteroids pass into breast milk. This causes undesirable effects such as suppression of growth and damage to endogenous corticosteroid production in the child. Therefore, it is recommended that mothers taking pharmacological doses of corticosteroids should not breastfeed.

Fertility

Steroids may increase or decrease motility and number of spermatozoa in some patients.

4.7. Effects on ability to drive and use machines

DEKORT has no negative effect on ability to drive and use machines.

4.8. Undesirable effects

Adverse reactions are listed according to system organ class and frequency:
Very common (1/10), common (1/100 to <1/10), uncommon (1/1000 to <1/100), rare (1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be predicted based on the available data).

The following adverse reactions have been reported with dexamethasone and the degree of frequency is not known (cannot be predicted based on the available data).

Immune system disorders:

Not known: Anaphylactoid reactions, fatigue, exacerbation or masking of infections.

Endocrine disorders

Not known: Menstrual irregularities, development of cushingoid state, development delay in children, secondary adrenocortical and pituitary unresponsiveness particularly in times of stress, as in trauma, surgery and illness, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetic patients, hirsutism.
Decreased carbohydrate and glucose tolerance, hyperglycemia, glycosuria.

Metabolism and nutritional disorders

Not known: Negative nitrogen balance due to protein catabolism

Nervous system disorders

Not known: Convulsions, increased intracranial pressure and consequent papilloedema

Eye disorders

Not known: Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos

Cardiac disorders

Not known: Congestive heart failure, thromboembolism

Vascular disorders

Not known: Hypertension

Gastrointestinal disorders

Not known: Peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine particularly in patients with inflammatory bowel disease, pancreatitis, abdominal distention,

ulcerative esophagitis, elevation in serum liver enzyme levels, increased appetite, nausea

Skin and subcutaneous tissue disorders
Not known: Delay in wound healing, thin fragile skin, ecchymoses, erythema, increased sweating, burning or itching in the perineal area (following I.V. injection), allergic dermatitis, angioneurotic edema

Musculoskeletal and connective tissue disorders
Not known: Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones, tendon rupture

Renal and urinary disorders
Not known: Sodium retention, fluid retention, potassium loss, hypokalemic alkalosis

General disorders and administration site conditions
Not known: Thromboembolism, increased weight and appetite, nausea, psychic disorders

The adverse reactions which may be observed only with parenteral corticosteroid treatment are as follows:

Eye disorders
Rare: Blindness

Skin and subcutaneous tissue disorders
Rare: Atrophy, hyper- or hypo-pigmentation, sterile abscess

Musculoskeletal and connective tissue disorders
Not known: Charcot type arthropathy following intra-articular administration

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 in accordance with local requirements.

4.9. Overdose
Acute reactions and death are unlikely to occur with overdose of glucocorticoid. There is no requirement for the treatment of chronic toxicity symptoms unless there is a condition which would lead to hypersensitivity to glucocorticoids. In case of such special condition, gastric lavage should be performed and symptomatic therapy should be instituted. When hypersensitivity reactions and anaphylaxis are observed, adrenalin and aminophylline should be administered and the patient should be kept in a warm and quiet environment.

Dexamethasone has no special antidote. Its plasma half-life is approximately 190 minutes.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Systemic corticosteroids

ATC code: H02AB02

Dexamethasone, the active substance of DEKORT, is a glucocorticoid with high anti-inflammatory activity and synthesized by fluoro-prednizolone molecule through the binding of methyl group to position 16 of fluoro-prednisolone.

In contrast to other synthesized corticosteroids which induce many undesirable effects, these potential adverse reactions occur less frequently and being less severe with dexamethasone, which enables corticosteroid therapy to be instituted in patients who are intolerant to other corticosteroids.

Although dexamethasone is superior to other corticosteroids with higher anti-inflammatory, anti-rheumatic and anti-allergic potency, it has only minor mineralocorticoid activities. Undesirable effects, such as loss of appetite, weight loss, severe headache, dizziness, muscle weakness which are normally observed during treatment with other corticosteroids do not occur in patients treated with dexamethasone and the drug product does not induce sodium retention and potassium loss (except use at large doses), and ultimately all these features provide great convenience in clinical practice. As it does not induce hypertension and almost completely lacks the sodium- and water- retaining, it enables an effective treatment for most patients with cardiovascular diseases.

5.2. Pharmacokinetic properties

General properties

Dexamethasone is a white to practically white crystalline powder. It is slightly soluble in acetone, methanol, anhydrous ethanol or dioxane. It is very slightly soluble in chloroform. It is very slightly soluble in ether, it is practically insoluble in water.

As dexamethasone 21-phosphate disodium is dissolved in water 3000 times more than hydrocortisone; it is convenient for intramuscular, intravenous, intrasynovial injections and soft tissue infiltration.

Absorption

As it is absorbed very rapidly, response in intramuscular administrations is as rapid as that in intravenous administrations. Its effect is exerted within two hours following injection into joint.
At therapeutic doses, soft tissue injections and intrasynovial administrations do not lead to the hormonal effects observed in long-term corticosteroid treatments.

Distribution

Binding of dexamethasone to plasma proteins is less than for most other corticosteroids. Corticosteroids are rapidly distributed to body tissues.

Biotransformation

Corticosteroids are mostly metabolized in liver.

Elimination

It is excreted mainly via the urine.

Linearity/ Non-linearity

Data is not available.

Other Special Populations

Geriatric population:

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In particular, the increased risk of diabetes mellitus, fluid retention and hypertension in elderly patients treated with corticosteroids should be considered.

Pediatric population:
The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids, which is similar in pediatric and adult population.

5.3 Preclinical safety data
The active substance of the drug product has been used in clinic for many years. Studies regarding the safety and efficacy profile of dexamethasone have been completed. Negative effects which may arise from its use are included in related sections 4.4, 4.6, 4.8 and 4.9.

5. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium citrate dihydrate
Sodium hydroxide
Sodium metabisulphite
Creatinine
Phenol
Water for injection

6.2 Incompatibilities
It has no known incompatibility.

6.3 Shelf life
48 months

6.4 Special precautions for storage
Store at room temperature below 25°C and protect from light.

6.5 Nature and contents of container
2 ml Type 1 amber colored glass ampoules with ring.
Each cardboard box contains 1 ampoule of 2 ml.

6.6 Special precautions for disposal and other handling
Any unused material should be disposed according to local disposal regulations.

6. MARKETING AUTHORIZATION HOLDER
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece - ISTANBUL/TÜRKİYE

7. MARKETING AUTHORIZATION NUMBER
85/88

8. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 10.03.1967
Date of last renewal : 05.04.2006

10. DATE OF REVISION OF THE TEXT