and the condition of the patient. Localised therapy is generally preferred because it minimises adverse effects. When systemic therapy is required, the oral route is preferred for ease in regulation of dose and the variety in regimens.

Oradexon Organon injections are used when the severity of the condition indicates an acute and strong relief of the symptoms, or when oral therapy is not feasible. Oradexon Organon injections can be given by intravenous (i.v.), intramuscular (i.m.) or local injection. Oradexon Organon injections can also be diluted with an infusion fluid or be injected directly into the infusion line.

Intravenous injections of massive doses should be given slowly, over a period of several minutes.

Intramuscular administration should be given by deep intramuscular injection, to prevent atrophy of the subcutaneous adipose tissues.

Intra-articular injections should be given under strictly aseptic conditions as glucocorticoids decrease the resistance to infection.

Oradexon Organon injections can be diluted with any of the following infusion fluids, or injected directly into the infusion line without causing precipitation of the ingredients.

When diluted with these infusion fluids, Oradexon Organon injections will keep its potency for at least 24 hours (at room temperature and in daylight conditions).

Infusion fluids: sodium chloride 0.9%, anhydrous glucose 5%, invert sugar 10%, sorbitol 5%, Ringer's solution, Hartmann's solution (Ringer-lactate), Rheomacrodex, Isodex, Haemaccel.

The dosage of Oradexon Organon injection depends on the severity of the condition and the response of the patient. Undesirable effects, such as suppression of the hypothalamus-pituitary-adrenal (HPA) axis, may be minimised by using the lowest effective dose for the minimum period, preferably in the morning and if disease control will allow
alternate day therapy. Systemic dexamethasone administered in the evening is more likely to cause clinically significant HPA suppression. Alternate day dosing is not appropriate for patients with established adrenal insufficiency. Frequent patient review is required to appropriately titrate the dose against disease activity. If no favourable response is noted within a couple of days, continuation of glucocorticoid therapy is undesirable.

**For systemic therapy** in adults, daily doses of 0.05-0.20 mg/kg body weight are usually sufficient. As soon as symptoms diminish, the dose should be reduced under continuous observation of the clinical picture to the lowest possible level, or tapered off completely by following the withdrawal schedule below. Oradexon Organon should only be administered to children with caution, since glucocorticoids can induce growth retardation. The daily dose should be determined by the physician for each child individually.

**For emergencies** (e.g. anaphylaxis, acute severe asthma, cerebral oedema) substantially higher doses are required. An initial dose of 10-20 mg i.v. is followed by 6 mg i.v. or i.m. every 6 hours, until a satisfactory result has been obtained. Thereafter the dosage has to be tapered off gradually.

**For local therapy**, the following doses are recommended:
- intra-articularly: 2-4 mg in large and 0.8-1 mg in small joints;
- intrabursally: 2-4 mg; in tendon sheaths: 0.4-1 mg.

The frequency of these injections may vary from every 3-5 days to every 2-3 weeks.

**During prolonged therapy** any intercurrent illness, trauma or surgical procedure will require a temporary increase in dosage.

**Withdrawal of prolonged therapy**

In patients who have received dexamethasone for more than 3 weeks, withdrawal should not be abrupt. How dose reduction should be carried out (tapered off over weeks or months) depends largely on whether the disease is likely to relapse as the dose of systemic glucocorticoids is reduced. Clinical assessment of disease activity may therefore be needed during withdrawal. If the disease is unlikely to relapse on withdrawal but there is uncertainty about hypothalamus-pituitary-adrenal (HPA) suppression, the dose of systemic dexamethasone may be reduced rapidly to physiological doses. Once a daily dose of approx. 1.5 mg dexamethasone sodium phosphate is reached, dose reduction should be slower to allow the HPA-axis to recover.

Abrupt withdrawal of systemic dexamethasone treatment, which has continued for up to 3 weeks is appropriate if it is considered that the disease is unlikely to relapse. Abrupt withdrawal of doses up to approx. 8 mg dexamethasone sodium phosphate for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression, in the majority of patients.

In the following patient groups, gradual withdrawal of systemic dexamethasone therapy should be considered even after courses lasting 3 weeks or less:
- Patients who have had repeated courses of systemic dexamethasone (or other corticosteroids), particularly if taken for more than 3 weeks.
- Patients who may have reasons for adrenocortical insufficiency other than exogenous dexamethasone (or other corticosteroids), particularly if taken for more than 3 weeks.

When a short course has been prescribed within one year of cessation of long-term therapy (months or years).
- Patients who may have reasons for adrenocortical insufficiency other than exogenous dexamethasone (or other corticosteroids) therapy.
- Patients receiving doses of systemic dexamethasone sodium phosphate higher than approx. 8 mg.
- Patients repeatedly taking doses in the evening.
- Patients who during systemic treatment encounter stresses such as trauma, surgery or infection and who are at risk of adrenal insufficiency should receive additional systemic dexamethasone cover during these periods. This includes patients who have finished a course of systemic dexamethasone of less than three weeks duration in the week prior to the stress.

Too rapid reduction of dexamethasone dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. Characteristic symptoms of a "withdrawal syndrome" that may occur are fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.
When treating **Acute Respiratory Distress Syndrome (ARDS)**, therapy with corticosteroids should start within the first two weeks of onset of ARDS (see also section 4.4 “Special warnings and precautions for use”).

### 4.3 Contraindications

**Systemic therapy:**
- gastric and duodenal ulcer;
- acute infections: viral infections and systemic fungal infections (bacterial infections: see section 4.4 “Special warnings and precautions for use”);
- hypersensitivity to glucocorticoids or one of the excipients;
- parasitic infections;
- vaccination with live vaccines (see section 4.4 “Special warnings and precautions for use”)

**Local therapy**
- local infection in or near the joint to be treated, e.g. septic arthritis caused by gonorrhea or tuberculosis;
- bacteremia or systemic fungal infection;
- articular instability;
- hypersensitivity to glucocorticoids or one of the other excipients.

### 4.4 Special warnings and precautions for use

**Adrenal cortical atrophy** develops during prolonged therapy and may persist for years after stopping 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 (see “withdrawal of prolonged therapy” above). During prolonged therapy any intercurrent illness, trauma or surgical procedure will require a temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced.

**Anti-inflammatory/Immunosuppressive effects.** Glucocorticoid therapy is non-specific, suppresses the symptoms and signs of disease and decreases the resistance to infections. The clinical presentation may often be atypical and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised. Strong antimicrobial therapy should accompany glucocorticoid therapy when necessary.

**Vaccines** should not be given to individuals with glucocorticoid therapy-induced immunosuppression. Vaccination with live vaccines, e.g. **Chickenpox** (Varicella) is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and even the dose may need to be increased.

Glucocorticoids can cause dose-related **growth retardation** in infancy, childhood and adolescence, which may be irreversible. Therefore, Oradexon Organon should only be used in children with caution.

The common adverse effects of systemic glucocorticoids may be associated with more serious consequences in **old age**, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

The prolonged and repeated use of glucocorticoids in **weight-bearing joints** may result in (further) joint degeneration. This is probably related to over-use of an affected joint following the relief of pain and other symptoms.

Particular care is required when considering the use of systemic glucocorticoids in patients with the following conditions and **frequent patient monitoring** is necessary:
- Osteoporosis (post-menopausal women are particularly at risk);
- Hypertension or congestive heart failure;
- Existing or previous history of severe affective disorders (especially previous steroid psychosis);
- Diabetes mellitus (or a family history of diabetes);
- History of tuberculosis;
- Glaucoma (or a family history of glaucoma);
- Previous glucocorticoid-induced myopathy;
- Liver failure;
- Renal insufficiency;
There are no adequate data from the use of dexamethasone in pregnant women to predict any effect on the embryonic or foetal development. When administered for prolonged periods or repeatedly during pregnancy, systemic glucocorticoids increase the risk of intra-uterine growth retardation (IUGR). There is no evidence for an increased incidence of IUGR following short-term treatment, such as prophylactic treatment for neonatal respiratory distress syndrome. In this case (to prevent respiratory distress syndrome), glucocorticoids are essential. Patients with pre-eclampsia or fluid retention require close monitoring. Dexamethasone should, for maternal indications, not be used during pregnancy unless clearly necessary. Adrenal suppression in the neonate following prenatal glucocorticoid exposure is to be expected. No data are available on the transfer of dexamethasone into breast milk. Because corticosteroids are in general excreted into breast milk, and given the lack of experience, breast feeding is discouraged during Oradexon therapy.

4.7 Effects on ability to drive and use machines
Glucocorticoids may cause mood changes (e.g. euphoria or depression) or visual disturbances. If affected, caution should be exercised in driving and operating machinery.

4.8 Undesirable effects
The incidence of predictable undesirable effects of glucocorticoids correlates with the dosage, timing of administration and duration of treatment. The clinician must balance the therapeutic effects of glucocorticoids with their risk for adverse effects, using the lowest possible effective doses for the shortest possible period of time, preferably by dosing in the morning on an alternate day dosing regimen. Early recognition and appropriate management of adverse effects can minimise the potential severe complications of glucocorticoid therapy.

The following adverse reactions have been associated with short-term glucocorticoid therapy:

- Epilepsy;
- Peptic ulceration.

Corticosteroids should not be used for the management of head injury or stroke because it is unlikely to be of benefit and may even be harmful.

The results of a randomized, placebo-controlled study suggest an increase in mortality if methylprednisolone therapy starts more than two weeks after the onset of Acute Respiratory Distress Syndrome (ARDS). Therefore, treatment of ARDS with corticosteroids should be initiated within the first two weeks of onset of ARDS (see also section 4.2 “Posology and method of administration”).

4.5 Interaction with other medicinal products and other forms of interaction
Rifampin, rifabutin, carbamazepine, phenobarbitone, phenytoin, primidone and aminoglutethimide enhance the metabolism of glucocorticoids and the therapeutic effects may be reduced. The desired effects of hypoglycaemic agents (including insulin), antihypertensives and diuretics are antagonised by glucocorticoids.

The effects of anticholinesterases are antagonised by glucocorticoids in myasthenia gravis. Concurrent use of potassium-depleting diuretics (e.g. acetazolamide, loop diuretics, thiazide diuretics or carbenoxolone) and glucocorticoids may result in severe hypokalaemia.

The efficacy of coumarin anticoagulants may be altered by concurrent glucocorticoid therapy and close monitoring of the International Normalised Ratio or prothrombin time is required.

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

Combination of corticosteroids with ulcer-inducing agents (e.g. NSAID’s) enhances the risk of peptic ulceration.

4.6 Pregnancy and lactation
Dexamethasone readily crosses the placenta. There are indications for a harmful effect of glucocorticoids on the foetus in animal experiments like abnormalities of foetal development including cleft palate or lip and effects on brain growth and development.
Hypersensitivity including anaphylaxis and allergic skin reactions. **Gastric duodenal ulceration**, with possible haemorrhage.

The following adverse reactions have been associated with **prolonged** systemic glucocorticoid therapy:

**Endocrine/metabolic.** Suppression of the hypothalamic-pituitary-adrenal axis, growth suppression in infancy, childhood and adolescence, menstrual irregularity and amenorrhoea. Cushingoid facies, hirsutism, weight gain, increased appetite and impaired carbohydrate tolerance with increased requirement for antidiabetic therapy. Negative protein and calcium balance.

**Anti-inflammatory and immunosuppressive effects.** Increased susceptibility to and severity of infections with suppression of clinical symptoms and signs, opportunistic infections and recurrence of dormant tuberculosis. The risk of developing severe chickenpox (Varicella) with possible fatal outcome.

**Musculoskeletal.** Osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture and proximal myopathy.

**Fluid and electrolyte disturbance.** Sodium and water retention, oedema, hypertension, potassium loss and hypokalaemic alkalosis.

**Neuropsychiatric.** Nervousness, euphoria, psychological dependence, depression, insomnia and aggravation of schizophrenia. Increased intracranial pressure with papilloedema in children (pseudotumour cerebri), usually after withdrawal. Aggravation of epilepsy.

**Ophthalmic.** Increased intraocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning and exacerbation of ophthalmic viral or fungal diseases.

**Gastrointestinal.** Dyspepsia, peptic ulceration with perforation and haemorrhage, acute pancreatitis and candidiasis.

**Dermatologic.** Impaired healing, skin atrophy, bruising, telangiectasia, striae and acne.

**General.** Leucocytosis and thrombo-embolism.

### 4.9 Overdose

It is difficult to define an excessive dose of a glucocorticoid as the therapeutic dose will vary according to indication and patient requirements. Massive i.v. glucocorticoid doses given as a pulse in emergencies are relatively free from hazardous effects. Exaggeration of glucocorticoid related effects may occur. Treatment should be symptomatic and supportive as necessary.

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Oradexon Organon injection contains as active ingredient dexamethasone sodium phosphate, which is rapidly hydrolysed to dexamethasone. Dexamethasone is a synthetic glucocorticoid with approximately a 7 times higher anti-inflammatory potency than prednisolone and 30 times that of hydrocortisone.

Glucocorticoids are produced and secreted by the adrenal cortex and are an intrinsic part of the hypothalamus-pituitary-adrenal axis (HPA-axis). In physiological concentrations glucocorticoids, both naturally occurring (hydrocortisone or cortisone) or synthetic (like dexamethasone) exert a broad range of effects on multiple organ systems and tissues; they affect carbohydrate, protein, lipid and calcium metabolism and have effects on fluid and electrolyte balance and are important for support of normal cardiovascular structure and function and the normal function of skeletal muscle.

In target tissues glucocorticoids interact with specific receptor proteins to regulate, via the expression of glucocorticoid-responsive genes, protein synthesis. As a consequence of the time required for changes in gene expression and protein synthesis, most effects of glucocorticoids are not immediate, but become apparent after several hours. This fact is of clinical significance, because a delay generally is seen before beneficial effects of glucocorticoid therapy are observed.

Dexamethasone is therapeutically used mostly because of its antiinflammatory and immunosuppressive properties. Dexamethasone has virtually no mineralocorticoid activity which makes it suitable for use in patients with cardiac failure or hypertension.
5.2 Pharmacokinetic properties
After administration of Oradexon Organon injection, dexamethasone sodium phosphate is rapidly hydrolysed to dexamethasone. After an i.v. dose of 20 mg, dexamethasone plasma levels peak within 5 minutes. Dexamethasone is bound (up to 77%) by plasma proteins, mainly albumin. There is high uptake of dexamethasone by the liver, kidney and adrenal glands. Metabolism in the liver is slow and excretion is mainly in the urine, largely as unconjugated steroids. The plasma half-life is 3.0-4.5 hours but, as the effects significantly outlast plasma concentrations of steroids, the plasma half-life is of little relevance and the use of the biological half-life is more applicable. The biological half-life of dexamethasone is 36-54 hours. Therefore Oradexon Organon is especially suitable in conditions where continuous glucocorticoid action is desirable.

5.3 Preclinical safety data
In animal studies, cleft palate was observed. This was seen in rats, mice, hamsters, rabbits, dogs and primates. In some cases this was combined with defects to the central nervous system and the heart. In primates, effects to the brain were seen. Moreover, intra-uterine growth can be delayed. All these effects were seen at high dosages.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
5.25 mg/mL: disodium edetate, glycerol, methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium hydroxide and phosphoric acid, water for injections
5 mg/mL: disodium edetate, glycerol, sodium hydroxide and phosphoric acid, water for injections.

6.2 Incompatibilities
None known.

6.3 Shelf life
5.25 mg/mL: 2 years
5 mg/mL: 3 years

6.4 Special precautions for storage
5.25 mg/mL: Store below 25°C, protected from light.
5 mg/mL: Store in a refrigerator (2°C – 8°C). Do not freeze. Store in the original package.

6.5 Nature and contents of container
5.25 mg/mL 2 mL in 2-mL vial
5 mg/mL 1 mL in 2-mL vial
The vials are made of colourless glass.

6.6 Instructions for use and handling
Not applicable.

7. MARKETING AUTHORISATION HOLDER
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