

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Danalone Syrup

2. Qualitative and quantitative composition

Each 1ml of syrup contains 3mg of prednisolone-

It also contains 0.86 mg of sodium, 0.36 g sucrose, 36.1 mg ethanol , 0.23 g propylene glycol and 1 mg benzoic acid.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Syrup

Colourless to slightly yellowish, clear liquid, with typical vanilla-apricot odour.

4. Clinical particulars

4.1 Therapeutic indications

Glucocorticoid with anti-inflammatory activity.

This medicine is intended for the treatment of glucocorticoid responsive inflammations, such as: endocrine disorders, rheumatic disorders, hematologic disorders, collagen diseases, ophthalmic diseases, dermatologic diseases, respiratory diseases, neoplastic diseases, gastrointestinal diseases, allergic and edematous conditions.

4.2 Posology and method of administration

The lowest dosage that will produce an acceptable result should be used (see section 4.4); when it is possible to reduce the dosage, this must be accomplished by stages. 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.

Adults: The dose used will depend upon the disease, its severity, and the clinical response obtained. The following regimens are for guidance only. Divided dosage is usually employed.

Short-term treatment: 20mg (6.7ml) to 30mg (10ml) daily for the first few days, subsequently reducing the daily dosage by 2.5mg (0.8ml) or 5mg (1.67ml) every two to five days, depending upon the response.

Rheumatoid arthritis: 7.5mg (2.5ml) to 10mg (3.3ml) daily. For maintenance therapy the lowest effective dosage is used.

Most other conditions: 10mg (3.3ml) to 100mg (33.3ml) daily for one to three weeks, then reducing to the minimum effective dosage.

Children: Fractions of the adult dosage may be used (e.g. 75% at 12 years, 50% at 7 years and 25% at 1 year) but clinical factors must be given due weight.

Danalone may be given early in the treatment of acute asthma attacks in children. For children over 5 years use a dose of 30-40mg (10-13.3ml) prednisolone. For children aged 2-5 years use a dose of 20mg (6.7ml) prednisolone. Those already receiving maintenance steroid tablets should receive 2mg/kg prednisolone up to a maximum dose of 60mg (20ml). The dose of prednisolone may be repeated for children who vomit; but intravenous steroids should be considered in children who are unable to retain orally ingested medication. Treatment for up to three days is usually sufficient, but the length of course should be tailored to the number of days necessary to bring about recovery. There is no need to taper the dose at the end of treatment.

For children under 2 years, Danalone can be used early in the management of moderate to severe episodes of acute asthma in the hospital setting, at a dose of 10mg (3.3ml) for up to three days.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Systemic infections, unless specific anti-infective therapy is employed.

- Live virus immunisation.

4.4 Special warnings and precautions for use

In patients who have received more than physiological doses of systemic corticosteroids (approximately 7.5mg prednisolone or equivalent) for greater than three weeks, withdrawal should not be abrupt. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during 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 equivalent to 7.5mg (2.5ml) prednisolone is reached, dose reduction should be slower to allow the HPA axis to recover.

Abrupt withdrawal of systemic corticosteroid treatment, which has continued up to three weeks is appropriate if it is considered that the disease is unlikely to relapse. Abrupt withdrawal of doses of up to 40mg daily of prednisolone, or equivalent for three 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 corticosteroid therapy should be *considered* even after courses lasting three weeks or less:

- Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than three 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 corticosteroid therapy, been stopped following prolonged therapy they may need to be temporarily reintroduced.
- Patients receiving doses of systemic corticosteroid greater than 40mg daily of prednisolone (or equivalent).
- Patients repeatedly taking doses in the evening.

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. 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.

Suppression of the HPA axis and other undesirable effects may be minimised by using the lowest effective dose for the minimum period, and by administering the daily requirement as a single morning dose or whenever possible as a single morning dose on alternate days. Frequent patient review is required to appropriately titrate the dose against disease activity (see section 4.2).

Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. 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.

Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. Patients without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. If the patient is a child parents must be given the above advice. Passive immunisation with varicella zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous three months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment.

Corticosteroids should not be stopped and the dose may need to be increased.

Patients should be advised to take particular care to avoid exposure to measles and to seek immediate advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin may be needed.

Live vaccines should not be given to individuals with impaired immune responsiveness caused by high doses of corticosteroids. The antibody response to other vaccines may be diminished.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

Because of the possibility of fluid retention, care must be taken when corticosteroids are administered to patients with renal insufficiency or hypertension or congestive heart failure.

Corticosteroids may worsen diabetes mellitus, osteoporosis, hypertension, glaucoma and epilepsy and therefore patients with these conditions or a family history of them should be monitored frequently.

Care is required and frequent patient monitoring necessary where there is a history of severe affective disorders (especially a previous history of steroid psychosis), previous steroid myopathy, peptic ulceration, hypothyroidism, recent myocardial infarction or patients with a history of tuberculosis.

In patients with liver failure, blood levels of corticosteroid may be increased, as with other drugs which are metabolised in the liver. Frequent patient monitoring is therefore necessary.

Paediatric population: Corticosteroids cause dose-related growth retardation in infancy, childhood and adolescence, which may be irreversible.

Use in the Elderly: The common adverse effects of systemic corticosteroids 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.

Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8 Undesirable effects). Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses/systemic exposure (see also section 4.5 Interaction with other medicinal products and other forms of interaction), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most adverse reactions resolve after either dose reduction or withdrawal of the medicine, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should also be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

Particular care is required when considering the use of systemic corticosteroids in patients with existing or a previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.

Danalone also contains 0.86 mg of sodium per 1 ml of syrup. To be taken into consideration by patients on a controlled sodium diet.

This medicinal product contains 4.6 % v/v ethanol (alcohol) per 60 ml bottle, i.e 36.1 mg ethanol per 1 ml of Danalone syrup. Total ethanol content in this package:2,166 mg.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision 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.

Scleroderma renal crisis

Caution is required in patients with systemic sclerosis because of an increased incidence of (possibly fatal) scleroderma renal crisis with hypertension and decreased urinary output observed with a daily dose of 15 mg or more prednisolone. Blood pressure and renal function (s-creatinine) should therefore be routinely checked. When renal crisis is suspected, blood pressure should be carefully controlled

4.5 Interaction with other medicinal products and other forms of interaction

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Rifampicin, rifabutin, carbamazepine, phenobarbitone, phenytoin, primidone, ephedrine and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced.

Mifepristone may reduce the effect of corticosteroids for 3-4 days.

Erythromycin and ketoconazole may inhibit the metabolism of some corticosteroids.

Ciclosporin increases plasma concentration of prednisolone. The same effect is possible with ritonavir.

Oestrogens and other oral contraceptives may potentiate the effects of glucocorticoids and dosage adjustments may be required if oral contraceptives are added to or withdrawn from a stable dosage regimen.

The desired effects of hypoglycaemic agents (including insulin), anti-hypertensives and diuretics are antagonised by corticosteroids.

The growth promoting effect of somatotropin may be inhibited by the concomitant use of corticosteroids.

Steroids may reduce the effects of anticholinesterases in myasthenia gravis and cholecystographic x-ray media.

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

Concomitant use of aspirin and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) with corticosteroids increases the risk of gastro-intestinal bleeding and ulceration.

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

The hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics, and carbenoxolone, are enhanced by corticosteroids. The risk of hypokalaemia is increased with theophylline and amphotericin. Corticosteroids should not be given concomitantly with amphotericin, unless required to control reactions.

The risk of hypokalaemia also increases if high doses of corticosteroids are given with high doses of bambuterol, fenoterol, formoterol, ritodrine, salbutamol, salmeterol and terbutaline. The toxicity of cardiac glycosides is increased if hypokalaemia occurs with corticosteroids.

Concomitant use with methotrexate may increase the risk of haematological toxicity.

High doses of corticosteroids impair the immune response and so live vaccines should be avoided (see also section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy:

The ability of corticosteroids to cross placenta varies between individual drugs, however, 88% of prednisolone is inactivated as it crosses the placenta.

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 man. However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intrauterine growth retardation.

Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

Patients with pre-eclampsia or fluid retention require close monitoring.

Depression of hormone levels has been described in pregnancy but the significance of this finding is not clear.

Breast-feeding

Corticosteroids are excreted in small amounts in breast milk. However doses of up to 40mg daily of prednisolone are unlikely to cause systemic effects in the infant. Infants of mothers taking higher doses than this may have a degree of adrenal suppression but the benefits of breast feeding are likely to outweigh any theoretical risk.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

The incidence of predictable undesirable effects, including hypothalamo-pituitary-adrenal (HPA) suppression, correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment (see section 4.4).

The following side effects may be associated with the long-term systemic use of corticosteroids.

Not known (cannot be estimated from available data)

System organ class	Frequency	Undesirable effects
Infections and infestations	Not known	Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis (see section 4.4).
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Not known	Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.
Blood and lymphatic system disorders	Not known	Leukocytosis
Immune system disorders	Not known	Hypersensitivity including anaphylaxis has been reported.
Endocrine disorders	Not known	Suppression of the HPA axis. Cushingoid. Impaired carbohydrate intolerance with increased requirement for anti-diabetic therapy, manifestation of latent diabetes mellitus.
Metabolism and nutrition disorders	Not known	Sodium and water retention, hypokalaemia, hypokalaemic alkalosis, increased appetite, negative protein and calcium balance.
Psychiatric disorders ^a	Not known	Euphoric mood, psychological dependence, depressed mood, insomnia, aggravation of

		schizophrenia.
Nervous system disorders	Not known	Dizziness, headache. Aggravation of epilepsy.
Eye disorders	Not known	Glaucoma, papilloedema, posterior subcapsular cataracts, central serous chorioretinopathy, exophthalmos, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases. and vision, blurred
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Not known	Myocardial rupture following recent myocardial infarction. Congestive cardiac failure (in susceptible patients).
Vascular disorders	Not known	Hypertension, embolism.
Respiratory, thoracic and mediastinal disorders	Not known	Hiccups
Gastrointestinal disorders	Not known	Dyspepsia, nausea, vomiting, abdominal distension, abdominal pain, diarrhoea, oesophageal ulceration, candidiasis, pancreatitis acute. Peptic ulceration with perforation and haemorrhage.
Skin and subcutaneous tissue disorders	Not known	Skin Atrophy, skin striae, acne, telangiectasia, hyperhidrosis, rash, pruritus, urticaria, hirsutism.
Musculoskeletal and connective tissue disorders	Not known	Myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, myalgia.
Renal and urinary disorders	Not known	Scleroderma renal crisis ^b
Reproductive system and breast disorders	Not known	Menstruation irregular, amenorrhoea.
General disorders and administration site conditions	Not known	Impaired healing, malaise.
Investigations	Not known	Weight increased.
Injury, poisoning and procedural complications	Not known	Tendon rupture, contusion (bruising).

a) A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia have been reported. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown

b) Scleroderma renal crisis

Amongst the different subpopulations the occurrence of scleroderma renal crisis varies. The highest risk has been reported in patients with diffuse systemic sclerosis. The lowest risk has been reported in patients with limited systemic sclerosis (2%) and juvenile onset systemic sclerosis (1%)

Withdrawal Symptoms

Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (see section 4.4).

A 'withdrawal syndrome' may also occur including fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.

In some instances, withdrawal symptoms may involve or resemble a clinical relapse of the disease for which the patient has been undergoing treatment.

Other effects that may occur during withdrawal or change of corticosteroid therapy include benign intracranial hypertension with headache and vomiting and papilloedema caused by cerebral oedema. Latent rhinitis or eczema may be unmasked.

Paediatric population:

Increased intracranial pressure with papilloedema in children (pseudotumour cerebri) -usually after treatment withdrawal.

Growth retardation in infancy, childhood and adolescence.

Reporting of suspected adverse reactions

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>.

4.9 Overdose

Treatment is unlikely to be needed in cases of acute overdosage.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Glucocorticoids, ATC code: H02AB06

Prednisolone is four times as active as hydrocortisone on a weight for weight basis.

5.2 Pharmacokinetic properties

Absorption

Prednisolone is readily absorbed from the gastrointestinal tract with peak plasma concentrations achieved by 1-2 hours after an oral dose. Plasma prednisolone is mainly protein bound (70-90%), with binding to albumin and corticosteroid-binding globulin. The plasma half-life of prednisolone, after a single dose, is between 2.5-3.5 hours.

Distribution

The volume of distribution and clearance of total and unbound prednisolone are concentration dependent, and this has been attributed to saturable protein binding over the therapeutic plasma concentration range.

Biotransformation

Prednisolone is extensively metabolised, mainly in the liver, but the metabolic pathways are not clearly defined.

Elimination

Over 90% of the prednisolone dose is excreted in the urine, with 7-30% as free prednisolone, and the remainder being recovered as a variety of metabolites.

5.3 Preclinical safety data

No additional data of relevance.

6. Pharmaceutical particulars

6.1 List of excipients

Sucrose

Propylene glycol

Glycerin

Alcohol 95%

Saccharin sodium

Apricot vanilla flavor E0408317

Benzoic acid
Citric acid anhydrous
Disodium EDETATE
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

store below 25°C

Once opened, and use within 6 months.

6.5 Nature and contents of container

Amber (Type III) glass bottle containing 60ml, with child - proof cap, polypropylene plastic screw cap, a 5ml plastic syringe.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. Manufacturer

TRIMA, Israel Pharmaceutical Products
Maabarot Ltd., Kibbutz Maabarot 40230.

8. Marketing authorisation holder

Megapharm Ltd.,
P.O. Box 519, Hod-Hasharon 45105.

9. Marketing authorisation number(s)

133-81-31155-00

10. Revised in August 2021 according to MOHs guidelines

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