SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sintredius

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient of Sintredius is prednisolone as the sodium phosphate ester.
Each 1 ml oral solution contains 1 mg prednisolone (as sodium phosphate).

Each 5 ml single-dose container contains 5 mg of prednisolone (as sodium phosphate).
Each 5 ml single-dose container contains 0.5 mmole sodium per dose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution.
The solution is a clear, light brown solution free from particulate matters.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sintredius oral solution is indicated for the treatment of:

Rheumatological disorders and connective tissue diseases such as:

- rheumatoid arthritis (for primary chronic disease and maintenance therapy)
- systemic lupus erythematosus (non-organ threatening disease)
- mild-moderate juvenile dermatomyositis

Severe or debilitating allergic conditions, not treatable in a conventional manner such as:

- bronchial asthma in children
- bronchial asthma in adults (for maintenance therapy)

Sarcoidosis in children and for maintenance therapy in adults

Acquired haemolytic anaemia (autoimmune, for maintenance therapy)

4.2 Posology and method of administration

Posology

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.

The medicinal product should preferably be taken as a single dose in the morning. However, divided daily dosages may be employed if required.

Note to the prescriber:

This 5 ml single-dose unit presentation should not be prescribed for doses exceeding 30 mg daily, because opening more than 6 containers in a day may increase the risk of dosing errors. For this reason, indications for Sintredius have been restricted to those where a large proportion of patients and a large proportion of doses (maintenance phase) in a particular patient will be 30 mg/day or below.

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:
20 to 30 mg daily for the first few days, subsequently reducing the daily dosage by 2.5 or 5 mg every two to five days, depending upon the response.

Rheumatoid arthritis:
7.5 to 10 mg daily. For maintenance therapy the lowest effective dosage is used.

Most other indicated conditions:

Indications for Sintredius have been restricted to those where a large proportion of patients and a large proportion of doses (maintenance phase) in a particular patient will be 30 mg or below.
10 to 30 mg of Sintredius should be taken daily for one to three weeks, then reducing to the minimum effective dosage.

For the administration of higher doses in particular haematological forms, dermatologic forms, etc., the use of a more appropriate prednisolone presentation (e.g. high dosage tablets) is recommended, to reduce the risk of dosing errors associated to opening several Sintredius containers.

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.

For treatment of bronchial asthma:
Children under 2 years: up to 10 mg daily.
Children 2-5 years inclusive: up to 20 mg daily.
Children older than 5 years: 30 mg daily or more (up to 40 mg daily) may be used. To reduce the risk of dosing errors, should the doctor prescribe more than 30 mg daily, a more appropriate prednisolone presentation (e.g. high dosage tablets) should be used.

Corticosteroids cause growth retardation in infancy, childhood and adolescence which may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time. In order to minimise suppression of the hypothalamo-pituitary adrenal axis and growth retardation, treatment should be administered where possible as a single dose on alternate days.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Tuberculosis, peptic ulcer, psychosis, ocular herpes simplex. Tropical worm infections, systemic infections including fungal infections, unless specific anti-infective therapy is employed. Live virus immunization.

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.

Suppression of the HPA axis and other undesirable effects may be minimized 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 dosage section).

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 recognized.

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 immunization 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 3 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 metabolized in the liver. Frequent patient monitoring is therefore necessary.

Physicians should be aware that corticoids have been reported to precipitate porphyria. As well, one case of a reversible Steven-Johnson-Syndrome (SJS) was reported in connection with prednisolone treatment.

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.

Chorioretinopathy may result in impaired vision, including loss of vision.

Regular checkups with doctors (including vision checkups in three month-intervals) are advised during long term treatment.

At high doses, sufficient calcium intake and sodium restriction, as well as potassium levels should be monitored.

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.

Use in Children: 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.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

"Patients should carry 'Steroid treatment' cards which give clear guidance on the precautions to be taken to minimize risk and which provide details of prescriber, drug, dosage and the duration of treatment."

Withdrawal

In patients who have received more than physiological doses of systemic corticosteroids (approximately 7.5 mg prednisolone or equivalent) for greater than 3 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 of 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 3 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 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 corticosteroid therapy should be considered even after courses lasting 3 weeks or less:

• Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater 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 corticosteroid therapy,

• Patients receiving doses of systemic corticosteroid greater than 40mg daily of prednisolone,

• Patients repeatedly taking doses in the evening.

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 reintroduced.

4.5 Interaction with other medicinal products and other forms of interaction

Rifampicin, rifabutin, carbamazepine, phenobarbitone, phenytoin, primidone, ephedrine and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced. Therefore it may be necessary to adjust the dose accordingly.

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 antagonized 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 warnings).

In rare cases the concomitant treatment with corticosteroids and fluoroquinolones may increase the risk of tendon rupture.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Animal studies indicate that administration of pharmacological doses of glucocorticoids during pregnancy may increase the fetus risk of intrauterine growth retardation, adult cardiovascular and/or metabolic disease and may have an effect on the glucocorticoid receptor density, and neurotransmitter turnover or neurobehavioural development.

Glucocorticoids caused cleft palate formation in animal experiments. There is an ongoing discussion on the possibility of an increased risk of oral cleft formation in the human fetus as a result of the administration of glucocorticoids during the first trimester.

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

During pregnancy, Sintredius oral solution should only be prescribed when the benefits to the mother and child outweigh the risks. The lowest effective dose of Sintredius oral solution needed to maintain adequate disease control should be used. Patients with pre-eclampsia or fluid retention require close monitoring.

Breastfeeding

Glucocorticoids are excreted in small amounts in breast milk (up to 0.23% of an individual dose). 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.

The milk/plasma concentration ratio increases with increasing doses (e.g. 25 % of the serum concentration are found in the breast milk with 80 mg prednisolone daily). Therefore, when high doses of prednisolone are given, it is recommended to avoid breastfeeding for 4 h after a dose.

Fertility

After high prednisolone doses (30 mg/day for at least 4 weeks) reversible disturbances of spermatogenesis has been observed, which lasted for several months after stop taking the medicine.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Data reported under this section originate from post authorization and spontaneous reporting, therefore estimation of frequency of adverse reaction could not be established.

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.

Infections and Infestations

Infection susceptibility increased, opportunistic infection, latent tuberculosis (see section 4.4).

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Kaposi's sarcoma (see section 4.4).

Blood and lymphatic system disorders

Leukocytosis.

Immune system disorders

Hypersensitivity, anaphylactic reaction.

Endocrine disorders

Suppression of the HPA axis.

Cushingoid.

Carbohydrate intolerance, diabetes mellitus exacerbated.

Metabolism and nutrition disorders

Sodium retention, fluid retention, hypokalaemia, hypokalaemic alkalosis, increased appetite, electrolyte imbalance, protein total abnormal

Psychiatric disorders

Dependence.

Affective disorder: irritability, euphoric mood, depressed mood, affect lability, suicidal ideation.

Psychotic disorder: mania, delusions, hallucinations, schizophrenia aggravated.

Abnormal behavior, anxiety, sleep disorder.

Cognitive disorder: confusion, amnesia.

A wide range of psychiatric reactions including the above mentioned 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.

Nervous system disorders

Dizziness, headache, epilepsy aggravated.

Intracranial pressure increased, papilloedema, epilepsy.

Eye disorders

Glaucoma, papilloedema, posterior subcapsular cataract, chorioretinopathy, vision, blurred (see also section 4.4), exophthalmos, corneal thinning, scleral thinning, eye infection viral, eye infection fungal.

Ear and labyrinth disorders

Vertigo

Cardiac disorders

Myocardial rupture (post infarct), cardiac failure congestive.

Frequency "not known": Bradycardia*

Vascular disorders

Hypertension, embolism.

Respiratory, thoracic and mediastinal disorders

Hiccups.

Gastrointestinal disorders

Dyspepsia, nausea, vomiting, abdominal distension, abdominal pain, diarrhoea, oesophageal ulcer, candidiasis, pancreatitis acute.

Peptic ulcer haemorrhage, peptic ulcer perforation.

Skin and subcutaneous tissue disorders

Skin atrophy, skin striae, acne, telangiectasia, hyperhidrosis, rash, pruritus, urticaria, hirsutism, Stevens-Johnson syndrome.

Musculoskeletal and connective tissue disorders

Myopathy, osteoporosis, multiple spinal fractures, osteonecrosis, myalgia.

Renal and urinary disorders

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%).

Reproductive system and breast disorders

Menstruation irregular, amenorrhoea.

Congenital, familial and genetic disorders

Porphyria

General disorders and administration site conditions

Impaired healing, malaise.

Investigations

Weight increased, intraocular pressure increased.

Injury, poisoning and procedural complications

Tendon rupture, contusion.

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.

Pediatric population

The following side effects have been reported in the pediatric population.

Growth retardation in infancy, childhood and adolescence.

Intracranial pressure increased with papilloedema (pseudo tumour cerebri) after treatment withdrawal.

For psychiatric reactions in children, refer to the paragraph “Psychiatric disorders”.

*Following high doses

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
Additionally, you should also report to Kamada Ltd. to email address:
pharmacovigilance@kamada.com

4.9 Overdose

Treatment is unlikely to be needed in cases of acute over dosage.

Should alterations of the electrolytic balance occur within prolonged therapy at high doses, it would be appropriate to adjust the intake of sodium and potassium. Corticosteroids increase the urinary excretion of calcium.

In case of overdose, the clinical control of patient's vital functions, jointly with the common measures for elimination of the non-absorbed drug (gastric lavage, vegetal charcoal etc), are recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: glucocorticoids, ATC code: H02AB06

Sintredius oral solution contains the equivalent of 1.0 mg/ml of prednisolone in the form of the 21-disodium phosphate ester. Prednisolone sodium phosphate is a synthetic glucocorticoid with the same general properties as prednisolone itself and other compounds classified as corticosteroids. Prednisolone is four times as active as hydrocortisone on a weight for weight basis.

Prednisolone sodium phosphate is very soluble in water, and is therefore less likely to cause local gastric irritation than prednisolone alcohol, which is only slightly soluble. This is important when high dosages are required, as in immunosuppressive therapy.

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.

Metabolism

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

Excretion

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

There are no preclinical safety data that could be of relevance to the prescriber that are not already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, Glycerol, Disodium phosphate anhydrous, Honey flavour, Vanilla/cream flavour, Masking flavour, Sodium dihydrogen phosphate monohydrate, Disodium edetate (EDTA), Water for injections.

6.2 Incompatibilities

None known.

6.3 Shelf life

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

Single dose container; Once opened: in case of administration of partial doses, the opened container must be discarded once the required dose is removed.

Pouch: The product can be used till 14 days after the opening of the pouch.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container

Single-dose polyethylene containers containing 5 ml of oral solution, grouped in strips of five containers. All opened units should be discarded once the required dose is removed. Each strip is packaged in a PET/Al/PE thermo-welded over-pouch. Each unit carton contains two pouches, together with a measuring spoon (dosing 3.75 ml, 2.5 ml and 1.25 ml, corresponding to partial doses).

Pack size of 10 single-dose containers.

6.6 Special precautions for disposal

For detailed instructions for use refer to the Patient Information Leaflet in every pack.

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

7 Manufacturer

Genetics S.p.A., Salerno, Italy, for

Dompé Farmaceutici S.p.A., Milano, Italy

Registration Holder

Kamada Ltd., Beit Kama

8 Registration Number 168-82-35801

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