- ULCERATIVE COLITIS/REGIONAL ENTERITIS REMEDY -

**PREDONEMA® Enema 20 mg**

< Prednisolone sodium phosphate >

Prescription drug

**Storage**

Store at room temperature.

**Expiration date**

Indicated on the package.

**Cautions**

This product should be used immediately after opening an aluminum-foil bag because of instability to light.

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**CONTRAINDICATIONS** (This product is contraindicated in the following patients.)

Patients with a history of hypersensitivity to any of the components of this product.

**RELATIVE CONTRAINDICATIONS** (As a general rule, this product is contraindicated in the following patients. If the use of this product is considered essential, it should be administered with care.)

1. Patients with infections without effective antibacterial agents or patients with systemic fungal disease [Infections may be aggravated because of immunosuppression.]
2. Patients with peptic ulcer [Peptic ulcer may be aggravated because of a reduction in the function of gastric mucosal barrier.]
3. Patients with psychosis [Psychosis may be aggravated because of a possible effect on central nervous system.]
4. Patients with tuberculosis disease [Tuberculous disease may be aggravated because of immunosuppression.]
5. Patients with herpes simplex keratitis [Herpes simplex keratitis may be aggravated because of immunosuppression.]
6. Patients with posterior capsular cataract [Posterior capsular cataract may be aggravated because of a possible effect on the lens fibers.]
7. Patients with glaucoma [Glaucma may be aggravated because of an increase in intraocular pressure.]
8. Patients with hypertension [Hypertension may be aggravated because of retention of sodium and water.]
9. Patients with electrolyte abnormality [Electrolyte abnormality may be aggravated because of retention of sodium and water.]
10. Patients with thrombosis [Thrombosis may be aggravated because of increased blood clotting.]
11. Patients with the unhealed surgical wound of the viscus [Wound healing may be delayed.]
12. Patients with a history of acute myocardial infarction [Cardiac rupture has been reported to occur.]

**DESCRIPTION**

**Product description**

<table>
<thead>
<tr>
<th>Brand name</th>
<th>PREDONEMA® Enema 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient/ content per container (60 mL)</td>
<td>Prednisolone sodium phosphate 22 mg (20 mg as prednisolone phosphate): The Japanese Pharmacopoeia (JP)</td>
</tr>
<tr>
<td>Inactive ingredients</td>
<td>Carboxy vinyl polymer, Disodium hydrogen phosphate hydrate, Ethyl parahydroxybenzoate, Butyl parahydroxybenzoate, Disodium edetate hydrate, Sodium hydroxide</td>
</tr>
<tr>
<td>Appearance/ description</td>
<td>This product occurs as a slightly viscous, colorless transparent solution.</td>
</tr>
<tr>
<td>Size (Container)</td>
<td></td>
</tr>
<tr>
<td>Identification code (package material)</td>
<td>KP-009</td>
</tr>
</tbody>
</table>

**INDICATIONS**

Ulcerative colitis, regional enteritis

**DOSAGE AND ADMINISTRATION**

The usual adult dose of this product for enema use (rectal infusion) is 22 mg of prednisolone sodium phosphate (20 mg as prednisolone phosphate). The dosage may be adjusted depending on patients’ ages and symptoms.

**PRECAUTIONS**

1. Careful Administration (This product should be administered with care in the following patients.)

   (1) Patients with infections
   [Infections may be aggravated because of immunosuppression.]
(2) Patients with diabetes mellitus

[Diabetes may be aggravated because of promotion of gluconeogenesis (hyperglycemia).]

(3) Patients with osteoporosis

[Osteoporosis may be aggravated because of inhibition of osteogenesis and impairment of calcium metabolism.]

(4) Patients with renal failure

[Symptoms may be aggravated.]

(5) Patients with hypothyroidism

[Adverse reactions are likely to develop because of a prolonged half-life of the drug.]

(6) Patients with hepatic cirrhosis

[Adverse reactions are likely to develop in patients with chronic hepatic disease because of a prolonged blood half-life of the drug.]

(7) Patients with fatty liver

[Fatty liver may be aggravated because of a possible effect on lipid metabolism.]

(8) Patients with fat embolism

[Fat embolism may be aggravated because of a possible effect on lipid metabolism.]

(9) Patients with myasthenia gravis

[Symptoms may be temporarily aggravated at the beginning of use.]

(10) Elderly patients

[See the section of “Use in the Elderly.”]

2. Important Precautions

(1) Since administration of this product may cause serious adverse reactions such as induced infection, secondary adrenocortical insufficiency, peptic ulcer, diabetes mellitus, and mental disorder, attention should be paid to the following items prior to the use of this product.

1) This product should be administered, especially taking indications and symptoms into account. This product should not be administered, if sufficient efficacy is expected by other therapy.

2) Sufficient care and observation should be conducted for development of adverse reactions during administration. In addition, patients should be protected from stress, and appropriate measures such as an increased dose should be taken at accidents and surgery.

3) Since varicella or measles infected during administration of this product may be fatally aggravated, attention should be paid to the following items:

a) A history of varicella or measles and the presence or absence of vaccination should be checked prior to administration of this product.

b) In patients with no history of varicella or measles, sufficient care and observation should be conducted to protect from infection of varicella or measles. If infected or suspected to be infected with varicella or measles, patients should be instructed to consult a doctor, with appropriate measures taken.

c) Even in patients with a history of varicella or measles and vaccination, attention should be paid to a possible infection of varicella or measles during administration of this product.

4) Withdrawal symptoms such as fever, headache, anorexia, weakness, myalgia, arthralgia, and shock may occur after repeated administration of this product is suddenly discontinued. Thus, appropriate measures are necessary for discontinuation of administration, such as a gradual reduction in dosage. If any of withdrawal symptoms occurs, readministration or increased dosage should be immediately taken.

(2) In hepatitis B virus carrier patients taking adrenocorticoid agents, hepatitis may occur because of proliferation of hepatitis B virus. Be cautious about the sign of proliferation of hepatitis B virus and the appearance of the symptoms by monitoring for liver function test values or hepatitis virus markers continuously during and after the period of administration of this product. If any of the abnormal findings is observed, a reduction in the dose of this product should be considered and appropriate measures such as administration of antiviral agents should be taken. In the patient with HBs antigen negative before administration of this product, onset of hepatitis because of hepatitis B virus has been reported.

(3) Since administration of corticosteroid has been reported to aggravate asthmatic attack in patients with bronchial asthma, close attention should be paid to asthmatic patients with hypersensitivity to drugs, foods, and additives.

(4) Since immune function may decrease in patients taking high doses of this product for a long term, or discontinuing long-term dosing within 6 months, inoculation of a live vaccine may increase or sustain infections derived from the vaccine. Therefore, these patients must not be inoculated with a live vaccine.

3. Drug Interactions

Precautions for Coadministration (This product should be administered with care when coadministered with the following drugs.)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Signs, symptoms and treatment</th>
<th>Mechanism and risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates:</td>
<td></td>
<td>Coadministration has been reported to attenuate the action of this product.</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td></td>
<td>These drugs induce cytochrome P450 to promote the metabolism of this product.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salicylate derivatives:</td>
<td></td>
<td>Coadministration has been reported to attenuate the action of this product.</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td>This product facilitates renal excretion and hepatic metabolism of salicylate derivatives, reducing the serum concentrations of the derivatives.</td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td>Coadministration has been reported to attenuate the action of anticoagulants.</td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
<td>This product facilitates blood coagulation.</td>
</tr>
<tr>
<td>Oral antidiabetes:</td>
<td></td>
<td>Coadministration has been reported to attenuate the actions of these drugs.</td>
</tr>
<tr>
<td>Aceto-hexamide</td>
<td></td>
<td>This product facilitates gluconeogenesis in the liver, and</td>
</tr>
<tr>
<td>Insulin preparations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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suppresses glucose consumption in the peripheral tissues.

Coadministration may induce hypokalemia. This product facilitates excretion of potassium in the renal tubule.

Activated vitamin D₃ preparations: Alfacalcidol etc.

Since coadministration may induce hypercalciuria and urolithiasis, sufficient examination and observation should be regularly conducted, with attention to dosage.

The mechanism of action is unknown. This product facilitates excretion of calcium in the urine by inhibiting resorption of calcium in the renal tubule and promoting bone resorption. Activated vitamin D₃ preparations facilitate excretion of calcium in the urine by promoting calcium absorption from the intestinal tract.

Cyclosporin

It has been reported that the high doses of corticosteroid increase the blood concentra-tions of cyclosporin coadministered.

This product inhibits the metabolism of cyclosporin.

Macrolide antibiotics: Erythromycin

Corticosteroids have been reported to enhance the action of this product.

The metabolism of this product may be inhibited.

4. Adverse Reactions

Incidence of adverse reactions has not been investigated in this product (drug-use results surveys, etc.).

(1) Clinically significant adverse reactions (Incidence unknown)

If the following adverse reactions are observed, administration of this product should be immediately discontinued, and appropriate measures be taken.

1) Induced infection and exacerbation of infections

Induced infection and exacerbation of infections may occur, and hepatitis may occur because of proliferation of hepatitis B virus. Patients should be carefully monitored and if any of the abnormal findings is observed, appropriate measures should be taken.

2) Secondary adrenocortical insufficiency and diabetes mellitus

3) Peptic ulcer, gastrointestinal perforation and gastrointestinal bleeding

Since peptic ulcer, gastrointestinal perforation and gastrointestinal bleeding have been reported, patients should be carefully monitored. If any of abnormal findings is found, appropriate measures such as discontinuation of administration should be taken.

4) Pancreatitis

5) Mental aberration, depression, and convulsions

6) Osteoporosis, aseptic necrosis of the femoral and humeral heads, and myopathy

7) Glaucoma, posterior capsular cataract, central serous chorioretinopathy, and multifocal posterior retinal pigment epitheliopathy

Since repeated administration of this product may cause increased intraocular pressure, glaucoma, posterior capsular cataract (symptom: blurred vision), and central serous chorioretinopathy (CSC)/multifocal posterior retinal pigment epitheliopathy (MPPE) (symptoms: decreased vision, distortion or reduction of vision, and distorted central portion of visual field), regular ophthalmological examinations are recommended. Localized retinal detachment is found in CSC, leading to extensive retinal detachment in MPPE.

8) Thrombosis

9) Myocardial infarction, cerebral infarction, and aneurysm

Since myocardial infarction, cerebral infarction, or aneurysm may occur, patients should be carefully monitored in the case of long-term administration.

10) Shock and anaphylactic reaction

Since shock or anaphylactic reaction may occur, patients should be carefully monitored. If dyspnoea, generalized flushing, angioedema, or urticaria is observed, administration should be discontinued, and appropriate measures be taken.

11) Asthmatic attack

Since administration of adrenocortical agents has been reported to exacerbate asthma attack in patients with bronchial asthma, attention should be paid to the patients.

(2) Other adverse reactions

If the following adverse reactions are observed, appropriate measures such as discontinuation of the administration should be taken:

<table>
<thead>
<tr>
<th>Symptom (incidence unknown)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
</tr>
<tr>
<td>Menstrual disorder, Cushing’s syndrome-like symptoms</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Diarrhea, nausea/vomiting, stomachache, heartburn, abdomen enlarged feeling, thirst, anorexia, increased appetite</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
</tr>
<tr>
<td>Euphoria, insomnina, headache, dizziness</td>
</tr>
<tr>
<td>Musculo-skeletal</td>
</tr>
<tr>
<td>Myalgia, arthralgia</td>
</tr>
<tr>
<td>Administration site</td>
</tr>
<tr>
<td>Local irritating symptoms</td>
</tr>
<tr>
<td>Lipid/protein metabolic</td>
</tr>
<tr>
<td>Moon face, buffalo hump, negative nitrogen balance, fatty liver</td>
</tr>
<tr>
<td>Humoral/electolytic</td>
</tr>
<tr>
<td>Edema, increased blood pressure, hypokalemic alkalosis</td>
</tr>
<tr>
<td>Ophthalmologic</td>
</tr>
<tr>
<td>Retinal disorder, exophthalmos, etc.</td>
</tr>
<tr>
<td>Hematologic</td>
</tr>
<tr>
<td>Leukocytosis</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Dermatologic</th>
<th>Acne, hypertrichosis, depilation, pigment deposition, ecchymosis, purpura, striae, pruritus, abnormal sweating, facial erythema, panniculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Others</td>
<td>Fever, fatigue, steroid nephropathy, weight increase, increases or decreases in number and mobility of spermatozoa, urolithiasis, disturbance of wound healing, thinning and fragility of skin/connective tissue</td>
</tr>
</tbody>
</table>

5. Use in the Elderly
Since long-term administration of this product to the elderly is likely to cause adverse reactions such as induced infection, diabetes mellitus, osteoporosis, hypertension, posterior capsular cataract, and glaucoma, this product should be administered with care.

6. Use during Pregnancy, Delivery or Lactation
(1) This product should be administered to pregnant women or women who may be pregnant only if the expected therapeutic benefits outweigh the potential risks associated with treatment.

[It has been reported that teratogenicity may occur in animal studies (rats, mice, rabbits, and hamsters) of this product, and adrenal insufficiency in newborns.]

(2) Nursing should be discontinued during the administration period of this product.

[This product may be excreted in the breast milk.]

7. Pediatric Use
(1) Since this product may inhibit growth in children, a careful observation should be conducted when this product is administered in children.

(2) Intracranial hypertension or hypertensive encephalopathy may occur in children.

8. Precautions concerning Use
The nozzle of enema container should be carefully inserted into the rectum because of possible damage to the rectal mucosa.

9. Other Precautions
(1) It has been reported that vaccination of patients treated with corticosteroids causes neuropathy or lack of antibody response.

(2) It has been reported that pneumatosis cystoides intestinalis or mediastinal emphysema develops during administration of oral prednisolone preparations.

PHARMACOKINETICS
Bioequivalence
After a single dose of PREDONEMA Enema 20 mg or its standard preparation (prednisolone phosphate injection 20 mg) was administered by rectal infusion to healthy adults in a fasted state in a crossover manner, the plasma concentrations of the unchanged form were determined, and the pharmacokinetic parameters (AUC and Cmax) obtained were statistically analyzed. As a result, bioequivalence of both preparations was confirmed.1)

<table>
<thead>
<tr>
<th></th>
<th>Standard preparation</th>
<th>PREDONEMA Enema 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC 0-24 (ng•hr/mL)</td>
<td>866.85 ± 305.23</td>
<td>954.16 ± 347.52</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>145.10 ± 43.27</td>
<td>158.61 ± 49.36</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>2.20 ± 0.34</td>
<td>2.10 ± 0.63</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>2.44 ± 0.32</td>
<td>2.50 ± 0.26</td>
</tr>
</tbody>
</table>

The plasma concentrations, and pharmacokinetic parameters (AUC and Cmax) may vary by patient selection, and the number and time point of plasma sampling.

PHARMACOLOGY
Rectal administration of prednisolone phosphate enema at 0.3 and 0.1 mg/kg significantly decreased the ulcerative areas in rat ulcerative-colitis model induced by intraserosal administration of acetic acid.2)

PHYSICOCHEMISTRY
Nonproprietary name:
Prednisolone sodium phosphate (JAN)

Another name:
Prednisolone phosphate disodium

Chemical name:
11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 21-(disodium phosphate)

Molecular formula:
C21H27Na2O8P

Molecular weight:
484.39

Structural formula:

Description:
Prednisolone sodium phosphate occurs as a white to pale yellow powder. It is freely soluble in water, soluble in methanol, and practically insoluble in ethan (99.5). It has hygroscopicity.

PRECAUTIONS FOR HANDLING
The long-term stability study (at a temperature of 25℃ and a relative humidity of 60% for 3 years) of the final-package product showed that the product was within the range of the specifications in appearance and content, thereby
demonstrating that PREDNEMA Enema 20 mg remained stable for 3 years under the usual distribution conditions in the market.3)

PACKAGING
PREDONEMA Enema 20 mg
A box of 60 mL x 7

REFERENCES
1) Nishiyama K. et al., Examination of bioequivalence of prednisolone sodium phosphate. (In-house data)
3) Abe H. et al., Stability study of PREDONEMA Enema 20 mg. (In-house data)

REQUEST FOR LITERATURE SHOULD BE MADE TO:
A request for in-house data mentioned in the References can also be made to the following.
Kyorin Pharmaceutical Co, Ltd. Drug Information Center
6, Kanda surugadai 4-chome, Chiyoda-ku, Tokyo 101-8311, Japan
TEL: 0120-409-341 (Toll-free)
9:00 to 17:30 (Monday through Friday exclusive of national holidays)

<How to Use PREDONEMA Enema 20 mg>

1. Heating on a water bath (as required)
   When this product is placed in low-temperature surroundings, administration may chill the hypogastric region. In such a case, heat this product in the aluminum-foil bag to around body temperature on a water bath.

2. Taking out the container from the bag
   Take out the container from the aluminum-foil bag just before use.
   § Use this product immediately after taking out from the bag, because it is unstable to light.

3. Setting the stopper (as required)
   Because distance for insertion of the nozzle varies individually, excessive insertion may injure the rectal mucosa.
   Fit the enclosed stopper on the nozzle for safety, for example, in the case of first use.
   § How to fit the stopper
   Insert the nozzle into a hole of the disk stopper and settle the disk stopper at a distance of about 4 to 6 cm from the top of the nozzle, as illustrated below.

4. Applying a lubricant (as required)
   Apply a lubricant (petrolatum, olive oil, or water) when the nozzle is difficult to be inserted.

5. How to hold the container at opening
   Grasp lightly the trunk of the container, with the nozzle upward and the logotype of “PREDONEMA” toward you, as illustrated below.
   § Since a strong grasp of the container at opening may spill the drug solution, grasp the trunk lightly.

6. How to remove the “Tip”
   Grasp the circular flange and bend the narrow part of the container back and forth to remove the “Tip” to release the drug solution. Even if the “Tip” is not completely separated, the solution will be released by dislocating the tip. Bending right and left (sideways) or diagonally may cause the leak of the drug solution.

7. Inserting the nozzle and injecting the drug solution
   (1) Insert the nozzle slowly into the anus with care.
       § Don’t insert the nozzle forcibly into the anus because of a possible damage to the rectal mucosa.
   (2) After slow injection of the drug solution in a left lateral decubitus position, remove the nozzle slowly from the anus while grasping the container.

8. Changing the posture (as required)
   Change the posture, as required.

Manufactured and marketed by:
Kyorin Pharmaceutical Co., Ltd.
6, Kanda Surugadai 4-chome, Chiyoda-ku, Tokyo 101-8311, Japan