1. NAME OF THE MEDICINAL PRODUCT

Novalor Syrup.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains Choroquine Phosphate 80mg. For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Novalor Syrup is presented as a clear syrup for oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Novalor is indicated for:
- Treatment of rheumatic arthritis including juvenile idiopathic arthritis.
- Treatment of lupus erythematosus (discoid or systemic)
- Management of light-sensitive skin eruptions (Photo allergic reactions).
- Treatment of hepatic amoebiasis.

4.2 Posology and method of administration

Posology

Doses are expressed in terms of Choroquine Phosphate.

Treatment of rheumatoid arthritis, Juvenile idiopathic arthritis and Lupus Erythematosus:
Adults: 250mg daily. Up to a maximum of 2.5mg/kg daily.
Children: 3mg/kg daily.
In rheumatoid arthritis, response may not be apparent for up to 6 months, but if there is no improvement by then, treatment should be stopped. Precautions for patients on long term therapy should be observed.

Treatment of Light-sensitive skin eruptions:
Adults: 250mg daily. Up to a maximum of 2.5mg/kg daily only during periods of intense light exposure.
Children: 3mg/kg daily during only during periods of intense light exposure.

Treatment of hepatic amoebiasis:
Adults: 500mg daily for 2 days, then 250mg daily for 2 to 3 weeks.
Children: Not recommended.

Method of administration

Novalor is for Oral administration.
Oral bioavailability is increased when Novalor is taken with food. However, the drug should be taken only as directed by the physician. Duration of therapy should be appropriate to the indication and should not exceed the prescribed dose by the physician.

4.3 Contraindications

- Patients with known hypersensitivity to chloroquine or 4-aminoquinoline compounds
- Retinal or visual field disease.
- Usage in pregnancy should be avoided except in preventive therapy where in the judgment of the physician, the benefits outweigh the risks.
- Patients with epilepsy

4.4 Special warnings and precautions for use

Irreversible retinal damage and corneal changes may develop during long term therapy and after the drug has been discontinued. Ophthalmic examination prior to, and at 3-6 monthly intervals during use is

recommended to forestall incidences of keratopathy and retinopathy if patients are receiving chloroquine:
- At continuous high doses for longer than 12 months
- As weekly treatment for longer than 3 years
- When total consumption exceeds 1.6g/kg (cumulative dose 100g)

Patients should be advised to stop taking the drug immediately and seek the advice of their doctor if any disturbances of vision occur.
Bone marrow suppression may occur rarely so full blood counts should be carried out during extended treatment. Caution is required if drugs known to induce blood disorders are used concurrently.
Caution should be observed in patients with hepatic impairment particularly cirrhosis or under treatment with potentially hepatotoxic drugs Use with caution in patients with impaired hepatic function.
Use with caution in patients with porphyria as the disease may be precipitated. This may be especially apparent in patients with a high alcohol intake.
Use with caution in patients with a renal impairment.
Use with caution in patients with a history of epilepsy, convulsions and other neurological disorders.
Use with caution in patients with psoriasis as chloroquine may precipitate a severe attack.
Use with caution in patients with severe gastro-intestinal disease.
Use with caution in patients with myasthenia gravis and in patients with glucose-6-phosphate dehydrogenase deficiency, as there may be risk of haemolysis.
Chloroquine has been shown to cause severe hypoglycaemia including loss of consciousness that could be life threatening in patients treated with and without antidiabetic medications. Patients treated with chloroquine should be warned about the risk of hypoglycaemia and the associated clinical signs and symptoms. Patients presenting with clinical symptoms suggestive of hypoglycaemia during treatment with chloroquine should have their blood glucose level checked and treatment reviewed as necessary.
A small number of cases of diffuse parenchymal lung disease have been identified in patients taking chloroquine. A response after therapy with steroids has been observed in some of these cases.
Cases of drug rash with eosinophilia and systemic symptoms (DRESS) syndrome have been identified in patients taking chloroquine. Recovery after discontinuation of treatment and response after therapy with steroids has been observed.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltese insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

There is increased risk of inducing cardiac arrhythmias including ventricular arrhythmias, bradycardias and cardiac conduction defect if chloroquine is used with halofantrine or other arrhytmogenic drugs such as amiodarone, droperidol and moxifloxacin.
There is risk of convulsions when chloroquine is given with mefloquine.
Absorption of chloroquine can be reduced by antacids and kaolin. Dosing should be separated by at least 4 hours interval.
Chloroquine may antagonize the antiepileptic activity of carbamazepine and valproate.
Chloroquine increases risk of convulsions with mefloquine (anti-malarial drug).
Activity of chloroquine may be affected when given with other antimalarials like quinine, mefloquine, amodiaquine, artemisinin or pyrimethamine-sulphadoxine.
Concomitant use of drugs such as multidrug and toxin extrusion protein (MATE1) inhibitors (e.g., ciprofloxacin, cimetidine, omeprazole, pyrimethamine) may inhibit the metabolism of chloroquine and impact the renal clearance of chloroquine, which could theoretically lead to increased levels of chloroquine and potentially overdosage (see section 4.9). In addition, care should be taken when alkalinization of urine occurs as this may reduce chloroquine renal excretion.
Chloroquine may possibly increase the plasma concentration of digoxin.
When co-administered with ciclosporin, chloroquine increases plasma ciclosporin concentration resulting in increased risk of toxicity.
Chloroquine has been reported to reduce the bioavailability of praziquantel. Caution is advised during co-administration.
Chloroquine has the potential to increase symptoms of myasthenia gravis and thus diminish effect of neostigmine and pyridostigmine.
Concomitant administration of chloroquine with rabies vaccine may affect the antibody response.
Concomitant administration of chloroquine inactivates oral typhoid vaccine, so the vaccine should be completed at least three days before the first dose of chloroquine.

4.6 Pregnancy and Lactation

Pregnancy

Should not be used during pregnancy unless, in the judgement of the physician, potential benefit outweighs the risk. When given at high doses throughout pregnancy it has been reported to give rise to foetal abnormalities including visual loss, ototoxicity and cochlea-vestibular dysfunction.

There has been concern about the potential teratogenic effects of chloroquine because of a few case reports including defects in hearing and vision. Two of 169 infants, born to women given chloroquine 300mg weekly throughout pregnancy, had birth defects compared with 4 of 454 control infants whose mothers had not received antimalarials; the difference was not significant. The data suggested that chloroquine in the recommended prophylactic doses is not a strong teratogen and that its proved antimalarial benefits outweigh any possible risk of low grade teratogenicity.

Usage in pregnancy should be avoided except in preventive therapy where in the judgment of the physician, the benefits outweigh the risks. Also it has been reported that chloroquine prophylaxis during pregnancy did not affect the bithweight of neonates compared with a control group.

Lactation

Studies have suggested that it is safe for mothers to breastfeed when they are receiving chloroquine for treatment of malaria. Although chloroquine and its metabolite are excreted into breast milk, it has been estimated that the amount that would be consumed by an infant is well below the therapeutic range and separate chemoprophylaxis for the infant is required.

There appear to be no data on the excretion of hydroxychloroquine in milk after doses appropriate for the prevention or treatment of malaria, but hydroxychloroquine has been detected in breast milk from 2 mothers receiving doses of 400mg daily for SLE or rheumatoid arthritis. One group of workers estimated that, calculated on a body-weight basis, a 9-month old infant could receive about 2% of a maternal dose via breast feeding.

4.7 Effects on ability to drive and use machines

At start of treatment chloroquine has a temporary effect on visual accommodation, causing blurred and/or double vision. Therefore patients should be advised that the product may affect their ability to drive or operate machinery.

4.8 Undesirable effects

The following CIOMS frequency rating is used when applicable:

Very common ≥ 10%; Common ≥ 1 and < 10%; Uncommon ≥ 0.1 and < 1%; Rare ≥ 0.01 and < 0.1%; Very rare < 0.01%; Not known (frequency cannot be estimated from available data)

Cardiac disorders

- Uncommon: cardiomyopathy has been reported during long term therapy at high doses, which may result in cardiac failure and in some cases a fatal outcome.
- Rare: cardiac arrhythmias, including QT prolongation, torsade de pointes, ventricular tachycardia and ventricular fibrillation have been reported with therapeutic doses of chloroquine as well as with overdose. The risk is greater if chloroquine is administered at high doses. Fatal cases have been reported.
- Not known - hypotension.

Nervous system disorders

- Very common: headache
- Common: convulsions have been reported rarely (these may result from cerebral malaria).
- Uncommon: neuropathy
- Rare: polyneuropathy
- Not known: acute extrapyramidal disorders (such as dystonia, dyskinesia, tongue protrusion, torticollis).

Psychiatric disorders

- Very common: insomnia
- Common: depression
- Rare: psychiatric disorders such as anxiety, agitation, confusion, hallucinations, delirium
- Not known: suicidal behaviour

Eye disorders

- Common: transient blurred vision
- Rare: reversible corneal opacity, cases of retinopathy as well as cases of irreversible retinal damage have been reported during long term, high dose therapy.
- Not known: maculopathy and macular degeneration have been reported and may be irreversible, macular

defects of colour vision, optic atrophy, scotomas, field defects, blindness and pigmented deposits, difficult in focusing, diplopia.
Gastro-intestinal disorders
- Very common: gastrointestinal disturbances such as nausea, vomiting, diarrhoea.
- Not known: abdominal cramps
Blood and lymphatic system disorders
- Rare: bone marrow depression, including aplastic anaemia, agranulocytosis, pancytopenia, thrombocytopenia, neutropenia
Hepatobiliary disorders
- Rare: changes in liver function, including hepatitis and abnormal liver function tests
- Immune system disorders
- Common: allergic and anaphylactic reactions, including angioedema
Ear and labyrinth disorders
- Uncommon: ototoxicity such as tinnitus, hypoacusis, nerve deafness.
Musculoskeletal and connective tissue disorders
- Uncommon: myopathy
Skin and subcutaneous tissue disorders
- Very common: pruritis,
- Common: skin eruptions, urticaria
- Uncommon: alopecia, bluish-black pigmentation of the nails and mucosae (long term use).
- Rare: exacerbation of psoriasis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
- Very rare: exfoliative dermatitis and similar desquamation-type events.
- Not known: depigmentation, photosensitivity, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome)
Metabolism and nutrition disorders
- Not known: hypoglycaemia

4.9 Overdose
Chloroquine is highly toxic in overdose and children are particularly susceptible.

Symptoms:
The chief symptoms of overdosage include circulatory collapse due to a potent cardiotoxic effect, respiratory arrest and coma. Symptoms may progress rapidly after initial headache, drowsiness, visual disturbances, nausea and vomiting. Cardiac complications may occur without progressively deepening coma.
Death may result from circulatory or respiratory failure or cardiac arrhythmia. If there is no demonstrable cardiac output due to arrhythmias, asystole or electromechanical dissociation, external chest compression should be persisted with for as long as necessary, or until adrenaline and diazepam can be given (see below).

Treatment:
Gastric lavage should be carried out urgently (as soon as possible within 2 hours of the overdose), first protecting the airway and instituting artificial ventilation where necessary. There is a risk of cardiac arrest following aspiration of gastric contents in more serious cases. Activated charcoal left in the stomach may reduce absorption of any remaining chloroquine from the gut (minimum 5 times the suspected maximum dose of chloroquine phosphate). Circulatory status (with central venous pressure measurement), respiration, plasma electrolytes and blood gases should be monitored, with correction of hypokalaemia and acidosis if indicated. Cardiac arrhythmias should not be treated unless life threatening; drugs with quinidine-like effects should be avoided. Intravenous sodium bicarbonate 1-2mmol/kg over 15 minutes may be effective in conduction disturbances, and DC shock is indicated for ventricular tachycardia and ventricular fibrillation.
Early administration of the following has been shown to improve survival in cases of serious poisoning:
1. Adrenaline infusion 0.25micrograms/kg/min initially, with increments of 0.25micrograms/kg/min until adequate systolic blood pressure (more than 100mg/Hg) is restored; adrenaline reduces the effects of chloroquine on the heart through its inotropic and vasoconstrictor effects.
2. Diazepam infusion (2mg/kg over 30 minutes as a loading dose, followed by 1-2mg/kg/day for up to 2-4 days). Diazepam may minimise cardiotoxicity.

Acidification of the urine, haemodialysis, peritoneal dialysis or exchange transfusion have not been shown to be of value in treating chloroquine poisoning. Chloroquine is excreted very slowly, therefore cases of overdosage require observation for several days.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarials, Aminoquinolines, ATC code: P01B A01
Choroquine is a 4-aminoquinoline. It possesses anti-inflammatory properties and has been used with some benefit in a range of inflammatory conditions which often have an immunological basis.
Mechanism of Action
The mode of action in these conditions is unclear but it does appear that chloroquine might have some immunosuppressive effects.

5.2 Pharmacokinetic properties

Chloroquine is rapidly and almost completely absorbed from the gastrointestinal tract when given orally and is widely distributed into body tissues such as the kidneys, liver, lungs and spleen and is strongly bound in melanin-containing cells such as those in the eyes and skin. It also crosses the placenta. Chloroquine is eliminated very slowly from the body and it may persist in tissues for months or even years after stopping therapy. It is metabolised in the liver mainly to monodesethylchloroquine with smaller amounts of bisdesethylchloroquine (didesethylchloroquine) and other metabolites being formed. Chloroquine and its metabolites are excreted in the urine. Chloroquine and its monodesethyl metabolite are both distributed into breast milk.

5.3 Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, Sodium Propyl Hydroxybenzoate, Aqua Anethi, Purified Water.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

60ml Amber coloured PET bottles with aluminium screw caps supplied with a measuring cup dosing device.

6.6 Special precautions for disposal

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

7. Marketing authorisation holder

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