128x270

NIMEGEN Soft Cap.
(Isotretinoin)

DESCRIPTION
NIMEGEN Capsules are light purple, oval and soft. They come in a white opaque blister of 10 capsules ; 3 such blisters in a printed box with a package insert.

COMPOSITION
Each capsule contains: Isotretinoin 10mg, Methyl parahydroxybenzoate 0.18mg and Propyl parahydroxybenzoate 0.07mg.

PHARMACOLOGICAL ACTION
Isotretinoin is an orally active retinoic acid derivative for the treatment of severe refractory nodulocystic acne. The pharmacological profile of the isotretinoin suggests that it acts primarily by reducing sebaceous gland size and sebum production, and as a result alters skin surface lipid composition. Bacterial skin microflora is reduced, probably as a result of decreased sebum secretion.

PHARMACOKINETICS
Time-related blood concentrations can be predicted on the basis of linear pharmacokinetics.
Absorption
Peak plasma concentrations(C max) of approximately 250mg/ml have been achieved in healthy volunteers and in patients with cystic acne one to four hours (t max) after administration of 80-100mg isotretinoin. Taking isotretinoin with food increases bioavailability up to two fold relative to fasting conditions, probably as a result of easier absorption of this highly lipophilic medication. Furthermore, there was an overall decrease in fluctuations in systemic availability when isotretinoin is ingested with food.
Distribution
Isotretinoin is extensively bound to plasma proteins (99.9%), with the result that the free active fraction of the drug is less than 0.1% of the total over a wide range of therapeutic concentrations. Albumin appears to be the major binding protein. The volume of distribution of isotretinoin is not known in man since it is not available as an intravenous preparation. Isotretinoin crosses the placental barrier in amounts that lead to congenital deformities. Owing to its lipophilicity, there is a high probability that isotretinoin is excreted into the breast milk. It is therefore contraindicated in nursing mothers.
Metabolism
The major blood metabolite of isotretinoin is 4-oxo-isotretinoin, which is rapidly formed following oral administration of the drug. Isotretinoin also isomerizes in vivo via an alternative metabolic pathway to tretinoin (all-trans retinoic acid). Glucuronidation of the metabolites has not been conclusively demonstrated in man but is strongly suggested by animal studies. Investigations in humans and the dog point to an enterohepatic recirculation of isotretinoin, which would contribute to the observed inter-individual variability in plasma concentrations.
Elimination
Isotretinoin appears to be eliminated almost exclusively by hepatic metabolism and biliary excretion. Following oral administration of isotretinoin, the elimination half-life of unchanged drug has ranged from 7-39 hours (mean: approximately 20 hours)in both healthy volunteers and patients with cystic acne. The mean elimination half-life of the 4-oxo metabolite in patients with cystic acne is slightly longer (25 hours, range : 17-50 hours) than that of the parent drug.
Pharmacokinetic in special clinical situation
Since isotretinoin is contraindicated in patients with renal or hepatic impairment, there is no information of the pharmacokinetics of the drug in this population.

INDICATIONS
Severe forms of acne (nodulo-cystic forms) which are resistant to previous therapy, particularly cystic acne and acne conglobata, especially when the lesions involve the trunk. NIMEGEN should only be prescribed by physicians who are experienced in the use of systemic retinoids - preferably dermatologists - and understand the risk of teratogenicity if NIMEGEN is used during pregnancy.

DOSAGE & ADMINISTRATION
Oral administration. The therapy should be started with 0.5mg/kg daily. It is not unusual for the acne to be aggravated for a short period at the beginning of treatment. Efficacy and side effects vary according to the individual patient; after about four weeks, therefore, dosage for the maintenance treatment should be adjusted within the range of 0.1-1.0mg/kg daily to meet individual needs. The maximum dosage of 1mg/kg daily should be given for only a limited period of time. Treatment usually lasts a total of 16 weeks. When assessing the result of the therapy, it should be borne in mind that there is often a further improvement after discontinuation of treatment. There should be an interval of at least 8 weeks before restarting treatment, which should be resumed in accordance with the above dosage guidelines. The capsules are taken with meals, low doses once daily and higher amounts as a single dose or in several doses spread over the day.

CONTRAINDICATIONS
1) Hepatic or renal insufficiency
2) Hyperlipidemia : When the serum lipid level is more than double the normal value
3) Hypervitaminosis A
4) Diabetes mellitus
5) Hypersensitivity to isotretinoin
6) Conditions predisposing to hypertriglyceridemia such as high alcohol intake, or history of hypertriglyceridemia, family history of obesity
7) Pregnancy & reproduction

NIMEGEN is highly teratogenic. It is therefore contraindicated not only in women who are pregnant or who may become pregnant while undergoing treatment but in all women of childbearing potential. There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking NIMEGEN in any amount even for short periods. Potentially all exposed fetuses can be affected.
NIMEGEN is contraindicated in women of childbearing potential unless the female patient meets the following conditions:
- She has severe disfiguriing cystic acne resistant to standard therapies.
- She is reliable in understanding and carrying out instruction.
- She is capable of complying with the mandatory contraceptive measures.
- She is informed by her physician of the hazards of becoming pregnant during and one month after treatment with NIMEGEN and she is warned of the possibility of contraceptive failure.
- She confirms that she has understood the precaution.
- She has a negative pregnancy test within two weeks prior to start of the therapy. Monthly repetition of pregnancy test is recommended.
- She uses effective contraception without any interruption for one month before beginning NIMEGEN therapy, during therapy and for one month following discontinuation of therapy.
- She starts NIMEGEN therapy only on the second or third day of the next normal menstrual period.
- In the event of relapse treatment she must also use the same uninterrupted and effective contraceptive measures one month prior to, during and one month after NIMEGEN therapy.
  Even female patients who normally do not apply contraception because of a history of infertility should be advised to do so while taking NIMEGEN following the above guidelines. Should pregnancy occur in spite of these precautions during treatment with NIMEGEN or in the month following, there is a great risk of very severe malformation of the fetus (involving in particular the central nervous system, the heart and the large blood vessels). There is also an increased risk of spontaneous abortion. Major human fetal abnormalities related to NIMEGEN administration have been documented, including hydrocephalus, microcephalus, abnormalities of the external ear(micropinna, small or absent external auditory canals), microphthalmia, cardiovascular abnormalities, facial dysmorphia, thymus gland abnormalities, parathyroid hormone deficiency and cerebellar malformation.

8) Nursing mothers
   NIMEGEN must not be given to nursing mothers

GUIDELINES FOR PATIENTS
The patients attention should be drawn to the following:
- The strict precautions relating to women of childbearing potential.
- NIMEGEN is prescribed for the patients sole use. Under no circumstances should they be passed on to third parties.
- The patients should adhere strictly to guidelines. They should be instructed to consult you in the event of side effects such as headaches, disturbances of vision, nausea, diarrhea, pain in muscle or joints.
- The soft capsules should be swallowed whole without chewing, during a meal or with a glass of milk.
- NIMEGEN should be kept in the packing in which it is received, and this should be, firmly closed, protected from heat and light, and out of reach of children.

SIDE EFFECTS
They are reversible, disappearing on discontinuation of treatment and dose-related in terms of their incidence and degree of severity. In the proper dosage, tolerance of this drug is generally acceptable in view of the severity of the disease. They can be attenuated by appropriate treatment.

MUCOCUTANEOUS SIDE EFFECTS : Cheilitis, Dermatitis facialis, Dryness of nasal mucosa, Epistaxis, Blepharoconjunctivitis.
SYSTEMIC SIDE EFFECTS : Headache, Arthralgia-myalgia
CHANGES IN LABORATORY PARAMETERS : Serum lipoproteins
The following are sometimes elevated to a greater or lesser degree : SPGT(ALAT), SGOT(ASAT), CPK, uric acid.
CNS DISTURBANCES : behavioural disorders, depression and seizures.
Patients should be monitored for signs of depression and if necessary the appropriate treatment given.

Symptoms associated with hypervitaminosis A
The following symptoms are the most frequently reported unwanted effects with NIMEGEN : dryness of the skin, dryness of the mucosae eg. Of the lips, the nasal mucosa (epistaxis), the pharynx(hoarseness), the eyes (conjunctivitis, reversible corneal opacities and intolerance to contact lenses).
Skin and appendages disorders
Exanthema, pruritus, dermatitis facialis, sweating, pyogenic granuloma, paronychia, nail dystrophy, increased formation of granulation tissue, persistent hair thinning, reversible alopecia, acne fulminans, hirsutism, hyperpigmentation, photosensitivity.
Musculo-skeletal system disorders
Muscle pain, joint pain, hyperostosis and other bone changes, tendonitis, NIMEGEN in not intended for long-term therapeutic use, and the possibility of this side effect occurring if it is used improperly for long-term treatment should be borne in mind.
Psychiatric and central nervous system disorder
Behavioural disorders, depression, headaches, increased intracranial pressure, seizures.
Rare (may affect up to 1 in 1,000 people):
Depression, depression aggravated, aggressive tendencies, anxiety, mood alterations.
Very rare (may affect up to 1 in 10,000 people):
Suicide, suicide attempt, suicidal ideation, psychotic disorder, abnormal behavior.
Sensory disorders
Isolated cases of visual disturbances, impaired hearing at certain frequencies photophobia, dark-adaption disturbances (decreased night vision), lenticular cataract, keratitis.
Gastro-Intestinal system disorders
Nausea, inflammatory bowel diseases such as colitis, ileitis and haemorrhage have been reported to occur.
Liver and biliary system disorders
Transitory and reversible increases in transaminases, some cases of hepatitis. In many such cases the changes have been within the normal range and values have returned to baseline levels during treatment. In other cases, however, it has been necessary to reduce the dose or discontinue treatment with NIMEGEN.
Respiratory system disorders
Bronchospasm.
Disorders of the blood
Decrease in white cell count, red blood cell parameters, increase of decrease in platelet count, elevated sedimentation rate.
Laboratory findings
Increase in serum triglyceride and cholesterol levels, hyperuricaeomia. Decrease in HDL have also been observed, particularly at high dosages and in predisposed patients (with a family history of lipid metabolism disorders, diabetes, obesity or alcoholism). These changes, too, are dose-related, and values return to nomal on reduction of the dosage or withdrawal of the drug. Every patient must be warned about the possible occurrence of side effects.
Resistance mechanism disorders
Local or systemic infections due to Gram positive microorganisms (Staphylococcus aureus).
Miscellaneous reactions
Lymphadenopathy, hematuria and proteinuria, pancreatitis [especially patients with high serum triglyceride levels (>800mg) treated with isotretinoin are at the risk of developing pancreatitis], vasculitis (for example Wegener's granulomatosis).
Post marketing:
Sexual dysfunction including erectile dystunction and decreased libido have also been reported.

PRECAUTIONS/WARNINGS:
1 Weigh the potential risks against the expected benefits of therapy, taking into account the possibility of long-term adverse reactions.
2) Monitor serum lipids and hepatic function regularly, also glycemia in diabetics.
3) Avoid prolonged exposure to sunlight.
4) Patients receiving isotretinoin should not donate blood during or for 30days after therapy, because of the risk of the developed fetus of a pregnant patient who may receive such blood.
Psychiatric disorders
Depression, depression aggravated, anxiety, aggressive tendencies, mood alterations, psychotic symptoms, and very rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with Isotretinoin. Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary. However, discontinuation of Isotretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary. Awareness by family or friends may be useful to detect mental health deterioration.

DRUG INTERACTION
1) Concurrent therapy with NIMEGEN and vitamin A must be avoided, as symptoms of hypercitaminosis A may be intensified.
2) Combination of tetracycline with NIMEGEN is contraindicated as concurrent use may increase the potential for development of pseudomotor cerevri.
3) Concurrent administration of Etretinate and Tretinoin is also contraindicated.
4) The effect of microdosed progesterone preparation of "minipills" may by disminished and thus such preparations should not be used during therapy with NIMEGEN.

SYMPTOMS & TREATMENT OR OVERDOSAGE:
Symptoms : Hypertriglycerifemia, increased cholesterol value and LDH value, hypervitaminosis A.
Treatment : In Case of hypervitaminosis A, the drug should be discontinued and supportive measures including gastric lavage to be applied.

STORAGE
Light-resistant container. Store below 30℃ Keep out of reach of children.
SHELF LIFE : 3 Years
PACKS : 30 soft capsules
CONTROLLED MEDICINE/UBAT TERKAWAL

MEDICA KOREA

MEDICA KOREA CO.,LTD.
904-6, Sangsin-ri, Hyangnam-myeon, Hwaseong-city, Gyeonggi-do,Korea.

Marketing Authorisation Holder
The Zyfas Medical Co.,
No. 7 Jalan Molek 3/10 Taman Molek, Johor Bahru

Revised Date : 09/05/2019