Niva-Fol™ Tablets

Description

Niva-Fol™ Tablets is an orally administered prescription dietary supplement specifically formulated for the dietary management of patients with unique nutritional needs requiring increased folate levels. Niva-Fol™ Tablets should be administered under the supervision of a licensed medical practitioner.

Each oval coated pink tablet debossed with "N080" contains the following dietary ingredients:

<table>
<thead>
<tr>
<th>Supplement Facts</th>
<th>Servings Per Container: 90</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily Values not established for patients with unique nutritional needs who are in need of supplementation as directed by a licensed medical practitioner.</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Amount per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B6 (as Pyridoxine HCl)</td>
<td>25 mg</td>
<td>1250%</td>
</tr>
<tr>
<td>Folacin (Vitamin B9)</td>
<td>2.5 mg</td>
<td>625%</td>
</tr>
<tr>
<td>Vitamin B12 (as Cyanocobalamin)</td>
<td>2 mg</td>
<td>33333%</td>
</tr>
</tbody>
</table>

Other Ingredients: Carmine, Calcium Carbonate, Magnesium Stearate, Stearic Acid, Starch, Croscarmellose Sodium, Silicon Dioxide, and Shellac. Contains no sugar, salt, yeast, milk, egg, shellfish, preservatives, artificial flavors or color.

Since additives, preservatives, bioavailability enhances, colors and/or flavors of natural origin, etc. are preferred over synthetics, it may be the case that product color, appearance and/or taste may vary slightly over time; and it may be necessary to substitute excipients during the manufacturing process as needed to preserve product appearance and continuity in order to avoid confusion in the marketplace and ensure the highest therapeutic target, safety and quality.

Warning: Carmine - haram for Mulsims.

FOLATE MECHANISM OF ACTION

FOLATE is essential for the production of certain coenzymes in many metabolic systems such as purine and pyrimidine synthesis. It is also essential in the synthesis and maintenance of nucleoprotein in erythropoiesis. It also promotes white blood cell (WBC) and platelet production in folate-deficiency anemia. Folate is associated with methylation and transformylation biochemistry.

FOLATE REGULATION

The Federal Register Notices from 1971 to 1973 established that increased folate was proper therapy in megaloblastic anemias of tropical and nontropical sprue, nutritional origin, pregnancy, infancy and childhood. Folate metabolism can be affected by malabsorption issues which differ widely among...
population groups. The March 5, 1996 Federal Register Notice (61 FR 8760) states that "The agency concluded that the scientific literature did not support the superiority of any one source of folate over others, and that the data were insufficient to provide a basis for stating that a specific amount of folate is more effective than another amount". The actual amount and source of folate require a licensed medical practitioner's supervision to achieve a satisfactory maintenance level, and may exceed the 0.8 mg UL. The Federal Register Notice of August 2, 1973 (38 FR 20750) specifically states that "dietary supplement preparations are available without a prescription (21 CFR 121.1134). Levels higher than dietary supplement amounts are available only with a prescription. Oral preparations supplying more than 0.8 mg of folate per dosage unit would be restricted to prescription dispensing and that a dietary supplement furnishing 0.8 mg could be prescribed when a maintenance level of 0.8 mg per day was indicated... When clinical symptoms have subsided and the blood picture and/or CSF folate levels have become normal, a maintenance level should be used. Patients should be kept under close supervision and adjustment of the maintenance level made if relapse appears imminent. In the presence of alcoholism, hemolytic anemia, anticonvulsant therapy, or chronic infection, the maintenance level may need to be increased." In the Letter Regarding Dietary Supplement Health Claim for Folic Acid, Vitamin B6, and Vitamin B12 and Vascular Disease (Docket No. 99P-3029) dated November 28, 2000, FDA wrote "... high intakes of folate may partially and temporarily correct pernicious anemia while the neurological damage of vitamin B12 deficiency progresses. IOM/NAS (1998) set the UL for all adults of 1 mg per day because of devastating and irreversible neurological consequences of vitamin B12 deficiency, the data suggesting that pernicious anemia may develop at a younger age in some racial or ethnic groups, and the uncertainty about the extent of the occurrence of vitamin B12 deficiency in younger age groups (IOM/NAS, 1998)". Summary: This product is a dietary management product that - due to advanced folate levels, requires administration under the care of a licensed medical practitioner, and the most appropriate way to do that is to provide the product as prescription for pedigree reporting and safety monitoring. The ingredients, indication or claims of this product are not to be construed to be drug claims.

**ALLERGY STATEMENT**

This product has been manufactured in a facility that also manufactures products containing fish, egg, wheat, milk, soy and shellfish. Individuals with allergic tendencies to these substances should use discretion.

**INTERACTIONS**

Talk to your healthcare practitioner and/or pharmacist before taking or using any prescription or over-the-counter medicines or herbal/health supplements alongside this product.

**CONTRAINDICATIONS**

This product is contraindicated in patients with a known hypersensitivity to any of the components contained in this product. This product is contraindicated for individuals with conditions for which any of the ingredients are contraindicated.

**WARNINGS**

Caution is recommended in patients with a history of bipolar illness. Mood elevation is possible in this population.

Caution is also recommended in patients taking anticonvulsant medications as folate may interfere with anticonvulsant medication, and may lower seizure threshold. Furthermore, it has been reported that anticonvulsant medications interfere with folate metabolism, but the exact action is unclear; therefore caution is recommended with patients in this therapeutic group.
Folinic acid may enhance the toxicity of fluorouracil. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly formyl-THF and fluorouracil. Concomitant granulocytopenia and fever were present in some but not all of the patients. The concomitant use of formyl-THF with trimethoprim-sulfamethoxazole for the acute treatment of Pneumocystis carinii pneumonia in patients with HIV infection was associated with increased rates of treatment failure and mortality in a placebo controlled study. Patients undergoing cancer treatment should consult their licensed medical practitioner for advice.

PRECAUTIONS

Folate alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B12 is deficient. Folate in doses above 0.1 mg daily may obscure pernicious anemia in that hematologic remission may occur while neurological manifestations progress.

INDICATIONS AND USAGE

Niva-Fol Tablets is indicated for patients in need of dietary supplementation as determined by a licensed medical practitioner.

Niva-Fol Tablets should be administered under the supervision of a licensed medical practitioner.

ADVERSE REACTIONS

Allergic reactions have been reported following the use of oral and parenteral folate. Mild transient diarrhea, polycythemia vera, itching, transitory exanthema and the feeling of swelling of the entire body has been associated with cobalamin. Nausea, vomiting, diarrhea, transient skin rash, flushing, epigastric pain, and constipation have been associated with acetylcysteine.

Call your medical practitioner about side effects.

PHARMACOLOGY

FOLATE

Folates are best known for reducing the incidence of fetal neural tube defects (NTDs). NTDs are congenital malformations produced by failure of the neural tube to form and close properly during embryonic development. During the first four weeks of pregnancy - when many women do not even realize that they have conceived, adequate maternal folate intake is essential to reduce the risk of NTDs. As the postnatal period approaches there is increased demand again for folate regardless of lactation status. Folate is involved in transformylation and methylation metabolism as well as - indirectly, succinylation metabolism (through the "methyl trap" hypothesis). Folate plays a central role in the formation of nucleic acid precursors, such as thymidylic acid and purine nucleotides, which are essential for nucleic acid synthesis and cell division. IOM/NAS (1998) noted that the evidence for a protective effect from folate supplements is much stronger than that for food folate. Other dietary ingredients are added to folate as cofactors, coenzymes and co-metabolites; in studies by Czeizel and Dudas (1992) and Berry et al. (1999), factors other than folate intakes may affect the magnitude of risk reduction or participate in a co-protective effect with folate.

KEEP THIS PRODUCT OUT OF THE REACH OF CHILDREN.

DRUG INTERACTIONS

Drugs which may interact with folate include:

- Antiepileptic drugs (AED): The AED class including, but not limited to, phenytoin, carbamazepine,
primidone, valproic acid, fosphenytoin, valproate, phenobarbital and lamotrigine have been shown to impair folate absorption and increase the metabolism of circulating folate.

- Additionally, concurrent use of folic acid has been associated with enhanced phenytoin metabolism, lowering the level of the AED in the blood and allowing breakthrough seizures to occur. Caution should be used when prescribing this product among patients who are receiving treatment with phenytoin and other anticonvulsants.

- Capecitabine: Folinic acid (5-formyltetrahydrofolate) may increase the toxicity of Capecitabine.

- Cholestyramine: Reduces folic acid absorption and reduces serum folate levels.

- Colestipol: Reduces folic acid absorption and reduces serum folate levels.

- Cycloserine: Reduces folic acid absorption and reduces serum folate levels.

- Dihydrofolate Reductase Inhibitors (DHFRI): DHFRIs block the conversion of folic acid to its active forms, and lower plasma and red blood cell folate levels. DHFRIs include aminopterin, methotrexate, pyrimethamine, triamterene, and trimethoprim.

- Fluoxetine: Fluoxetine exerts a noncompetitive inhibition of the 5-methyltetrahydrofolate active transport in the intestine.

- Isotretinoin: Reduced folate levels have occurred in some patients taking isotretinoin.

- L-dopa, triamterene, colchicine, and trimethoprim may decrease plasma folate levels.

- Nonsteroidal Anti-inflammatory Drugs (NSAIDs): NSAIDs have been shown to inhibit some folate dependent enzymes in laboratory experiments. NSAIDs include ibuprofen, naproxen, indomethacin and sulindac.

- Oral Contraceptives: Serum folate levels may be depressed by oral contraceptive therapy.

- Methylprednisolone: Reduced serum folate levels have been noted after treatment with methylprednisolone.

- Pancreatic Enzymes: Reduced serum folate levels have occurred in some patients taking pancreatic extracts, such as pancreatin and pancrelipase.

- Pentamidine: Reduced folate levels have been seen with prolonged intravenous pentamidine.

- Pyrimethamine: High levels of folic acid may result in decreased serum levels of pyrimethamine.

- Smoking and Alcohol: Reduced serum folate levels have been noted.

- Sulfasalazine: Inhibits the absorption and metabolism of folic acid.

- Metformin treatment in patients with type 2 diabetes decreases serum folate.

- Warfarin can produce significant impairment in folate status after a 6-month therapy.

- Folinic acid may enhance the toxicity of fluorouracil.

- Concurrent administration of chloramphenicol and folic acid in folate-deficient patients may result in antagonism of the haematopoietic response to folate.

- Caution should be exercised with the concomitant use of folinic acid and trimethoprim-sulfamethoxazole for the acute treatment of Pneumocystis carinii pneumonia in patients with HIV infection as it is associated with increased rates of treatment failure and mortality in a placebo controlled study.

**Drugs which may interact with vitamin B$_{12}$ (Methylcobalamin):**

- Antibiotics, cholestyramine, colchicines, colestipol, metformin, para-aminosalicylic, and potassium chloride may decrease the absorption of vitamin B$_{12}$.

- Nitrous oxide can produce a functional vitamin B$_{12}$ deficiency.

**REFERENCES**

PREGNANCY and NURSING MOTHERS

Niva-Fol™ Tablets is not intended for use as a prenatal/postnatal multivitamin for lactating and nonlactating mothers. This product contains B vitamins in reduced form. Talk with your medical practitioner before using if pregnant or lactating.

DOSAGE AND ADMINISTRATION

One to two tablets daily or as directed by a licensed medical practitioner.

HOW SUPPLIED

Niva-Fol™ Tablets are oval coated pink tablets debossed with "N080", and dispensed in bottles of 90 tablets.

STORAGE


KEEP THIS OUT OF REACH OF CHILDREN.

All prescriptions using this product shall be pursuant to state statutes as applicable. This is not an Orange Book product.

Call your medical practitioner about side effects. You may report side effects by calling 877-977-0687.

Product Code: 75834-080-90

*This product is a prescription-folate with or without other dietary ingredients that - due to increased folate levels (AUG 2 1973 FR20750), requires an Rx on the label because of increased risk associated with masking of B₁₂ deficiency (pernicious anemia). Based on our assessment of the risk of obscuring pernicious anemia, this product requires licensed medical supervision, an Rx status, and a National Drug Code (NDC) - or similar product code, as required by pedigree reporting requirements and supply-chain control as well as - in some cases, for insurance-reimbursement applications.

This product may - under certain circumstances, be dispensed through a certified mail-order program so long as there is record of prescription AND confirmation that the patient is under licensed medical supervision. This product is not an Orange Book (OB) rated product, therefore all prescriptions using this product shall be pursuant to state statutes as applicable.
Rx
Manufactured for:
Nivagen Pharmaceuticals, Inc
Sacramento, CA 95827
Made in USA
4/15

PRINCIPAL DISPLAY PANEL - 90 Tablet Bottle Label

NIVAGEN
PHARMACEUTICALS

75834-080-90

Niva-Fol
Prescription
Vitamin
B₉-Containing
Dietary
Supplement

Rx
90 Tablets
Made in USA

Supplement Facts

<table>
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<tr>
<th>Serving Size: 1 Tablet</th>
<th>Amount per Serving</th>
<th>% Daily Value</th>
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<tbody>
<tr>
<td></td>
<td>pyridoxine HCl</td>
<td>25 mg</td>
</tr>
<tr>
<td></td>
<td>Folic Acid (Vitamin B₉)</td>
<td>2.5 mg</td>
</tr>
<tr>
<td></td>
<td>Vitamin B12 (as Cyanocobalamin)</td>
<td>2 mcg</td>
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Other Ingredients: Carnitine, Calcium Carbonate, Magnesium Stearate, Stearic Acid, Starch, Crosscarmellose Sodium, Silicon Dioxide, and Pellitol. Contains no sugar, salt, yeast, egg, milk, gluten, artificial flavors or color.
### Active Ingredient/Active Moiety

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<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
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<tbody>
<tr>
<td>Pyridoxine Hydrochloride (UNII: 68Y4CF58BV) (PYRIDOXINE - UNII:KV2JZ1B6Z)</td>
<td>Pyridoxine Hydrochloride</td>
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<td>Folic Acid (UNII: 935E97BOY8) (FOLIC ACID - UNII:935E97BOY8)</td>
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<td>Cyanocobalamin (UNII: P6YC3EG204) (CYANOCOBALAMIN - UNII:P6YC3EG204)</td>
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### Inactive Ingredients

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### Packaging

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### Marketing Information

<table>
<thead>
<tr>
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<tr>
<td>DIETARY SUPPLEMENT</td>
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### Supplement Facts

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**Labeler** - Nivagen Pharmaceuticals, Inc. (052032418)

Revised: 6/2015