

**NAPROXEN- naproxen tablet**  
**Northwind Pharmaceuticals**

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NDC: 51655-626-52

MFG: 68462-0190-05

Naproxen tablets 500 MG

30 Tablets

Rx Only

Lot#:

Exp. Date:

Each tablet contains 500 mg naproxen USP

Dosage: See medication guide

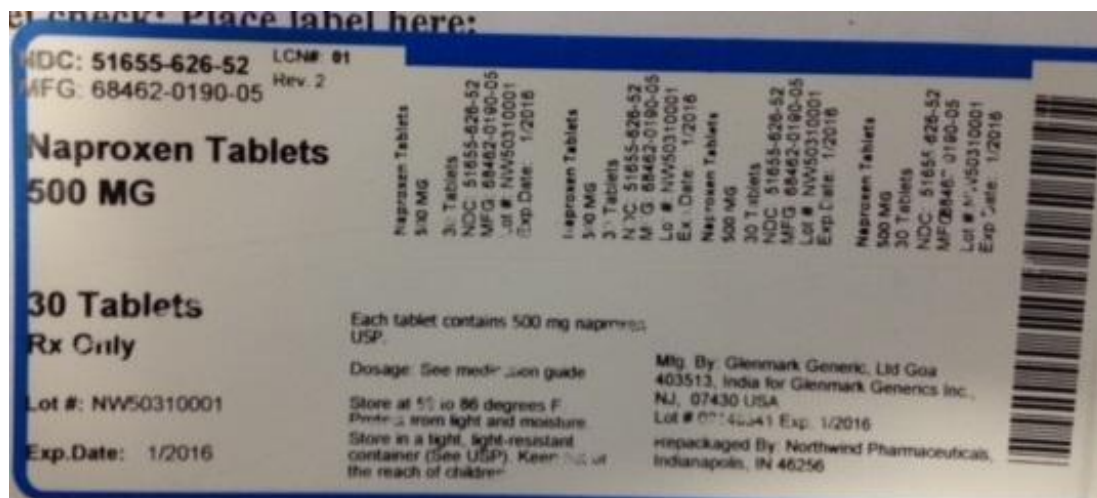
Store at 59-86 degrees F. Protect from light and moisture.

Store in a tight, light-resistant container (See USP) Keep out of the reach of children.

Mfg By: Glenmark Generic, Ltd Goa 403513 India for Glenmark Generics Inc,

NJ, 07430 USA Lot#: Exp Date:

Repackaged by: Northwind Pharmaceuticals, Indianapolis, IN 46256



NDC: 51655-626-20

MFG: 68462-0190-05

Naproxen tablets 500 MG

20 Tablets

Rx Only

Lot#:

Exp. Date:

Each tablet contains 500 mg naproxen USP

Dosage: See medication guide

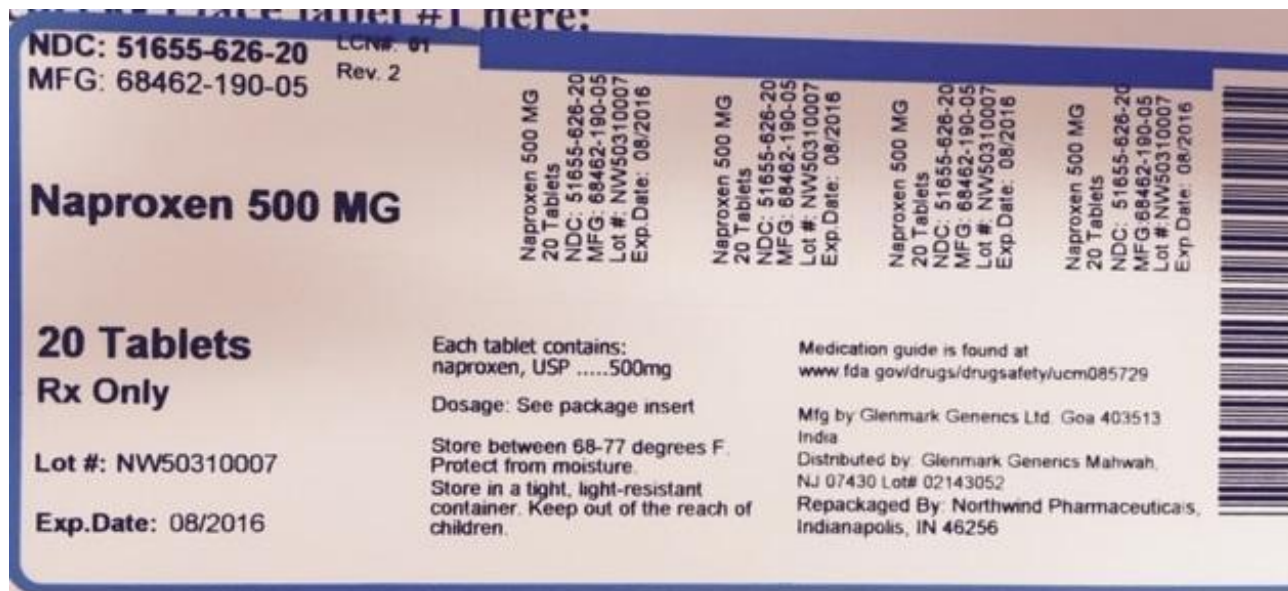
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Repackaged by: Northwind Pharmaceuticals, Indianapolis, IN 46256



NDC: 51655-626-25

MFG: 68462-0190-05

Naproxen tablets 500 MG

60 Tablets

Rx Only

Lot#:

Exp. Date:

Each tablet contains 500 mg naproxen USP

Dosage: See medication guide

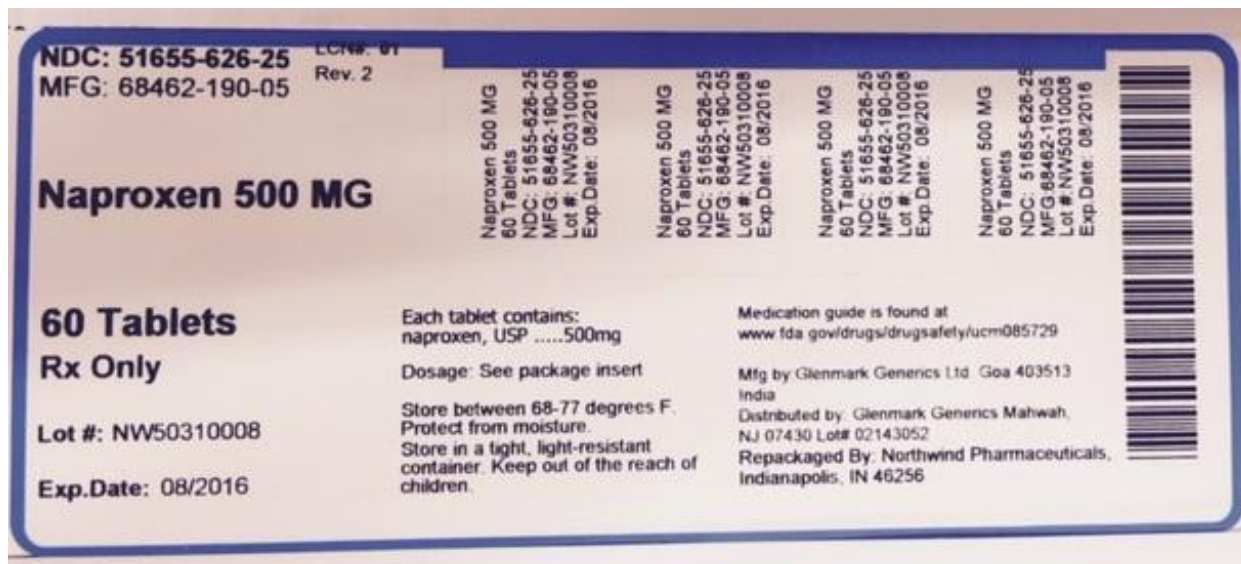
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Mfg By: Glenmark Generic, Ltd Goa 403513 India for Glenmark Generics Inc,

NJ, 07430 USA Lot#: Exp Date:

Repackaged by: Northwind Pharmaceuticals, Indianapolis, IN 46256



NDC: 51655-626-83

MFG: 68462-0190-05

Naproxen tablets 500 MG

180 Tablets

Rx Only

Lot#:

Exp. Date:

Each tablet contains 500 mg naproxen USP

Dosage: See medication guide

Store at 59-86 degrees F. Protect from light and moisture.

Store in a tight, light-resistant container (See USP) Keep out of the reach of children.

Mfg By: Glenmark Generic, Ltd Goa 403513 India for Glenmark Generics Inc,

NJ, 07430 USA Lot#: Exp Date:

Repackaged by: Northwind Pharmaceuticals, Indianapolis, IN 46256



## Patient Medication Guide

NAPROXEN- naproxen tablet

NAPROXEN SODIUM- naproxen sodium tablet

Glenmark Generics Inc., USA

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Medication Guide for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases:

with longer use of NSAID medicines in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a “coronary artery bypass graft (CABG).”

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:

can happen without warning symptoms may cause death

The chance of a person getting an ulcer or bleeding increases with:

taking medicines called “corticosteroids” and “anticoagulants” longer use smoking drinking alcohol older age having poor health

NSAID medicines should only be used:

exactly as prescribed at the lowest dose possible for your treatment for the shortest time needed

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:

different types of arthritis menstrual cramps and other types of short-term pain

Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?

Do not take an NSAID medicine:

if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine for pain right before or after heart bypass surgery

Tell your healthcare provider:

about all your medical conditions. about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. Keep a list of your medicines to show to your healthcare provider and pharmacist. if you are pregnant. NSAID medicines should not be used by pregnant women late in their pregnancy. if you are breastfeeding. Talk to your doctor.

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)? Serious side effects include: Other side effects include:

heart attack stomach pain

stroke constipation

high blood pressure diarrhea

heart failure from body swelling (fluid retention) gas

kidney problems including kidney failure  
heartburn  
bleeding and ulcers in the stomach and intestine  
nausea  
low red blood cells (anemia)  
vomiting  
life-threatening skin reactions  
dizziness  
life-threatening allergic reactions  
liver problems including liver failure  
asthma attacks in people who have asthma

Get emergency help right away if you have any of the following symptoms:

shortness of breath or trouble breathing  
slurred speech  
chest pains  
swelling of the face or throat  
weakness in one part or side of your body

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:

nausea  
there is blood in your bowel movement or it is black and sticky like tar  
more tired or weaker than usual  
itching your skin or eyes look yellow  
unusual weight gain  
stomach pain  
skin rash or blisters with fever  
flu-like symptoms  
swelling of the arms and legs, hands and feet  
vomit blood

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines. Some of these NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

NSAID medicines that need a prescription \* Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAID, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke.

Generic Name Tradename

Celecoxib Celebrex®

Diclofenac Cataflam®, Voltaren®, Arthrotec™ (combined with misoprostol)

Diflunisal Dolobid®

Etorolac Lodine®, Lodine® XL

Fenoprofen Nalfon®, Nalfon® 200

Flurbiprofen Ansaid®

Ibuprofen Motrin®, Tab-Profen®, VVicoprofen®\*\* (combined with hydrocodone),

Combunox™ (combined with oxycodone)

Indomethacin Indocin®, Indocin® SR, Indo-Lemmon™, Indomethagan™

Ketoprofen Oruvail®

Ketorolac Toradol®

Mefenamic Acid Ponstel®

Meloxicam Mobic®

Nabumetone Relafen®

Naproxen Naprosyn®, Anaprox®, Anaprox® DS, EC-Naproxyn®, Naprelan®, Naprapac®  
(copackaged with lansoprazole)

Oxaprozin Daypro®

Piroxicam Feldene®

Sulindac Clinoril®

Tolmetin Tolectin®, Tolectin DS®, Tolectin® 600

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:  
Glenmark Generics Ltd  
Colvale-Bardez, Goa 403 513  
India

Manufactured for:

Glenmark Generics Inc., USA  
Mahwah, NJ 07430

January 2009

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Glenmark Generics Inc., USA

## **DESCRIPTION**

Naproxen USP is a propionic acid derivative related to the arylacetic acid group of nonsteroidal anti-inflammatory drugs.

The chemical names for naproxen USP and naproxen sodium USP are (S)-6-methoxy- $\alpha$ -methyl-2-naphthaleneacetic acid and (S)-6-methoxy- $\alpha$ -methyl-2-naphthaleneacetic acid, sodium salt, respectively. Naproxen USP and naproxen sodium USP have the following structures, respectively:

Naproxen USP has a molecular weight of 230.26 and a molecular formula of C<sub>14</sub>H<sub>14</sub>O<sub>3</sub>. Naproxen sodium USP has a molecular weight of 252.23 and a molecular formula of C<sub>14</sub>H<sub>13</sub>NaO<sub>3</sub>.

Naproxen USP is an odorless, white to off-white crystalline substance. It is lipid-soluble, practically insoluble in water at low pH and freely soluble in water at high pH. The octanol/water partition coefficient of naproxen USP at pH 7.4 is 1.6 to 1.8. Naproxen sodium USP is a white to creamy white, crystalline solid, freely soluble in water at neutral pH.

Naproxen tablets USP are available as light orange colored tablets containing 250 mg of naproxen USP, light orange colored tablets containing 375 mg of naproxen USP and light orange colored tablets containing 500 mg of naproxen USP for oral administration. The inactive ingredients are microcrystalline cellulose, croscarmellose sodium, iron oxides, povidone and magnesium stearate.

Naproxen sodium tablets USP are available as blue tablets containing 275 mg of naproxen sodium USP and as blue tablets containing 550 mg of naproxen sodium USP for oral administration. The inactive ingredients are croscarmellose sodium, colloidal silicon dioxide, povidone, magnesium stearate, microcrystalline cellulose and talc. The coating suspension for the naproxen sodium 275 mg tablet may contain Opadry blue 03F50544. The coating suspension for the naproxen sodium 550 mg tablet may contain Opadry blue 03F50544.

## **CLINICAL PHARMACOLOGY**

### **Pharmacodynamics**

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The sodium salt of naproxen has been developed as a more rapidly absorbed formulation of naproxen for use as an analgesic. The mechanism of action of the naproxen anion, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

### **Pharmacokinetics**

Naproxen and naproxen sodium are rapidly and completely absorbed from the gastrointestinal tract with an in vivo bioavailability of 95%. The different dosage forms of naproxen are bioequivalent in terms of extent of absorption (AUC) and peak concentration (C<sub>max</sub>); however, the products do differ in their pattern of absorption. These differences between naproxen products are related to both the chemical

form of naproxen used and its formulation. Even with the observed differences in pattern of absorption, the elimination half-life of naproxen is unchanged across products ranging from 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days, and the degree of naproxen accumulation is consistent with this half-life. This suggests that the differences in pattern of release play only a negligible role in the attainment of steady-state plasma levels.

## Absorption

### Immediate Release

After administration of naproxen tablets, peak plasma levels are attained in 2 to 4 hours. After oral administration of naproxen sodium, peak plasma levels are attained in 1 to 2 hours. The difference in rates between the two products is due to the increased aqueous solubility of the sodium salt of naproxen used in naproxen sodium.

### Distribution

Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough C<sub>ss</sub> 36.5, 49.2 and 56.4 mg/L with 500, 1000 and 1500 mg daily doses of naproxen, respectively). The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma (see PRECAUTIONS, Nursing Mothers).

## Metabolism

Naproxen is extensively metabolized in the liver to 6-O-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes. Both naproxen and 6-O-desmethyl naproxen are further metabolized to their respective acylglucuronide conjugated metabolites.

## Excretion

The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (<1%), 6-O-desmethyl naproxen (<1%) or their conjugates (66% to 92%). The plasma half-life of the naproxen anion in humans ranges from 12 to 17 hours. The corresponding half-lives of both naproxen's metabolites and conjugates are shorter than 12 hours, and their rates of excretion have been found to coincide closely with the rate of naproxen disappearance from the plasma. Small amounts, 3% or less of the administered dose, are excreted in the feces. In patients with renal failure metabolites may accumulate (see WARNINGS: Renal Effects).

## Special Populations

### Pediatric Patients

In pediatric patients aged 5 to 16 years with arthritis, plasma naproxen levels following a 5 mg/kg single dose of naproxen suspension (see DOSAGE AND ADMINISTRATION) were found to be similar to those found in normal adults following a 500 mg dose. The terminal half-life appears to be similar in pediatric and adult patients. Pharmacokinetic studies of naproxen were not performed in pediatric patients younger than 5 years of age. Pharmacokinetic parameters appear to be similar following administration of naproxen suspension or tablets in pediatric patients.

### Geriatric Patients

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly, although the unbound fraction is <1% of the total naproxen concentration. Unbound trough naproxen concentrations in elderly subjects have been reported to range from 0.12% to 0.19% of total naproxen concentration, compared with 0.05% to 0.075% in younger subjects. The clinical significance of this finding is unclear, although it is possible that the increase in free naproxen concentration could be associated with an increase in the rate of adverse events per a given dosage in some elderly patients.

## Race

Pharmacokinetic differences due to race have not been studied.

## Hepatic Insufficiency

Naproxen pharmacokinetics has not been determined in subjects with hepatic insufficiency.

## Renal Insufficiency

Naproxen pharmacokinetics has not been determined in subjects with renal insufficiency. Given that naproxen, its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment. Naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine clearance <30 mL/min) (see WARNINGS: Renal Effects).

## **INDICATIONS & USAGE**

Carefully consider the potential benefits and risks of naproxen, naproxen sodium and other treatment options before deciding to use naproxen and naproxen sodium tablets. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see WARNINGS).

Naproxen as naproxen or naproxen sodium tablets are indicated:

- For the relief of the signs and symptoms of rheumatoid arthritis
- For the relief of the signs and symptoms of osteoarthritis
- For the relief of the signs and symptoms of ankylosing spondylitis
- For the relief of the signs and symptoms of juvenile arthritis

Naproxen as naproxen suspension is recommended for juvenile rheumatoid arthritis in order to obtain the maximum dosage flexibility based on the patient's weight.

Naproxen as naproxen and naproxen sodium tablets are also indicated:

- For relief of the signs and symptoms of tendonitis
- For relief of the signs and symptoms of bursitis
- For relief of the signs and symptoms of acute gout
- For the management of pain
- For the management of primary dysmenorrhea

## **CONTRAINDICATIONS**

Naproxen and naproxen sodium are contraindicated in patients with known hypersensitivity to naproxen and naproxen sodium.

Naproxen and naproxen sodium should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS: Anaphylactoid Reactions and PRECAUTIONS: Preexisting Asthma).

Naproxen and naproxen sodium are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

## **WARNINGS**

### **CARDIOVASCULAR EFFECTS**

Cardiovascular Thrombotic Events



Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see CONTRAINDICATIONS).

### Hypertension

NSAIDs, including naproxen and naproxen sodium, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including naproxen and naproxen sodium, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

### Congestive Heart Failure and Edema

Fluid retention, edema, and peripheral edema have been observed in some patients taking NSAIDs. Naproxen and naproxen sodium should be used with caution in patients with fluid retention, hypertension, or heart failure. Since each naproxen sodium tablet contains 25 mg or 50 mg of sodium (about 1 mEq per each 250 mg of naproxen), this could be considered in patients whose overall intake of sodium must be severely restricted.

### Gastrointestinal Effects

#### Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including naproxen and naproxen sodium, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal.

These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only 1 in 5 patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general

health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population. To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of an NSAID or aspirin potentiated the risk of bleeding (see PRECAUTIONS - Drug Interactions). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated.

NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated.

### Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, hypovolemia, heart failure, liver dysfunction, salt depletion, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state (see WARNINGS: Advanced Renal Disease ).

### Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of naproxen or naproxen sodium in patients with advanced renal disease. Therefore, treatment with naproxen and naproxen sodium is not recommended in these patients with advanced renal disease. If naproxen or naproxen sodium therapy must be initiated, close monitoring of the patient's renal function is advisable.

### Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to naproxen or naproxen sodium. Naproxen and naproxen sodium should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS: Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

### Skin Reactions

NSAIDs, including naproxen and naproxen sodium, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

### Pregnancy

In late pregnancy, as with other NSAIDs, naproxen and naproxen sodium should be avoided because it

may cause premature closure of the ductus arteriosus.

## **PRECAUTIONS**

### **General**

Naproxen-containing products such as naproxen, naproxen sodium tablets and other naproxen products should not be used concomitantly since they all circulate in the plasma as the naproxen anion.

Naproxen and naproxen sodium cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids and the patient should be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

Patients with initial hemoglobin values of 10 g or less who are to receive long-term therapy should have hemoglobin values determined periodically.

The pharmacological activity of naproxen and naproxen sodium in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Because of adverse eye findings in animal studies with drugs of this class, it is recommended that ophthalmic studies be carried out if any change or disturbance in vision occurs.

### **Hepatic Effects**

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including naproxen and naproxen sodium. Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. These laboratory abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with naproxen or naproxen sodium.

If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (eg, eosinophilia, rash, etc.), naproxen or naproxen sodium should be discontinued.

Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose.

### **Hematological Effects**

Anemia is sometimes seen in patients receiving NSAIDs, including naproxen and naproxen sodium. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including naproxen and naproxen sodium, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving either naproxen or naproxen sodium who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should

be carefully monitored.

### Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, naproxen and naproxen sodium should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

### Information for Patients

Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

Naproxen and naproxen sodium, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS: Cardiovascular Effects).

Naproxen and naproxen sodium, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see WARNINGS: Gastrointestinal Effects: Risk of Ulceration, Bleeding, and Perforation)

Naproxen and naproxen sodium, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (eg nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should be informed of the signs of an anaphylactoid reaction (eg, difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see WARNINGS).

In late pregnancy, as with other NSAIDs, naproxen and naproxen sodium should be avoided because it may cause premature closure of the ductus arteriosus.

Caution should be exercised by patients whose activities require alertness if they experience drowsiness, dizziness, vertigo or depression during therapy with naproxen.

### Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (eg, eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, naproxen and naproxen sodium should be discontinued.

## Drug Interactions

### ACE-inhibitors

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

### Antacids and Sucralfate

Concomitant administration of some antacids (magnesium oxide or aluminum hydroxide) and sucralfate can delay the absorption of naproxen.

### Aspirin

When naproxen as naproxen or naproxen sodium tablet is administered with aspirin, its protein binding is reduced, although the clearance of free naproxen or naproxen sodium is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of naproxen and naproxen sodium and aspirin is not generally recommended because of the potential of increased adverse effects.

### Cholestyramine

As with other NSAIDs, concomitant administration of cholestyramine can delay the absorption of naproxen.

### Diuretics

Clinical studies, as well as postmarketing observations, have shown that naproxen and naproxen sodium can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see WARNINGS: Renal Effects ), as well as to assure diuretic efficacy.

### Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

### Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. Naproxen, naproxen sodium and other nonsteroidal anti-inflammatory drugs have been reported to reduce the tubular secretion of methotrexate in an animal model. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

### Warfarin

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone. No significant interactions have been observed in clinical studies with naproxen and coumarin-type anticoagulants. However, caution is advised since interactions have been seen with other nonsteroidal agents of this class. The free fraction of warfarin may increase substantially in some subjects and naproxen interferes with platelet function.

### Selective Serotonin Reuptake Inhibitors (SSRIs)

There is an increased risk of gastrointestinal bleeding when selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs. Caution should be used when NSAIDs are administered concomitantly with SSRIs.

## Other Information Concerning Drug Interactions

Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as coumarin-type anticoagulants, sulphonylureas, hydantoins, other NSAIDs, and aspirin. Patients simultaneously receiving naproxen and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

Naproxen and other nonsteroidal anti-inflammatory drugs can reduce the antihypertensive effect of propranolol and other beta-blockers.

Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

## Drug/Laboratory Test Interactions

Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-di-nitrobenzene used in this assay. Although 17-hydroxycorticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.

Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

## Carcinogenesis

A 2-year study was performed in rats to evaluate the carcinogenic potential of naproxen at rat doses of 8, 16, and 24 mg/kg/day (50, 100, and 150 mg/m<sup>2</sup>). The maximum dose used was 0.28 times the systemic exposure to humans at the recommended dose. No evidence of tumorigenicity was found.

## Pregnancy

### Teratogenic Effects

Pregnancy Category C: Reproduction studies have been performed in rats at 20 mg/kg/day (125 mg/m<sup>2</sup>/day, 0.23 times the human systemic exposure), rabbits at 20 mg/kg/day (220 mg/m<sup>2</sup>/day, 0.27 times the human systemic exposure), and mice at 170 mg/kg/day (510 mg/m<sup>2</sup>/day, 0.28 times the human systemic exposure) with no evidence of impaired fertility or harm to the fetus due to the drug. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women. Naproxen and naproxen sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Nonteratogenic Effects

There is some evidence to suggest that when inhibitors of prostaglandin synthesis are used to delay preterm labor there is an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus and intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction and abnormal prostaglandin E levels in preterm infants. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

### Labor and Delivery

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. Naproxen-containing products are not recommended in labor and delivery because, through its prostaglandin synthesis inhibitory effect, naproxen may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage. The effects of naproxen and naproxen sodium on labor and

delivery in pregnant women are unknown.

#### Nursing Mothers

The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.

#### Pediatric Use

Safety and effectiveness in pediatric patients below the age of 2 years have not been established. Pediatric dosing recommendations for juvenile arthritis are based on well-controlled studies (see DOSAGE AND ADMINISTRATION). There are no adequate effectiveness or dose-response data for other pediatric conditions, but the experience in juvenile arthritis and other use experience have established that single doses of 2.5 to 5 mg/kg (as naproxen suspension, see DOSAGE AND ADMINISTRATION), with total daily dose not exceeding 15 mg/kg/day, are well tolerated in pediatric patients over 2 years of age.

#### Geriatric Use

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose.

Experience indicates that geriatric patients may be particularly sensitive to certain adverse effects of nonsteroidal anti-inflammatory drugs. Elderly or debilitated patients seem to tolerate peptic ulceration or bleeding less well when these events do occur. Most spontaneous reports of fatal GI events are in the geriatric population (see WARNINGS).

Naproxen is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Geriatric patients may be at a greater risk for the development of a form of renal toxicity precipitated by reduced prostaglandin formation during administration of nonsteroidal anti-inflammatory drugs (see WARNINGS: Renal Effects).

### **ADVERSE REACTIONS**

Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are listed below. In general, reactions in patients treated chronically were reported 2 to 10 times more frequently than they were in short-term studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea. The most frequent complaints reported related to the gastrointestinal tract.

A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking daily doses of 1500 mg naproxen compared to those taking 750 mg naproxen (see CLINICAL PHARMACOLOGY).

In controlled clinical trials with about 80 pediatric patients and in well-monitored, open-label studies with about 400 pediatric patients with juvenile arthritis treated with naproxen, the incidence of rash and prolonged bleeding times were increased, the incidence of gastrointestinal and central nervous system reactions were about the same, and the incidence of other reactions were lower in pediatric patients than in adults.

In patients taking naproxen in clinical trials, the most frequently reported adverse experiences in approximately 1% to 10% of patients are:

Gastrointestinal (GI) Experiences, including: heartburn\*, abdominal pain\*, nausea\*, constipation\*,

diarrhea, dyspepsia, stomatitis

Central Nervous System: headache\*, dizziness\*, drowsiness\*, lightheadedness, vertigo

Dermatologic: pruritus (itching)\*, skin eruptions\*, ecchymoses\*, sweating, purpura

Special Senses: tinnitus\*, visual disturbances, hearing disturbances

Cardiovascular: edema\*, palpitations

General: dyspnea\*, thirst

\*Incidence of reported reaction between 3% and 9%. Those reactions occurring in less than 3% of the patients are unmarked.

In patients taking NSAIDs, the following adverse experiences have also been reported in approximately 1% to 10% of patients.

Gastrointestinal (GI) Experiences, including: flatulence, gross bleeding/perforation, GI ulcers (gastric/duodenal), vomiting

General: abnormal renal function, anemia, elevated liver enzymes, increased bleeding time, rashes

The following are additional adverse experiences reported in <1% of patients taking naproxen during clinical trials and through postmarketing reports. Those adverse reactions observed through postmarketing reports are italicized.

Body as a Whole: anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills and fever)

Cardiovascular: congestive heart failure, vasculitis, hypertension, pulmonary edema

Gastrointestinal: gastrointestinal bleeding and/or perforation, hematemesis, pancreatitis, vomiting, colitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn's disease), nonpeptic gastrointestinal ulceration, ulcerative stomatitis, esophagitis, peptic ulceration

Hepatobiliary: jaundice, abnormal liver function tests, hepatitis (some cases have been fatal)

Hemic and Lymphatic: eosinophilia, leucopenia, melena, thrombocytopenia, agranulocytosis, granulocytopenia, hemolytic anemia, aplastic anemia

Metabolic and Nutritional: hyperglycemia, hypoglycemia

Nervous System: inability to concentrate, depression, dream abnormalities, insomnia, malaise, myalgia, muscle weakness, aseptic meningitis, cognitive dysfunction, convulsions

Respiratory: eosinophilic pneumonitis, asthma

Dermatologic: alopecia, urticaria, skin rashes, toxic epidermal necrolysis, erythema multiforme, erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, systemic lupus erythematoses, bullous reactions, including Stevens-Johnson syndrome, photosensitive dermatitis, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa. If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.

Special Senses: hearing impairment, corneal opacity, papillitis, retrobulbar optic neuritis, papilledema

Urogenital: glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis, raised serum creatinine

Reproduction (female): infertility

In patients taking NSAIDs, the following adverse experiences have also been reported in <1% of patients.

Body as a Whole: fever, infection, sepsis, anaphylactic reactions, appetite changes, death



Cardiovascular: hypertension, tachycardia, syncope, arrhythmia, hypotension, myocardial infarction

Gastrointestinal: dry mouth, esophagitis, gastric/peptic ulcers, gastritis, glossitis, eructation

Hepatobiliary: hepatitis, liver failure

Hemic and Lymphatic: rectal bleeding, lymphadenopathy, pancytopenia

Metabolic and Nutritional: weight changes

Nervous System: anxiety, asthenia, confusion, nervousness, paresthesia, somnolence, tremors, convulsions, coma, hallucinations

Respiratory: asthma, respiratory depression, pneumonia

Dermatologic: exfoliative dermatitis

Special Senses: blurred vision, conjunctivitis

Urogenital: cystitis, dysuria, oliguria/polyuria, proteinuria

## NAPROXEN

naproxen tablet

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:51655-626(NDC:68462-190)
<b>Route of Administration</b>	ORAL		

### Active Ingredient/Active Moiety

<b>Ingredient Name</b>	<b>Basis of Strength</b>	<b>Strength</b>
NAPROXEN (UNII: 57Y76R9ATQ) (NAPROXEN - UNII:57Y76R9ATQ)	NAPROXEN	500 mg

### Product Characteristics

<b>Color</b>	orange	<b>Score</b>	2 pieces
<b>Shape</b>	OVAL	<b>Size</b>	16mm
<b>Flavor</b>		<b>Imprint Code</b>	G;32;500
<b>Contains</b>			

### Packaging

#	<b>Item Code</b>	<b>Package Description</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
1	NDC:51655-626-52	30 in 1 BOTTLE, DISPENSING		
2	NDC:51655-626-20	20 in 1 BOTTLE, DISPENSING		
3	NDC:51655-626-25	60 in 1 BOTTLE, DISPENSING		
4	NDC:51655-626-83	180 in 1 BOTTLE, DISPENSING		

### Marketing Information

<b>Marketing Category</b>	<b>Application Number or Monograph Citation</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
ANDA	ANDA078250	05/28/2014	

**Labeler** - Northwind Pharmaceuticals (036986393)

**Registrant** - Northwind Pharmaceuticals (036986393)

**Establishment**

Name	Address	ID/FEI	Business Operations
Northwind Pharmaceuticals		036986393	repack(51655-626)

Revised: 1/2015

Northwind Pharmaceuticals