

## **PRODUCT INFORMATION**

**<sup>N</sup>FIORINAL<sup>®</sup>-C 1/4, 1/2**  
(acetylsalicylic acid-caffeine-codeine-butalbital)

Capsules

Combination Analgesic

Novartis Pharmaceuticals Canada Inc.  
385, boul. Bouchard  
Dorval, Quebec  
H9S 1A9

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## **PRODUCT INFORMATION**

### **NAME OF DRUG**

<sup>N</sup>FIORINAL<sup>®</sup>-C 1/4, 1/2  
(acetylsalicylic acid-caffeine-codeine-butalbital)

### **THERAPEUTIC CLASSIFICATION**

Combination Analgesic

### **ACTION AND CLINICAL PHARMACOLOGY**

#### **Pharmacokinetics:**

The behaviour of the individual components is described below.

#### ***Acetylsalicylic acid (ASA)***

ASA is a salicylate that binds to the cyclooxygenase enzyme leading to a reduction in prostaglandin activity. The systemic availability of ASA after an oral dose is highly dependent on the dosage form, the presence of food, the gastric emptying time, gastric pH, antacids, buffering agents, and particle size. These factors affect not necessarily the extent of absorption of total salicylates but more the stability of ASA prior to absorption.

During the absorption process and after absorption, ASA is mainly hydrolyzed to salicylic acid and distributed to all body tissues and fluids, including fetal tissues, breast milk, and the central nervous system (CNS). Highest concentrations are found in plasma, liver, renal cortex, heart, and lung. In plasma, about 50% - 80% of the salicylic acid and its metabolites are loosely bound to plasma proteins.

The clearance of total salicylates is subject to saturable kinetics; however, first-order elimination kinetics are still a good approximation for doses up to 650 mg. The plasma half-life for ASA is

about 12 minutes and for salicylic acid and/or total salicylates is about 3 hours.

The elimination of therapeutic doses is through the kidneys either as salicylic acid or other biotransformation products. The renal clearance is greatly augmented by an alkaline urine as is produced by concurrent administration of sodium bicarbonate or potassium citrate.

The biotransformation of ASA occurs primarily in the hepatocytes. The major metabolites are salicyluric acid (75%), the phenolic and acyl glucuronides of salicylate (15%), and gentisic and gentisuric acid (1%).

See **SYMPTOMS AND TREATMENT OF OVERDOSAGE** for toxicity information.

### *Caffeine*

Caffeine is a CNS stimulant with primary effects on adenosine receptors. Like most xanthines, caffeine is rapidly absorbed and distributed in all body tissues and fluids, including the CNS, fetal tissues, and breast milk.

Caffeine is cleared rapidly through metabolism and excretion in the urine. The plasma half-life is about 3 hours. Hepatic biotransformation prior to excretion results in about equal amounts of 1-methylxanthine and 1-methyluric acid. Of the 70% of the dose that has been recovered in the urine, only 3% was unchanged drug.

See **SYMPTOMS AND TREATMENT OF OVERDOSAGE** for toxicity information.

### *Codeine*

Codeine is an opiate which acts on the CNS through agonistic action on opiate receptors. Codeine is readily absorbed from the gastrointestinal tract. It is rapidly distributed from the intravascular spaces to the various body tissues, with preferential uptake by parenchymatous organs such as the liver, spleen, and kidney. Codeine and its active metabolite morphine cross the blood-brain barrier, and is found in fetal tissue and breast milk. The plasma concentration does not correlate

with brain concentration or relief of pain; however, codeine is not bound to plasma proteins and does not accumulate in body tissues.

The plasma half-life is about 2.9 hours. The elimination of codeine is primarily via the kidneys, and about 90% of an oral dose is excreted by the kidneys within 24 hours of dosing. The urinary secretion products consist of free and glucuronide-conjugated codeine (about 70%), free and conjugated norcodeine (about 10%), free and conjugated morphine (about 10%), normorphine (4%), and hydrocodone (1%). The remainder of the dose is excreted in the feces.

At therapeutic doses, the analgesic effect reaches a peak within 2 hours and persists between 4 and 6 hours. Patients who lack functional CYP2D6 genes do not metabolize codeine to morphine and may experience less analgesic effect.

See **SYMPTOMS AND TREATMENT OF OVERDOSAGE** for toxicity information.

### ***Butalbital***

Butalbital is a short to intermediate-acting barbiturate which is thought to act on the CNS through enhanced gamma-aminobutyric acid (GABA) binding to GABA A receptors. Butalbital is well absorbed from the gastrointestinal tract and is expected to distribute to most of the tissues in the body. Barbiturates, in general, may appear in breast milk and readily cross the placental barrier. They are bound to plasma and tissue proteins to a varying degree and binding increases directly as a function of lipid solubility.

Elimination of butalbital is primarily via the kidney (59% - 88% of the dose) as unchanged drug or metabolites. The plasma half-life is about 35 hours. The elimination half-life of butalbital is about 61 hours (range: 35 to 88 hours). Urinary excretion products included parent drug (about 3.6% of the dose), 5-isobutyl-5-(2,3 dihydroxypropyl) barbituric acid (about 24% of the dose), 5-allyl-5(3-hydroxy-2-methyl-1-propyl) barbituric acid (about 4.8% of the dose), products with the barbituric acid ring hydrolyzed with excretion of urea (about 14% of the dose), as well as unidentified materials. Of the material excreted in the urine, 32% was conjugated.

The *in vitro* plasma protein binding of butalbital is 45% over the concentration range of 0.5 - 20 mcg/mL. This falls within the range of plasma protein binding (20% - 45%) reported with other barbiturates such as phenobarbital, pentobarbital, and secobarbital sodium. The plasma-to-blood concentration ratio was almost unity indicating that there is no preferential distribution of butalbital into either plasma or blood cells.

See **SYMPTOMS AND TREATMENT OF OVERDOSAGE** for toxicity information.

### **INDICATIONS AND CLINICAL USE**

FIORINAL<sup>®</sup>-C (ASA-caffeine-codeine-butalbital) is indicated for the relief of tension-type headache.

Evidence supporting the efficacy of FIORINAL<sup>®</sup>-C is derived from 2 multi-clinic trials that compared patients with tension-type headache randomly assigned to 4 parallel treatments: FIORINAL<sup>®</sup>-C, codeine, FIORINAL<sup>®</sup> (ASA-caffeine-butalbital), and placebo. Response was assessed over the course of the first 4 hours of each of 2 distinct headaches, separated by at least 24 hours. FIORINAL<sup>®</sup>-C proved statistically significantly superior to each of its components (FIORINAL<sup>®</sup>, codeine) and to placebo on measures of pain relief.

Evidence supporting the efficacy and safety of FIORINAL<sup>®</sup>-C in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because repeated use of FIORINAL<sup>®</sup>-C may cause medication overuse headaches and codeine and butalbital are habit-forming and potentially abusable (see **WARNINGS and PRECAUTIONS, Abuse and Dependence**).

#### **Pediatrics:**

FIORINAL<sup>®</sup>-C has not been studied in pediatrics and should not be administered to children < 18 years of age.

Regardless of clinical setting, the use of codeine, including FIORINAL<sup>®</sup>-C, is not recommended in patients below the age of 18 years due to increased safety concerns (see **PRECAUTIONS/Pediatric Use**).

### **CONTRAINDICATIONS**

FIORINAL<sup>®</sup>-C (ASA-caffeine-codeine-bitalbital) is contraindicated under the following conditions:

1. Hypersensitivity or intolerance to ASA, caffeine, codeine or butalbital or to any of the components.
2. Patients with a hemorrhagic diathesis (e.g., hemophilia, hypoprothrombinemia, von Willebrand's disease, thrombocytopenia, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage).
3. Patients with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to ASA or other nonsteroidal anti-inflammatory drugs. Anaphylactoid reactions have occurred in such patients.
4. Peptic ulcer or other serious gastrointestinal lesions.
5. Patients with porphyria.
6. In patients with a history of abuse or overdose due to alcohol, hypnotics, analgesics and psychotropic drugs.
7. Respiratory insufficiency.
8. Pneumonia.
9. Acute asthma attack.
10. Coma.
11. Pregnancy and breast-feeding.
12. Labour and delivery
13. Patients known to be CYP2D6 ultra-rapid metabolizers for whom there is an increased risk of developing symptoms of opioid toxicity, even at commonly prescribed doses (see **WARNINGS**).

## **WARNINGS**

Therapeutic doses of ASA can cause anaphylactic shock and other severe allergic reactions. It should be ascertained if the patient is allergic to ASA, although a specific history of allergy may be lacking.

Significant bleeding can result from ASA therapy in patients with peptic ulcer or other gastrointestinal lesions, and in patients with bleeding disorders.

Thrombocytopenia has been reported in association with the use of ASA, and may be the underlying cause of the increased risk of bleeding, intracerebral hemorrhage and hemorrhagic stroke observed in patients treated with ASA as an antiplatelet therapy.

ASA administered pre-operatively may prolong the bleeding time.

A possible association between Reye's syndrome and the use of salicylates has been suggested but not established. Reye's syndrome has also occurred in many patients not exposed to salicylates. However, caution is advised when prescribing salicylate-containing medications for young adults with influenza or chickenpox.

### **Ultra-Rapid Metabolizers of Codeine:**

Codeine is metabolized by the liver enzyme CYP2D6 into morphine, its active metabolite. Some individuals may be extensive or ultra-rapid metabolizers due to a specific CYP2D6\*2x2 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labelled dosage regimens, individuals who are extensive or ultra-rapid metabolizers may experience overdose symptoms such as extreme sleepiness, confusion, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal. If the patient is a CYP2D6 ultra-rapid metabolizer and a nursing mother,

higher levels of morphine may be present in breast milk and may result in symptoms of opioid toxicity in the infant, which may be fatal. Therefore, the use of FIORINAL<sup>®</sup>-C (ASA-caffeine-codeine-butalbital) is contraindicated in patients known to be ultra-rapid metabolizers, as well as in nursing mothers (see **CONTRAINDICATIONS**).

The prevalence of this CYP2D6 phenotype varies widely by ethnic group and has been estimated at 0.5 to 1% in Chinese, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of patients with head injuries.

Cases of acute pancreatitis have been reported with the use of codeine and should therefore be considered as a possible side effect of this compound.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Butalbital and codeine are both habit-forming and potentially abusable. Consequently, the extended use of FIORINAL<sup>®</sup>-C is not recommended (see **PRECAUTIONS, Abuse and Dependence**).

FIORINAL<sup>®</sup>-C is associated with exacerbation of headache (medication overuse headaches) in susceptible patients. Repeated use of FIORINAL<sup>®</sup>-C can lead to “rebound” headaches as each dose wears off. With repeated doses physical and psychological dependence can develop. In addition to dependence, butalbital-containing products can lead to tolerance, and at higher doses



can produce withdrawal symptoms after discontinuation (see **PRECAUTIONS, Abuse and Dependence**).

## **PRECAUTIONS**

### **General:**

Because of its ASA content, FIORINAL<sup>®</sup>-C (ASA-caffeine-codeine-butalbital) should be used with caution in patients with a history of bleeding tendencies, in patients on anticoagulant therapy and in patients with underlying hemostatic defects and with extreme caution in patients with peptic ulceration.

Precautions should be taken when administering salicylates to persons with known allergies. Hypersensitivity to ASA is particularly likely in patients with nasal polyps and relatively common in those with asthma.

Long-term use of preparations containing barbiturates and/or codeine may lead to habituation and physical dependence. FIORINAL<sup>®</sup>-C, because of its codeine and butalbital content, should be avoided in patients with head injury, in whom a depressed CNS is suspected. Similarly, it should not be used in patients with actual or a predisposition towards respiratory depression.

### **Respiratory:**

Codeine, including FIORINAL<sup>®</sup>-C, is not recommended for use in any patient in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, lung infections, multiple trauma or extensive surgical procedures.

FIORINAL<sup>®</sup>-C should be prescribed with caution for certain special-risk patients, such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, coagulation disorders, head injuries, elevated intracranial pressure, acute abdominal conditions, hypothyroidism, urethral stricture, Addison's disease, prostatic hypertrophy, peptic ulcer, or in osteomalacia and osteoporosis.

**Occupational Hazards:**

Barbiturate-containing preparations may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a vehicle or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of FIORINAL<sup>®</sup>-C with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:**

Long-term studies have been conducted in mice and rats with ASA, alone or in combination with other drugs, in which no evidence of carcinogenesis was seen. No adequate studies have been conducted in animals to determine whether butalbital has a potential for carcinogenesis, mutagenesis or impairment of fertility. Codeine is not mutagenic *in vitro* or *in vivo* and no carcinogenic potential was seen in 2- year rat and mouse studies. A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the rat, doses at the 120 mg/kg level, in the toxic range for the adult animal, were associated with an increase in embryo resorption at the time of implantation. In another study a single 100 mg/kg dose of codeine administered to pregnant mice reportedly resulted in delayed ossification in the offspring.

**Use in Pregnancy:**

FIORINAL<sup>®</sup>-C is contraindicated during pregnancy (see **CONTRAINDICATIONS**) because the codeine component of FIORINAL<sup>®</sup>-C significantly increases the rate of malformations if used in the first trimester of pregnancy (deformities of the respiratory tract, slight increase in cleft lip and palate). In the last trimester of pregnancy, codeine may cause withdrawal symptoms in the neonate (also in the foetus if therapy is discontinued before birth).

***Teratogenicity***

Animal reproduction studies have not been conducted with FIORINAL<sup>®</sup>-C.

Although FIORINAL<sup>®</sup>-C was not implicated in the birth defect, a female infant was born with lissencephaly, pachygyria and heterotopic gray matter. The infant was born 8 weeks prematurely to a woman who had taken an average of 90 FIORINAL<sup>®</sup>-C each month from the first few days of pregnancy. The child's development was mildly delayed and from one year of age she had partial simple motor seizures.

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital containing drug during the last 2 months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5 mg/kg, which was tapered without further seizure or other withdrawal symptoms.

In controlled studies involving 41,337 pregnant women and their offspring, there was no evidence that ASA taken during pregnancy caused stillbirth, neonatal death or reduced birth weight. In controlled studies of 50,282 pregnant women and their offspring, ASA administration in moderate and heavy doses during the first four lunar months of pregnancy showed no teratogenic effect.

Therapeutic doses of ASA in pregnant women close to term may cause bleeding in mother, fetus, or neonate. During the last 6 months of pregnancy, regular use of ASA in high doses may prolong pregnancy and delivery.

Dependence and withdrawal signs have been reported in newborns whose mothers took opiates regularly during pregnancy. These signs include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. Signs usually appear during the first few days of life.

Reproduction studies have been performed in rabbits and rats at doses up to 150 times the human dose and have revealed no evidence of impaired fertility due to codeine.

### ***Labour and Delivery***

Ingestion of ASA prior to delivery may prolong delivery or lead to bleeding in the mother or neonate. FIORINAL<sup>®</sup>-C is contraindicated before delivery and during labour or in case of risk of premature labour since codeine crosses the placental barrier and can lead to respiratory depression in the neonate (newborns are particularly sensitive to opioids). Administration of opioids during labour may produce gastric stasis and increase the risk of vomiting and aspiration pneumonia in the mother. If the mother has received FIORINAL<sup>®</sup>-C during labour, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see **SYMPTOMS AND TREATMENT OF OVERDOSAGE**).

### **Nursing Women:**

ASA, caffeine and barbiturates are excreted into human breast milk, but the significance of their effects on nursing infants is not known. FIORINAL<sup>®</sup>-C is contraindicated in women who are breast-feeding (see **CONTRAINDICATIONS**). Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. **However, some women are ultra-rapid metabolisers of codeine** (see **CONTRAINDICATIONS, Ultra-Rapid Metabolisers of Codeine**). **These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breast-fed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death in nursing infants.**

Since there is a risk of infant exposure to codeine and morphine through breast milk, FIORINAL<sup>®</sup>-C is contraindicated in breast-feeding. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about any use of codeine during breast-feeding.

### **Pediatric Use:**

Safety and efficacy in patients younger than 18 years of age have not been studied.

### **Geriatric Use:**

Clinical studies of FIORINAL<sup>®</sup>-C did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Butalbital 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.

**Laboratory Tests:**

In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

**Drug Interactions:**

The concomitant use of alcohol or other CNS depressants may have an additive effect, and patients should be warned accordingly.

The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

In patients receiving concomitant corticosteroids and chronic use of ASA, withdrawal of corticosteroids may result in salicylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.

The prolonged ingestion of barbiturates gives rise to enzyme induction. This increases the rate of metabolism of certain drugs, including oral anticoagulants and oral contraceptives, thus reducing their effectiveness.

FIORINAL<sup>®</sup>-C may enhance the effects of:

1. Oral antidiabetic agents and insulin, causing hypoglycemia by contributing an additive effect if dosage of FIORINAL<sup>®</sup>-C exceeds maximum recommended daily dosage.
2. Oral anticoagulants, causing bleeding by inhibiting prothrombin formation in the liver and displacing anticoagulants from plasma protein binding sites.
3. 6-mercaptopurine and methotrexate, causing bone marrow toxicity and blood dyscrasias by displacing these drugs from secondary binding sites, and, in the case of methotrexate, also reducing its excretion.
4. Non-steroidal anti-inflammatory agents, increasing the risk of peptic ulceration and bleeding by contributing additive effects.
5. Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlorthalidopoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

FIORINAL<sup>®</sup>-C may diminish the effects of:

Uricosuric agents such as probenecid and sulfinpyrazone, reducing their effectiveness in the treatment of gout. ASA competes with these agents for protein binding sites.

**Drug/Laboratory Test Interactions:**

ASA may interfere with the following laboratory determinations in blood: serum amylase, fasting blood glucose, cholesterol, protein, aspartate aminotransferase (AST), uric acid, prothrombin time and bleeding time. ASA may interfere with the following laboratory determinations in urine: glucose, 5-hydroxyindoleacetic acid, Gerhardt ketone, vanillylmandelic acid (VMA), uric acid, diacetic acid, and spectrophotometric detection of barbiturates.

Codeine may increase serum amylase levels.

### **Abuse and Dependence:**

FIORINAL<sup>®</sup>-C products have the potential for being abused and thus, continuous daily use should be avoided.

### ***Codeine***

Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic medications.

### ***Butalbital***

**Barbiturates may be habit-forming:** Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1,500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than twofold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decreasing the daily dosage as tolerated by the patient.

### **Information for Patients:**

1. Patients should be informed that FIORINAL<sup>®</sup>-C contains ASA and should not be taken by patients with an ASA allergy.
2. FIORINAL<sup>®</sup>-C may impair the mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking FIORINAL<sup>®</sup>-C.
3. Alcohol and other CNS depressants may produce an additive CNS depression when taken with FIORINAL<sup>®</sup>-C and should be avoided.
4. Codeine and butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.
5. For information on use in geriatric patients, see **PRECAUTIONS, Geriatric Use**.
6. Nursing mothers taking codeine can also have higher morphine levels in their breast milk if they are ultra-rapid metabolizers. These higher levels of morphine in breast milk may lead to life-threatening or fatal side effects in nursing babies. Since there is a risk of infant exposure to codeine and morphine through breast milk, FIORINAL<sup>®</sup>-C is contraindicated in breast-feeding. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about any use of codeine during breast-feeding.

### **ADVERSE REACTIONS**

#### **Commonly Observed:**

The most commonly reported adverse events associated with the use of FIORINAL<sup>®</sup>-C (ASA-caffeine-codeine-butalbital) and not reported at an equivalent incidence by placebo-treated patients were nausea and/or abdominal pain, drowsiness and dizziness. Less frequent adverse reactions are constipation, rash, miosis, lightheadedness and gastrointestinal disturbances including nausea, vomiting and flatulence. Several cases of dermatological reactions including



toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported.

**Associated with Treatment Discontinuation:**

Of the 382 patients treated with FIORINAL<sup>®</sup>-C in controlled clinical trials, three (0.8%) discontinued treatment with FIORINAL<sup>®</sup>-C because of adverse events. One patient each discontinued treatment for the following reasons: gastrointestinal upset; lightheadedness and heavy eyelids; and drowsiness and generalized tingling.

**Incidence in Controlled Clinical Trials:**

The following table summarizes the incidence rates of the treatment emergent adverse events reported by at least 1% (rated as frequent) of the FIORINAL<sup>®</sup>-C treated patients in controlled clinical trials comparing FIORINAL<sup>®</sup>-C to placebo, and provides a comparison to the incidence rates reported by the placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

**Adverse Events Reported by at Least 1% of FIORINAL<sup>®</sup>-C Treated Patients During Placebo Controlled Clinical Trials**

Incidence Rate of Adverse Events		
Body System/Adverse Event	FIORINAL <sup>®</sup> -C (N = 382)	Placebo (N = 377)
<b>Central Nervous</b>		
Drowsiness	2.4%	0.5%
Dizziness/Lightheadedness	2.6%	0.5%
Intoxicated Feeling	1.0%	0.0%
<b>Gastrointestinal</b>		
Nausea/Abdominal Pain	3.7%	0.8%

**Other Treatment Emergent Adverse Events Reported During Controlled Clinical Trials:**

The listing that follows represents the proportion of the 382 patients exposed to FIORINAL<sup>®</sup>-C while participating in the controlled clinical trials who reported, on at least one occasion, an adverse event of the type cited. All reported adverse events, except those already presented in the previous table, are included and are rated as infrequent (i.e. less than 1% but occurring in at least 1/1000 patients). It is important to emphasize that, although the adverse events reported did occur while the patient was receiving FIORINAL<sup>®</sup>-C, the adverse events were not necessarily caused by FIORINAL<sup>®</sup>-C. Adverse events are classified by body system and frequency.

**Central nervous:** headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, and sluggishness.

**Autonomic nervous:** dry mouth and hyperhidrosis.

**Gastrointestinal:** vomiting, difficulty swallowing, and heartburn.

**Cardiovascular:** tachycardia.

**Musculoskeletal:** leg pain and muscle fatigue.

**Genitourinary:** diuresis.

**Miscellaneous:** pruritus, fever, earache, nasal congestion, and tinnitus.

**Post-Marketing Reported Adverse Events:**

Voluntary reports of adverse drug events, temporally associated with FIORINAL<sup>®</sup>-C, that have been received since market introduction and that were not reported in clinical trials by the patients treated with FIORINAL<sup>®</sup>-C, are listed below. Many or most of these events may have no causal relationship with the drug and are listed according to body system.

**Central nervous:** Abuse, addiction, anxiety, depression, disorientation, hallucination, hyperactivity, insomnia, libido decrease, nervousness, neuropathy, psychosis, sedation, sexual activity increase, slurred speech, twitching, unconsciousness, vertigo.

**Autonomic nervous:** epistaxis, flushing, miosis, salivation.

**Gastrointestinal:** anorexia, appetite increased, constipation, diarrhea, esophagitis, gastroenteritis, gastrointestinal spasm, hiccup, mouth burning, pyloric ulcer.

**Cardiovascular:** chest pain, hypotensive reaction, palpitations, syncope.

**Skin:** erythema, erythema multiforme, exfoliative dermatitis, hives, rash, toxic epidermal necrolysis, Stevens-Johnson syndrome, lichenoid eruption.

**Urinary:** kidney impairment, urinary difficulty.

**Miscellaneous:** allergic reaction, anaphylactic shock, cholangiocarcinoma, drug interaction with erythromycin (stomach upset), edema.

The following adverse drug events may be borne in mind as potential effects of the components of FIORINAL<sup>®</sup>-C. Potential effects of high dosage are listed in the **SYMPTOMS and TREATMENT of OVERDOSAGE** section below.

**ASA:** occult blood, hemolytic anemia, iron deficiency anemia, dyspepsia, nausea, peptic ulcer, prolonged bleeding time, acute airway obstruction, nephropathy toxic when taken in high doses for prolonged periods, urine uric acid decreased, hepatitis.

**Caffeine:** tachycardia, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

**Codeine:** nausea, vomiting, drowsiness, lightheadedness, constipation, pruritus.

**Butalbital:** incoordination, difficulty thinking, poor memory, faulty judgment, decreased attention, emotional lability, exaggeration of personality traits.

### **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

For management of a suspected drug overdose, contact your regional Poison Control Centre.
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The toxic effects of acute overdosage of FIORINAL<sup>®</sup>-C (ASA-caffeine-codeine-butalbital) are attributable mainly to the barbiturate and codeine components, and, to a lesser extent, ASA. Because toxic effects of caffeine occur in very high dosages only, the possibility of significant caffeine toxicity from FIORINAL<sup>®</sup>-C overdosage is unlikely.

#### **Symptoms:**

- 1) Acute barbiturate poisoning: drowsiness, confusion and coma, with reduced or absent reflexes; prominent, persistent respiratory depression; hypotension, followed by circulatory

collapse and a typical shock-like state in severe intoxication; respiratory complications, renal failure, and, possibly, death.

- 2) Acute ASA poisoning: principal toxic effects include hyperpnea; hypercapnia; acid-base disturbances with the development of metabolic acidosis, especially in children; and gastrointestinal irritation with vomiting and abdominal pain. Also, acetone odour in breath, tinnitus, sweating, hyperthermia, dehydration, hypoprothrombinemia with spontaneous bleeding, restlessness, delirium, convulsions and coma may occur.
- 3) Acute caffeine poisoning: insomnia, restlessness, tinnitus and flashes of light; tachycardia and extrasystoles; tremor, delirium and coma, following high doses in the region of 10 g. Death has not been reported with caffeine overdosage.
- 4) Acute codeine poisoning: symptoms will be more pronounced with the capsules containing the higher doses. These include the triad of: pinpoint pupils, marked depression of respiration, and loss of consciousness. Convulsions may occur.

**Note:** Because large doses of barbiturate alone may cause marked respiratory and CNS depression, an even more profound depressant effect may be expected after an overdosage of FIORINAL<sup>®</sup>-C.

The dangers of FIORINAL<sup>®</sup>-C overdosage are increased when the drug is ingested in the presence of alcohol, phenothiazines, minor tranquilizers and/or narcotics.

### **Treatment:**

The management of acute FIORINAL<sup>®</sup>-C overdosage may involve the treatment of the toxic effects of all its constituents, with the possible exception of caffeine, which is toxic in very high doses only. Generally, it is the management of the barbiturate intoxication, the correction of the acid-base imbalance due to salicylism and the reversal of the effects of codeine which demand most attention. The therapeutic procedures most commonly employed are:

Elimination of the offending drug:

- 1) Emesis: if the patient is conscious, induce vomiting mechanically or with syrup of ipecac (15 to 30 mL).
- 2) Perform gastric lavage followed by the administration of activated charcoal if the pharyngeal and laryngeal reflexes are present and if less than 4 hours have elapsed since ingestion. Do not attempt gastric lavage on the unconscious patient unless cuffed endotracheal intubation has been performed to prevent aspiration and pulmonary complications.
- 3) Catharsis: Following gastric lavage, a saline cathartic (sodium or magnesium sulfate 30 g in 250 mL of water) may be introduced and left in the stomach.
- 4) Encourage diuresis by administration of i.v. fluids assisted, if necessary, by 100 to 150 mL 25% mannitol solution given slowly i.v. Note: Mannitol should not be mixed with blood in a transfusion set, as red cell crenation and agglutination may occur.
- 5) Alkalinization of the urine (see caution): i.v. isotonic sodium bicarbonate solution accelerates urinary excretion of barbiturates. Maximum alkalinization may be more successfully attained if the sodium bicarbonate infusion is accompanied by acetazolamide 250 mg given as a single i.v. injection every 6 hours. (Caution: perform urinary alkalinization with care in children).
- 6) Peritoneal dialysis and hemodialysis have been used with success in acute barbiturate intoxication and may be life saving. However, before embarking on either method, weigh the risks inherent to these procedures against the risk of not using them at all.

Maintenance of adequate pulmonary ventilation: Respiratory depression is an early and often profound manifestation of acute barbiturate poisoning. Meticulous attention to this aspect of treatment is essential. Perform pharyngeal and tracheal suction diligently to remove excess mucous secretions. Judicious administration of oxygen is also indicated. However, oxygen without assisted respiration must be used with caution, as its use in hypoventilation hypoxia may result in further respiratory depression and hypercapnia. In more critical cases, endotracheal intubation or tracheotomy, with or without assisted respiration, may be necessary.

Correction of hypotension: Vigorous treatment is essential, as circulatory collapse and renal failure are frequent causes of death.

- 1) Mild cases: the usual head down position and other supportive measures may be adequate.
- 2) Severe cases: Vasopressors (dopamine, levarterenol) may be given i.v. with the usual precautions and serial blood pressure monitoring.

Narcotic antagonism: naloxone injection may reverse the respiratory depression caused by codeine and should be used until respiration improves. Typically, a dose of 0.4-2 mg is given parenterally and may be repeated if an adequate response is not achieved. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

**Note:** Respiratory depression caused by barbiturates will not respond to narcotic antagonists. Unwitting overdosage with narcotic antagonists may occur in an attempt to reverse respiratory depression caused by mixed barbiturate-codeine intoxication.

Special features due to salicylate overdose:

- 1) The prominent features of salicylate intoxication are metabolic acidosis and electrolyte disturbance, and these require evaluation and correction. Sodium bicarbonate 400 mg (5 mEq)/kg as a 1% solution in 5% dextrose water is not only effective in correcting acidosis, but effectively and rapidly accelerates salicylate excretion by the kidneys. The administration of sodium bicarbonate must be carefully monitored with frequent blood pH and plasma CO<sub>2</sub> content determinations, as large amounts of sodium bicarbonate may result in severe alkalosis, particularly in children. THAM, an osmotic alkalizing diuretic, also greatly increases the excretion of salicylate. This is given as a 0.3 molar solution at a rate not exceeding 5 mL/kg/hour. Potassium deficiency may occur and should be corrected.
- 2) Treat hyperthermia and dehydration with ice packs and i.v. fluids.
- 3) Treat hypoprothrombinemia with vitamin K<sub>1</sub> 50 mg given daily i.v.

- 4) Hemodialysis, peritoneal dialysis or exchange transfusion are indicated in very severe salicylate intoxication. However, in FIORINAL<sup>®</sup>-C overdose, these measures are indicated mainly for barbiturate intoxication but would be effective for both.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

General supportive measures:

- 1) Good nursing care is of prime importance, particularly in the comatose patient, and should include regular observation and accurate recording of the vital signs and depth of coma, maintenance of a free airway, frequent turning, and other routine measures usually adopted with unconscious patients.
- 2) Careful supervision and recording of fluid intake and output is essential.
- 3) Take blood samples to determine barbiturate blood concentrations and for electrolyte and other pertinent blood studies.

**Toxic and Lethal Doses (for adults):**

ASA: toxic blood level greater than 30 mg/100 mL; lethal dose 10-30 g

Caffeine: toxic dose greater than 1 g; (25 capsules); lethal dose 6.5-10 g

Codeine: toxic dose 240 mg (8 capsules); lethal dose 0.5-1 g

Butalbital: toxic dose 1 g (20 capsules); lethal dose 2-5 g

**DOSAGE AND ADMINISTRATION**

**Adults (18 years and older):**

1 or 2 capsules at once, followed if necessary, by 1 capsule every 4 to 6 hours, up to 6 capsules daily, or as prescribed.

FIORINAL<sup>®</sup>-C (ASA-caffeine-codeine-bitalbital) should not be administered to children younger than 18 years of age.

Codeine, including FIORINAL<sup>®</sup>-C, should be prescribed at the lowest effective dose for the shortest period of time. Dosing should be as needed every 4 to 6 hours and not on scheduled intervals.

Extended and repeated use of this product is not recommended because of the potential for physical dependence.

Patients should be instructed to seek the advice of a physician if no effective pain relief is achieved after 3 days of treatment.

### **PHARMACEUTICAL INFORMATION**

#### **Drug Substance:**

##### ***Acetylsalicylic acid (ASA)***

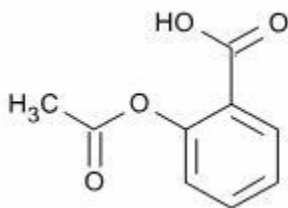
Common name: Acetylsalicylic acid (ASA)

Chemical name: benzoic acid, 2-(acetyloxy)-

Molecular formula: C<sub>9</sub>H<sub>8</sub>O<sub>4</sub>

Molecular mass: 180.16

Structural formula:



##### ***Caffeine***

Common name: Caffeine

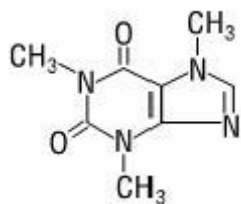
Chemical name: 1,3,7-trimethylxanthine

Molecular formula: C<sub>8</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub>

Molecular mass: 194.19



Structural formula:



### ***Codeine***

Common name: Codeine phosphate

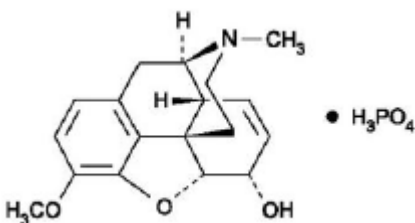
Chemical name: 7,8-Didehydro-4,5 $\alpha$ -epoxy-3-methoxy-17-methylmorphinan-6 $\alpha$ -ol phosphate

(1:1) (salt) hemihydrate

Molecular formula:  $C_{18}H_{24}NO_7P$

Molecular mass: anhydrous molecular weight 397.37

Structural formula:



### ***Butalbital***

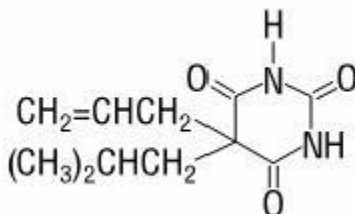
Common name: Butalbital

Chemical name: 5-allyl-5-isobutylbarbituric acid

Molecular formula:  $C_{11}H_{16}N_2O_3$

Molecular mass: molecular weight 224.26

Structural formula:




**Storage:**


Store at room temperature between 15-30°C.

Keep out of reach and sight of children.

**AVAILABILITY OF DOSAGE FORMS****FIORINAL<sup>®</sup>-C 1/4 Capsules:**

Each hard gelatin oblong capsule, white opaque body with blue opaque cap, printed with “FIORINAL-C1/4” and "  " in black ink contains the following active ingredients: butalbital USP 50 mg, caffeine USP 40 mg, ASA USP 330 mg, codeine phosphate USP 15 mg. Nonmedicinal ingredients: cornstarch, talc, microcrystalline cellulose and stearic acid. Bottles of 100.

**FIORINAL<sup>®</sup>-C 1/2 Capsules:**

Each hard gelatin oblong capsule, light blue opaque body with blue opaque cap, printed with “FIORINAL-C 1/2” and "  " in black ink contains the following active ingredients: butalbital USP 50 mg, caffeine USP 40 mg, ASA USP 330 mg, codeine phosphate USP 30 mg. Nonmedicinal ingredients: cornstarch, talc, microcrystalline cellulose and stearic acid. Bottles of 100 and 500.

**PART III: CONSUMER INFORMATION**

**<sup>N</sup>FIORINAL®-C 1/4, 1/2**  
**(acetylsalicylic acid-caffeine-codeine-butalbital)**

This leaflet is part III of a three-part "Product Monograph" published when FIORINAL®-C was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FIORINAL®-C. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION****What the medication is used for:**

FIORINAL®-C, is used for the relief of tension-type headache.

FIORINAL®-C is recommended for adults 18 years and older.

**What it does:**

FIORINAL®-C consists of acetylsalicylic acid (ASA), caffeine, codeine and butalbital. ASA reduces pain, fever and inflammation. Caffeine is a mild stimulant which may enhance pain-relieving effects. Codeine is a narcotic used to relieve pain and butalbital is a sedative that causes relaxation. This combination is used to relieve tension-type headaches.

**When it should not be used:**

You should NOT take FIORINAL®-C if you:

- have a history of allergic reactions to ASA, caffeine, codeine, butalbital or any other components of the FIORINAL®-C capsules (see "What the nonmedicinal ingredients are")
- have a condition that predisposes to bleeding such as hemophilia, hypoprothrombinemia, von Willebrand's disease, thrombocytopenia, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage
- have nasal polyps, allergic reaction or bronchospastic reactivity to ASA or other nonsteroidal anti-inflammatory drugs (NSAIDs)
- have stomach ulcers or other serious stomach or bowel sores
- have a disease called porphyria
- have a history of drug abuse or drug overdose due to alcohol, sleeping pills, drugs to treat pain or any other prescription or illegal drugs
- have severe asthma, severe lung problems or other breathing difficulties
- have pneumonia (a lung infection)
- are pregnant, in labour or delivery, or breast-feeding
- metabolize codeine at a much faster rate than the general population.

FIORINAL®-C is not recommended in children less than 18 years old.

**What the medicinal ingredients are:**

ASA (acetylsalicylic acid), caffeine, codeine and butalbital.

**What the nonmedicinal ingredients are:**

FIORINAL®-C capsules contain the following non-medicinal ingredients: cornstarch, microcrystalline cellulose, stearic acid and talc.

**What dosage forms it comes in:**

FIORINAL®-C 1/4 capsules contain 330 mg ASA, 40 mg caffeine, 15 mg codeine phosphate and 50 mg butalbital.

FIORINAL®-C 1/2 capsules contain 330 mg ASA, 40 mg caffeine, 30 mg codeine phosphate and 50 mg butalbital.

**WARNINGS AND PRECAUTIONS**

**Keep FIORINAL®-C out of the reach of children. You should not give FIORINAL®-C to anyone as inappropriate use may have severe medical consequences.**

**BEFORE you use FIORINAL®-C talk to your doctor or pharmacist if you:**

- are allergic to ASA as it can cause anaphylactic shock and other severe allergic reactions
- have nasal polyps or asthma
- have a history of blocked bowels, stomach ulcers, sores in your stomach or bowel or any other serious stomach problems
- have a history of bleeding
- will be having surgery
- have severe liver or kidney disease
- have a blood clotting disorder or are taking blood thinners
- have recently suffered a head injury or elevated pressure in your brain
- have problems with your thyroid gland
- have narrowing of the urethra caused by injury or disease
- have Addison's disease
- have an enlarged prostate gland
- have softening or weakening of bones or osteoporosis
- have any allergies to any medicines, food, dyes or preservatives
- have the flu, or chickenpox
- are pregnant, may become pregnant, in labour or delivery, or breastfeeding
- have reacted strongly to other codeine-containing drugs in the past (i.e. got sleepy, confused and/or had trouble breathing) even when taking the dose recommended by your doctor.

FIORINAL®-C is not recommended for **anyone** who has or is at risk for breathing problems such as:

- lung infections, or respiratory conditions
- neuromuscular disorders
- severe heart problems
- recent multiple traumas or extensive surgical procedures

**Some people metabolize codeine at a much faster rate than the general population, which may lead to accidental overdose, if this should happen to you, seek help immediately (see PROPER USE OF THIS MEDICINE: Overdose, below for symptoms of overdose and what to do if it happens). If you know that you metabolize codeine rapidly, tell your doctor BEFORE starting this medication.**

FIORINAL®-C is a controlled medication. Butalbital and codeine are both habit-forming (tolerance, mental and physical dependence) and potentially abusable. Some patients, particularly those who have abused drugs in the past, may have a higher risk of abusing or developing an addiction while taking barbiturate- or opioid-containing products, such as FIORINAL®-C. Physical dependence may lead to withdrawal side effects when you stop taking this medicine. Continuous daily use of FIORINAL®-C should be avoided as medication overuse (rebound) headaches may result in addition to the tolerance and dependence risks. Patients should take FIORINAL®-C only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

While there are important differences between physical dependence and addiction, each is a reason for close medical supervision and honest discussions with your doctor. If you have questions or concerns about abuse, addiction or physical dependence, please tell your doctor.

ASA may increase the risk of Reye's syndrome, a rare but often fatal condition. Caution should be used in administering ASA-containing medications to young adults who have fever, flu or chicken pox. FIORINAL®-C should not be administered to children.

Before you have any medical tests done, tell the person in charge that you are taking FIORINAL®-C. ASA and codeine may interfere with the results of certain tests done in blood and urine.

### **Driving and operating machinery**

FIORINAL®-C may impair the mental and/or physical abilities required for performance of potentially hazardous task such as driving a car or operating machinery. If you experience drowsiness or dizziness, such tasks should be avoided. Avoid alcohol as it can increase drowsiness and dizziness.

### **Pregnancy, labour and delivery, and breastfeeding**

FIORINAL®-C should not be used during pregnancy because it may cause withdrawal symptoms in the newborn baby. When taken close to delivery it may make delivery longer or lead to bleeding and other serious complications in the mother or in the newborn baby.

FIORINAL®-C should not be used during breast-feeding as FIORINAL®-C passes into breast milk and may harm a nursing infant. High levels of morphine in breast milk may lead to life-threatening side in nursing babies or death.

## **INTERACTIONS WITH THIS MEDICATION**

Tell your doctor or pharmacist if you are taking or have recently taken any other prescription or over-the-counter medicines, vitamins or natural health products during your treatment with FIORINAL®-C.

Check with your doctor or pharmacist before taking any other medication with FIORINAL®-C.

### **Tell your doctor if you are taking any of the following medications:**

- alcohol and other CNS depressants (such as sleeping pills, muscle relaxants, pain killers, allergy medication (antihistamines), drugs used to treat anxiety, panic attacks and seizures)
- monoamine oxidase (MAO) inhibitors (e.g., phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- corticosteroids
- oral drugs to treat diabetes and/or insulin
- blood thinners such as warfarin
- drugs used to suppress the immune system such as 6-mercaptopurine and methotrexate
- NSAIDs (non-steroidal anti-inflammatory drugs) to treat pain such as ibuprofen and naproxen
- tranquilizers such as chlordiazepoxide
- drugs used to treat gout such as probenecid and sulfinpyrazone
- birth control pills.

## **PROPER USE OF THIS MEDICATION**

Take FIORINAL®-C exactly as directed by your doctor.

### **Usual dose (adults 18 years and older):**

Take 1 or 2 capsules at once, followed if necessary, by 1 capsule every 4 to 6 hours. Do not take more than 6 capsules daily or as prescribed.

Your doctor should prescribe FIORINAL®-C at the lowest effective dose for the shortest period of time. Take FIORINAL®-C every 4 to 6 hours, as needed.

FIORINAL®-C comes as a capsule to take by mouth.

Let your physician know rapidly if no effective pain relief is achieved after 3 days of treatment.

### **Overdose:**

The most important sign of overdose is decreased breathing (abnormally slow or weak breathing), dizziness, confusion or extreme drowsiness. If you accidentally take too much FIORINAL®-C, call your doctor and/or your local emergency number and/or a Regional Poison Control Centre immediately, or go to a hospital emergency and take any remaining tablets and the container with you, even though you may not feel sick.

### Missed Dose:

If you forget to take a dose of FIORINAL<sup>®</sup>-C, do not worry. Take the missed dose as soon as you remember it. However, if it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. Do not take a double dose to make up for the missed one.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, FIORINAL<sup>®</sup>-C may cause unwanted reactions called side effects. Not all of these side effects may occur. Check with your doctor if the unwanted effects do not go away during treatment or become bothersome.

The following side effects may occur during treatment:

- nausea, vomiting, indigestion and/or stomach pain
- drowsiness, lightheadedness and dizziness
- constipation and gas
- skin rash and itching
- small pupils
- fast or irregular heart beat
- irritability
- tremor
- lack of coordination
- difficulty thinking
- poor memory and judgement
- decreased attention
- mood swings
- exaggeration of personality traits.

If any of these side effects affects you severely, tell your doctor.

### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist right away		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Uncommon	<b>Reye's syndrome:</b> rash on the palms of hands and feet, severe vomiting, high fever, weakness, confusions, headache, fast breathing leading to unresponsiveness and death			√

### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist right away		Stop taking drug and seek
	<b>Allergic reactions:</b> itching, rash, hives, difficulty breathing or swallowing not present before using this medicine			√
Unknown	<b>Pancreatitis:</b> severe stomach pain with radiation through to the back, nausea and vomiting		√	
	<b>Serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson syndrome erythema multiforme and exfoliative dermatitis:</b> fever, itching, skin sores			√
	<b>Anemia:</b> fatigue, breathing difficulties, irregular heart beat or pale skin	√		
	<b>Stomach ulcer:</b> heartburn, long lasting stomach pain, loss of appetite and weight loss		√	
	Prolonged bleeding time	√		
	<b>Hepatitis:</b> loss of appetite, dark urine, yellowing of eyes and skin		√	
	Blood in the stool		√	

*This is not a complete list of side effects. For any unexpected effects while taking FIORINAL<sup>®</sup>-C, contact your doctor or pharmacist.*

## HOW TO STORE IT

- store your FIORINAL<sup>®</sup>-C capsules at room temperature (between 15-30°C)
- keep out of reach and sight of children
- discard any expired medicine or medicine no longer needed.

## **REPORTING SUSPECTED SIDE EFFECTS**

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

1. Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
2. Call toll-free at 1-866-234-2345
3. Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701E  
Ottawa, Ontario  
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect<sup>™</sup> Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.novartis.ca>  
or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at:  
1-800-363-8883

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

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