PRODUCT MONOGRAPH

^{N}CODOFEN®

(Hydrocodone bitartrate 7.5 mg-Ibuprofen 200 mg)

Tablets

Opioid/NSAID combination analgesic

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THERAPEUTIC CLASSIFICATION

Opioid/NSAID combination analgesic

ACTION AND CLINICAL PHARMACOLOGY

Hydrocodone Component

Hydrocodone is a centrally acting semisynthetic opioid antitussive and analgesic. The precise mechanism of analgesic action of hydrocodone and other opioids is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood, mental clouding, constipation and, in overdose, respiratory depression.

Ibuprofen Component

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that possesses analgesic and antipyretic activities. The mode of action, like that of other NSAIDs, is not completely understood, but may be related to inhibition of cyclooxygenase activity and prostaglandin synthesis. Ibuprofen is a peripherally acting analgesic. Ibuprofen does not have any known effects on opiate receptors.

CODOFEN combines the analgesic effects of the centrally acting analgesic hydrocodone with the peripherally acting NSAID analgesic, ibuprofen.

Pharmacokinetics

Hydrocodone bitartrate and ibuprofen are well absorbed in the gastrointestinal tract from oral CODOFEN. In a single oral dose study, 31 adult male and female subjects dosed with two CODOFEN tablets gave a mean hydrocodone C_{max} of 27.3 ng/mL occurring at T_{max} 1.7 hours; the mean half-life was 4.5 hours and the mean AUC $_{0-\infty}$ was 216 ng/mL*hr. The mean ibuprofen

C_{max} was 30.2 mcg/mL occurring at T_{max} 1.8 hours; the mean half-life was 2.2 hours and the mean $AUC_{0-\infty}$ was 136 mcg/mL*hr.

Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation, and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxy metabolites. The effects of renal disease on the clearance of hydrocodone are unknown.

When taken with food, the rate of ibuprofen absorption is reduced but the overall extent is unchanged. Ibuprofen, given alone, is rapidly metabolized and eliminated in the urine. Two major human urinary metabolites isolated are 2 to 4' (2-hydroxy-2-methylpropyl) phenylpropionic acid and 2 to 4' (2-carboxypropyl) phenylpropionic acid. Within 24 hours of dosing, 45 to 79% of a dose is recovered as these 2 metabolites, with conjugated ibuprofen constituting the other significant urinary metabolite. Ibuprofen is 99% protein-bound.

Clinical Trials

The contribution of each component of CODOFEN (i.e. ibuprofen and hydrocodone) to analgesic efficacy, with respect to time of onset, pain scores and duration of action, was demonstrated in randomised, controlled clinical trials; duration of action was estimated to between four to six hours.

In five pivotal single-dose studies of post-surgical pain (abdominal/gynecological, orthopedic), 319 patients received one or two tablets of CODOFEN. CODOFEN produced greater efficacy, based on comparisons of pain relief scores, pain intensity difference scores, and duration of effect, than placebo or either of its individual components given alone at the same dose. In the only efficacy trial with direct comparison of the one versus two tablet dose, no difference in dose response was seen.

In a 30-day repeat-dosing study in which 309 pain patients were taking fixed one or two tablet doses of CODOFEN three times a day, drug-related adverse events, especially those related to the opioid component of the formulation, were significantly increased in the two tablet dosing arm of the study.

INDICATIONS AND CLINICAL USE

CODOFEN (hydrocodone bitartrate-ibuprofen) tablets are indicated for the short term management of acute moderate pain. CODOFEN is not indicated for the treatment of chronic pain conditions, such as rheumatoid arthritis and osteoarthritis, since the safety and efficacy of CODOFEN have not been systematically explored in these patient populations.

CONTRAINDICATIONS

CODOFEN (hydrocodone bitartrate-ibuprofen) contraindications are:

Hypersensitivity: Known hypersensitivity to hydrocodone and/or ibuprofen. Patients hypersensitive to other opioids or non-steroidal anti-inflammatory drugs (NSAIDs) may exhibit cross-sensitivity. Complete or partial syndrome of nasal polyps, asthma, anaphylaxis, urticaria, rhinitis or other allergic manifestations precipitated by ASA or other NSAIDs. Asthmatic patients with triad asthma (the syndrome of nasal polyps, asthma and hypersensitivity to ASA or other NSAIDs) may be at particular risk of severe hypersensitivity reactions. Fatal anaphylactoid reactions have occurred in such individuals.

Systemic Lupus Erythematosus: anaphylaxis-like reactions with fever may occur with ibuprofen treatment, particularly when ibuprofen had been administered previously. Aseptic meningitis has been reported.

Gastrointestinal: Active peptic ulcer, history of recurrent ulceration or active gastrointestinal inflammatory disease.

Hepatic Impairment: Significant hepatic impairment or active liver disease.

Renal Impairment: Severely impaired or deteriorating renal function (creatinine clearance < 30 mL/min).

Obstetrics: Ibuprofen may inhibit labour, prolong pregnancy or cause post partum bleeding.

Acute Respiratory Depression, Acute Asthma or other obstructive airway disease: Severe CNS depression, convulsive disorders, *cor pulmonale*, suspected surgical abdomen.

Increased cerebrospinal or intracranial pressure, head injury: in the presence of an intracranial lesion associated with increased intracranial pressure and whenever ventilatory function is depressed.

Concomitant MAO inhibitors (or within 14 days of such therapy): Opioid use in combination with MAO inhibitors has occasionally precipitated unpredictable, severe, and occasionally fatal reactions in patients who have received such agents within 14 days. The mechanism of these reactions is unclear, but may be related to pre-existing hyperphenylalaninemia.

WARNINGS

Gastrointestinal System (GI)

Serious GI toxicity, such as peptic ulceration, perforation, and gastrointestinal bleeding, sometimes severe and occasionally fatal can occur at any time, with or without symptoms, during non-steroidal anti-inflammatory drug (NSAID) treatment including CODOFEN (hydrocodone bitartrate-ibuprofen).

Minor upper GI symptoms, such as dyspepsia, are common, usually developing early in therapy. Be vigilant for ulceration and bleeding in NSAID-treated patients even if previous GI tract symptoms were absent. The incidence of these complications increases with increasing doses; therefore do not take more than the recommended dose.

Use in the Elderly

Patients older than 65 years and frail or debilitated patients are most susceptible to a variety of adverse reactions from NSAIDs: the incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal ulceration and bleeding.

Because the elderly may be more sensitive to the renal and gastrointestinal effects of non-steroidal anti-inflammatory agents as well as possible increased risk of respiratory depression with opioids, extra caution should be used when treating the elderly with CODOFEN.

Patients prone to gastrointestinal tract irritation, particularly those with a history of peptic ulcer, diverticulosis or other gastrointestinal tract inflammatory diseases, such as ulcerative colitis and Crohn's disease should be under close medical supervision when using CODOFEN. In these cases the physician must weigh the benefits of treatment against the possible hazards.

Patients taking any NSAIDS including ibuprofen should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur without warning at any time during treatment.

No studies, to date, have identified any other patient groups not at risk of developing ulceration and bleeding. Factors associated with increased risk include: prior history of serious GI events, excess alcohol intake, smoking, age, female gender and concomitant oral steroid and anticoagulant use. Studies to date show that all NSAIDs can cause GI tract adverse events.

There is no information on safety and efficacy during the long-term use of this combination drug.

Renal Function

Even in patients with lesser impairment (e.g. creatinine clearance >30 mL/min and <60 mL/min), NSAIDs may produce renal function deterioration.

Aseptic Meningitis

Aseptic meningitis with fever and coma has been observed on rare occasions in patients on ibuprofen therapy. Although probably more likely to occur in systemic lupus erythematosus and related mixed connective tissue diseases, it has also been reported in other patients. Therefore, be aware that signs or symptoms such as stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness, may be ibuprofen related meningitis.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of head injury patients.

Acute Abdominal Conditions

Opioid administration obscures the diagnosis or clinical course of patients with acute abdominal conditions.

Abuse and Dependence

Hydrocodone can produce drug dependence, and therefore has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration. Prescribe and administer with the same degree of caution appropriate to other oral narcotic drugs.

Respiratory Depression

Hydrocodone produces dose-related respiratory depression by directly acting on the brain stem respiratory centres. If respiratory depression occurs, it may be antagonized by the use of naloxone and other supportive measures when indicated.

Occupational Hazards

Hydrocodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Caution patients accordingly.

CNS Depression

Patients receiving other narcotic analgesics, general anaesthetics, phenothiazines or other tranquilizers, tricyclic antidepressants, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with hydrocodone may exhibit an additive CNS depression. When such combined therapy is contemplated, reduce the dose of one or both agents.

Use with other NSAIDs

Neither the safety nor efficacy of such combinations has been established.

PRECAUTIONS

General

As with any opioid analgesic agent CODOFEN (hydrocodone bitartrate-ibuprofen) tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind. Patients should report to their physician signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash or edema.

Patients with Special Diseases or Conditions

Respiratory tract

Hydrocodone suppresses the cough reflex. As with all opioids, caution should be exercised when CODOFEN is used postoperatively and in patients with pulmonary disease.

At high doses or in opioid-sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory centres. Hydrocodone also affects the centre that controls respiratory rhythm, and may produce irregular and periodic breathing.

Renal Effects

Caution should be used when initiating treatment with CODOFEN in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with CODOFEN. Caution is also recommended in patients with pre-existing kidney disease (see **WARNINGS - Renal Disease).**

As with other NSAIDS, long-term administration of ibuprofen has resulted in renal papillary necrosis and other renal pathology changes. 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 NSAID 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 for this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Ibuprofen metabolites are eliminated primarily by the kidneys. The extent to which the metabolites may accumulate in patients with renal failure has not been studied. Patients with significantly impaired renal function should be closely monitored.

Genitourinary tract

Some NSAIDs are known to cause persistent urinary symptoms (bladder pain, dysuria, and urinary frequency), haematuria or cystitis. Symptom onset may occur at any time after NSAID therapy initiation. Should urinary symptoms occur, CODOFEN treatment must be stopped immediately to obtain recovery. This should be done before any urological investigations or treatments are carried out.

Hepatic Effects

As with other nonsteroidal anti-inflammatory drugs, ibuprofen has been reported to cause borderline elevations of one or more liver function tests in up to 15% of patients. 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 reactions while on therapy with ibuprofen. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs.

Although such reactions are rare, if abnormal liver test results persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), ibuprofen should be discontinued.

Fluid and Electrolyte Balance

Fluid retention and edema have been observed in patients treated with ibuprofen. Therefore, as with many other nonsteroidal anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. Use CODOFEN cautiously in heart failure, cardiac decompensation, hypertension or other conditions predisposing to fluid retention.

With nonsteroidal anti-inflammatory treatment there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with β-adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics.

Haematological Effects

Drugs inhibiting prostaglandin biosynthesis interfere with platelet function to some degree. Therefore, patients who may be adversely affected by such an action should be carefully observed when CODOFEN is administered.

Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anaemia and agranulocytosis) associated with non-steroidal anti-inflammatory drugs use are rare, but could occur with severe consequences.

Ibuprofen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range), in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Infection

In common with other anti-inflammatory drugs, the antipyretic and anti-inflammatory activity of CODOFEN may mask the usual signs of infection (fever and inflammation).

Ophthalmology

Blurred and/or diminished vision, scotomata, and/or changes in colour vision have been reported with ibuprofen and other non-steroidal anti-inflammatory drug use. If a patient develops such complaints, discontinue CODOFEN, and obtain an ophthalmologic examination that includes central visual fields and colour vision testing.

Cross-sensitivity

Patients sensitive to any nonsteroidal anti-inflammatory drug may also be sensitive to any other NSAIDs.

Stevens-Johnson Syndrome (a severe form of erythema multiforme) and toxic necrolysis have been reported with ibuprofen therapy, but only rarely.

Use In Children

The safety and effectiveness of CODOFEN in the pediatric population below the age of 18 has not been established.

Pregnancy

Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of ductus arteriosus), use of CODOFEN during late pregnancy should be avoided. As with other drugs

known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. As there are no adequate and well-controlled studies of CODOFEN in pregnant women, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects

CODOFEN, administered to rabbits at 5.72 times the maximum clinical dose based on body weight, a maternally toxic dose, resulted in an increase in the percentage of litters and fetuses with any major abnormality and an increase in the number of litters and fetuses with one or more nonossified metacarpals (a minor abnormality). CODOFEN, administered to rats at 10 times the maximum recommended clinical dose based on body weight, a maternally toxic dose, did not result in any reproductive toxicity. There are no adequate and well-controlled studies in pregnant women.

Nonteratogenic Effects

Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labour and Delivery

As with other drugs known to inhibit prostaglandin synthesis, an increase incidence of dystocia and delayed parturition occurred in rats. Administration of CODOFEN is not recommended during labour and delivery.

Nursing Mothers

It is not known whether hydrocodone is excreted in human milk. Furthermore, because of the possible adverse effects prostaglandin-inhibiting drugs have on neonates, CODOFEN is not recommended for use in nursing mothers.

Carcinogenicity, Mutagenicity and Impairment of Fertility

The carcinogenic and mutagenic potential of CODOFEN has not been investigated. The ability of CODOFEN to impair fertility has not been assessed.

Drug Interactions

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

Acetylsalicylic acid (ASA) or other NSAIDS: Using CODOFEN in addition to any other NSAIDs, including over the counter ASA and ibuprofen, is not recommended due to possibly additive side effects.

Anticholinergics: Concurrent anticholinergic use with hydrocodone preparations may produce paralytic ileus.

Antidepressants: MAO inhibitors or tricyclic antidepressants given with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

CNS depressants: Patients receiving other opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with hydrocodone preparations may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

Coumarin-type anticoagulants: Several short-term controlled studies failed to show that ibuprofen significantly affected prothrombin times or a variety of other clotting factors when administered to individuals on coumarin-type anticoagulants.

However, numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding. Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function, the physician should be cautious when administering CODOFEN to patients on anticoagulants.

Diuretics: Because of its fluid retention properties, high doses of ibuprofen can decrease the diuretic and antihypertensive effects of diuretics and increase diuretic dosage may thus be required. Patients with impaired renal function who are taking potassium-sparing diuretics should not take ibuprofen preparations.

Furosemide: Ibuprofen reduces the natriuretic effect of furosemide and thiazide in some patients; this effect has been attributed to renal prostaglandin synthesis inhibition. During concomitant therapy, patients should be observed closely for diuretic efficacy and signs of renal failure (see **PRECAUTIONS**, Renal effects.)

Glucocorticoids: Numerous studies have shown that concomitant NSAID use with oral glucocorticoids increases the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.

H_2 Antagonists: Due to the limited information available regarding the potential for interaction between H_2 antagonists and opioid analgesics, the physician should exercise caution when coprescribing CODOFEN and H_2 antagonists.

Hypoglycemic agents: Ibuprofen may increase hypoglycemic effects of oral antidiabetic agents and insulin.

Lithium: Ibuprofen has been shown to elevate plasma lithium concentration and reduce renal lithium clearance. This effect has been attributed to renal prostaglandin synthesis inhibition by ibuprofen. Thus, when CODOFEN and lithium are administered concurrently, observe patients for signs of lithium toxicity.

MAO Inhibitors: Concomitant use of opioids with MAO inhibitors (or within 14 days of such therapy) has occasionally precipitated unpredictable, severe, and occasionally fatal reactions. The mechanism of these reactions is unclear, but may be related to preexisting hyperphenylalaninemia. Some reactions have been characterised by coma, severe respiratory depression, cyanosis and hypotension and have resembled the syndrome of acute narcotic overdose. In other reported reactions, the predominant manifestations have been hyperexcitability, convulsions, tachycardia, hyperpyrexia and hypertension. It is not known that other opioids such as hydrocodone are free of such reactions. The usefulness and safety of narcotic antagonists in the treatment of these reactions is unknown.

Methotrexate: Ibuprofen, like other NSAIDS, has been reported to competitively inhibit methotrexate accumulation *in vitro*, indicating that ibuprofen could enhance methotrexate toxicity. Use caution when co-administering CODOFEN and 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.

Other Drugs: Although ibuprofen binds extensively to plasma proteins, interactions with other protein-bound drugs occur rarely. Nevertheless, caution should be observed when other drugs, also having a high affinity for protein binding sites, are used concurrently. Some observations have suggested a potential for ibuprofen to interact with furosemide, pindolol, digoxin, phenytoin and lithium salts. However, the mechanism and clinical significance of these observations are presently not known. No interactions have been reported when ibuprofen has been used in conjunction with probenecid, thyroxine, steroids, antibiotics or benzodiazepines.

Information to be Provided by Physicians to the Patient

Physicians are advised to discuss the following issues with patients:

Interference with Cognitive and Motor Performance

CODOFEN, like other opioid-containing analgesics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Gastrointestinal

CODOFEN has side effects like other drugs containing ibuprofen. These side effects can cause discomfort. Rarely, they are more serious, such as gastrointestinal bleeding, and may result in hospitalization and even fatal outcomes. If persistent dyspepsia or other symptoms or signs suggesting gastrointestinal ulceration or bleeding is experienced, instruct the patient to contact a physician immediately.

Pregnancy

Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in animals**.**

Nursing

CODOFEN is not recommended for nursing mothers because of possible adverse prostaglandin-inhibition effects on neonates.

Concomitant Medication

Alcohol and other CNS depressants may produce an additive CNS depression when taken with CODOFEN, and should be avoided.

ADVERSE REACTIONS

The observed adverse events in clinical trials of CODOFEN were as would be expected for a NSAID/opioid combination product. Adverse event rates generally increased with increasing daily dose. The most frequently observed adverse experiences in patients receiving one tablet of CODOFEN an average of three to four times daily included headache (27%), constipation (22%), nausea (21%), dizziness (14%) and dyspepsia (12%); in addition, patients experienced the following adverse events at an incidence of between three and nine percent; abdominal pain, asthenia, infection, anxiety, insomnia, nervousness, diarrhea, dry mouth, flatulence, edema, pruritus and sweating. In trials which included active comparator, the overall incidence rates of adverse experiences for patients receiving either one tablet of CODOFEN or acetaminophen 600 mg with codeine 60 mg were similar.

The following table highlights adverse events which were observed to occur with greater frequency in patients taking higher doses of CODOFEN:

Table 1
Dose-Related Adverse Reactions

Adverse Event	Observed Frequency (%)		
	1 Tablet Codofen (200/7.5 mg)	2 Tablet Codofen (400/15 mg)	Active Comparator
Gastrointestinal			
Nausea	21.3	35.9	21.1
Vomiting	5.3	13.1	7.8
Nervous System			
Somnolence	20.1	28.8	20.3
Dizziness	13	31.4	10.9
Insomnia	5.9	9.8	3.5
Skin and Appendages			
Pruritis	8.3	18.3	6.6
Sweating	3.6	10.5	2.3

The following table summarizes adverse events, according to body system, observed in pivotal clinical trials in patients receiving single doses of study medication.

Table 2
Counts (%) of Patients with AEs by Body System and Treatment Group

	Placebo	Hydrocodone (7.5 mg)	Ibuprofen (200 mg)	Codofen (200/7.5 mg)
No. of Patients	261	61	60	119
No. of Patients with any AEs	45 (17.2%)	1 (1.6%)	6 (10.0%)	19 (16.0%)
Body as a Whole	6 (2.3%)	1 (1.6%)	0 (0.0%)	2 (1.7%)
Fever	5 (1.9%)	1 (1.6%)	0 (0.0%)	1 (0.8%)
Headache	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
Chills	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Edema (Facial)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pain Abdo	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pain Chest	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory System	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dyspnea	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Digestive System	8 (3.1%)	0 (0.0%)	6 (10.0%)	4 (3.4%)
Nausea	6 (2.3%)	0 (0.0%)	1 (1.7%)	4 (3.4%)
Flatulence	1 (0.4%)	0 (0.0%)	5 (8.3%)	0 (0.0%)
Dry Mouth	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dyspepsia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nervous System	33 (12.6%)	0 (0.0%)	0 (0.0%)	12 (10.1%)
Somnolence	29 (11.1%)	0 (0.0%)	0 (0.0%)	10 (8.4%)
Dizziness	3 (1.1%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
Anxiety	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
Abnormal Dreams	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)

Tremor	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Vertigo	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Skin & Appendages	1	(0.4%)	0	(0.0%)	0	(0.0%)	1	(0.8%)
Sweating	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Pruritus	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(0.8%)
Special Senses	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Taste Pervers	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Urogenital/Nervous	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Urin Retent	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Cardiovascular System	3	(1.1%)	0	(0.0%)	0	(0.0%)	1	(0.8%)
Hypertension	2	(0.8%)	0	(0.0%)	0	(0.0%)	1	(0.8%)
Vasodilation	1	(0.4%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Palpitation	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone and/or ibuprofen.

Signs and Symptoms

Hydrocodone Component: A serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis) extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Ibuprofen Component: Symptoms include gastrointestinal irritation with erosion and haemorrhage or perforation, kidney damage, liver damage, heart damage, hemolytic anaemia, agranulocytosis, thrombocytopenia, aplastic anaemia, and meningitis. Other symptoms may include headache, dizziness, tinnitus, confusion, blurred vision, mental disturbances, skin rash, stomatitis, edema, reduced retinal sensitivity, corneal deposits, and hyperkalemia.

Treatment: Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. Naloxone, a narcotic antagonist, can reverse respiratory depression and coma

associated with opioid overdose or unusual sensitivity to opioids, including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered intravenously with simultaneous efforts at respiratory resuscitation. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous 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. Oxygen, intravenous fluids, vasopressor and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug. In cases where consciousness is impaired, it may be unadvisable to perform gastric lavage. If gastric lavage is performed, little drug will likely be recovered if more than an hour has elapsed since ingestion. Ibuprofen is acidic and is excreted in the urine; therefore, it may be beneficial to administer alkali and induce diuresis. In addition to supportive measures the use of oral activated charcoal may help to reduce the absorption and reabsorption of ibuprofen. Dialysis is not likely to be effective for renal clearance of ibuprofen because it is very highly bound to plasma proteins.

DOSAGE AND ADMINISTRATION

CODOFEN tablets are indicated for the short term management of moderate acute pain. The safety and efficacy of CODOFEN has not been established for the management of chronic pain conditions, such as osteoarthritis and rheumatoid arthritis, and therefore CODOFEN is not indicated for such use.

Adults: The recommended dose is one tablet every 4 to 6 hours. Dosage should not exceed 6 tablets in a 24-hour period.

Table 3
OPIOID ANALGESICS: APPROXIMATE ANALGESIC EQUIVALENCES[1]

DRUG	Equivalent Dose (mg)[2] (compared to morphine 10 mg IM)		Duration of Action (hours)
	Parenteral	Oral	
Strong Opioid Agonists:			
Morphine (single dose)	10	60[3]	3-4
(chronic dose)	10	20-30[3]	3-4
Hydromorphone	1.5-2	6-7.5	2-4
Anileridine	25	75	2-3
Levorphanol	2	4	4-8
Meperidine[4]	75	300	1-3
Oxymorphone	1.5	5(rectal)	3-4
Methadone[5]	5-8	10-15	3-4
Heroin			
Weak Opioid Agonists:			
Codeine	120	200	3-4
Hydrocodone	-	15-30	3-6
Oxycodone	5-10	10-15[6]	2-4
Propoxyphene	50	100	
Mixed Agonist-Antagonists[7]:			
Pentazocine[4]	60	180	3-4
Nalbuphine	10		3-6
Butorphanol	2		3-4

[1] References:
Cancer Pain: A Monograph on the Management of Cancer Pain, Health and Welfare Canada 1984.
Foley K.M., New Engl. J.Med.313:84-95,1985.
Aronoff, G.M. and Evans, W.O., In: Evaluation and Treatment of Chronic Pain, 2nd Ed., G.M. Aronoff (Ed.), Williams and Wilkins, Baltimore,pp.359-368,1992.
Cherny, N.I. and Portenoy, R.K., In: Textbook of Pain, 3rd Ed., P.D. Wall and R. Melzack (Eds.), Churchill Livingstone, London, pp.1437-1467,1994.

[2] Most of this data was derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain.

[3] For acute pain, the oral or rectal dose of morphine is six times the injectable dose. However, for chronic dosing, clinical experience indicates that this ratio is 2-3:1 (i.e., 20-30 mg of oral or rectal morphine is equivalent to 10 mg of parenteral morphine).

[4] These drugs are not recommended for the management of chronic pain.

[5] Extremely variable equianalgesic dose. Patients should undergo individualized titration starting at an equivalent to 1/10 of the morphine dose.

[6] In combination with acetaminophen or ASA. For acute pain, single entity oral oxycodone is twice as potent as oral morphine.

[7] Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

PHARMACEUTICAL INFORMATION

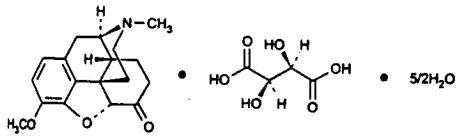
Drug Substance

Trade Name: CODOFEN: hydrocodone bitartrate and ibuprofen fixed combination.

Common Name: Hydrocodone bitartrate

Chemical Name: 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one

Structural Formula:



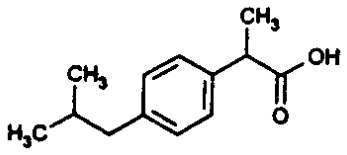
Molecular Formula: $C_{18}H_{21}NO_3\ C_4H_6O_6\ 2½H_2O$ **Molecular Weight:** 494.5

Drug Substance

Common Name: Ibuprofen

Chemical Name: (±)-2-(*p*-isobutylphenyl) propionic acid

Structural Formula:



Molecular Formula: $C_{13}H_{18}O_2$ **Molecular Weight:** 206.29

Description

Hydrocodone Bitartrate*:* White needle-shaped crystalline solid with a melting point of 137 to 143°C. It is insoluble in ether and chloroform and has a pH 3.6.

Ibuprofen*:* white crystalline solid with a melting point of 75 to 77°C and a pKa of ~5.2. Solubility at 25°C: very slightly soluble in water (pH 3.4 to 7.5 at 0.04 to 6.56 mg/mL) and very soluble in alcohol, methanol, acetone and chloroform.

Composition

Each CODOFEN tablet contains of 7.5 mg hydrocodone bitartrate USP and 200 mg ibuprofen USP. It also contains as inactive ingredients, colloidal silicon dioxide NF; microcrystalline cellulose NF; croscarmellose sodium NF, corn starch NF, hydroxypropyl methylcellulose USP and magnesium stearate NF and colouring (Opadry YS-3-7011 and Opadry YS-1-7003: Hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, polysorbate 80 and propylene glycol).

Stability and Storage Recommendation

Store at controlled room temperature, between 15 to 30°C. Do not use beyond expiry date indicated on the label.

AVAILABILITY OF DOSAGE FORM

Each white, round, convex, CODOFEN (hydrocodone bitartrate-ibuprofen) film-coated tablet engraved with 'VP' over the Knoll triangle on one side only, contains hydrocodone bitartrate 7.5 mg and ibuprofen 200 mg. CODOFEN tablets are supplied in HDPE bottles of 100 and 500, and blister packs of 4 x 25.

INFORMATION FOR THE CONSUMER

Please read this leaflet carefully before you take CODOFEN tablets. This provides a summary of the information available on your medicine. Please do not throw away this leaflet until you have finished your medicine; you may need to read it again. This leaflet does not contain all the information on CODOFEN Tablets. For further information or advice, ask your doctor or pharmacist.

Information about your Medicine

The name of your medicine is CODOFEN Tablets. It contains a combination of ibuprofen and hydrocodone which are both medications for pain relief. Tolerance to CODOFEN can develop with continued use and it can be obtained only by prescription from your doctor. The decision to use CODOFEN Tablets is one that you and your doctor should make jointly, taking into account your individual preferences and medical circumstances.

The Purpose of Your Medicine

CODOFEN Tablets are intended to provide short term relief of your acute moderate pain. CODOFEN should not be used to treat chronic pain conditions such as rheumatoid arthritis or osteoarthritis since neither the safety nor efficacy of CODOFEN has been established in patients with these conditions.

How Your Medicine Works

CODOFEN is a combination of two pain relieving ingredients: ibuprofen and hydrocodone. Ibuprofen works by reducing the production of pain-producing substances called prostaglandins, often in the painful area. Hydrocodone works in the Central Nervous System (brain and spinal cord) to reduce the awareness of pain.

What your doctor or dentist, and pharmacist need to know about you

Medical professionals need certain information about you to decide whether you can take CODOFEN safely. Make sure they know whether you have:

- an allergy to aspirin (ASA or acetylsalicylic acid), ibuprofen or other pain relievers,
- side effects from medication for arthritis, rheumatism, sore joints, or other pain relievers that you have taken in the past,
- a history of stomach upset or ulcer,
- liver disease,
- kidney disease,
- other medical problems,
- all medications you are currently taking, including over the counter products.

If you are seeing more than one doctor, be sure they know you are taking CODOFEN.

Are you pregnant or breast-feeding?

If you are pregnant or intend to become pregnant, inform your doctor. CODOFEN is not recommended during pregnancy. CODOFEN is also not recommended while breast-feeding, since it is not known whether the ingredients pass into breast milk.

What are the side effects?

Like any other medication, CODOFEN can produce side effects. The most common side effects are stomach problems, nausea, sleepiness, and dizziness.

Some side effects cause only mild discomfort, but are important for your doctor to know about. Inform your doctor as soon as possible if any of the following occur.

- bloody or black, tarry stools
- stomach pain, nausea, vomiting, indigestion, diarrhea, rectal itching or bleeding
- yellow discolouration of skin or eyes
- "flu-like" symptoms
- itching, rash, hives, swelling
- shortness of breath, wheezing, troubled breathing or tightness in chest
- swelling of feet or lower legs
- blurred vision or any visual disturbance or hearing problem
- changes in the amount or colour of your urine (such as dark, red or brown)
- mental confusion, depression, headache, dizziness, lightheadedness
- any other unusual effect

What about taking other drugs or alcohol at the same time?

Aspirin (ASA), ASA-containing compounds, other ibuprofen products, and drugs used to relieve pain and/or swelling must not be taken while you are taking CODOFEN, unless your doctor directs otherwise. Be aware that other drugs and alcohol may interact with CODOFEN to make you drowsy, dizzy or lightheaded. Make sure your doctor is aware of all other drugs you are taking.

Am I okay to drive?

CODOFEN can make you drowsy, dizzy or lightheaded, and decrease your alertness. Do not drive, operate machinery, or undertake other hazardous or complex tasks until you know your reaction to CODOFEN. Avoid these activities if you are drowsy.

Can children take CODOFEN?

The safety and effectiveness of CODOFEN in children has not been established. Children should therefore not take CODOFEN.

Have you been given the correct tablets?

CODOFEN tablets are white, round, and convex with the Knoll triangle logo overlaid with ‘VP' on one side.

How to take CODOFEN

The recommended adult dose is one tablet every 4-6 hours. Do not take more than 6 tablets in a 24 hour period or for more than 5 days unless your doctor tells you to do so. CODOFEN should not be used to treat chronic pain conditions such as rheumatoid arthritis or osteoarthritis as it has not been tested for efficacy or safety in these conditions.

Storage

Protect your tablets from heat. Store at temperatures between 15°C- 30°C.

Remember

Use CODOFEN only as directed and do not give it to anyone else. If you require more information, consult your pharmacist or doctor. Keep this and all other medications out of the reach of children. If you think you are experiencing side effects, stop taking the tablets and notify your doctor immediately.

PHARMACOLOGY

The pharmacologies of ibuprofen and hydrocodone bitartrate have been previously characterized and are well known.

TOXICOLOGY

The preclinical CODOFEN safety evaluation assessed the potential toxicity of three different active ingredient ratios, 1:80, 1:40 and 1:27 hydrocodone bitartrate to ibuprofen, prepared with appropriate excipients. Compared with the intended clinical dosing regimen, the ibuprofen proportions remained constant at 200 mg while the hydrocodone bitartrate concentration proportion varied over the range of 2.5, 5.0 and 7.5 mg. Thus, the 1:27 blend used in toxicology studies is comparable, with respect to drug proportions, to the marketed formulation of CODOFEN; the 1:40 and 1:80 blends have diminishing proportions of hydrocodone compared with ibuprofen. In the following tables, studies described which used the 1:27 blend are shaded for the purposes of clarity. The ibuprofen active controls received a dose equivalent to the ibuprofen contained in the CODOFEN combination. Active ingredients constitute approximately 68% of the final blend or formulation used to produce the tablets used in the clinical trials.

Table 4
Short Term Toxicity

Species/ Strain	Compound	Sex No./Grp	Observation (days)	LD_{50} Active mg/kg	Important findings
Mouse CD-1	Codofen 1:80	M/5	14	1240	Prostration, dyspnea, Straub tail, convulsions (higher Codofen doses). GI toxicity dose-related, similar to Ibuprofen.
		F/5	14	1512	
	Ibuprofen	M/5	14	1186	
		F/5	14	2372	
Rat Sprague Dawley	Codofen 1:80	M/5	14	1006	Ibuprofen and Codofen toxicity similar. GI lesions, inflammation, haemorrhage seen with both drugs (Codofen higher doses).
		F/5	14	802	
	Ibuprofen	M/5	14	<1186	
		F/5	14	< 839	
Rat Sprague Dawley	Codofen 1:40	M/5	14	808	Codofen toxicity attributed to Ibuprofen.
		F/5	14	709	
	Ibuprofen	M/5	14	714	
		F/5	14	< 505	

Table 5
Long Term Toxicity

Species/ Strain	Sex No./Group	Observation (days)	Compound (Ratio)	Active mg/kg	Important findings
Rat Sprague Dawley	4/sex	7	Control	0	Significant GI toxicity was seen, as was some renal toxicity.
			V (1:80)	65	
			V (1:80)	130	
			V (1:80)	260	
			V (1:80)	520	
Monkey Cynomolgus	1/sex	14	Control	0	Some liver, renal toxicity, weight loss, anorexia seen.
			V (1:80)	25/300	
			V (1:80)	50	
			V (1:80)	100	
			V (1:80)	200	
Rat Sprague Dawley	10/sex	30	Control	0	Codofen toxicity similar to Ibuprofen. GI toxicity, ulcers responsive anaemia, weight loss, ↓eating, ↑liver, spleen weights.
			V (1:80)	40	
			V (1:80)	80	
			V (1:80)	160	
			Ibuprofen	160	
Rat Sprague Dawley	20/sex	90	Control	0	Codofen higher dose toxicity similar to Ibuprofen. GI toxicity, ulcers, interstitial nephritis, renal tubular nephritis, Gastritis seen with both drugs, greater with Ibuprofen.
			V (1:27)	33	
			V (1:27)	66	
			V (1:27)	132	
			Ibuprofen	131	
			V (1:27)	99	
			Ibuprofen	96	
Monkey Cynomolgus	3/sex	30	Control	0	Similar clinical signs seen for both drugs: anorexia, ataxia. One death in high dose Codofen Ibuprofen group. Pyloric ulcer seen with Codofen.
			V (1:80)	65	
			V (1:80)	130	
			V (1:80)	260	
			Ibuprofen	257	

Table 6
Reproductive Studies

Species /Strain	Sex No./Group	Observation (days)	Compound (Ratio)	Active (mg/kg)	Important Findings
Rat Sprague-Dawley	24/F	6 to 15	Control	0	Severe maternal toxicity, at >200 mg/kg. Few embryotoxic effects, fetal abnormalities.
			V (1:27)	50	
			V (1:27)	100	
			V (1:27)	200	
			V (1:27)	166	
Rabbit NZW	5/F	6 to 18	Control	0	MTD in pregnant rabbits is 90 mg/kg/day, ↓eating, weight gain no effect on embryonic & fetal development. Sex ratios were normal
			V (1:27)	10	
			V (1:27)	25	
			V (1:27)	70	
			V (1:27)	90	
Rabbit NZW	16/F	6 to 18	Control	0	Transient food, weight reductions. No embryo toxicity, fetal growth retardation. Increase in both major and minor abnormalities at high Codofen dose; relationship to treatment not clear.
			V (1:27)	10	
			V (1:27)	33	
			V (1:27	95	

Genotoxicity Studies

No genotoxicity studies have been performed with CODOFEN. The genotoxicity for the components has been previously characterized.

REFERENCE

1. Wideman G, Keffer M, Morris EJ, Doyle R, Jiang JG, Beaver WT. Analgesic Efficacy of a Combination of Hydrocodone with Ibuprofen in Post-operative Pain. Clin Pharmacol Ther 1999; 65(1):66.