PRODUCT MONOGRAPH

Muscle and Back Pain Platinum Relief

Methocarbamol and Ibuprofen Caplets

500mg/200mg

Muscle Relaxant/Analgesic

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Control Number 231400

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Methocarbamol and Ibuprofen Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	**Tablet:** Methocarbamol 500 mg and ibuprofen 200 mg	None. For a complete listing see Dosage Forms, Composition and Packaging section.

INDICATIONS AND CLINICAL USE

Adults and Children (>12 years of age): Muscle and Back Pain Platinum Relief is indicated for the effective relief of pain associated with muscle spasm such as back pain, tense neck muscles, strains and sprains.

Geriatrics (> 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. Therefore, the use of Muscle and Back Pain Platinum Relief in this population is not recommended (See *Warnings and Precautions, Special Populations, Geriatrics*).

Pediatrics (< 12 years of age): Muscle and Back Pain Platinum Relief is not indicated for children <12 years of age.

CONTRAINDICATIONS

- Known hypersensitivity to methocarbamol or ibuprofen. Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the *Dosage Forms, Composition and Packagin*g section of the product monograph. There is a potential for cross-reactivity between different NSAIDs and ibuprofen, and patients sensitive to other carbamate derivatives and methocarbamol.

- Active peptic ulcer, a history of recurrent ulceration or active inflammatory disease of the G.I. system, such as ulcerative colitis and Crohn's disease.[56]

- The combination drug product should not be used in patients who have significant hepatic impairment or active liver disease.[56]

- Severely impaired or deteriorating renal function (creatinine clearance <30 mL/min).[56] Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored.

- Patients with the complete or partial syndrome of nasal polyps, or in whom asthma, anaphylaxis, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse effects.

- Not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.

- Children (equal to or greater than 12 years of age) with kidney disease or who have suffered significant fluid loss due to vomiting, diarrhea or lack of fluid intake, should not be given ibuprofen.

- Ibuprofen is contraindicated in patients with systemic lupus erythematosus, as an anaphylaxis-like reaction with fever may occur, particularly when ibuprofen has been administered previously.

- Ibuprofen should not be used during pregnancy or by nursing mothers.

- Ibuprofen should not be used right before or after heart surgery.

Serious Warnings and Precautions

- Use with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention (See *WARNINGS AND PRECAUTIONS, Cardiovascular* and *Fluid and Electrolyte Balance;* and *DRUG INTERACTIONS, Antihypertensives*).
- Use with caution in patients who might be prone to gastrointestinal tract irritation, particularly those with a history of diverticulosis, or other inflammatory disease of the gastrointestinal tract such as ulcerative colitis or Crohn's disease (See *WARNINGS AND PRECAUTIONS, Gastrointestinal* and *DRUG INTERACTIONS, Coumarin-type anticoagulants*).
- Use with caution in patients at greatest risk of renal toxicity, such as those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly (See *WARNINGS AND PRECAUTIONS, Renal*).
- Ibuprofen use during pregnancy/nursing should be avoided (See *WARNINGS AND PRECAUTIONS, Special Populations: Pregnant Women and Nursing Women*).
- If persistent urinary symptoms, hematuria and cystitis occur, the drug should be stopped immediately (See *WARNINGS AND PRECAUTIONS, Genitourinary*).

General

In common with other anti-inflammatory drugs, ibuprofen may mask the usual signs of infection.

Methocarbamol may produce false positive tests for urinary 5-hydroxyindoleacetic acid (5-HIAA) and vanillymandelic acid (VMA).

Carcinogenesis and Mutagenesis

Not applicable.

Cardiovascular

Congestive heart failure in patients with marginal cardiac function, elevated blood pressure and palpitations have been reported following ibuprofen administration.[56]

Dependence/Tolerance

Not applicable.

Ear/Nose/Throat

Patients with complete or partial syndrome of nasal polyps should not use this drug.

Endocrine and Metabolism

Not applicable.

Fluid and Electrolyte Balance

Fluid retention and edema have been observed in patients treated with ibuprofen. Therefore, as with many other NSAIDs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. Ibuprofen should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

With NSAID 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. Serum electrolytes should be monitored periodically during long-term therapy, especially in those who are at risk.

Gastrointestinal

Serious GI toxicity, such as peptic ulceration, perforation and gastrointestinal bleeding, [68] sometimes severe and occasionally fatal, can occur at any time, with or without symptoms in patients treated with NSAIDs including ibuprofen.

Minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy. Physicians should remain alert for ulceration and bleeding in patients treated with nonsteroidal anti-inflammatory drugs, even in the absence of previous GI tract symptoms.

In patients observed in clinical trials of such agents, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. The risk continues beyond one year and possibly increases. The incidence of these complications increases with increasing dose.

Combination methocarbamol/ibuprofen should be given under close medical supervision to patients prone to gastrointestinal irritation, particularly those with history of peptic ulcer, diverticulosis or ulcerative colitis and Crohn's Disease.[56] In these cases the physician must weigh the benefits of treatment against the possible hazards.

Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and instruct them to contact a physician immediately if they experience persistent dyspepsia or other symptoms or signs suggestive of gastrointestinal ulceration or bleeding. Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients by checking their haemoglobin periodically and by being vigilant for the signs and symptoms of ulceration and bleeding and should inform the patients of the importance of this follow-up.

If ulceration is suspected or confirmed, or if GI bleeding occurs, Muscle and Back Pain Platinum Relief should be discontinued immediately, appropriate treatment instituted and the patient monitored closely.

No studies, to date, have identified any group of patients not at risk of developing ulceration and bleeding. A prior history of serious GI events and other factors such as excess alcohol intake, smoking, age, female gender and concomitant oral steroid and anticoagulant use have been associated with increased risk. Studies to date show that all NSAIDs can cause GI tract adverse events. Although existing data does not clearly identify differences in risk between various NSAIDs, this may be shown in the future.

Genitourinary

Some NSAIDs are known to cause persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with an NSAID. Some cases have become severe on continued treatment. Should urinary symptoms occur, treatment with ibuprofen/methocarbamol combination must be stopped immediately to obtain recovery. This should be done before any urological investigations of treatments are carried out.

Hematologic

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees; therefore, patients who may be adversely affected by such an action should be carefully observed when ibuprofen is administered.

Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anaemia and agranulocytosis) associated with the use of NSAIDs are rare, but could occur with severe consequences.

Hepatic/Biliary/Pancreatic

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with nonsteroidal anti-inflammatory drugs.

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

During long-term therapy, liver function tests should be monitored periodically. If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

The frequency of acute liver injury among 311,716 patients who were prescribed ibuprofen was 1.6/100,000. For NSAID users as a group, the only factors that had an independent effect on the occurrence of acute liver injury were the simultaneous use of hepatotoxic medication or the

presence of rheumatoid arthritis.[24] Based on these data, the short-term use of ibuprofen as an analgesic/antipyretic should not be of concern regarding the development of liver disease.

Immune
In occasional cases with some NSAIDs (ibuprofen) the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea, vomiting, fever, or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissue disease etc.) seem to be pre-disposed. Therefore, in such patients, the physician must be vigilant to the development of this complication.

Neurologic
Some patients may experience drowsiness, dizziness, vertigo or insomnia with the use of ibuprofen. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

Methocarbamol has potential to cause drowsiness and dizziness. The patient should be cautioned against the operation of motor vehicles or machinery. Since methocarbamol may possess a general CNS depressant effect, patients taking Muscle and Back Pain Platinum Relief should be cautioned about combined effects with alcohol and other CNS depressants.

Ophthalmologic
Blurred and/or diminished vision has been reported with the use of ibuprofen. If such symptoms develop this drug product should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug product for an extended period of time.

Peri-Operative Considerations
Not applicable.

Psychiatric
Some patients may experience depression with the use of ibuprofen.

Renal
Long-term administration of nonsteroidal anti-inflammatory drugs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state.

Like other NSAIDs, ibuprofen inhibits renal prostaglandin synthesis, which may decrease renal function and cause sodium retention. Renal blood flow and glomerular filtration rate decreased in patients with mild impairment of renal function who took 1200 mg/day of ibuprofen for one week. Renal papillary necrosis has been reported. A number of factors appear to increase the risk of renal toxicity. In comparative clinical trials involving 7624 ibuprofen-treated, 2822 ASA-treated and 2843 placebo-treated patients, adverse reactions involving renal function were reported by 0.6% of the ibuprofen group, 0.3% of the ASA group and 0.1% of the placebo group.

The analysis included data from trials which employed doses greater than 1200 mg, used for longer periods than OTC recommendations and by patients being treated for serious conditions.[83] Ibuprofen and its metabolites are eliminated primarily by the kidneys; therefore the drug should be used with great caution in patients with impaired renal function. In these cases, utilisation of lower doses of Muscle and Back Pain Platinum Relief should be considered and patients carefully monitored. Methocarbamol may also affect renal function if therapy lasts 5 days or more.

During long-term therapy kidney function should be monitored periodically.

Respiratory
Not applicable.

Sensitivity/Resistance
Patients sensitive to any one of the nonsteroidal anti-inflammatory drugs may be sensitive to any of the other NSAIDs also.

Sexual Function/Reproduction
Not applicable.

Skin
Not applicable.

Special Populations

Pregnant Women: Muscle and Back Pain Platinum Relief is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition (see Toxicology).

Caution should be exercised in prescribing Muscle and Back Pain Platinum Relief to women who are trying to conceive, during the first and second trimester of pregnancy, or if breastfeeding (see Toxicology).

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. Because of the known effects of NSAIDs on the fetal cardiovascular system, use

of ibuprofen 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. Administration of ibuprofen is not recommended during pregnancy.

Nursing Women: Methocarbamol was detected in the breast milk of dogs. Assuming small amounts of methocarbamol are also excreted in human breast milk, it is doubtful any adverse clinical effects would be seen in the nursing infant. Newborns with neonatal tetanus have been treated with larger doses of intravenous or oral methocarbamol without ill effects from the drug.[33] One study showed an ibuprofen concentration of 13 ng/mL 30 minutes after ingesting 400 mg.[78] The milk: plasma ratio was 1:126. This translates to an infant exposure of 0.0008% of the maternal dose. It is not known to what extent, if any, ibuprofen crosses the human placenta. No adverse effect has been detected in children 6 months of age who were administered ibuprofen.

Pediatrics (< 12 years of age): The combination methocarbamol/ibuprofen has not been studied in children. Furthermore, the safety and efficacy of methocarbamol (other than in the management of tetanus) in children younger than 12 years of age also have not been established; therefore, Muscle and Back Pain Platinum Relief should not be administered to children in this age group.

Geriatrics (> 65 years of age): 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. The chance of stomach bleeding is higher if you are: age 60 or older, have had stomach ulcers or bleeding problems, take a blood thinner or steroid drug, take with other drugs containing an NSAID like acetylsalicylic acid (ASA), ibuprofen, naproxen, or prescription anti-inflammatory drugs, have 3 or more alcoholic drinks every day while using this product. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal ulceration and bleeding.[56]

For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision.

The OTC dose of 1200 mg ibuprofen per day for up to 7 days is reported to be safe for the over 65 years of age group.[52, 53]

Monitoring and Laboratory Tests

For Monitoring and Laboratory Tests related to the use of Muscle and Back Pain Platinum Relief, see *WARNINGS AND PRECAUTIONS, Fluid and Electrolyte Balance, Gastrointestinal, Hematologic, Hepatic, Renal and Special populations: Geriatrics*.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Post-Market Adverse Drug Reactions

Ibuprofen[56]

The following adverse reactions have been noted in patients treated with doses (≥ 1200 mg/day). Note: Reactions listed below under Causal Relationship Unknown are those which occurred under circumstances where a causal relationship could not be established. However, in these reported events, the possibility of a causal relationship to ibuprofen cannot be excluded.

Gastrointestinal

The adverse reactions most frequently seen with prescribed ibuprofen therapy involve the gastrointestinal system.

Incidence 3 to 9%: nausea, epigastric pain, heartburn.

Incidence 1 to 3%: diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the gastrointestinal tract (bloating or flatulence).

Incidence less than 1%: gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, hepatitis, jaundice, abnormal liver function AST, serum bilirubin and alkaline phosphatase.

Allergic

Incidence less than 1%: anaphylaxis.

Causal relationship unknown: fever, serum sickness, lupus erythematosus.

Central Nervous System

Incidence 3 to 9%: dizziness.

Incidence 1 to 3%: headache, nervousness.

Incidence less than 1%: depression, insomnia.

Causal relationship unknown: paresthesias, hallucinations, dream abnormalities.

Aseptic meningitis and meningoencephalitis, in one case accompanied by eosinophilia in the cerebrospinal fluid, have been reported in patients who took ibuprofen intermittently and did not have any connective tissue disease.

Dermatologic
Incidence 3 to 9%: rash (including maculopapular type).

Incidence 1 to 3%: pruritus.

Incidence less than 1%: vesiculobullous eruptions, urticaria, erythema multiforme. Causal relationship unknown: alopecia, Stevens-Johnson syndrome.

Cardiovascular
Incidence less than 1%: congestive heart failure in patients with marginal cardiac function, elevated blood pressure.

Causal relationship unknown: arrhythmias (sinus tachycardia, sinus bradycardia, palpitations).

Special Senses
Incidence 1 to 3%: tinnitus.

Incidence less than 1%: amblyopia (blurred and/or diminished vision, scotomata and/or changes in colour vision). Any patient with eye complaints during ibuprofen therapy should have an ophthalmological examination.

Causal relationship unknown: conjunctivitis, diplopia, optic neuritis.

Hematologic
Incidence less than 1%: leukopenia and decreases in hemoglobin and hematocrit.

Causal relationship unknown: hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes (e.g. purpura, epistaxis, hematuria, menorrhagia).

Renal
Causal relationship unknown: decreased creatinine clearance, polyuria, azotemia.

Like other non-steroidal anti-inflammatory drugs, ibuprofen inhibits renal prostaglandin synthesis, which may decrease renal function and cause sodium retention. Renal blood flow and glomerular filtration rate decreased in patients with mild impairment of renal function who took 1200 mg/day of ibuprofen for one week. Renal papillary necrosis has been reported. A number of factors appear to increase the risk of renal toxicity (See *WARNINGS AND PRECAUTIONS*).

Hepatic
Incidence less than 1%: hepatitis, jaundice, abnormal liver function (AST, serum bilirubin, and alkaline phosphatase).

Endocrine
Causal relationship unknown: gynecomastia, hypoglycemic reaction.

Menstrual delays of up to two weeks and dysfunctional uterine bleeding occurred in nine patients taking ibuprofen, 400 mg t.i.d., for three days before menses.

Metabolic
Incidence 1 to 3%: decreased appetite, edema, fluid retention.

Fluid retention generally responds to drug discontinuation.

Methocarbamol

May cause drowsiness,[58] dizziness,[58] blurred vision[74] light headedness, somnolence,[58] vertigo,[58] anorexia, headache, fever, nausea, allergic reactions such as urticaria, pruritus, rash, skin eruptions, conjunctivitis with nasal congestion.[80]

Oral administration of methocarbamol may cause the urine in some patients, following elimination from the body, to turn brown, black, blue or green after a period of time.[81]

DRUG INTERACTIONS

Overview
Muscle and Back Pain Platinum Relief is not recommended for concomitant use with any other NSAIDs, including ASA. Documented or possible drug interactions with Muscle and Back Pain Platinum Relief include acetaminophen, digoxin, anticoagulants, oral antidiabetic agents and insulin, antihypertensives, diuretics, methotrexate, lithium and other protein-bound drugs.

Since methocarbamol may possess a general CNS depressant effect, patients taking Muscle and Back Pain Platinum Relief should be cautioned about combined effects with alcohol and other CNS depressants.

Drug-Drug Interactions

Acetaminophen
Although interactions have not been reported, concurrent use with ibuprofen is not advisable; it may increase the risk of adverse renal effect.

Acetylsalicylic acid (ASA) or other NSAIDs
The use of ibuprofen in addition to any other NSAID, including ASA, is not recommended due to the possibility of additive side effects. Animal studies show that acetylsalicylic acid given with NSAIDs including ibuprofen, yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-acetylsalicylic acid drug. Single dose bioavailability studies in normal volunteers have failed to show an effect of acetylsalicylic acid on ibuprofen blood levels. Correlation clinical studies have not been conducted.

Antacids[11]
A bioavailability study has shown that there was no interference with the absorption of ibuprofen when given in conjunction with an antacid containing aluminum hydroxide and magnesium hydroxide.

Anti-hypertensives
Ibuprofen can interfere with blood pressure control in certain patients under treatment for mild to moderate hypertension.

Prostaglandins are an important factor in cardiovascular homeostasis and inhibition of their synthesis by NSAIDs may interfere with circulatory control. NSAIDs may elevate blood pressure in patients receiving antihypertensive medication. Two meta analyses,[6, 7] have observed this relationship for NSAIDs as a class and for certain NSAIDs in particular, but ibuprofen did not significantly affect blood pressure in either meta analysis. Consistent with this lack of effect, a study by Davies et al[13] showed that ibuprofen 1600 mg/day for 14 days did not attenuate the antihypertensive effect of two ß-adrenergic blockers. Houston et al[14] showed no effect of three weeks' therapy with ibuprofen on the antihypertensive efficacy of verapamil, but it is not known whether this lack of interaction extends to other classes of calcium channel blockers.

When renal perfusion pressure is reduced both prostaglandins and angiotensin II are important mediators of renal autoregulation.[22] As a class, the combination of an NSAID and angiotensin converting enzyme inhibitor theoretically may have the potential to decrease renal function. One study found a clinically significant decrease in renal function in 4 of 17 patients treated with hydrochlorothiazide and fosinopril who received ibuprofen 2400 mg/day for one month.[16] In contrast, Minuz[43] found no effect on the antihypertensive effect of enalapril or on plasma renin or aldosterone following two days' treatment with ibuprofen 1200 mg/day.

The relationship of ibuprofen and antihypertensives is clearly not well defined. The benefits of concomitant medication should be analysed and compared to the potential risks before being prescribed. If ibuprofen is being recommended for long-term use, then periodic monitoring of blood pressure may be useful. Blood pressure monitoring is not necessary if ibuprofen is being recommended for short-term use as an analgesic.

Coumarin-type[40, 15]
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, concurrent therapy of ibuprofen with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary.[56] Several short-term controlled studies failed to show that ibuprofen significantly affected prothrombin time or a variety of other clotting factors when administered to individuals on coumarin-type anticoagulants. Nevertheless, the physician should be cautious when administering ibuprofen to patients on anticoagulants.

Digoxin[30]
Ibuprofen has been shown to increase serum digoxin concentration. Increased monitoring and dosage adjustments of digitalis glycoside may be necessary during concurrent ibuprofen therapy and following discontinuation of ibuprofen therapy.

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

Clinical studies, as well as random observations, have shown that ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with ibuprofen, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

H-2 antagonists
In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Hypoglycaemic Agents
Ibuprofen may increase hypoglycemic effects of oral antidiabetic agents and insulin.[56]

Lithium[57]
Plasma lithium levels should be carefully monitored in patients taking combination therapy of ibuprofen and lithium. Ibuprofen has been shown to decrease the renal lithium clearance and increase plasma lithium levels.

Methotrexate[48]
Ibuprofen and other NSAIDs have been reported to reduce renal tubular secretion of methotrexate in-vitro. This may enhance the toxicity of methotrexate. Caution should be used when ibuprofen is administered concomitantly with methotrexate.

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, and phenytoin.

However, the mechanisms 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, antibiotics (e.g. cyclosporine), phenytoin, corticosteroids or benzodiazepines.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbs have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Consult a physician if symptoms persist for longer than 5 days.

The safety issues to consider when developing a dosage regimen of Muscle and Back Pain Platinum Relief for individual patients is applicable to:

- Elderly patients older than 65 years who are frail or debilitated and consideration should be given to a starting dose lower than the one usually recommended (See *WARNINGS AND PRECAUTIONS, Elderly*).

Recommended Dose and Dosage Adjustment

***Adults and Children over 12*:** 1 to 2 caplets every 4-6 hours. Do not exceed 6 caplets in 24 hours, unless recommended by a physician.

Missed Dose
Take the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to take your medicine and skip your missed dose. Do not take two doses at the same time.

Administration
See *Recommended Dose and Dosage Adjustment.*

OVERDOSAGE

Symptoms of Overdose
Methocarbamol overdose toxicity or death has not been reported. One adult survived the deliberate ingestion of 22 to 30 g of methocarbamol without serious toxicity. Another survived 30 to 50 g. The principal symptom was drowsiness in both cases. However, 3 deaths have been

reported when methocarbamol was combined with alcohol and other drugs.

Clinical findings associated with major ibuprofen overdose include abdominal pain, nausea, vomiting, lethargy and drowsiness. Other CNS symptoms include headache, tinnitus, CNS depression, dizziness, drowsiness, seizures, apnea and stupor, rarely progressing to coma. Examination may reveal hyper- or hypothermia, abnormal respiration ranging from hyperventilation to respiratory depression, hypotension, sinus tachycardia or bradycardia, and abnormal neurological and neuromuscular activity with ataxia, nystagmus, and seizure activity. Subsequently, renal dysfunction with oliguria or anuria may supervene, and clinical evidence of bleeding due to hypoprothrombinemia and thrombocytopenia may occur later. An elevated anion gap metabolic acidosis can be seen following large ingestions.

Treatment of Overdose

Acute ibuprofen overdose does not normally result in significant morbidity or mortality, although serious toxicity has been reported following very large overdoses. Deaths have been rare. Treatment is directed towards specific clinical signs and symptoms, and is generally supportive.

Adverse effects associated with ibuprofen overdose usually depend on the amount of drug ingested and time elapsed; however, because each individual response may vary, each occurrence of overdose has to be evaluated individually. In general, ingestion of up to 200 mg/kg will not cause symptoms of toxicity, and observation at home is recommended. If symptoms are to appear, they will occur within 4 hours of poisoning, and the patient should be taken to a medical facility.

For overdoses >200 mg/kg (ibuprofen), the patient should be referred to a medical facility and gastrointestinal decontamination with administration of activated charcoal (1 gm/kg) should be instituted. However, little drug is likely to be captured if the time elapsed after ingestion is greater than 1 hour. Because seizures can occur in children with ibuprofen overdose, emesis should not be induced at this level of overdose. The onset of symptoms is usually within 4 hours of ingestion so the patient should be observed for at least this period of time.

For overdoses greater than 400 mg/kg (ibuprofen), in-hospital observation is indicated. Initial laboratory tests should include arterial blood gases, electrolyte levels, blood urea nitrogen (BUN), creatinine, and liver function studies.

In pediatric patients, the estimated amount of ibuprofen ingested per body weight may be helpful to predict the potential for development of toxicity although each case must be evaluated. Ingestion of less than 100 mg/kg is unlikely to produce toxicity. Pediatric patients ingesting 100 to 200 mg/kg may be managed with induced emesis and a minimal observation time of at least four hours. Pediatric patients ingesting 200 to 400 mg/kg of ibuprofen should have immediate gastric emptying and at least four hours observation. Pediatric patients ingesting greater than 400 mg/kg require immediate medical referral, careful observation and appropriate supportive therapy. Ipecac-induced emesis is not recommended in overdoses greater than 400 mg/kg because of the risk for convulsions and the potential for aspiration of gastric contents.

Methocarbamol overdose treatment: Within ½ to 1 hour of ingestion, gastric lavage and/or emesis may reduce absorption. Supportive measures include maintenance of an adequate airway, monitoring urinary output and vital signs and the administration of i.v. fluids, if necessary. There is no experience with forced diuresis or with dialysis in the treatment of methocarbamol overdose. Likewise, the usefulness of hemodialysis in managing methocarbamol overdose is unknown.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

A bioavailability study has demonstrated that methocarbamol and ibuprofen when taken (orally) in combination, are bioequivalent to methocarbamol and ibuprofen when taken individually. This indicates that the absorption and bioavailability of these drugs is independent of each other's presence. There is no pharmacological interaction between methocarbamol and ibuprofen. Methocarbamol is a muscle relaxant and ibuprofen is an analgesic with antipyretic and anti-inflammatory properties.

Mechanism of Action

Methocarbamol:

Methocarbamol is effective in reducing muscle spasm and pain in acute musculo-skeletal disorders secondary to trauma and inflammation.[17,70] Each drug of the combination of methocarbamol and acetylsalicylic acid contributed to the therapeutic effects against acute painful skeletal muscle problems of spasm, pain and tenderness.[69,18] The precise mechanism of action is not known. Methocarbamol is thought to act on the central nervous system, perhaps depressing polysynaptic reflexes.

Ibuprofen:

Ibuprofen, like all nonsteroidal anti-inflammatory drugs (NSAIDs), is an analgesic, antipyretic, and anti-inflammatory medication.[42, 45, 19] There is strong evidence to support the view that the main mechanism of action of ibuprofen (like other NSAIDs) is related to decreasing prostaglandin biosynthesis.[34, 2, 41]

Prostaglandins are naturally-occurring fatty acid derivatives that are widely distributed in the tissues. They are believed to be a common factor in the production of pain, fever, and inflammation. Prostaglandins are believed to sensitise tissues to pain- and inflammation-producing mediators such as histamine, 5-hydroxytryptamine, and kinins. The enzyme catalyzing the committed step in prostaglandin biosynthesis is prostaglandin endoperoxide synthase, also known as cyclooxygenase. There is significant evidence that the main mechanism of

analgesic/antipyretic action of NSAIDs is prostaglandin biosynthesis inhibition.[82] Other pharmacologic effects such as lysosome and plasma membrane stabilisation have been observed, but the potential relevance of these effects to ibuprofen-induced analgesia and antipyresis is unclear.

Pharmacokinetics

Methocarbamol

Absorbtion: Orally administered methocarbamol is well absorbed from the gastrointestinal tract. Animal studies indicate that absorption occurs in the small intestine.[10]

Distribution: In a comparative bioavailability study, following oral administration peak plasma concentration was reached in approximately 45 minutes when methocarbamol was administered in combination with ibuprofen. The plasma half life of methocarbamol administered alone was 1.25 ± 0.27 hours and 1.30 ± 0.29 hours when administered in combination. In a dose proportionality study of single doses of 500 mg, 1500 mg and 3000 mg, it was shown that kinetics of methocarbamol are not linear. However, rates of elimination suggest that no accumulation is expected with chronic dosing every 6 hours.[20]

Metabolism: Methocarbamol has been shown to be metabolized in humans by dealkylation, hydroxylation and conjugation with glucuronic acid and sulfate, presumably in the liver. Two metabolites identified are:

3-(2-hydroxyphenoxy), 1, 2-propanediol-1-carbamate
3-(4-hydroxy-2-methoxyphenoxy)-1, 2-propanediol-1-carbamate.

Excretion: Studies in humans dosed with radio-labelled (C^{14}) methocarbamol indicated that 97-99% of the administered radioactivity was recovered in the urine over 3 days.[8] Extremely small amounts of unchanged methocarbamol have also been recovered in the feces.[8]

Ibuprofen

Absorption: Ibuprofen is rapidly and almost completely absorbed. Peak serum concentration occurs within 1-2 hours in adults.[4, 29] In a comparative bioavailability study, following oral administration peak plasma concentration was reached in approximately 1.6 hours for ibuprofen alone and in approximately 1.3 hours when ibuprofen was administered in combination with methocarbamol. The plasma half-life of ibuprofen administered alone was 2.11 ± 0.43 hours, and 2.08 ± 0.37 hours when administered in combination. Food decreases the rate but not the extent of absorption.[4]

Distribution: The volume of distribution in adults after oral administration is 0.1 - 0.2 L/kg.[3]

At therapeutic concentrations ibuprofen is highly bound to whole human plasma and to site II of purified albumin.[77] There is no appreciable plasma accumulation of ibuprofen or its metabolites with repeated doses.[4]

In humans, drug concentrations have been found in the synovial fluid of inflamed tissue approximately 5-12 hours after oral administration.[35, 37]

Metabolism: Cytochrome P450 (CYP) 2C9 has been identified as the most important catalyst for formation of all oxidative metabolites of R-(-) and S-(+) ibuprofen.[9]

Excretion: Approximately 80% of a dose is recovered in urine, primarily as carboxymetabolites and conjugated hydroxymetabolites.[3] Ibuprofen does not appear to induce the formation of drug metabolising enzymes in the rat.[39]

There is no evidence of a differential metabolism or elimination of ibuprofen in the elderly. A pharmacokinetic evaluation of ibuprofen in geriatric subjects (65 to 78 years) compared with young adult subjects (22 to 35 years) found that there was no clinically significant difference in the kinetic profiles of ibuprofen for these age groups.[28] Furthermore, there was no statistically significant difference between the two populations in the urinary excretion pattern of the drug and its major metabolites.[28]

Special Populations and Conditions

Breast Milk and Placental Transport:
The high protein binding and lower pH of breast milk versus plasma tend to inhibit the excretion of ibuprofen into breast milk.[78]

Ibuprofen excretion in breast milk following ingestion of one 400 mg ibuprofen tablet every 6 hours for five doses was below the level (i.e. 1 µg/mL) of detection.[5] However, a later study using a more sensitive assay showed ibuprofen to be rapidly excreted in breast milk 30 minutes following oral ingestion of 400 mg of ibuprofen at a concentration of 13 ng/mL. A milk:plasma ratio of 1:126 was determined and the exposure of a suckling infant was calculated to be approximately 0.0008% of the maternal dose.[78] It is not known whether ibuprofen crosses the placenta. Animal studies have shown that methocarbamol crosses the placenta.[10]

STORAGE AND STABILITY

Muscle and Back Pain Platinum Relief should be stored in closed containers under room temperature (15-30°C) conditions. Protect from light.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each white and grey coloured, caplet shaped, bilayer film coated tablets, debossing with ‘P449’ on grey side and plain on white side contains methocarbamol 500 mg and ibuprofen 200 mg.

Muscle and Back Pain Platinum Relief are available in blisters of 9/18/27 and bottles of 40/50/60/80/100/200.

In addition to methocarbamol and ibuprofen, the caplets contain: Colloidal silicon dioxide, FD&C Blue No. 2, ferric oxide (red), hypromellose, magnesium stearate, maize starch, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, sodium lauryl sulphate, sodium starch glycolate, stearic acid.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

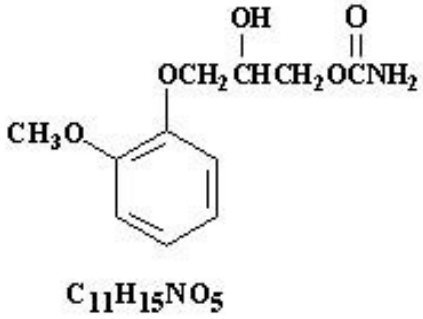
Drug Substance

Proper Name: Methocarbamol

Chemical Name: 1, 2-Propanediol, 3-(2-methoxyphenoxy)-, 1-carbamate
(±)-3-(0-methoxyphenoxy)-1, 2-propanediol 1-carbamate

Molecular formula and molecular mass: $C_{11}H_{15}NO_5$, 241.25

Structural Formula:



Physicochemical properties:	White powder or crystals.
Solubility:	Solubility in water at 20°C, 2.5 g/100 mL. Soluble in alcohol and propylene glycol.
pH value:	1% solution in water approximate pH 6-8.
Melting Point:	92 - 94°C

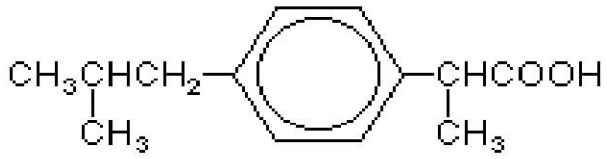
Drug Substance

Proper name: Ibuprofen

Chemical name: (±)-2-(p-isobutyl phenyl)propionic acid
Benzene acetic acid, α-methyl-4-(2-methylpropyl),
(±)-p-isobutyl hydratropic acid

Molecular formula and molecular mass: $C_{13}H_{18}O_2$, 206.28

Structural formula:



$C_{13}H_{18}O_2$

Physiochemical properties: White or almost white powder or crystals with a characteristic odour.

Solubility: Low solubility in water: soluble 1 in 1.5 of alcohol, 1 in 1 of chloroform, 1 in 2 of ether, and 1 in 1.5. of acetone. Ibuprofen is also soluble in an aqueous solution of alkali hydroxides and carbonates.

pH value: 4.6 - 6.0, in a solution of 1 in 20.

Melting Point: 75 - 77°C

CLINICAL TRIALS

Bioequivalence Studies

A randomized, single dose, open label, two treatment, two period, two sequence crossover, comparative bioavailability study of Muscle and Back Pain Platinum Relief (methocarbamol/ibuprofen) 500 mg/200 mg caplets of Vita Health Products Inc., and Robax Platinum® (containing methocarbamol/ibuprofen) 500 mg/200 mg caplets of Wyeth Consumer Healthcare Inc., Canada was conducted in 24 healthy, adult, Asian male subjects under fasting conditions. The results for ibuprofen and methocarbamol are summarized in the following tables.

Summary Table of the Comparative Bioavailability Data
IBUPROFEN
(1 x 500/200 mg)
From measured data
Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means #	90% Confidence Interval#
AUC_T (ng.hr/mL)	44746.77 48119.89 (45.34)	43713.59 46591.88 (41.77)	102.81	97.77 – 108.11
AUC_∞ (ng.hr/mL)	46854.65 50153.04 (43.68)	45976.50 48758.77 (40.27)	102.37	97.43 – 107.55
C_{max} (ng/mL)	13219.33 14088.77 (35.90)	14044.57 14651.09 (31.95)	95.12	87.21 – 103.76
T_{max}§ (hr)	1.96 (43.03)	1.59 (54.89)		
$T_{½}$§ (hr)	1.79 (21.84)	1.88 (27.20)		

* Muscle and Back Pain Platinum Relief (methocarbamol/ibuprofen) 500 mg/200 mg caplets (Vita Health Products Inc. Canada)

† Robax Platinum® (methocarbamol/ibuprofen) 500 mg/200 mg caplets caplets (Wyeth Consumer Healthcare Inc, purchased in Canada)

§ Expressed as the arithmetic mean (CV %) only

Based on the least square mean estimate

Summary Table of the Comparative Bioavailability Data METHOCARBAMOL (1 x 500/200 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means #	90% Confidence Interval#
AUC_T (ng.hr/mL)	23822.49 24816.65 (27.24)	23805.21 24959.89 (29.29)	99.33	91.94- 107.31
AUC_∞ (ng.hr/mL)	24565.45 25545.19 (26.72)	24433.32 25574.42 (28.84)	99.77	92.58- 107.52
C_{max} (ng/mL)	10296.23 10839.23 (33.17)	9100.48 9557.56 (32.06)	113.03	98.03 - 130.31
T_{max}§ (hr)	0.89 (53.82)	0.89 (53.30)		
$T_{½}$§ (hr)	1.49 (22.06)	1.63 (21.22)		

* Muscle and Back Pain Platinum Relief (methocarbamol/ibuprofen) 500 mg/200 mg caplets (Vita Health Products Inc.Canada)

† Robax Platinum® (methocarbamol/ibuprofen) 500 mg/200 mg caplets caplets (Wyeth Consumer Healthcare Inc, purchased in Canada)

§ Expressed as the arithmetic mean (CV %) only

Based on the least square mean estimate

Published Literature
Methocarbamol has been studied in muscle relaxation models including tetanus therapy,[73] muscle spasms,[75] painful muscle conditions,[17, 26, 55, 70] and in combination with analgesics,[23, 38, 69] with positive results. In gynecological postoperative patients, methocarbamol reduced the use of narcotics and other sedatives for pain and discomfort.[26]

A double-blind, randomized study showed that ibuprofen 400 mg every 4 hours for a total of 3 doses relieved muscle soreness following exercise significantly better than acetaminophen 1000 mg and placebo.[21]

A double-blind, randomized study showed that ibuprofen 400 mg relieved headache pain significantly better than acetaminophen 1000 mg and placebo.[49] Another double-blind, placebo-controlled, randomized study showed that ibuprofen 400 mg began to exert a significant analgesic effect on headache within 30 minutes after dosing.[50] One study confirmed that ibuprofen 400 mg provided a significantly faster onset of relief as measured by first perceptible relief, meaningful relief, per cent attaining complete relief, and superior overall analgesic efficacy compared to acetaminophen 1000 mg for relief of episodic tension-type headache.[51]

Ibuprofen has been studied in other pain models including dental,[71] muscle contraction headache,[76] soft tissue injury,[72, 44] post surgery,[66, 67] dysmenorrhea,[59, 61, 62, 63, 64, 65] and migraine,[54] with equally effective pain relief results.

Comparative Bioavailability Studies
In a comparative bioavailability study in humans after a single dose of combination (methocarbamol 500 mg and ibuprofen 200 mg) drug product, and single-drug methocarbamol 500 mg or ibuprofen 200 mg, the following pharmacological parameters were determined:

Parameter	Orally administered Combination Drug	Orally administered Single Drug
Methocarbamol mean t_{max}	0.72 ± 0.35 hours	1.01 ± 0.52 hours
Ibuprofen mean t_{max}	1.36 ± 1.04 hours	1.65 ± 0.96 hours
Methocarbamol mean $t_{½}$	1.30 ± 0.29 hours	1.25 ± 0.27 hours
Ibuprofen mean $t_{½}$	2.08 ± 0.37 hours	2.11 ± 0.43 hours
Methocarbamol mean C_{max}	8686.37 ± 2635.47 ng/ml	7698.73 ± 2657.59 ng/mL
Ibuprofen mean C_{max}	20376.2 ± 5592.44 ng/ml	18435.6 ± 4582.87 ng/mL
Methocarbamol k_{el}/hr.	0.556 ± 0.116	0.579 ± 0.116
Ibuprofen k_{el}/hr.	0.344 ± 0.065	0.342 ± 0.067

The results of this study show that Methocarbamol 500 mg and Ibuprofen 200 mg administered as a combination drug product are bioequivalent to Methocarbamol 500 mg and Ibuprofen 200 mg when administered individually.

DETAILED PHARMACOLOGY

Methocarbamol [8, 10, 27]

Human pharmacokinetic studies show rapid peaking of blood levels at under two hours.

In a comparative bioavailability study, the 500 mg dose administered individually produced peak plasma level at about 1 hour and in about 45 minutes when administered in combination with ibuprofen. The C_{max} was 7698 ng/mL for methocarbamol when administered alone relative to 8686 ng/mL when administered in combination. In about 6 hours the amount of methocarbamol level in plasma dropped to below 700 ng/mL for both individual and combination administrations.

Acute animal studies of methocarbamol levels in viscera have shown the highest concentrations in the liver and kidneys. Pharmacokinetic studies in dogs show that a single dose is cleared from the body in about three days. Animal studies have also shown that methocarbamol crosses the placental and blood-brain barriers.[10]

Some accumulation of methocarbamol at the usual dosage levels can be expected among patients with cirrhosis of the liver. At the six-hour point, plasma levels of methocarbamol in cirrhotics were about six times the normal. No alteration of methocarbamol metabolism was found in six patients with chronic renal failure and in a group of young-elderly.

In animal studies, the synergistic prolongation of hexobarbital sleeping time by methocarbamol was suggestive of an action on supraspinal brain centres.[60]

Ibuprofen

Animal Pharmacology

After single oral doses of 20 to 150 mg/kg of C^{14} labelled ibuprofen in rats, the peak plasma level occurred at or before the earliest time examined (20 minutes in the 20 mg/kg group and 45 minutes in the 150 mg/kg group) and peak levels occurred with 45 minutes of dosing in nearly all tissues examined. The concentration in plasma and tissue decreased to very low levels by six hours after the 20 mg/kg dose and by 17 hours after the 150 mg/kg dose. Sixteen to 38% of the daily dose of ibuprofen was excreted in the urine.[12]

A similar dose was given to dogs for periods of up to six months with no evidence of accumulation of the drug or its metabolites.[12]

Inhibition of Platelet Aggregation in Animals

Like many other NSAIDs, ibuprofen inhibits platelet aggregation, as demonstrated by preventing

platelet disposition in aortopulmonary arterial bypass grafts in the dog.[25] The drug's protective action against fatal pulmonary embolism in rabbits injected intravenously with arachidonic acid may also relate to platelet inhibition.[31, 32] Various prostaglandins and thromboxane A_2 (TXA_2), are important factors in normal platelet aggregation. Cyclooxygenase inhibition reduces TXA_2 production and release, thereby reducing platelet aggregation.[46] Ibuprofen may also reduce platelet membrane fluidity, which reduces aggregation,[47] but it is not known to what extent TXA_2 synthesis inhibition is involved in this effect.

Human Pharmacology

Two metabolites of lbuprofen were isolated from the urine of patients who had been treated for one month with the drug. The metabolites were identified as 2-4', (2-hydroxy-2-methylpropyl) phenylpropionic acid (metabolite A) and 2-4' (2-carboxpropyl) phenylpropionic acid (metabolite B). About 1/3 of the dose was excreted in the urine of patients as metabolite B, 1/10 as unchanged ibuprofen and 1/10 as metabolite A. The remainder of the dose could not be identified in the urine.[12]

Effect of Ibuprofen on Platelet Aggregation, Bleeding and Clotting Times in Normal Volunteers

Platelet aggregation studies using the method of Sekhar were performed. Platelet aggregation fell significantly at a dosage of 1800 mg per day of ibuprofen when given over a period of 28 days.

lbuprofen was also found to influence ADP induced aggregation to a lesser extent than that influenced by collagen. Platelet aggregation induced by recalcification of citrated platelet-rich plasma (a thrombin induced reaction) was not influenced by ibuprofen treatment. Likewise, ibuprofen did not affect whole blood clotting time on recalcification or prothrombin time. Bleeding time performed two hours after the administration of ibuprofen showed a significant dose related increase.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Acute Animal Toxicity

LD_{50} was determined in rats with oral combined drugs (methocarbamol 2.5 and ibuprofen 1 w/w) and individually administered methocarbamol and ibuprofen as follows:

	LD_{50} (mg/kg)
Methocarbamol / Ibuprofen (2.5/1)	2367.7
Methocarbamol	3576.2
Ibuprofen	762.9

The LD_{50} of the combination drug was 2367.7 mg/kg. It contained 676.5 mg of ibuprofen and

1691.2 mg of methocarbamol. The ibuprofen component of the combination is close to the LD_{50} of ibuprofen of 762.9 mg/kg. This suggests that ibuprofen was solely responsible for the toxicity/mortality of the animals dosed with the mixture. The results also indicate that the mixture of ibuprofen and methocarbamol (1:2.5 w/w) does not affect the acute oral toxicity of either constituent drug in rats.

Methocarbamol

Subacute Toxicity

Oral administration to dogs of dosages of 200, 400, 600 and 1000 mg/kg/day produced no gross signs of toxicity during the 30-day observation period. At 1200 mg/kg/day, transitory tremor, loss of righting reflex and salivation were seen. Ataxia, which was slightly more persistent, was also observed.[79]

Chronic Toxicity

Oral administration in rats of dosages up to 1600 mg/kg/day for 13 weeks produced toxic effects only at the higher levels. At 1600 mg/kg/day, there was sprawling of the hind limbs and waddling gait during the first 6-8 weeks of the study. Doses of 800 mg/kg/day and higher resulted in significant reduction in body weight. There were no histologic changes.[79]

Ibuprofen

Single Dose Toxicity Studies

Single dose toxicity studies have been conducted using mice,[4] rats,[4] and dogs.[12]

The LD_{50} values for ibuprofen, expressed as mg/kg of body weight are as follows:

Mouse:[4]	Oral	800 mg/kg
	Intraperitoneal	320 mg/kg
Rat:	Oral	1600 mg/kg
	Subcutaneous	1300 mg/kg

Acute signs of poisoning were prostration in mice, and sedation, prostration, loss of righting reflex and laboured respiration in rats. Death occurred within 3 days from perforated gastric ulcers in mice and intestinal ulceration in rats, irrespective of the route of administration.

Following single ibuprofen doses of 125 mg/kg and above to dogs effects were observed including emesis, transient albuminuria, faecal blood loss and erosions in the gastric antrum and pylorus; no ill effects were seen with 20 or 50 mg/kg doses.

Multiple Dose Studies

The no-effect level was determined using groups of 10 male and 10 female rats which were dosed

orally for 26 weeks with 180, 60, 20 or 7.5 mg/kg ibuprofen in 0.4% hydroxyethyl cellulose. The control group consisted of 20 males and 20 females which received 0.4% hydroxyethyl cellulose. Rats were weighed three times daily and blood samples were obtained in the final week of dosing. The rats were sacrificed the day after the last dose and the internal organs examined.

Rats receiving ibuprofen for 26 weeks grew normally except for males on 180 mg/kg/day, which gained significantly less weight than the controls. One male rat receiving 180 mg/kg/day died due to intestinal lesions and the death was thought to be treatment-related. Both males and females receiving 180 mg/kg/day were anaemic; leukocyte count and plasma glutamic pyruvic transaminase activities were not significantly altered. The organ to body weight ratio of males given 180 mg/kg/day was typically greater than normal. For some organs, this was because the males weighed less than the controls. Organs that were enlarged were the liver, kidney, and spleen. The same organs were also enlarged in females receiving 180 mg/kg/day, although these females were similar in body weight to the controls. In addition, the combined seminal vesicle and prostate weight was subnormal and uterine weight was increased. The thyroid gland of males receiving 180, 60, 20 mg/kg/day exhibited a slight increase in weight, which was the same for the three doses, however no such increase was observed in the females. There were no significant histological changes observed in rat tissues except for the presence of intestinal ulcers in 1 male and 3 females receiving 180 mg/kg/day.

The above experiment was adapted to establish whether the effects of ibuprofen treatment on rats were reversible when dosing ended.[12] In this instance, rats were administered 180, 60, or 20 mg/kg/day ibuprofen for 13 weeks instead of 26 weeks, whereupon half the animals in each group were sacrificed and the remaining rats were maintained, undosed, for three weeks and then sacrificed. Haematological examinations were performed after 4, 8, and 12 weeks of treatment.

Results obtained from the dosing phase of this 13-week experiment reflected the results obtained previously, where rats were dosed for 26 weeks. Males receiving 180 mg/kg/day had enlarged kidneys, spleen, and testes; while those on lower doses had normal organ weights. Females on all three doses had enlarged kidneys, the extent of which was dose-dependent. Enlargement of the liver and ovaries was observed in females receiving 180 mg/kg/day, and of the spleen and ovaries of those on 60 mg/kg/day. None of the enlarged organs were histologically abnormal. Three weeks following withdrawal of treatment, the organ to body weight ratios had completely or almost completely returned to normal. Rats receiving 180 mg/kg/day were anaemic from week 4 of dosing and when examined after the final dose, were found to have intestinal lesions. These effects were not seen at the lower doses, thereby confirming the results of the first experiment.

Since the highest dose of 180 mg/kg/day was only moderately toxic, an additional group of rats was dosed with 540 mg/kg/day.[12] All these rats died or were killed *in extremis* after 4 days' dosing. All had intestinal ulceration with peritonitis, and some also had slight renal tubular dilation.

The primary toxic effect of ibuprofen in rats is intestinal damage. Ibuprofen alters the organ to body weight ratio of certain organs, such as the liver, kidneys, gonads, and the secondary sex

organs, although no histological abnormalities have occurred and the effect is reversible. The liver and kidney enlargement may be a reflection of work hypertrophy associated with the metabolism and excretion of the compound, whereas the significance of the effect on other organs is unknown. When administered in lethal doses, ibuprofen produces mild kidney lesions in addition to the intestinal damage.

Carcinogenic Potential
Thirty male and 30 female rats were given 180 mg/kg/day of ibuprofen orally for 55 weeks and 60 mg/kg/day for the next 60 weeks. The only specific pathological effect observed was intestinal ulceration. There was no evidence of tumour induction and it is concluded that lbuprofen is not carcinogenic in the rat.[1, 4]

Teratology Study in Rabbits
New Zealand white rabbits were given 0, 7.5, 20 and 60 mg/kg daily of ibuprofen from day 1 to day 29 of pregnancy. The mean foetal weight was unaffected; litter size was unaffected at the lower doses. Congenital malformations did occur in both treated and untreated groups with no consistent pattern except for one litter of 4 young with cylcopia. The results of this experiment indicate that ibuprofen is not teratogenic when given in toxic doses to rabbits.[12]

Teratology Study in Rats
Newly-mated female albino rats were given ibuprofen in doses of 0, 7.5, 20, 60 and 180 mg/kg/day from day 1 to day 20 of pregnancy; ibuprofen exhibited no embryotoxic or teratogenic effects even when administered at ulcerogenic doses.[12]

Penetration into Animal Foetus
Rabbits and rats in late pregnancy were given Ibuprofen single oral doses of 60 and 20 mg/kg respectively of C^{14} labelled ibuprofen. Rabbits were killed three hours after dosing and rats killed 1.5 hours after dosing when maternal and foetal blood was collected. Similar concentrations of radioactive ibuprofen were detected in both the mother and foetus indicating that the drug and its metabolites readily crossed the placental barrier into the foetal circulation.[12]

Various species showed evidence of transfer of Methocarbamol to the fetus. However, several studies of various species showed no teratogenic potential for methocarbamol.[79]

REFERENCES

1. Adams SS, Bough RG, Cliffe EE, Dickenson W, Lessel B, McCullough KF, Mills RF, Nicholson JS, Williams GA: Some aspects of the pharmacology, metabolism and toxicology of ibuprofen. l. Pharmacology and metabolism. Rheumotol Phys Med. Suppl, Rheum Phys Med.1970;10: Suppl 10:9-26

2. Adams SS, Cliffe EE, Lessel B, Nicholson JS: Some biological properties of 2-(4 isobutylphenyl)-proponic acid. J. Pharm Sci 1967, 56:1686

3. Davies NM: Clinical pharmacoketics of ibuprofen. The first 30 years. Clin Pharmacokinet 1998; 34: 101-154.

4. Adams SS, Buckler JW: Ibuprofen and flurbiprofen. Clinics in Rheum Diseases 1979; 5: No 2, 359-379.

5. Albert KS, Gernaat RN: The pharmacokinetics of ibuprofen. Am J Med 1984 77(1A): 40-46.

6. Johnson AG, Nguyen TV, Day RO: Do non-steroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Ann Intern Med 1994; 121: 289-300.

7. Pope JE, Anderson JJ, Felson DT: A meta-analysis of the effects of non-steroidal anti-inflammatory drugs on blood pressure. Arch Intern Med 1993; 153: 477-484.

8. Bruce RB, Turnbull LB, Newman JH: Metabolism of methocarbamol in the rat, dog and human. J Pharm Sc 1971; 60(1): 104-106.

9. Leeman TD, Transon C, Bonnabry C, Dayer P: A major role for cytochrome $P450_{TB}$ (CYP2C subfamily) in the actions of non-steroidal anti-inflammatory drugs. Drugs Exp Clin Res 1993; 19: 189-195.

10. Campbell AD, Coles FK, Eubank LL, Huf EG: Distribution metabolism of methocarbamol. J Pharmacol Exp Ther 1961; 131: 18-25.

11. Gontarz N, Small RE, Comstock TJ, Stalker DJ, Johnson SM, Willis HE: Effects of antacid suspension on the pharmacokinetics of ibuprofen. Clin Pharm 1987; 7(5):413-416.

12. Adams SS, Bough RG, Cliffe EE, Lessel B, Mills RFN: Absorption, distribution and toxicity of ibuprofen. Toxicol Appl Pharmacol 1969; 15: 310-330.

13. Davies JG, Rawlins DC, Busson M: Effect of ibuprofen on blood pressure control by propranolol and benzofluazide. J Intern Med Res 1988; 16: 173-181.

14. Houston MC, Weir M, Gray J, Ginserg D, Szeto C, Kaihlenen PM, Sugimoto D, Lefkowitz M, Runde M: The effects of non-steroidal anti-inflammatory drugs on blood pressure of patients with hypertension controlled by verapamil. Arch Intern Med 1995; 155: 1049-1054.

15. Slattery JT, Levy G: Effect of ibuprofen on protein binding of warfarin in human serum. J Pharm Sci 1977; 66:1060.

16. Cook ME, Wallin JD, Thakur VD, Kadowitz PJ, McNamara DB, Garcia MM, Lipani JA, Poland M: Comparative effects of nabumetone, sulindac and ibuprofen on renal function. J Rheumatol 1997; 24: 1137-1144.

17. Dent RW, Ervin DK: Relief of acute musculoskeletal symptoms with intravenous methocarbamol: A placebo controlled study. Curr Ther Res 1976; 20(5): 661 665.

18. Dick-Smith JB. Ibuprofen, aspirin and placebo in the treatment of rheumatoid arthritis - a double-blind clinical trial. Med J Aust.1969; 2(17):853-859.

19. Dornan J , Reynolds WJ. Comparison of ibuprofen and acetylsalicylic acid in the treatment of rheumatoid arthritis. Can Med Assoc J. 1974;110 (12):1370-2.

20. Dose proportionality study to evaluate the single dose pharmacokinetics of methocarbamol in healthy male volunteers receiving 500 mg, 1500 mg, and 3000 mg orally [Study No. 11]. Data on file.

21. Braun RP, Lockhart EA, Bruno P: Delayed-onset muscle soreness (DOMS) - a new pain model to compare OTC analgesics. Med Sci Sports Exer 1994; 26: S14.

22. Fommei E, Ghione S, Palla L, Ragazzini A, Gazzetti P, Palombo C, Giaconi S: Inhibition of prostaglandins and angiotensin II: Effects on renal function in hypertensive patients. Agents Actions Suppl 1987; 22: 183-189.

23. Gready DM. Parafon Forte versus Robaxisal in skeletal muscle disorders: a double-blind study. Curr Ther Res Clin Exp. 1976; 20(5): 666-673.

24. Garcia Rodriguez LA, Williams R, Derby LE, Dean AD, Jick H. Acute liver injury associated with non-steroidal anti-inflammatory drugs and the role of risk factors. Arch Intern Med 1994; 154: 311-316.

25. Lillehei TJ, Metke MP, Dawnajee MK, Tago M, Lim MF, Kaye MP: Reduction of platelet deposition in aorta-coronary artery Gore-Tex bypass grafts in dogs by platelet inhibitors. Circulation 1980; 62: Suppl 3; 53.

26. Hudgins AP: Clinical evaluation of methocarbamol. Clin Med 1959; 2321-2324.

27. Huf EG, Coles FK, Eubank LL: Comparative plasma levels of mephenesin, mephenesin carbamate and methocarbamol. P.S.E.B.M. 1959; 102: 276-7.

28. Albert KS, Gillespie WR, Wagner JG, Pau A, Lockwood GF: Effects of age on the clinical pharmacokinetics of ibuprofen. Am J Med 1984; 77: 47-50.

29. Janssen GME, Venema JF: Ibuprofen: plasma concentrations in man. J Int Med Res 1985, 13:68-73

30. Jorgensen HS, Christensen HR, Kampmann JP. Interaction between digoxin and indomethacin or ibuprofen. Br J Clin Pharmacol 1991; 31(1): 108-110.

31. Dipasquale G, Mellace D: Inhibition of arachidonic acid induced mortality in rabbits with several non-steroidal anti-inflammatory agents. Agents Actions 1977; 7: 481-485.

32. Adesuyi SA, Ellis EF: The effect of ibuprofen dose on rabbit platelet aggregation and aortic PGI_2 synthesis. Thromb Res 1982; 28: 581-585.

33. Lampert M, Villarreal J, Lopez V, Garcia R, Lozaro J, Teran J, Ahan K, Rubin F. Methocarbamol in the management of tetanus. Texas State J Med; 62: 55-59.

34. Nozu K: Flurbiprofen: Highly potent inhibitor of prostaglandin synthesis. Biochim Biophys Acta 1978; 529: 493-496.

35. Makela A-L, Lempiainen M, Ylijoki H: Ibuprofen levels in serum and synovial fluid. Scand J Rheumatology 1981, 39(Suppl):15-17

36. Makela A-L, Lempiainen M, Yrjana T: Ibuprofen in the treatment of Juvenile rheumatoid arthritis: metabolism and concentration in synovial fluid. Br J Clin Pract 1979, 6 (Suppl): 23-27

37. Makela A-L, Lempiainen M, Yrjana T: Ibuprofen in the Treatment of JRA: Metabolism and Concentrations in Synovial Fluid. Br J Clin Pract, 1980, Suppl 6, Brufen Under Review, Wiesbaden, 23.

38. Middleton RSW: A comparison of two analgesic muscle relaxant combinations in acute back pain. Br J Clin Pract 1984; 38(3) 107-9.

39. Mills RFN, Adams SS, Cliffe EE, Dickinson W, Nicholson JS. The Metabolism of Ibuprofen. Xenobiotica 1973; Sep;3(9):589-598.

40. Penner JA, Abbrecht PH: Lack of interaction between ibuprofen and warfarin. Curr Ther Res Clin Exp1975; 18: 862-871.

41. Moncada S. Vane JR: Mode of action of aspirin-like drugs. Adv Intern Med 1979; 24: 1-22,

42. Motrin (Ibuprofen) past, present, and future. Proceedings of a symposium, Scottsdale, Arizona, December 2 and 3, 1983. Am J Med. 1984 Jul 13;77(1A):1 125.

43. Minuz P, Lechi A, Arosio E, Degan M, Capuzzo MG, Lechi C, Corsato M, Dalla Riva A, Velo GP: Antihypertensive activity of enalapril. Effect of ibuprofen and different salt intakes. J Clin Hypertens 1987; 3: 645-653.

44. Muckle DS: Comparative study of ibuprofen and aspirin in soft-tissue Injuries. Rheumatol and Rehabil. 1974; 13 (3):141-147.

45. Insel PA. Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In Molinoff PB, Ruddon RW, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. New York: McGraw-Hill, 1996: 617-657.

46. Utsunomiya T, Krausz MM, Dunham B, Valeri CR, Levine L, Shepro D, Hechtman HB: Modification of inflammatory response to aspiration with ibuprofen. Am J Physiol 1982; 243: H903-910.

47. Imai H, Muramatsu Y, Tsurumi K, Fujimura H: Platelet aggregation and liposome as a model system. Jap J Pharmacol 1981; 31: 92P.

48. Nierenberg DW: Competitive inhibition of methotrexate accumulation in rabbit kidney slices by non-steroidal anti-inflammatory drugs. J Pharmacol Exper Ther 1983; 226(1): 1-6.

49. Schachtel BP, Furey SA, Thoden WR: Nonprescription ibuprofen and acetaminophen in the treatment of tension-type headache. J Clin Pharmacol 1996; 36: 1120-1125.

50. Schachtel BP, Thoden WR: Onset of action of ibuprofen in the treatment of muscle-contraction headache. Headache 1988; 28: 471-474.

51. Packman EW, Doyle G, Koronkiewicz K, Jayawardena S, Cooper SA: Onset of analgesia of ibuprofen liquigels (400 mg) compared to acetaminophen caplets (1000 mg) in the treatment of tension headache. J Clin Pharmacol 1998; 38: 876.

52. Furey SA, Vargas R, McMahon FG. Renovascular effects of nonprescription ibuprofen in elderly hypertensive patients with mild renal impairment. Pharmacotherapy 1993; 13: 143-148.

53. Moore N. Van Ganse E, Le Parc JM, Wall R, Schneid H, Farhan M, Verriere F, Pelen F: The PAIN study: paracetamol, aspirin, and ibuprofen new tolerability study. Clin Drug Invest 1999; 18: 89-97.

54. Hamalainen MJ, Hoppu K, Valkeila E, Santavuori P. Ibuprofen or acetaminophen for the acute treatment of migraine in children: A double-blind, randomized, placebo-controlled, crossover study. Neurology 1997; 48: 103-107.

55. Preston EJ, Miller CB, Herbertson RK: A double-blind, multicentre trial of methocarbamol and cyclobenzaprine in acute musculoskeletal conditions. Today's Ther Trends 1984; 1(4) 1-11.

56. Product Monograph - Advil, 2002.

57. Ragheb M: Ibuprofen can increase serum lithium in lithium treated patients. J Clin Psychiatry 1987; 48: 161-163.

58. A.H. Robins: A double blind, parallel, placebo controlled, clinical experience trial of Robaxin in a setting of minimum restriction to obtain safety data among the probable OTC patient population. Protocol No. 17, Reference No. AHR-90-0100. April 20, 1990.

59. Corson SL and Bolognese RJ: Ibuprofen therapy for dysmenorrhea. J Reprod Med 1978; 20(5): 246-252.

60. Truitt EB, Little JM: A pharmacologic comparison of methocarbamol (AHR-85), the monocarbamate of 3-(o-methoxyphenoxy)-1,2-propanediol with chemically related inter neuronal depressant drugs. J Pharmacol Ther 1958;122:239.

61. Dawood MY: Over-the-counter (OTC) analgesics for the relief of menstrual cramps. J Clin Pharmacol 1994; 34: 1014.

62. Shapiro SS and Diem K: The effect of ibuprofen in the treatment of dysmenorrhea. Curr Ther Res 1981; 30(3): 327-334.

63. Larkin RM, Van Orden DE, Poulson AM, Scott JR.: Dysmenorrhea: treatment with an antiprostaglandin. Obstet and Gynecol 1979; 54(4): 456-460.

64. Milsom I, Andersch B: Effect of ibuprofen, naproxen sodium, and paracetamol on intrauterine pressure and menstrual pain in dysmenorrhea. Br J Obstet Gynaecol 1984; 91: 1129-1135.

65. Morrison JC, Ling FW, Forman EK, Bates GW, Blake PG, Vecchio TJ, Linden CV, O'Connell MJ. Analgesic efficacy of ibuprofen for treatment of primary dysmenorrhea. South Med J 1980; 73(8): 999-1002.

66. Bertin L, Pons G, d'Athis P, Lasfargues G, Maudelonde C, Duhamel JF, Olive G: Randomized, double-blind, multicenter, controlled trial of ibuprofen versus acetaminophen (paracetamol) and placebo for treatment of symptoms of tonsillitis and pharyngitis in children. J Ped 1991; 119: 811-814.

67. St. Charles CS, Matt BH, Hamilton MM, Katz BP: A comparison of ibuprofen versus acetaminophen with codeine in the young tonsillectomy patient. Otolaryngol Head Neck Surg 1997; 117: 76-82.

68. Thompson M, Anderson M: Studies of Gastrointestinal blood loss during Ibuprofen therapy. Rheumatol Phys Med . 1970; 10:Suppl 10:104-7.

69. Tisdale SA, Ervin DK: Controlled clinical trial of robaxisal. Curr Ther Res 1978; 23(2): 166-172.

70. Tisdale SA Jr, Ervin DK: A controlled study of methocarbamol (Robaxin®) in acute painful musculoskeletal conditions. Curr Ther Res 1975; 17(6): 525-530.

71. Greene JJ, Brown SR, Romeo DA, Schachtel BP: Efficacy and safety of ibuprofen (10 mg/kg) (IBU), acetaminophen (15 mg/kg) (APAP) and placebo (PBO) in the relief of orthodontic pain in children. J Clin Pharmacol 1995; 35: 929.

72. Lohokare SK, Jog V: Comparative study of suspensions of ibuprofen and paracetamol in soft tissue injuries in children. J Pain Symp Mgmt 1991; 6: 158.

73. Utterback RA, Tenney PH: Methocarbamol in the therapy of tetanus. Arch Neurol 1963; 9: 555-560.

74. Skeletal Muscle Relaxants (Systemic) Methocarbamol. USPDI 20th Edition, 2002.2779-2780.

75. Valtonen EJ: A double-blind trial of methocarbamol versus placebo in painful muscle spasm. Curr Med Res Opinion 1975; 3(6): 382-385.

76. Vecchio TJ, Heilman CJ, O'Connell MA: Efficacy of Ibuprofen in Muscle Contraction Headache. J Clin Therap 33(2):199, February 1983

77. Walson PD, Galletta G, Braden NJ, Alexander L: Ibuprofen, acetaminophen, and placebo treatment of febrile children. Clin Pharmacol Ther 1989, 46:9-17

78. Walter K, Dilger C: Ibuprofen in human milk. Br J Pharmacol 1997; 44: 211-212.

79. Robaxin - Monograph (U.S.).

80. Skeletal Muscle Relaxants 12:20. Methocarbamol. AHFS Drug Information 2002; 1364-1366.

81. Methocarbamol DrugDex Drug Evolution, Revised December 1999.

82. Adams SS, McCullough KF, Nicholson JS: The pharmacological properties of ibuprofen, an

anti-inflammatory, analgesic and anti-pyretic agent. Arch Int Pharmacodyn 1969, 178:155-129.

83. Rushford WAI: A double-blind crossover comparison of ibuprofen and distalgesic -G.P. Study. The Boots Company Ltd. Research Report.

84. Product Monograph: Robax Platinum, Control number 229825, Date of Revision: September 8, 2019.

85. Product Monograph: Ibuprofen+Methocarbamol Caplets, Control # 155330, Date of Preparation: January 04, 2013.

PART III: CONSUMER INFORMATION

Muscle and Back Pain Platinum Relief
Methocarbamol 500 mg, Ibuprofen 200 mg
Caplets

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

ABOUT THIS MEDICATION

What the medication is used for:
For effective relief of pain associated with muscle spasm such as back pain, tense neck, muscles, strains and sprains.

What it does:
Pain reliever and Muscle Relaxant.

When it should not be used:
Do not take Muscle and Back Pain Platinum Relief if you have or are:

- peptic ulcer disease or gastrointestinal bleeding or any other active inflammatory disease of the gastrointestinal tract (e.g. colitis, Crohn's disease),
- taking acetylsalicylic acid (ASA) or any other non-steroidal anti-inflammatory medication including any other ibuprofen product,
- allergic/hypersensitive to ibuprofen or other non-steroidal anti-inflammatory drugs (NSAIDs), ASA or other salicylates, methocarbamol or to any ingredient in the formulation or component of the container, or any of Muscle and Back Pain Platinum Relief ingredients (Refer to the nonmedicinal ingredients on outer carton or composition section),
- nasal polyps (swelling of the inside of the nose), or allergic manifestations such as asthma, anaphylaxis (sudden severe life threatening allergic reaction), urticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms,
- dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake,
- right before or after heart surgery,
- serious liver or kidney disease,
- Systemic Lupus Erythematosus,
- in your third trimester of pregnancy

What the medicinal ingredients are:
Methocarbamol and ibuprofen.

What the important nonmedicinal ingredients are:
Colloidal silicon dioxide, FD&C Blue No. 2, ferric oxide (red), hypromellose, magnesium stearate, maize starch, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, sodium lauryl sulphate, sodium starch glycolate, stearic acid.

What dosage forms it comes in:
Each caplet contains methocarbamol 500 mg and ibuprofen 200 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Caution in those with heart failure, high blood pressure or other conditions predisposing to fluid retention.
- Caution in those prone to gastrointestinal tract irritation, diverticulosis, or other inflammatory disease of the gastrointestinal tract such as ulcerative colitis or Crohn's disease.
- Caution in those at risk of kidney or liver problems, those taking diuretics and the elderly.
- Stop use immediately if you have difficulty or pain when urinating.
- The chance of stomach bleeding is higher if you are: age 60 or older, have had stomach ulcers or bleeding problems, take a blood thinner or steroid drug, take with other drugs containing an NSAID like acetylsalicylic acid (ASA), ibuprofen, naproxen, or prescription anti-inflammatory drugs, have 3 or more alcoholic

drinks every day while using this product.

BEFORE you use Muscle and Back Pain Platinum Relief talk to your doctor or pharmacist if:

- you have diabetes, high blood pressure, heart or thyroid disease, asthma, kidney or liver disease, glaucoma, blood clotting disorder (such as hemophilia), any other serious disease, are under doctor's care for any serious condition, you are trying to conceive, in your first or second trimester of pregnancy or if you breastfeeding, or taking any other drug including over the counter drugs.

May cause drowsiness or dizziness. Exercise caution in operating machinery or motor vehicles. Avoid alcohol. Use with caution in the elderly.

INTERACTIONS WITH THIS MEDICATION

Do not use this product if you are taking ASA.

Drugs that may interact with Muscle and Back Pain Platinum Relief include: acetaminophen, anticoagulants (blood thinners), digoxin, oral antidiabetic agents and insulin, diuretics, methotrexate, lithium, protein-bound drugs including probenecid, thyroxine, antibiotics (e.g. cyclosporine), phenytoin, corticosteroids or benzodiazapenes, other NSAIDs, or medications for high blood pressure. Tell your doctor or pharmacist what prescription drugs you are taking or plan to take.

PROPER USE OF THIS MEDICATION

Usual dose:
Adults and children over 12: Take 1 or 2 caplets every four to six hours as needed. Do not exceed 6 caplets in 24 hours, unless directed by a physician. Consult your physician if symptoms persist for more than 5 days.

Overdose:

In case of drug overdose, contact a doctor, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Continue to take 1-2 tablets every 4-6 hours as needed after a missed dose. Do not take twice the recommended dose following a missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Take with food or milk if stomach upset occurs.

Muscle and Back Pain Platinum Relief may occasionally produce unwanted side effects, such as heartburn, constipation, nausea, bloating, nervousness or sleeplessness.

Stop use and contact a doctor or pharmacist if these symptoms worsen or persist.

The risk of having side effects may be decreased by using the smallest dose for the shortest duration of time.

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

Symptom/effect		Talk with your doctor or pharmacist		Seek immediate emergency medical assistance
		Only if severe	In all cases	
Uncommon	Symptoms of severe allergic reaction (anaphylaxis), including: rash, severe itching/ redness, blisters, swelling, or trouble breathing			X
	Blood in vomit, bloody or black stools			X
	Abdominal pain, vomiting, diarrhea		X	
	Ringing or buzzing in the ears / dizziness		X	
	Change in vision including: blurred or diminished vision		X	
	Fluid retention		X	

This is not a complete list of side effects. For any unexpected effects while taking Muscle and Back Pain Platinum Relief contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected side effect associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

HOW TO STORE IT

Store at room temperature (15-30°C). Protect from light.

Keep out of reach of children. This package contains enough medicine to seriously harm a child.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Vita Health Products Inc., 150 Beghin Avenue, Winnipeg, MB R2J 3W2.

This leaflet was prepared by Vita Health Products Inc.

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