PRODUCT MONOGRAPH

ANALGESIC AND MUSCLE RELAXANT

Methocarbamol and Ibuprofen caplets

Caplets, 500 mg/400 mg

Muscle Relaxant/Analgesic

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Methocarbamol and Ibuprofen caplets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Caplet, 500 mg/400 mg	Pregelatinized starch *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

ANALGESIC AND MUSCLE RELAXANT (Methocarbamol and Ibuprofen caplets) is indicated for the following:

- Adults and Children over 12 years of age: For effective relief of pain associated with muscle spasms, such as back pain, tense neck muscles, strains and sprains.

For patients with an increased risk of developing CV and/or GI adverse events, other management strategies that do NOT include the use of NSAIDs should be considered first. (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS)

ANALGESIC AND MUSCLE RELAXANT is a nonprescription drug. Use should be limited to a single caplet to be taken no more than three times a day, as this provides the highest permitted nonprescription single dose (400 mg) and daily dose (1 200 mg) of ibuprofen. Use should be limited to the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events. If pain persists for more than 5 days consult a health care provider.

Methocarbamol has been studied in muscle relaxation models including tetanus therapy[1], muscle spasms[2], painful muscle conditions[3-6], and in combination with analgesics[7-9], with positive results. In gynecological postoperative patients, methocarbamol reduced the use of narcotics and other sedatives for pain and discomfort.[4]

Ibuprofen has been studied in pain models including dental[10-17], dysmenorrhea[18-23], fever[24-26], headache[27-28], migraine[29], muscle aches[30], post surgery[31-32], soft tissue injury[33-34], and sore throat[35], with effective pain relief results.

Geriatrics:

Evidence from clinical studies and post-market experience suggests that use in the geriatric population is associated with differences in safety (see **WARNINGS AND PRECAUTIONS**).

Pediatrics (≤ 12 years of age):

Safety and efficacy have not been established in the pediatric population.

CONTRAINDICATIONS

ANALGESIC AND MUSCLE RELAXANT is contraindicated in:

- the peri-operative setting of coronary artery bypass graft surgery (CABG). Although ANALGESIC AND MUSCLE RELAXANT has NOT been studied in this patient population, a selective COX-2 inhibitor NSAID studied in such a setting has led to an increased incidence of cardiovascular/thromboembolic events, deep surgical infections and sternal wound complications.
- the third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus and prolonged parturition
- severe uncontrolled heart failure
- known hypersensitivity to methocarbamol or ibuprofen, or to any of the components/excipients. There is a potential for cross-reactivity between different NSAIDs and ibuprofen, and patients sensitive to other carbamate derivatives and methocarbamol (see **WARNINGS AND PRECAUTIONS - *Hypersensitivity Reactions - Anaphylactoid Reactions***).
- history of asthma, urticaria, or allergic-type reactions after taking ASA or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance - rhinosinusitis, urticaria/ angioedema, nasal polyps, asthma). Fatal anaphylactoid reactions have occurred in such individuals. 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 reaction.
- active gastric / duodenal / peptic ulcer, active GI bleeding
- cerebrovascular bleeding or other bleeding disorders
- inflammatory bowel disease
- severe liver impairment or active liver disease
- severe renal impairment (creatinine clearance < 30 mL/min or 0.5 mL/sec) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when using NSAIDs and must be monitored) (see **WARNINGS AND PRECAUTIONS - *Renal***)
- known hyperkalemia (see **WARNINGS AND PRECAUTIONS - *Renal - Fluid and Electrolyte Balance***)

WARNINGS AND PRECAUTIONS

Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV) (see WARNINGS AND PRECAUTIONS - *Cardiovascular*).

ANALGESIC AND MUSCLE RELAXANT contains ibuprofen, a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing ANALGESIC AND MUSCLE RELAXANT to any patient with ischemic heart disease (including but NOT limited to acute myocardial infarction, history of myocardial infarction and/or angina), cerebrovascular disease (including but NOT limited to stroke, cerebrovascular accident, transient ischemic attacks and/or amaurosis fugax) and/or congestive heart failure (NYHA II-IV).

Use of NSAIDs, such as ibuprofen contained in ANALGESIC AND MUSCLE RELAXANT, can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure (see also WARNINGS AND PRECAUTIONS - *Renal - Fluid and Electrolyte Balance*).

Randomized clinical trials with ibuprofen have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing ANALGESIC AND MUSCLE RELAXANT.

Risk of Gastrointestinal (GI) Adverse Events (see WARNINGS AND PRECAUTIONS - *Gastrointestinal*).

Use of NSAIDs, such as ibuprofen contained in ANALGESIC AND MUSCLE RELAXANT, is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction and gastrointestinal bleeding).

General

Frail or debilitated patients may tolerate side effects less well and therefore special care should be taken in treating this population. **Use should be limited to a single caplet to be taken no more than three times a day, as this provides the highest permitted nonprescription single**

dose (400 mg) and daily dose (1 200 mg) of ibuprofen. Use should be limited to the shortest possible duration of treatment in order to minimize the potential risk for an adverse event. If pain persists for more than 5 days consult a health care provider. Caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Ibuprofen contained in ANALGESIC AND MUSCLE RELAXANT is NOT recommended for use with other NSAIDs, with the exception of low-dose ASA for cardiovascular prophylaxis, because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions (see **DRUG INTERACTIONS - *Drug/Drug Interactions - Acetylsalicylic acid (ASA) or other NSAIDs***).

Carcinogenesis and Mutagenesis

(See **PART II – TOXICOLOGY**)

Cardiovascular

ANALGESIC AND MUSCLE RELAXANT contains ibuprofen, a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing ANALGESIC AND MUSCLE RELAXANT to patients with risk factors for cardiovascular disease, cerebrovascular disease or renal disease, such as any of the following (NOT an exhaustive list):

- **Hypertension**
- **Dyslipidemia / Hyperlipidemia**
- **Diabetes Mellitus**
- **Congestive Heart Failure (NYHA I)**
- **Coronary Artery Disease (Atherosclerosis)**
- **Peripheral Arterial Disease**
- **Smoking**
- **Creatinine Clearance < 60 mL/min or 1 mL/sec**

Use of NSAIDs, such as ibuprofen contained in ANALGESIC AND MUSCLE RELAXANT, can lead to new hypertension or can worsen pre-existing hypertension, either of which may increase the risk of cardiovascular events as described above. Thus blood pressure should be monitored regularly. Consideration should be given to discontinuing ANALGESIC AND MUSCLE RELAXANT should hypertension either develop or worsen with its use.

Use of NSAIDs, such as ibuprofen contained in ANALGESIC AND MUSCLE RELAXANT, can induce fluid retention and edema, and may exacerbate congestive heart failure, through a renally-mediated mechanism (see **WARNINGS AND PRECAUTIONS - *Renal - Fluid and Electrolyte Balance***).

For patients with a high risk of developing an adverse CV event, other management strategies that do NOT include the use of NSAIDs should be considered first. **Use should be limited to a single caplet to be taken no more than three times a day, as this provides the highest permitted nonprescription single dose (400 mg) and daily dose (1 200 mg) of ibuprofen. Use should be limited to the shortest possible duration of treatment in order to minimize the potential risk for an adverse event. If pain persists for more than 5 days consult a health care provider.**

Congestive heart failure in patients with marginal cardiac function, elevated blood pressure and palpitations have been reported following ibuprofen administration.[36]

Endocrine and Metabolism

Corticosteroids: Patients with thyroid disease should not take this drug unless directed by a physician.

Gastrointestinal (GI)

Serious GI toxicity (sometimes fatal), such as peptic/duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, such as ibuprofen contained in ANALGESIC AND MUSCLE RELAXANT. Minor upper GI problems, such as dyspepsia, commonly occur at any time. Health care providers should remain alert for ulceration and bleeding in patients treated with ANALGESIC AND MUSCLE RELAXANT, even in the absence of previous GI tract symptoms. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **Use should be limited to a single caplet to be taken no more than three times a day, as this provides the highest permitted nonprescription single dose (400 mg) and daily dose (1 200 mg) of ibuprofen. Use should be limited to the shortest possible duration of treatment in order to minimize the potential risk for an adverse event. If pain persists for more than 5 days consult a health care provider.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered (see **WARNINGS AND PRECAUTIONS - *Special Populations - Geriatrics***).

Patients should be informed about the signs and/or symptoms of serious GI toxicity and instructed to discontinue using ANALGESIC AND MUSCLE RELAXANT and seek emergency medical attention if they experience any such symptoms. The utility of periodic laboratory monitoring has NOT been demonstrated, nor has it been adequately assessed. Most patients who develop a serious upper GI adverse event on NSAID therapy have no symptoms. Upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These

trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. Even short-term therapy has its risks.

Caution should be taken if prescribing ANALGESIC AND MUSCLE RELAXANT to patients with a prior history of peptic / duodenal ulcer disease or gastrointestinal bleeding as these individuals have a greater than 10-fold higher risk for developing a GI bleed when taking a NSAID than patients with neither of these risk factors. Other risk factors for GI ulceration and bleeding include the following: *Helicobacter* pylori infection, increased age, prolonged use of NSAID therapy, excess alcohol intake, smoking, poor general health status or concomitant therapy with any of the following:

- Anti-coagulants (e.g. warfarin)
- Anti-platelet agents (e.g. ASA, clopidogrel)
- Oral corticosteroids (e.g. prednisone)
- Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. citalopram, fluoxetine, paroxetine, sertraline)

There is no definitive evidence that the concomitant administration of histamine H_2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of ANALGESIC AND MUSCLE RELAXANT therapy when and if these adverse reactions appear.

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. In these cases the physician must weigh the benefits of treatment against the possible hazards.[36]

Genitourinary

Some NSAIDs are associated with 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 a NSAID. Should urinary symptoms occur, in the absence of an alternate explanation, treatment with ANALGESIC AND MUSCLE RELAXANT should be stopped to ascertain if symptoms disappear. This should be done before urological investigations or treatments are carried out.

Hematologic

NSAIDs inhibiting prostaglandin biosynthesis interfere with platelet function to varying degrees; patients who may be adversely affected by such an action, such as those on anti-coagulants or suffering from haemophilia or platelet disorders should be carefully observed when ANALGESIC AND MUSCLE RELAXANT is administered.

Anti-coagulants: Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy of ANALGESIC AND MUSCLE RELAXANT with warfarin requires close monitoring of the international normalized ratio

(INR).

Even with therapeutic INR monitoring, increased bleeding may occur.

Anti-platelet Effects: NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike acetylsalicylic acid (ASA), their effect on platelet function is quantitatively less, or of shorter duration, and is reversible.

Ibuprofen contained in ANALGESIC AND MUSCLE RELAXANT and other NSAIDs have no proven efficacy as anti-platelet agents and should NOT be used as a substitute for ASA or other anti-platelet agents for prophylaxis of cardiovascular thromboembolic diseases. Anti-platelet therapies (e.g., ASA) should NOT be discontinued. There is some evidence that use of NSAIDs with ASA can markedly attenuate the cardioprotective effects of ASA (see **DRUG INTERACTIONS - *Drug-Drug Interactions - Acetylsalicylic Acid (ASA) or other NSAIDs***).

Concomitant administration of ANALGESIC AND MUSCLE RELAXANT with low dose ASA increases the risk of GI ulceration and associated complications.

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

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

Hepatic/Biliary/Pancreatic

As with other NSAIDs, including ibuprofen, borderline elevations of one or more liver enzyme tests (AST, ALT, alkaline phosphatase) may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy.

The frequency of acute liver injury among 625 307 people, who received NSAIDs in England and Wales between 1987 and 1991, was examined.[37] There were 311 716 patients who were prescribed ibuprofen. The incidence of acute liver injury among ibuprofen users was 1.6/100 000; this was the lowest incidence among the 8 NSAIDs studied and was significantly lower than the incidence among users of ketoprofen, piroxicam, fenbrufen or sulindac. 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. 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.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including

jaundice and cases of fatal hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported with NSAIDs.

Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop (e.g., jaundice), or if systemic manifestations occur (e.g., eosinophilia, associated with 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.

Hypersensitivity Reactions

Anaphylactoid Reactions: As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to ibuprofen contained in ANALGESIC AND MUSCLE RELAXANT. In post-marketing experience, rare cases of anaphylactic/anaphylactoid reactions and angioedema have been reported in patients receiving ibuprofen contained in ANALGESIC AND MUSCLE RELAXANT. ANALGESIC AND MUSCLE RELAXANT should NOT be given to patients with the ASA-triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking ASA or other NSAIDs (see **CONTRAINDICATIONS**).

ASA-Intolerance: ANALGESIC AND MUSCLE RELAXANT should NOT be given to patients with complete or partial syndrome of ASA-intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps, asthma) in whom asthma, anaphylaxis, urticaria/angioedema, rhinitis or other allergic manifestations are precipitated by ASA or other NSAIDs. 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 reaction (see **CONTRAINDICATIONS**).

Cross-sensitivity: Patients sensitive to one NSAID may be sensitive to any of the other NSAIDs as well. There is potential for cross-reactivity between different NSAIDs and ibuprofen, and patients sensitive to other carbamate derivatives and methocarbamol (see **CONTRAINDICATIONS**).

Serious Skin Reactions: (see **WARNINGS AND PRECAUTIONS – *Skin)***

Immune

(see **WARNINGS AND PRECAUTIONS - *Infection - Aseptic Meningitis***)

Infection

Ibuprofen contained in ANALGESIC AND MUSCLE RELAXANT, in common with other NSAIDs, may mask signs and symptoms of an underlying infectious disease.

Aseptic Meningitis: Rarely, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissue diseases, etc.) seem to be pre-disposed. Therefore, in such patients, the health care provider must be vigilant to the development of this complication.

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia or depression with the use of NSAIDs, such as ibuprofen contained in ANALGESIC AND MUSCLE RELAXANT. If patients experience such adverse reaction(s), 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 ANALGESIC AND MUSCLE RELAXANT should be cautioned about combined effects with alcohol and other CNS depressants.

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

Ophtalmologic

Blurred and/or diminished vision has been reported with the use of NSAIDs. If such symptoms develop ANALGESIC AND MUSCLE RELAXANT should be discontinued and an ophthalmologic examination performed. Ophthalmologic examination should be carried out at periodic intervals in any patient receiving ANALGESIC AND MUSCLE RELAXANT for an extended period of time.

Peri-Operative Considerations

(see **CONTRAINDICATIONS - *Coronary Artery Bypass Graft Surgery***)

Psychiatric

(see **WARNINGS AND PRECAUTIONS – *Neurologic***)

Renal

Long-term administration of NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis, hematuria, low grade proteinuria and occasionally nephrotic syndrome.

Renal insufficiency due to NSAID use is seen in patients with pre-renal conditions leading to reduction in renal blood flow or blood volume. Under these circumstances, renal prostaglandins help maintain renal perfusion and glomerular filtration rate (GFR). In these patients, administration of a NSAID may cause a reduction in prostaglandin synthesis leading to impaired renal function. Patients at greatest risk of this reaction are those with pre-existing renal insufficiency (GFR < 60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets,

those with congestive heart failure, cirrhosis, liver dysfunction, taking angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, cyclosporine, diuretics, and those who are elderly. Serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short-term therapy with NSAIDs. Even patients at risk who demonstrate the ability to tolerate a NSAID under stable conditions may decompensate during periods of added stress (e.g., dehydration due to gastroenteritis). Discontinuation of NSAIDs is usually followed by recovery to the pre-treatment state.

Caution should be used when initiating treatment with NSAIDs, such as ibuprofen contained in ANALGESIC AND MUSCLE RELAXANT, in patients with considerable dehydration. Such patients should be rehydrated prior to initiation of therapy. Caution is also recommended in patients with pre-existing kidney disease.

A number of factors appear to increase the risk of renal toxicity. In comparative clinical trials involving 7 624 ibuprofen-treated, 2 822 ASA-treated and 2 843 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 1 200 mg, used for longer periods than OTC recommendations and by patients being treated for serious conditions[38] 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. Methocarbamol may also affect renal function if therapy lasts 5 days or more. Kidney function should be monitored periodically if treatment goes beyond the recommended 5 days.

Use should be limited to a single caplet to be taken **no more than** three times a day, as this provides the highest permitted nonprescription single dose (400 mg) and daily dose (1 200 mg) of ibuprofen. Use should be limited to the shortest possible duration of treatment in order to minimize the potential risk for an adverse event.

Advanced Renal Disease*:* (see **CONTRAINDICATIONS**)

Fluid and Electrolyte Balance: Use of NSAIDs, such as ibuprofen contained in ANALGESIC AND MUSCLE RELAXANT, can promote sodium retention in a dose-dependent manner, which can lead to fluid retention and edema, and consequences of increased blood pressure and exacerbation of congestive heart failure. Thus, caution should be exercised in prescribing ANALGESIC AND MUSCLE RELAXANT in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention (see **WARNINGS AND PRECAUTIONS - *Cardiovascular***).

Use of NSAIDs, such as ibuprofen contained in ANALGESIC AND MUSCLE RELAXANT, can increase the risk of hyperkalemia, especially in patients with diabetes mellitus, renal failure, increased age, or those receiving concomitant therapy with adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, cyclosporine, or some diuretics.

Electrolytes should be monitored periodically (see **CONTRAINDICATIONS**).

Respiratory

ASA-induced asthma is an uncommon but very important indication of ASA and NSAID sensitivity. It occurs more frequently in patients with asthma who have nasal polyps.

Sexual Function/Reproduction

The use of ibuprofen contained in ANALGESIC AND MUSCLE RELAXANT, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of ANALGESIC AND MUSCLE RELAXANT should be considered.

Skin

In rare cases, serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme have been associated with the use of some NSAIDs. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus, causality is NOT clear. These reactions are potentially life threatening but may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that if they experience a skin rash they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue.

Special Populations

Pregnant Women: **ANALGESIC AND MUSCLE RELAXANT 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 PART II -TOXICOLOGY).**

Caution should be exercised in prescribing ANALGESIC AND MUSCLE RELAXANT during the first and second trimesters of pregnancy (see PART II -TOXICOLOGY).

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryo-foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

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.[39]

The high protein binding and lower pH of breast milk versus plasma tend to inhibit the excretion of ibuprofen into breast milk.[40] One study showed an ibuprofen concentration of 13 ng/mL in breast milk 30 minutes following the ingestion by the nursing mother of 400 mg of ibuprofen.[41] The milk:plasma ratio was 1:126. This translates to an infant exposure of 0.0008% of the maternal dose. No adverse effect has been detected in children 6 months of age who were administered ibuprofen.

Pediatrics: (see **CONTRAINDICATIONS**)

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 12 years of age and less have not been established; therefore, ANALGESIC AND MUSCLE RELAXANT should not be administered to children in this age group.

Geriatrics: Patients older than 65 years (referred to in this document as older or elderly) and frail or debilitated patients are more 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 injury including ulceration and bleeding. Use should be limited to a single caplet to be taken no more than three times a day, as this provides the highest permitted nonprescription single dose (400 mg) and daily dose (1 200 mg) of ibuprofen. Use should be limited to the shortest possible duration of treatment in order to minimize the potential risk for an adverse event. If pain persists for more than 5 days consult a health care provider.

Monitoring and Laboratory Tests

Cardiovascular: Blood pressure should be monitored regularly during therapy with ANALGESIC AND MUSCLE RELAXANT.

Hematologic: Patients on long-term treatment with NSAIDs, including ibuprofen contained in ANALGESIC AND MUSCLE RELAXANT, should have their haemoglobin, hematocrit, and blood cell count checked if they exhibit any signs or symptoms of anemia or blood loss or blood dyscrasia.

Concurrent therapy of ANALGESIC AND MUSCLE RELAXANT with warfarin requires close monitoring of the international normalized ratio (INR) to be certain that no change in anticoagulant dosage is necessary.[36]

Hepatic: Patient with symptoms and/or signs of liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with ANALGESIC AND MUSCLE RELAXANT.

Renal: Renal function should be monitored in high-risk populations, such as elderly, patients with advanced renal disease, patients with cardiovascular disease and diabetes mellitus.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The types of adverse drug reactions expected with the combination of methocarbamol and ibuprofen are likely to be similar to those reported by each component individually. Central Nervous System (CNS) adverse reactions are the most commonly seen following oral administration of methocarbamol. The most commonly reported adverse reactions with ibuprofen are gastrointestinal, CNS and dermatological in nature.

This section summarizes adverse drug reaction data pooled from clinical trials, published investigations and post-marketing experience with methocarbamol and ibuprofen.

Methocarbamol

Methocarbamol may cause drowsiness[44], dizziness[44], blurred vision[45], lightheadedness, somnolence[44], vertigo[44], anorexia, headache, fever, nausea, allergic reactions such as urticaria, pruritus, rash, skin eruptions, conjunctivitis with nasal congestion[46].

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.[47]

Ibuprofen – Prescription Experience

The following adverse reactions were reported in patients treated with prescription doses of ibuprofen (≥ 1 200 mg/day).

Table 1. Most Common Adverse Drug Reactions (≥ 1%)

	Incidence (%)	Adverse Drug Reaction
Gastrointestinal	3 to 9%	Nausea, epigastric pain, heartburn
	1 to 3%	Diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the gastrointestinal tract (bloating or flatulence)
Central Nervous System	3 to 9%	Dizziness
	1 to 3%	Headache, nervousness
Dermatologic	3 to 9%	Rash (including maculopapular type)
	1 to 3%	Pruritus
Special Senses	1 to 3%	Tinnitus
Metabolic	1 to 3%	Decreased appetite, edema, fluid retention

Less Common Adverse Drug Reactions (< 1%)

The following is a list of adverse drug reactions occurring in < 1% of patients receiving ibuprofen. Reactions listed below under Causal Relationship Unknown are those which occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, the possibility of a relationship to ibuprofen cannot be excluded.

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

Allergic: Incidence less than 1%: Anaphylaxis (see Contraindications). Causal relationship unknown: fever, serum sickness, lupus erythematosus.

Central Nervous System: 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 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 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 haemoglobin and hematocrit. Causal relationship unknown: haemolytic anaemia, 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 1 200 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

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

Endocrine: Causal relationship unknown: gynecomastia, hypoglycaemic 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.

Ibuprofen - Nonprescription Experience (Literature)

The following adverse reactions were reported in patients treated with nonprescription doses of ibuprofen ($\leq$ 1 200 mg/day).

One researcher conducted an extensive analysis of published data concerning the relative safety of nonprescription doses of ibuprofen and acetaminophen.[48] Of a total of 96 randomized and blinded trials, there were 10 trials of seven days' duration or less where the safety of both drugs was directly compared. In three of these trials, the incidence of adverse events was higher with acetaminophen; there were no reported adverse events in six trials; and one trial reported a higher incidence with ibuprofen. In this subset of 10 studies, it was reported that gastrointestinal adverse events were found to be the most common type of event reported and were predominantly dyspepsia, nausea, or vomiting. None of the GI events appeared to warrant follow-up from which the author inferred there were no serious gastrointestinal events.

It was concluded: "Although we recognise that the above mentioned data are very selective and are based on information derived from a variety of trial designs and populations, it is nonetheless instructive for indicating a relatively low incidence of severe adverse reactions with both drugs when taken at their respective nonprescription dosages."

A double-blind, placebo-controlled study (N=1 246) was conducted to prospectively evaluate the gastrointestinal tolerability, as compared to placebo, of the maximum nonprescription dose and duration (1 200 mg/day for 10 consecutive days) of ibuprofen use in healthy subjects representative of a nonprescription analgesic user population.[49] Gastrointestinal adverse experiences were similar in the placebo and ibuprofen groups (67 out of 413, 16% with placebo vs. 161 out of 833, 19% with ibuprofen). There was no difference between the two groups in the proportion of discontinuing due to a gastrointestinal event. Gastrointestinal adverse experiences reported by ≥ 1% of subjects were: dyspepsia, abdominal pain, nausea, diarrhea, flatulence, and constipation. Seventeen (1.4%) subjects had positive occult blood tests: their frequency was comparable between treatments. When used as directed to treat episodic pain, nonprescription ibuprofen at the maximum dose of 1 200 mg/day for 10 days, is well tolerated.

In two multi-trial analyses[50-51], a meta analysis[52] and a literature review[48], single doses of ibuprofen had a low incidence of gastrointestinal drug reactions, comparable to that of acetaminophen and placebo. Reports from spontaneous reporting systems in the United Kingdom[53], France and the United States[54], where a prescription is not needed for ibuprofen at a daily dose up to 1 200 mg, confirm the medication's gastrointestinal safety and acceptability. A large-scale randomised trial[43] comparing nonprescription doses of acetylsalicylic acid, acetaminophen, and ibuprofen in 8 677 adults found that the rates of significant adverse reactions were: aspirin 18.7%, ibuprofen 13.7%, and acetaminophen 14.5%. Ibuprofen was not statistically different from acetaminophen. Total gastrointestinal events (including dyspepsia) and abdominal pain were less frequent with ibuprofen (4% and 2.8%, respectively) than with acetaminophen (5.3% and 3.9%) or aspirin (7.1% and 6.8%) [all $p < 0.035$]. It was concluded that "The overall tolerability of ibuprofen in this large-scale study was equivalent to that of paracetamol (acetaminophen) and better than that of [ASA]".

DRUG INTERACTIONS

Drug-Drug Interactions

Acetylsalicylic Acid (ASA) or Other NSAIDs: The use of ANALGESIC AND MUSCLE RELAXANT in addition to any NSAID, including over-the-counter ones (such as ASA and ibuprofen) for analgesic and/or anti-inflammatory effects is NOT recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions.

The exception is the use of low dose ASA for cardiovascular protection, when another NSAID is being used for its analgesic/anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions.

Some NSAIDs (e.g., ibuprofen) may interfere with the anti-platelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1.

Antacids: 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.[55]

Anti-coagulants: (see **WARNINGS AND PRECAUTIONS – *Hematologic - Anti-coagulants***)

Anti-hypertensives: NSAIDs may diminish the anti-hypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors.

Combinations of ACE inhibitors, angiotensin-II antagonists, or diuretics with NSAIDs might have an increased risk for acute renal failure and hyperkalemia. Blood pressure and renal function (including electrolytes) should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure.

When renal perfusion pressure is reduced both prostaglandins and angiotensin II are important mediators of renal autoregulation.[56] 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 2 400 mg/day for one month[57] In contrast, Minuz[58] found no effect on the antihypertensive effect of enalapril or on plasma renin or aldosterone following two days treatment with ibuprofen 1 200 mg/day.

Two meta-analyses[59-60], 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*[61] showed that ibuprofen 1 600 mg/day for 14 days did not attenuate the antihypertensive effect of two ß-adrenergic blockers. Antagonism of the antihypertensive effects of calcium channel blockers by NSAIDs has been reported in some studies[62-64], but not in others[65-68]. The discrepancies between the

results of these studies may be related to a number of factors. In positive studies, the changes in blood pressure with the addition of NSAIDs have generally been small (+4 mmHg to +8 mmHg) and the negative studies may not have been sufficiently powerful to detect such differences. Some of the negative studies were performed on healthy volunteers, who are likely to have fewer effects from NSAIDs on renal blood flow. NSAIDs have been shown to antagonize most antihypertensive drug classes.[69] A small interaction in susceptible patients with hypertension or renal impairment upon treatment with calcium channel blockers is likely for all NSAIDs. As such, caution is advised if NSAIDs and calcium channel blockers are used concomitantly. The antihypertensive effects of calcium channel blockers may be antagonized by concomitant administration of NSAIDs.[70]

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.

Anti-platelet Agents (including ASA): There is an increased risk of bleeding, via inhibition of platelet function, when anti-platelet agents are combined with NSAIDs, such as ibuprofen contained in ANALGESIC AND MUSCLE RELAXANT (see **WARNINGS AND PRECAUTIONS – *Hematologic - Anti-platelet Effects***).

CNS Depressants: Methocarbamol may interact with opioid analgesics, barbiturates, benzodiazepines, centrally acting muscle relaxants, chlorate hydrate, and other drugs affecting the CNS (e.g., sodium oxybate).[70]

Coumarin-type: 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. 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.[71-72]

Cyclosporine and Tacrolimus: Although this interaction has not been studied with ANALGESIC AND MUSCLE RELAXANT, co-administration of cyclosporine or tacrolimus and any NSAID may increase the nephrotoxic effect of cyclosporine or tacrolimus due to the NSAID's effect on renal prostaglandins. The concurrent use of NSAIDs and cyclosporine has resulted in increases in cyclosporine levels, nephrotoxicity, and increased plasma creatinine concentrations.[73-76] The deterioration in renal function is generally reversible upon discontinuation of the NSAID.[74] The mechanism for observed rises in cyclosporine concentrations is not known and may not occur with all NSAIDs.

Two cases have been reported in which short-term use (three to four doses) of ibuprofen was associated with anuria or oliguria in liver transplant patients receiving tacrolimus immunosuppression.[77] Tacrolimus concentrations were low to moderate in both patients, and the

time-course was suggestive of an interaction. A possible explanation for this interaction is a greater dependence on real prostaglandins by patients with liver dysfunction. The production of renal prostaglandins is inhibited by NSAIDs such as ibuprofen. If this suggested mechanism is correct, the interaction may occur with all NSAIDs. Thus, renal function should be monitored when ANALGESIC AND MUSCLE RELAXANT and either of these drugs is used in combination.[70]

Digoxin: No interaction data is available for the co-administration of ANALGESIC AND MUSCLE RELAXANT and digoxin. However, an increase serum digoxin level has been noted with ibuprofen. Increased monitoring and dosage adjustments of digitalis glycoside may be necessary during concurrent ibuprofen therapy and following discontinuation of ibuprofen therapy.[78]

Diuretics: Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics. This response has been attributed to inhibition of renal prostaglandin synthesis. Concomitant therapy with potassium-sparing diuretics may be associated with increased serum potassium, thus making it necessary to monitor levels. Patients with impaired renal function who are taking potassium-sparing diuretics should not take ibuprofen.

Glucocorticoids: Some studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI adverse events such as ulceration and bleeding. This is especially the case in older (> 65 years of age) individuals.

H_2 Antagonists: In studies with human volunteers, co-administration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Lithium: Monitoring of plasma lithium concentrations is advised when stopping or starting a NSAID, as increased lithium concentrations can occur.

Ibuprofen produced an elevation of plasma lithium levels and a reduction in renal lithium clearance in a study of eleven normal volunteers. The mean minimum lithium concentration increased 15% and the renal clearance of lithium was decreased by 19% during this period of concomitant drug administration. This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when ibuprofen and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.[79]

Methotrexate: 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.[80]

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

Selective Serotonin Reuptake Inhibitors (SSRIs): Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see **WARNINGS AND PRECAUTIONS - *Gastrointestinal***).

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. Combined phenytoin and ibuprofen therapy may result in an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor), especially in renally impaired patients.[70] 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, steroids, antibiotics (except quinolones) or benzodiazepines.

Drug-Food Interactions

When ANALGESIC AND MUSCLE RELAXANT were taken with a high fat, high calorie meal, the rate and extent of absorption of methocarbamol was reduced by 36% and 20%, respectively, and the rate of absorption of ibuprofen was reduced by 22%. The product should preferably be taken on an empty stomach, but if stomach upset occurs, take with food or milk.

Drug-Herb Interactions

The interaction of ANALGESIC AND MUSCLE RELAXANT with herbal medications or supplements has not been studied.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

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 ANALGESIC AND MUSCLE RELAXANT should be cautioned about combined effects with alcohol.

The patient should be cautioned against excess alcohol intake and smoking when taking ANALGESIC AND MUSCLE RELAXANT as these are risk factors for cardiovascular disease and for gastrointestinal ulceration and bleeding.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Elderly: Use should be limited to a single caplet to be taken no more than three times a day, as this provides the highest permitted nonprescription single dose (400 mg) and daily dose (1 200 mg) of ibuprofen. Use should be limited to the shortest possible duration of treatment in order to minimize the potential risk for an adverse event. If pain persists for more than 5 days consult a health care provider (see **WARNINGS AND PRECAUTIONS – *Special Populations - Geriatrics***).

Hepatic Impairment: ANALGESIC AND MUSCLE RELAXANT is contraindicated in patients with severe hepatic impairment (see **CONTRAINDICATIONS**).

Renal Insufficiency: As with other NSAID-containing drugs, ANALGESIC AND MUSCLE RELAXANT should be used with great caution in patients with renal insufficiency (GFR < 60 mL/min or 1 mL/s). Administration of ibuprofen at 1 200 mg/day for one week has been observed to affect renal function in patients with mild renal insufficiency. Methocarbamol may also affect renal function if therapy lasts 5 days or more (see **WARNINGS AND PRECAUTIONS – *Renal***, and **ADVERSE REACTIONS – *Renal***). Use should be limited to a single caplet to be taken **no more than** three times a day, as this provides the highest permitted nonprescription single dose (400 mg) and daily dose (1 200 mg) for ibuprofen. Use should be limited to the shortest possible duration of treatment to minimize the potential risk for an adverse event. If pain persists for more than 5 days, consult a health care provider. ANALGESIC AND MUSCLE RELAXANT is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min or 0.5 mL/sec) (see **CONTRAINDICATIONS**).

Recommended Dose and Dosage Adjustment

Adults and Children over 12 years of age: Unless recommended by a physician, do not take more than one (1) caplet every 4-6 hours or more than three (3) caplets in 24 hours, as this provides the highest permitted nonprescription single dose (400 mg) and daily dose (1 200 mg) for ibuprofen.

ANALGESIC AND MUSCLE RELAXANT should preferably be taken on an empty stomach, but if stomach upset occurs, take with food or milk.

Use should be limited to the shortest possible duration of treatment. If the condition persists for more than five days, the patient should consult a health care provider.

Missed Dose

Patients who miss one or more doses of ANALGESIC AND MUSCLE RELAXANT should not increase the dose of ANALGESIC AND MUSCLE RELAXANT to compensate for the missed dose or doses, but should resume to their normal dosing and schedule without exceeding the maximum allowed for 24 hours.

OVERDOSAGE

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

Symptoms

Methocarbamol overdose toxicity or death has not been reported. One adult survived the deliberate ingestion of 22-30 g of methocarbamol without serious toxicity. Another survived 30-50 g. The principal symptom was drowsiness in both cases. However, 3 deaths have been reported when methocarbamol was combined with alcohol and other drugs.

The toxicity of ibuprofen overdose is dependent upon the amount of drug ingested and the time elapsed since ingestion; individual responses may vary, thus making it necessary to evaluate each case separately. Although uncommon, serious toxicity and death have been reported with ibuprofen overdosage. The most frequently reported symptoms of ibuprofen overdose include abdominal pain, nausea, vomiting, lethargy and drowsiness. Other CNS symptoms include headache, tinnitus, CNS depression and seizures. Metabolic acidosis, coma, acute renal failure and apnoea (primarily in very young pediatric patients) may rarely occur. Cardiovascular toxicity, including hypotension, bradycardia, tachycardia and atrial fibrillation, have also been reported.

Therapeutic Measures

Methocarbamol overdose treatment: Within 1/2 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.

In cases of acute overdose, the stomach should be emptied through induction of emesis (in alert patients only) or gastric lavage. Emesis is most effective if initiated within 30 minutes of ingestion. Orally administered activated charcoal may help in reducing the absorption of ibuprofen when given less than 2 hours following ingestion. There is some evidence that repeated administration of activated charcoal may bind the medication that has diffused from the circulation.[81] Inducing diuresis may be helpful. The treatment of acute overdose is primarily supportive. Management of hypotension, acidosis and gastrointestinal bleeding may be necessary.

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 4 hours. Pediatric patients ingesting 200 to 400 mg/kg of ibuprofen should have immediate gastric emptying and at least 4 hours observation. Pediatric patients ingesting greater than 400 mg/kg require immediate medical referral, careful observation and appropriate supportive therapy. 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.

In adult patients, the dose reportedly ingested does not appear to be predictive of toxicity. The need for referral and follow-up must be judged by the circumstances at the time of the overdose ingestion. Symptomatic adults should be carefully evaluated, observed and supported.

ACTION AND CLINICAL PHARMACOLOGY

Methocarbamol

Mechanism of Action

The precise mechanism of action is not known. Methocarbamol is thought to act on the central nervous system, perhaps depressing polysynaptic reflexes.

Pharmacodynamics

Methocarbamol is effective in reducing muscle spasms and pain in acute musculoskeletal disorders secondary to trauma and inflammation.[3,6] Each drug of the combination of methocarbamol and aspirin contributed to the therapeutic effects against acute painful skeletal muscle problems of spasm, pain and tenderness.[9,82]

Pharmacokinetics

Absorption: Orally administered methocarbamol is well absorbed from the gastrointestinal tract. Animal studies indicate that absorption occurs in the small intestine.[83] 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.

Distribution: The distribution of methocarbamol in normal and pregnant dogs was investigated by Campbell *et al*.[83] Administration of unlabelled or ^{14}C-methocarbamol into a tied-off loop of the jejunum to anesthetized dogs demonstrated that the radioactivity related to methocarbamol was easily absorbed from the intestine and widely distributed in all body tissues (highest concentrations in the liver and kidneys) and fluids (including crossing the blood-brain barrier). Radioactivity related to methocarbamol also crossed the placenta into the fetus in the dog.[83]

Methocarbamol is 46 to 50% protein bound.[85]

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.[86] In a dose proportionality study of single doses of 500 mg, 1 500 mg and 3 000 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.[87]

Extremely small amounts of unchanged methocarbamol have also been recovered in the feces[86]

Special Populations and Conditions

Cirrhosis: Some accumulation of methocarbamol at the usual dosage levels can be expected among patients with cirrhosis of the liver. At the 6-hour point, plasma levels of methocarbamol in cirrhotics were about six times the normal.

Renal Insufficiency: No alteration of methocarbamol metabolism was found in 6 patients with chronic renal failure and in a group of young-elderly.

Ibuprofen

Mechanism of Action

Ibuprofen, like all non-steroidal anti-inflammatory drugs, is an analgesic, antipyretic, and anti-inflammatory medication.[88] 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.[89]

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 catalysing the committed step in prostaglandin biosynthesis is prostaglandin endoperoxide synthase, also know as cyclooxygenase. There is significant evidence that the main mechanism of analgesic/antipyretic action of NSAIDs is prostaglandin biosynthesis inhibition.[90] 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.

Pharmacodynamics

Consistent with the NSAID classification, ibuprofen exhibits anti-inflammatory activity at higher dosage ranges.[84] At lower adult single doses relevant to a nonprescription dosage (200 mg to 400 mg) ibuprofen relieves pain of mild to moderate intensity[115-119] and reduces fever[120-122]. Analogous to acetylsalicylic acid, the prototype of this class, this analgesic/antipyretic activity of ibuprofen occurs at lower doses than necessary for anti-inflammatory effects, which are thought to require sustained administration of higher individual doses.[42]

Clinical studies indicate a duration of clinical effect for up to 8 hours for fever and up to 6 hours for pain.

Pharmacokinetics

Absorption: Ibuprofen is rapidly and almost completely absorbed. Peak serum concentration occurs within 1-2 hours in adults.[92] 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.[92]

Distribution: The volume of distribution of ibuprofen in adults after oral administration is 0.1-0.2 L/kg.[40] In humans, drug concentrations have been found in the synovial fluid of inflamed tissue approximately 5-12 hours after oral administration.[93-94] In children (mean age 11 years), synovial fluid peak levels were reached within 5-6 hours of oral administration.[95]

At therapeutic concentrations ibuprofen is highly bound to whole human plasma and to site II of purified albumin.[40] There is no appreciable plasma accumulation of ibuprofen or its metabolites with repeated doses.[92]

Metabolism: Ibuprofen is a racemic mixture of R-(-) ibuprofen and S-(+) ibuprofen. R-(-) ibuprofen undergoes extensive enantiomeric conversion to S-(+) ibuprofen in humans, averaging between 53% and 65%.[96] S-(+) ibuprofen is believed to be the pharmacologically more active enantiomer. Two major metabolites, 2-[4-(2-carboxypropyl)phenyl]propionic acid and 2-[4-(2-hydroxy-2-methylpropyl]propionic acid, have been identified in plasma and urine.[97] The metabolites 1-hydroxyibuprofen and 3-hydroxyibuprofen have also been found in urine in very small concentrations.[98-99] Cytochrome P450 (CYP) 2C9 has been identified as the most important catalyst for formation of all oxidative metabolites of R-(-) and S-(+) ibuprofen.[100] Approximately 80% of a dose is recovered in urine, primarily as carboxymetabolites and conjugated hydroxymetabolites.[40] Ibuprofen does not appear to induce the formation of drug metabolising enzymes in the rat.[97]

Excretion: Ibuprofen's plasma half-life in adults is 1.5-2.0 hours.[101] Parent drug and metabolites are primarily excreted in the urine; bile and faeces are relatively minor elimination routes. Total recovery in urine is between 70% and 90% of the administered dose within 24 hours.[102]

Special Populations and Conditions

Geriatrics: 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.[103] Furthermore, there was no statistically significant difference between the two populations in the urinary excretion pattern of the drug and its major metabolites.

Pediatrics: The pharmacokinetics of ibuprofen have also been evaluated in children, in whom the metabolism has been shown to be similar to that reported for adults. Walson reported that for ibuprofen 10 mg/kg given to children under 12 years of age, peak plasma concentration occurred at 1.5 hours and then declined with a plasma half-life of 1.8 hours.[104] Thus, ibuprofen appears to exhibit a similar pharmacokinetic profile in all age groups examined.

STORAGE AND STABILITY

Store at room temperature (15-30°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

ANALGESIC AND MUSCLE RELAXANT (methocarbamol 500 mg and ibuprofen 400 mg): Capsule-shaped, coated, bilayer tablet, debossed with "P" on one side (white) and "E" and "S" separated by a score on the other side (purple). Supplied in bottles of 50 caplets and in blister packages of 18 (9 x 2) caplets.

Composition: The inactive ingredients in ANALGESIC AND MUSCLE RELAXANT include: colloidal silicon dioxide, croscarmellose sodium, FD&C blue No. 2, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, iron oxide red, sodium lauryl sulfate, and sodium starch glycolate.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substances

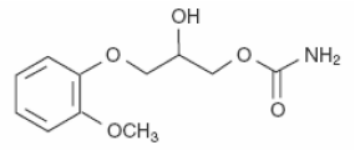
Methocarbamol

Proper name: Methocarbamol

Chemical name: 1,2-propanediol, 3-(2-methoxyphenoxy)-,1-carbamate, (±)-

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

Structural formula:



Physicochemical properties:

Physical Characteristics: White powder or crystals

Solubility: Solubility in water at 20°C: 2.5 g/100 mL. Soluble in alcohol and propylene glycol.

pKa and pH values: 1% solution in water approximate pH 6-8

Melting Point: 92 - 94°C

Ibuprofen

Proper name: Ibuprofen

Chemical name: 2-(4-isobutylphenyl)propionic acid

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

Structural formula:

Physicochemical properties:

Physical characteristics	White or almost white powder or crystals with a characteristic odour
Solubilities:	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.
pKa and pH values:	pH : 4.6 - 6.0, in a solution of 1 in 20
Melting Point:	75 - 77°C

CLINICAL TRIALS

Comparative Bioavailability Studies

A comparative bioavailability study was performed using 35 healthy human male volunteers under fasting and fed conditions. The rate and extent of absorption of methocarbamol and ibuprofen were measured and compared following a single dose of ANALGESIC AND MUSCLE RELAXANT (Methocarbamol and Ibuprofen caplets) 500 mg/400 mg caplets (Pharmascience Inc.) administered under fasting and fed conditions and a single dose of Robaxin® (methocarbamol) 500 mg tablets (Wyeth Consumer Healthcare Inc.) co-administered with a single dose of Advil® Extra Strength (ibuprofen) 400 mg tablets (Wyeth Consumer Healthcare Inc.) under fasting conditions. The results are summarized as follows:

Methocarbamol (1 x 500 mg methocarbamol/400 mg ibuprofen or 1 x 500 mg methocarbamol; fasting) From Measured Data Geometric Mean Arithmetic Mean (CV %)				
PARAMETER	**TEST[a]**	**REFERENCE[b]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng·h/mL)	18 968 19 837 (31.0)	18 836 19 686 (31.1)	100.70	95.26 – 106.45
AUC_I (ng·h/mL)	19 512 20 421 (31.5)	19 463 20 311 (30.7)	100.25	95.03 – 105.75
C_{max} (ng/mL)	7 443 7 707 (25.5)	7 101 7 391 (28.4)	104.82	95.03 – 115.63
T_{max}[c] (h)	0.83 (0.33 – 4.00)	0.83 (0.33 – 5.00)		
$T_{½}$[d] (h)	1.46 (18.5)	1.46 (16.0)		

[a] ANALGESIC AND MUSCLE RELAXANT (Methocarbamol and Ibuprofen caplets) 500 mg/400 mg caplets (Pharmascience Inc., Montréal, Québec, Canada).
[b] Robaxin® (methocarbamol) 500 mg tablets (Wyeth Consumer Healthcare Inc.) were purchased in Canada.
[c] Expressed as median (range) only.
[d] Expressed as arithmetic mean (CV%) only.

Methocarbamol (1 x 500 mg methocarbamol/400 mg ibuprofen; fed vs. fasting) From Measured Data Geometric Mean Arithmetic Mean (CV %)				
PARAMETER	**TEST[a]**	**REFERENCE[b]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng·h/mL)	14 982 15 955 (37.6)	18 968 19 837 (31.0)	78.98	74.72 – 83.50
AUC_I (ng·h/mL)	15 577 16 607 (38.6)	19 512 20 421 (31.5)	79.84	75.68 – 84.22
C_{max} (ng/mL)	4 670 4 969 (36.0)	7 443 7 707 (25.5)	62.74	56.88 – 69.21
T_{max}[c] (h)	1.50 (0.67 – 5.00)	0.83 (0.33 – 4.00)		
$T_{½}$[d] (h)	1.41 (20.0)	1.46 (18.5)		

[a] ANALGESIC AND MUSCLE RELAXANT (Methocarbamol and Ibuprofen caplets) 500 mg/400 mg caplets (Pharmascience Inc., Montréal, Québec, Canada) administered under fed conditions.
[b] ANALGESIC AND MUSCLE RELAXANT (Methocarbamol and Ibuprofen caplets) 500 mg/400 mg caplets (Pharmascience Inc., Montréal, Québec, Canada) administered under fasting conditions.
[c] Expressed as median (range) only.
[d] Expressed as arithmetic mean (CV%) only.

Ibuprofen (1 x 500 mg methocarbamol/400 mg ibuprofen or 1 x 400 mg ibuprofen; fasting) From Measured Data Geometric Mean Arithmetic Mean (CV %)				
PARAMETER	**TEST[a]**	**REFERENCE[b]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (mcg·h/mL)	132.362 133.855 (14.7)	130.157 131.546 (14.0)	101.69	99.25 – 104.20
AUC_I (mcg·h/mL)	139.656 141.578 (16.9)	137.095 138.871 (15.7)	101.87	99.07 – 104.74
C_{max} (mcg/mL)	37.016 37.482 (16.0)	38.501 39.025 (16.2)	96.14	89.49 – 103.30
T_{max}[c] (h)	1.25 (0.67 – 4.00)	1.25 (0.67 – 5.00)		
$T_{½}$[d] (h)	2.17 (17.0)	2.18 (13.9)		

[a] ANALGESIC AND MUSCLE RELAXANT (Methocarbamol and Ibuprofen caplets) 500 mg/400 mg caplets (Pharmascience Inc., Montréal, Québec, Canada).
[b] Advil® Extra Strength (ibuprofen) 400 mg tablets (Wyeth Consumer Healthcare Inc.) were purchased in Canada.
[c] Expressed as median (range) only.
[d] Expressed as arithmetic mean (CV%) only.

Ibuprofen (1 x 500 mg methocarbamol/400 mg ibuprofen; fed vs. fasting) From Measured Data Geometric Mean Arithmetic Mean (CV %)				
PARAMETER	**TEST[a]**	**REFERENCE[b]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (µg·h/mL)	117.076 118.074 (13.5)	132.362 133.855 (14.7)	88.45	86.32 – 90.63
AUC_I (µg·h/mL)	128.640 130.451 (15.0)	139.656 141.578 (16.9)	92.11	89.55 – 94.75
C_{max} (µg/mL)	28.527 29.274 (23.9)	37.016 37.482 (16.0)	77.07	71.73 – 82.80
T_{max}[c] (h)	1.75 (0.50 – 5.05)	1.25 (0.67 – 4.00)		
$T_{½}$[d] (h)	2.32 (24.6)	2.17 (17.0)		

[a]ANALGESIC AND MUSCLE RELAXANT (Methocarbamol and Ibuprofen caplets) 500 mg/400 mg caplets (Pharmascience Inc., Montréal, Québec, Canada) administered under fed conditions.
[b]ANALGESIC AND MUSCLE RELAXANT (Methocarbamol and Ibuprofen caplets) 500 mg/400 mg caplets (Pharmascience Inc., Montréal, Québec, Canada) administered under fasting conditions.
[c]Expressed as median (range) only.
[d]Expressed as arithmetic mean (CV%) only.

DETAILED PHARMACOLOGY

Methocarbamol[86,83,105]

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 7 698 ng/mL for methocarbamol when administered alone relative to 8 686 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.[83]

In animal studies, the synergic prolongation of hexobarbital sleeping time by methocarbamol was suggestive of an action on supraspinal brain centres.[106]

Ibuprofen

Animal

After single oral doses of 20 to 150 mg/kg of ^{14}C labelled ibuprofen 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 6 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.[107]

A similar dose was given to dogs for periods of up to 6 months with no evidence of accumulation of the drug or its metabolites.[107]

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.[108] The drug's protective action against fatal pulmonary embolism in rabbits injected intravenously with arachidonic acid may also relate to platelet inhibition.[109-110] Various prostaglandins and thromboxane A_2 (TXA_2) are important factors in normal platelet aggregation.[111] Cyclooxygenase inhibition reduces TXA_2 production and release, thereby reducing platelet aggregation. Ibuprofen may also reduce platelet membrane fluidity, which reduces aggregation[112], but it is not known to what extent TXA_2 synthesis inhibition is involved in this effect.

Human

Two metabolites of ibuprofen were isolated from the urine of patients who had been treated for one month with the drug. The metabolites were identified at 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.[107]

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 1 800 mg per day of ibuprofen when given over a period of 28 days.

Ibuprofen 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 2 hours after the administration of ibuprofen showed a significant dose related increase.

TOXICOLOGY

Methocarbamol

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)	2 367.7
Methocarbamol	3 576.2
Ibuprofen	762.9

The LD_{50} of the combination was 2 367.7 mg/kg. It contained 676.5 mg of ibuprofen and 1 691.2 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.

Subacute Toxicity: Oral administration to dogs of dosages of 200, 400, 600 and 1 000 mg/kg/day produced no gross signs of toxicity during the 30-day observation period. At 1 200 mg/kg/day, transitory tremor, loss of righting reflex and salivation were seen. Ataxia, which was slightly more persistent, was also observed.[113]

Chronic Toxicity: Oral administration in rats of dosages up to 1 600 mg/kg/day for 13 weeks produced toxic effects only at the higher levels. At 1 600 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.[113] There were no histological changes.

Penetration into Animal Foetus: Various species showed evidence of transfer of methocarbamol to the foetus. However, several studies of various species showed no teratogenic potential for methocarbamol.[113]

Ibuprofen

Single Dose Toxicity Studies: Single dose toxicity studies have been conducted using mice, rats, and dogs[107]. The LD_{50} values for ibuprofen, expressed as mg/kg of body weight are as follows:

Mouse:	Oral	800 mg/kg
	Intraperitoneal	320 mg/kg
Rat:	Oral	1 600 mg/kg
	Subcutaneous	1 300 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.[107] 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 on 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.[107] 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 ibuprofen is not carcinogenic in the rat.[114]

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 cyclopia. The results of this experiment indicate that ibuprofen is not teratogenic when given in toxic doses to rabbits.[107]

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.[107]

Penetration of Ibuprofen into the Rabbit and Rat Foetus: Rabbits and rats in late pregnancy were given single oral doses of 60 and 20 mg/kg respectively of C^{14} labelled ibuprofen. Rabbits were killed 3 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.[107]

REFERENCES

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

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

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

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

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

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

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

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

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

10. Cooper SA, Schachtel BP, Goldman E *et al*. Ibuprofen and acetaminophen in the relief of acute pain: A randomized, double-blind, placebo-controlled study. J Clin Pharmacol 1989; 29: 1026-1030.

11. Cooper SA. The relative efficacy of ibuprofen in dental pain. Compend Contin Educ Dent 1986; 7(8): 578-597.

12. Forbes JA, Kehm CJ, Grodin CD *et al*. Evaluation of ketorolac, ibuprofen, acetaminophen and an acetaminophen –codeine combination in post-operative oral surgery pain. Pharmacotherapy 1990; 10: 94S-105S.

13. Forbes JA, Edquist IA, Smith FG *et al*. Evaluation of bromfenac, aspirin, and ibuprofen in postoperative oral surgery pain. Pharmacotherapy 1991; 11: 64-70.

14. Forbes JA, Beaver WT, Jones KF *et al.* Analgesic efficacy of bromfenac, ibuprofen, and aspirin in postoperative oral surgery pain. Clin Pharmacol Ther 1992; 51: 343-352.

15. Jain AK, Ryan JR, McMahon FG *et al*. Analgesic efficacy of low dose ibuprofen in dental extraction pain. Pharmacotherapy 1986; 6: 318-322.

16. Mehlisch DR, Sollecito WA, Helfrick JF *et al.* Multicenter clinical trial of ibuprofen and acetaminophen in the treatment of post-operative dental pain. J Am Dent Assoc 1990; 121: 257-263.

17. Ngan P, Wilson S, Shanfeld JS *et al.* The effect of ibuprofen on the level of discomfort in patients undergoing orthodontic treatment. Am J Orthodon Dent Orthop 1994; 106: 88-95.

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

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

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

21. Larkin RM, Van Orden DE, Poulson AM, *et al*. Dysmenorrhea: Treatment with an antiprostaglandin. Obstet and Gynecol 1979; 54(4):456-460.

22. Milsom I and 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.

23. Morrison JC, Ling FW, Forman EK, *et al.* Analgesic efficacy of ibuprofen for treatment of primary dysmenorrhea. South Med J 1980; 73(8):999-1002.

24. Minor MG and Schachtel BP. Antipyretic efficacy of ibuprofen 200 mg in adults with acute upper respiratory tract infection (URI). J Clin Pharmacol 1990; 30: 846.

25. Jain AK, Vargas R, McMahon FG. The antipyretic effect of over-the-counter dosages of aspirin, acetaminophen and ibuprofen in endotoxin-induced fever. Clin Pharmacol Ther 1993; 53: 153.

26. Thoden WR and Lockhart EA: Antipyretic efficacy of ibuprofen and naproxen in flu-like upper respiratory illness. J Clin Pharmacol 1995; 35: 929.

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

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

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

30. 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.

31. Bertin L, Pons G, d'Athis P *et al.* 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.

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

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

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

35. Schachtel BP, Fillingim JM, Thoden WR *et al.* Sore throat pain in the evaluation of mild analgesics. Clin Pharmacol Ther 1988; 44: 704-711.

36. Product Monograph - Advil, 2002.

37. Garcia Rodriguez LA, Williams R, Derby LE *et al.* Acute liver injury associated with non-steroidal anti-inflammatory drugs and the role of risk factors. Arch Intern Med 1994;154: 311-316.

38. Robax ®Platinum Monograph Caplets Product Monograph, p. 9 Ref. 83. Wyeth Consumer Healthcare Inc., Missisauga, Ontario, Canada. Date of Preparation: December 16, 2003.

39. Lampert M, Villarreal J, Lopez V *et al*. Methocarbamol in the management of tetanus. Texas State J Med; 62: 55-59.

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

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

42. Flower RJ, Moncada S, Vane JR. Analgesic-antipyretics and anti-inflammatory agents; drugs employed in the treatment of gout. In: Gilman AG, Goodman LS, Rall TW, Murad F. Goodman and Gilman's The pharmacological basis of therapeutics. Toronto: Collier MacMillan, Canada 1985; 674-689, 700-703.

43. Moore N, Van Ganse E, Le Parc JM *et al*. The PAIN study: paracetamol, aspirin and ibuprofen new tolerability study. Clin Drug Invest 1999;18: 89-98.

44. Robax ®Platinum Monograph Caplets Product Monograph, p. 15 Ref. 58. Wyeth Consumer Healthcare Inc., Missisauga, Ontario, Canada. Date of Preparation: December 16, 2003.

45. Skeletal Muscle Relaxants (Systemic) Methocarbamol. USPDI 27th Edition, 2007.2632-2633.

46. Skeletal Muscle Relaxants 12:20. Methocarbamol. AHFS Drug Information 2009; 1418-1419.

47. Methocarbamol DrugDex Drug Evolution, Revised December 1999.

48. Rainsford KD, Roberts SC, Brown S. Ibuprofen and paracetamol: relative safety in non-prescription dosages. J Pharm Pharmacol 1997; 49: 345-376.

49. Doyle G, Furey S, Berlin R, Cooper S *et al*. Gastrointestinal safety and tolerance of ibuprofen maximum over-the-counter use. Aliment Pharmacol Ther 1999; 13:897-906.

50. Furey SA, Waksman JA, Dash BH. Nonprescription ibuprofen: side effect profile. Pharmacotherapy 1992; 12: 403-407.

51. DeArmond B, Francisco CA, Lin JS *et al*. Safetyprofile of over-the-counter naproxen sodium. Clin Therap 1995; 17: 587-601.

52. Kellstein DE, Waksman JA, Binstok G *et al*. The safety profile of nonprescription ibuprofen in multiple-dose use: a meta-analysis. J Clin Pharmacol 1999;39: 520-532.

53. Committee on Safety of Medicines (CSM) Update: Non-steroidal anti-inflammatory drugs and serious gastrointestinal adverse reactions. Br Med J 1986; 2: 292.

54. Ewell A, Toth F, Wolfe B *et al.* Thirteen year secular trend analysis of manufacturer-received Advil® spontaneous adverse experience reports. Pharmacoepidemiol Drug Safety 1998; 7: S101.

55. Gontarz N, Small RE, Comstock TJ *et al*. Effects of antacid suspension on the pharmacokinetics of ibuprofen. Clin Pharm 1987;7(5):413-416.

56. Fommei E, Ghione S, Palla L *et al*. Inhibition of prostaglandins and angiotensin II: Effects

on renal function in hypertensive patients. Agents Actions Suppl 1987; 22: 183-189.

57. Cook ME, Wallin JD, Thakur VD *et al*. Comparative effects of nabumetone, sulindac and ibuprofen on renal function. J Rheumatol 1997; 24: 1137-1144.

58. Minuz P, Lechi A, Arosio E *et al*.Antihypertensive activity of enalapril. Effect of ibuprofen and different salt intakes. J Clin Hypertens 1987; 3: 645-653.

59. 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.

60. 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.

61. 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.

62. Pancera P, Arosio E, Minuz P *et al*. Changes in peripheral hemodynamics and vasodilating prostaglandins after high-dose short-term ibuprofen in chronically treated hypertensive patients. Prostaglandins Leukot Essent Fatty Acids 1996; 54:217-222.

63. Harvey PJ, Wing LM, Beilby J *et al*. Effect of indomethacin on blood pressure control during treatment with nitrendipine. Blood Press 1995; 4:307-312

64. Minuz P, Pancera P, Ribul M *et al*. Amlodipine and haemodynamic effects of cyclo-oxygenase inhibition. Br J Clin Pharmacol 1995; 39:45-50.

65. Houston MC, Weir M, Gray J *et al*. 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.

66. Klassen DK, Jane LH, Young DY *et al*. Assessment of blood pressure during naproxen therapy in hypertensive patients with hypertension patients treated with nicardipine. AM J Hypertens 1995; 8:146-153.

67. Muck W, Heine PR, Schmage N *et al*. Steady-state pharmacokinetics of nimodipine during chronic administration of indomethacin in elderly healthy volunteers. Arzneimittelforschung 1995; 45:460-462.

68. Polonia J, Boaventura I, Gama G *et al*. Influence of non-steroidal anti-inflammatory drugs on renal function and 24h ambulatory blood pressure-reducing effect of enalapril and nifedipine gastrointestinal therapeutic system in hypertensive patients. J Hypertens 1995; 13:925-931.

69. Wong DG, Spence JD, Lamki L *et al*. Effect of non-steroidal anti-inflammatory drugs on

control of hypertension by beta-blockers and diuretics. Lancet 1986; 1:997-1001.

70. MICROMEDEX Healthcare Series [Internet]. Denver, CO: Thomson Reuters, 2002. [cited 2009 Oct 29]. http://www.thomsonhc.com.

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

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

73. Product Information. Lodine® oral capsule, oral Tablet, etodolac oral capsule, oral tablet. Wyeth Pharmaceuticals Inc., Philadelphia PA. , June 2005.

74. Harris KP, Jenkins D, Walls J. Nonsteroidal anti-inflammatory drugs and cyclosporine: a potentially serious adverse interaction. Transplantation 1988; 46:598-599

75. Branthwaite JP and Nicholls A. Cyclosporine and diclofenac interaction in rheumatoid arthritis (letter). Lancet 1991; 337:252.

76. Deray G, Le Hoang P, Aupetit B *et al*. Enhancement of cyclosporine A nephrotoxicity by diclofenac (letter). Clin Nephrol 1987; 27:213-214.

77. Sheiner PA, Mor E, Chodoff L *et al*. Acute renal failure associated with the use of ibuprofen in two liver transplant recipients on FK506. Transplantation 1994; 57:1132-1133.

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

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

80. Nierenberg DW. Competitive inhibition of methotrexate accumulation in rabbit kidney slices by non-steroidal anti-inflammatory drugs. J Pharmacol Exper Ther1983; 226(1): 1-6.

81. USP I: 2002: p.426-427.

82. 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.

83. Campbell AD, Coles FK, Eubank LL *et al*. Distribution metabolism of methocarbamol. J Pharmacol Exp Ther 1961; 131: 18-25.

84. Brooks CD, Schlagel CA, Sekhar NC, Sobota JT. Tolerance and pharmacology of

ibuprofen. Curr Ther Res 1973; 15:180-190.

85. Drugs Information Online, Methocarbamol, 2007. http://www.drugs.com

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

87. Robax® Platinum Caplets Product Monograph, p. 3, Ref. 20. Wyeth Consumer Healthcare Inc., Mississauga, Ontario, Canada. Date of Preparation: December 16, 2003.

88. 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.

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

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

91. Packman EW, Doyle G, Koronkiewicz K *et al.* 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.

92. Adams SS and Buckler JW. Ibuprofen and flurbiprofen. Clinics Rheum Dis 1979; 5: 359-379.

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

94. 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.

95. 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

96. Rudy AC, Knight PM, Brater DG *et al*. Enantioselective disposition of ibuprofen in elderly persons with and without renal impairment. J Pharmacol Exp Ther 1995; 273: 88-93.

97. Mills RFN, Adams SS, Cliffe EE, *et al.* The metabolism of ibuprofen. Xenobiotica 1973; 3(9):589.

98. Giachetti C, Zanolo G, Canali S. Topical administration of ibuprofen in man. Simultaneous determination of the drug and its metabolites in urine by high resolution gas

chromatography. J High Res Chromatogr Commun 1985; 8: 465-468.

99. Brooks CJW and Gilbert MT: Studies of urinary metabolites of 2-(4-isobutylphenyl)propionic acid by gas-liquid chromatography-mass spectrometry (GC-MS). J Chromatogr 1974; 99: 541-551.

100. Leeman TD, Tanson C, Bonnabry C *et al.* 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.

101. Dollery C: Ibuprofen. In Therapeutic Drugs, 1st ed, Churchill Livingstone, 11-14. 1991.

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

103. Albert KS, Gillespie WR, Wagner JG *et al.* Effects of age on the clinical pharmacokinetics of ibuprofen. Am J Med 1984; 77: 47-50.

104. Walson PD: Ibuprofen versus paracetamol for the treatment of fever in children. Br J Clin Pract 1990; 70: 19-21.

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

106. Truitt EB and 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.

107. Adams SS, Bough RG, Cliffe EE *et al.* Absorption, distribution and toxicity of ibuprofen. Toxicol Appl Pharmacol 1969; 15: 310-330.

108. Lillehei TJ, Metke MP, Dawnajee MK *et al.* Reduction of platelet deposition in aorto-coronary artery Gore-Tex bypass grafts in dogs by platelet inhibitors. Circulation 1980; 62: Suppl 3; 53.

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

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

111. Utsunomiya T, Krausz MM, Dunham B *et al.* Modification of inflammatory response to aspiration with ibuprofen. Am J Physiol 1982; 243:H903-910.

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

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

114. Adams SS, Bough RG, Cliffe EE *et al*. Some aspects of the pharmacology, metabolism and toxicology of ibuprofen. Rheum Phys Med Suppl 1970: 9-14.

115. Cooper SA, Needle SE, Kruger GO. Comparative analgesic potency of aspirin and ibuprofen. J Oral Surgery 1977; 35:898-903.

116. Gallardo F, Rossi E. Double-blind evaluation of naproxen and ibuprofen in periodontal surgery. Pharm Ther Dent 1980; 5:69-72.

117. Jain AK, Ryan JR, McMahon FG, Kuebel JO, Walters PJ, Noveck C. Analgesic efficacy of low doses of ibuprofen in dental extraction pain. Clin Pharmacol Ther 1984; 35:249.

118. Vecchio TJ, Heilman CJ, O'Connel MJ. Efficacy of ibuprofen in muscle extraction headache. Clin Pharmacol Ther 1983; 33:199.

119. Iles JD. Relief of postoperative pain by ibuprofen: a report of two studies. Can J Surg 1980;23:288-290.

120. Gaitonde BB, Dattani K, Morwani K. Antipyretic activity of ibuprofen (Brufen). J Assoc Physicians India 1973; 21:579-584.

121. Sheth UK, Gupta K, Paul T, Pispati PK. Measurement of antipyretic activity of ibuprofen and paracetamol in children. J Clin Pharmacol 1980; 20:672-675.

122. Simila S, Kouvalainen K, Keinanen S. Oral antipyretic therapy: evaluation of ibuprofen. Scand J Rheumatol 1976; 581-583.

PART III: CONSUMER INFORMATION
ANALGESIC AND MUSCLE RELAXANT
Methocarbamol and Ibuprofen caplets

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

ABOUT THIS MEDICATION

What the medication is used for:
ANALGESIC AND MUSCLE RELAXANT is used for effective relief of pain associated with muscle spasms, such as back pain, tense neck muscles, strains and sprains.

What it does:
Ibuprofen reduces pain, fever and inflammation. Methocarbamol is a muscle relaxant. Ibuprofen is a member of a class of drugs called non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs work within the body by decreasing the production of substances, called prostaglandins which are involved in the development of pain and inflammation. Methocarbamol is thought to act on the central nervous system

When it should not be used:
DO NOT TAKE ANALGESIC AND MUSCLE RELAXANT if you have
or are:

- stomach distress, stomach or gastric ulcers
- bleeding from the stomach or gut
- inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis)
- taking acetylsalicylic acid (ASA) or any other Non-Steroidal Anti-Inflammatory Drugs (NSAID) including any other ibuprofen product.
- right before or after heart surgery.
- heart disease or severe high blood pressure
- Bleeding in the brain or other bleeding disorders
- in your third trimester (after 28 weeks) of pregnancy
- allergic to methocarbamol, ibuprofen, ASA (Acetylsalicylic Acid) or other salicylates or other NSAIDs, or any of the non-medicinal ingredients in ANALGESIC AND MUSCLE RELAXANT (see the heading "What the non-medicinal ingredients are"). Allergic reactions may appear as hives, difficulty breathing, shock, skin reddening, rash or blisters, swelling of the face or throat, or sudden collapse.
- 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.
- Systemic Lupus Erythematosus.
- Serious liver disease or kidney disease
- high potassium in the blood

Patients who took a drug in the same class as ANALGESIC AND MUSCLE RELAXANT after a type of heart surgery (coronary artery bypass grafting (CABG)) were more likely to have heart attacks, strokes, blood clots in the leg(s) or lung(s), and infections or other complications than those who did NOT take that drug.

What the medicinal ingredients are:
Methocarbamol
Ibuprofen

What the non-medicinal ingredients are:
ANALGESIC AND MUSCLE RELAXANT also contain colloidal silicon dioxide, croscarmellose sodium, FD&C Blue No. 2, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, iron oxide red, sodium lauryl sulfate, and sodium starch glycolate.

What dosage forms it comes in:
Each caplet contains 500 mg of methocarbamol and 400 mg of ibuprofen.

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 taking ANALGESIC AND MUSCLE RELAXANT talk to your doctor or pharmacist if you have or are:

- High blood pressure
- Diabetes mellitus or on a low sugar diet
- Heart or thyroid disease
- Poor circulation to your extremities
- A current or past habit of smoking
- Kidney disease or urine problems
- Previous ulcer or bleeding from the stomach or gut
- Previous bleeding in the brain
- Liver disease
- Take drugs for depression, sedatives or any other medication

- Asthma, glaucoma, blood clotting disorder (such as hemophilia), any other serious disease, are under doctor's care for any serious condition
- Trying to conceive, in your first or second trimester of pregnancy or if you are breastfeeding

While taking this medication:

- fertility may be decreased. The use of ANALGESIC AND MUSCLE RELAXANT is not recommended in women trying to get pregnant. In women who have difficulty conceiving, stopping treatment with ANALGESIC AND MUSCLE RELAXANT should be considered.
- exercise caution when operating machinery or motor vehicles as ANALGESIC AND MUSCLE RELAXANT may cause drowsiness or dizziness. Avoid consuming alcohol.
- Use with caution in the elderly.
- Long-term continuous use may increase the risk of heart attack or stroke.

INTERACTIONS WITH THIS MEDICATION

Do not use this product if you are taking ASA.

Talk to your health care provider and pharmacist if you are taking any other medication (prescription or nonprescription) such as any of the following (this is NOT a complete list):

- Acetylsalicylic Acid (ASA) or other NSAIDs
  e.g., ASA, celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen
- Antacids
- Antidepressants
- Blood pressure medications
  - ACE (angiotensin converting enzyme) inhibitors
    e.g., enalapril, lisinopril, perindopril, ramipril
  - ARBs (angiotensin II receptor blockers)
    e.g., candesartan, irbesartan, losartan, valsartan
- Blood thinners e.g., warfarin, ASA, clopidogrel
- Corticosteroids (including glucocorticoids)
  e.g., prednisone
- Cyclosporin or Tacrolimus
- Digoxin
- Diuretics
  e.g., furosemide, hydrochlorothiazide
- Lithium
- Methotrexate
- Oral hypoglycemics (diabetes medications)
- Selective Serotonin Reuptake Inhibitors (SSRIs)
  e.g., citalopram, fluoxetine, paroxetine, sertraline

PROPER USE OF THIS MEDICATION

Usual dose:

Medical Condition	Usual Dose	Maximum Dose	Maximum Duration of Treatment
Pain associated with muscle spasms (for adults and adolescents over 12 years of age)	1 caplet every 4 to 6 hours	3 caplets per 24 hours	Not specified

Preferably, take on an empty stomach, but if stomach upset occurs, take with food or milk.

Take ANALGESIC AND MUSCLE RELAXANT only as directed by your health care provider. Do not take more than recommended or longer than five days. Use the lowest effective dose for the shortest duration.
If your condition persists for more than five days, consult a health care provider.

ANALGESIC AND MUSCLE RELAXANT should NOT be used in children 12 years of age and under since safety and effectiveness have NOT been established.

Overdose:

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

Missed Dose:
Continue to take 1 tablet 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

ANALGESIC AND MUSCLE RELAXANT may cause some side effects, such as heartburn, constipation, nausea, bloating, nervousness or sleeplessness especially when used for a long time or in large doses. The risk of having side effects may be decreased by using the smallest dose for the shortest duration of time. Stop use and contact a doctor or pharmacist if these symptoms worsen or persist

ANALGESIC AND MUSCLE RELAXANT may cause you to become drowsy or tired. Be careful when driving or participating in activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking ANALGESIC AND MUSCLE RELAXANT, do NOT drive or operate machinery.

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	

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 or chest tightness			✓
	Blood in vomit, Bloody or black stools, gastrointestinal ulcer with bleeding or perforation, jaundice, inflammation of pancreas or kidney			✓
	Heart failure and stroke, renal failure, asthma			✓
	Blurred vision, or any visual disturbance		✓	
	Any change in the amount or colour of your urine (red or brown)		✓	
	Any pain or difficulty experienced while urinating		✓	
	Swelling of the feet, lower legs; weight gain		✓	
	Vomiting or persistent indigestion, nausea, stomach pain or diarrhea		✓	
	Yellow discolouration of the skin or eyes, with or without itchy skin		✓	
	Malaise, fatigue, loss of appetite		✓	
	Headaches, stiff neck		✓	
	Mental confusion, depression		✓	
	Dizziness, lightheadedness		✓	
	Hearing problems		✓	

This is NOT a complete list of side effects. If you have any unexpected side effects while taking ANALGESIC AND MUSCLE RELAXANT, see your healthcare provider.

HOW TO STORE IT

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

Store at room temperature (15-30°C).

Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) 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.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Pharmascience Inc. at:
1-888-550-6060

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