

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

MOTRIN® Platinum Muscle & Body

Ibuprofen and Methocarbamol Tablets
Tablet, 200 mg ibuprofen and 500 mg methocarbamol, Oral
Analgesic/Muscle Relaxant

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Date of Initial Authorization:
[Feb 26,2015]
Date of Revision:
February 26, 2026

Submission Control Number: 302595

RECENT MAJOR LABEL CHANGES

3 SERIOUS WARNINGS AND PRECAUTIONS BOX		[08/2023]
7 WARNINGS AND PRECAUTIONS	Monitoring and Laboratory Tests	[08/2023]
7 WARNINGS AND PRECAUTIONS	7.1.1 Pregnant Women	[08/2023]

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Adults and children (>12 years of age):

MOTRIN® Platinum Muscle & Body (ibuprofen and methocarbamol caplets) is indicated for the effective relief of pain associated with muscle spasm such as back pain, tense neck muscles, strains and sprains.

1.1 Pediatrics

Pediatrics (< 12 years of age):

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use in children under 12 years of age. MOTRIN® Platinum Muscle & Body is not indicated for children <12 years of age.

1.2 Geriatrics

Geriatrics (> 65 years of age):

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. Therefore, the use of MOTRIN® Platinum Muscle & Body in this population is not recommended (See Warnings and Precautions, Special Populations, Geriatrics).

2 CONTRAINDICATIONS

- Known hypersensitivity to methocarbamol or ibuprofen. Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition and Packaging section of the product monograph. There is a potential for cross-reactivity between different NSAIDs and ibuprofen, and patients sensitive to other carbamate derivatives and methocarbamol.
- Active peptic ulcer, a history of recurrent ulceration or active inflammatory disease of the G.I. system, such as ulcerative colitis and Crohn's disease.
- The combination drug product should not be used in patients who have significant hepatic impairment or active liver disease.
- Severely impaired or deteriorating renal function (creatinine clearance <30mL/min). Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored.
- Patients with the complete or partial syndrome of nasal polyps, or in whom asthma, anaphylaxis, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse effects.

- Not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects (See 9 Drug Interactions).
- Children (equal to or greater than 12 years of age) with kidney disease or who have suffered significant fluid loss due to vomiting, diarrhea or lack of fluid intake, should not be given ibuprofen.
- Ibuprofen is contraindicated in patients with systemic lupus erythematosus, as an anaphylaxis-like reaction with fever may occur, particularly when ibuprofen has been administered previously.
- The third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus and prolonged parturition.
- Do not use right before or after heart surgery (see Peri-Operative Considerations).
- Ibuprofen should not be used in the presence of known hyperkalemia (also see Warnings and Precautions – Renal section).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Use with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention (See WARNINGS AND PRECAUTIONS, Cardiovascular and Fluid and Electrolyte Balance; and DRUG INTERACTIONS, Antihypertensives).
- Use with caution in patients who might be prone to gastrointestinal tract irritation, particularly those with a history of diverticulosis, or other inflammatory disease of the gastrointestinal tract such as ulcerative colitis or Crohn’s disease (See WARNINGS AND PRECAUTIONS, Gastrointestinal and DRUG INTERACTIONS, Coumarin-type anticoagulants).
- Use with caution in patients at greatest risk of renal toxicity, such as those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly (See WARNINGS AND PRECAUTIONS, Renal).
- If persistent urinary symptoms, hematuria and cystitis occur, the drug should be stopped immediately (See WARNINGS AND PRECAUTIONS, Genitourinary).
- Caution should be exercised in prescribing **MOTRIN® Platinum Muscle and body** if trying to conceive, during the first and second trimesters of pregnancy, or nursing. Use of NSAIDS at approximately 20 weeks of gestation or later may cause oligohydramnios, and renal dysfunction including renal failure (see WARNINGS AND PRECAUTIONS, Special Populations). **MOTRIN® Platinum Muscle and body** is CONTRAINDICATED for use during

the third trimester because of risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition) (see CONTRAINDICATIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

The safety issues to consider when developing a dosage regimen of MOTRIN® Platinum Muscle & Body for individual patients is applicable to:

- Elderly patients older than 65 years who are frail or debilitated and consideration should

be given to a starting dose lower than the one usually recommended (See WARNINGS AND PRECAUTIONS, Elderly).

- Use the lowest effective dose for the shortest duration.

4.2 Recommended Dose and Dosage Adjustment

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

4.5 Missed Dose

Take the missed dose as soon as you remember. If it is almost time for your next dose, wait until

then to take your medicine and skip your missed dose. Do not take two doses at the same time.

5 OVERDOSAGE

Symptoms of Overdose

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

Clinical findings associated with major ibuprofen overdose include abdominal pain, nausea, vomiting, lethargy and drowsiness, renal tubular acidosis. Other CNS symptoms include headache, tinnitus, CNS depression, dizziness, drowsiness, seizures, rhabdomyolysis, apnea

and stupor, rarely progressing to coma. Examination may reveal hyper- or hypothermia, abnormal respiration ranging from hyperventilation to respiratory depression, hypotension, sinus tachycardia, bradycardia and atrial fibrillation, and abnormal neurological and neuromuscular activity with ataxia, nystagmus, and seizure activity. Subsequently, renal dysfunction with oliguria or anuria may supervene, and clinical evidence of bleeding due to hypoprothrombinemia and thrombocytopenia may occur later. An elevated anion gap metabolic acidosis can be seen following large ingestions.

Treatment of Overdose

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

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

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

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

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

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet/ Ibuprofen 200 mg/ Methocarbamol 500 mg	Carnauba wax, colloidal silicon dioxide, FD&C yellow no. 6, hypromellose, microcrystalline cellulose, povidone, sodium lauryl sulphate, sodium starch glycolate, stearic acid, triacetin.

Each bi-layered MOTRIN® Platinum Muscle & Body coated caplet contains ibuprofen 200 mg and methocarbamol 500 mg and consists of an orange layer on one side and a white layer on the other side, with occasional orange specks on the white layer, occasional white specks on the orange layer, embossed with « MOTRIN » on the orange layer.

MOTRIN® Platinum Muscle & Body caplets are available in blisters of 18 and bottles of 40 caplets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

In common with other anti-inflammatory drugs, ibuprofen may mask the usual signs of infection. Methocarbamol may produce false positive tests for urinary 5-hydroxyindoleacetic acid (5- HIAA) and vanillymandelic acid (VMA).

If symptoms persist or get worse, or if new symptoms occur, patients should stop use and consult a physician.

Cardiovascular

Use of ibuprofen may precipitate congestive heart failure in patients with marginal cardiac function, elevated blood pressure and palpitations have been reported following ibuprofen administration.

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke. This risk may increase with dose and duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Driving and Operating Machinery

May cause drowsiness or dizziness. Exercise caution in operating machinery or motor vehicles.

Ear/Nose/Throat

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

Fluid and Electrolyte Balance

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

With NSAID treatment there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with β -adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics. Serum electrolytes should be monitored periodically during long-term therapy, especially in those who are at risk.

Gastrointestinal

Serious GI toxicity, such as peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal, can occur at any time, with or without symptoms in patients treated with NSAIDs including ibuprofen. The risk may increase with dose and duration of use.

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

In patients observed in clinical trials of such agents, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6

months and in about 2-4% of patients treated for one year. The risk continues beyond one year and possibly increases. The incidence of these complications increases with increasing dose.

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

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

If ulceration is suspected or confirmed, or if GI bleeding occurs, MOTRIN® Platinum Muscle & Body should be discontinued immediately, appropriate treatment instituted, and the patient monitored closely.

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

Genitourinary

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

Hematologic

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

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

Hepatic/Biliary/Pancreatic

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

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

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

The frequency of acute liver injury among 311,716 patients who were prescribed ibuprofen was 1.6/100,000. For NSAID users as a group, the only factors that had an independent effect on the occurrence of acute liver injury were the simultaneous use of hepatotoxic medication or the presence of rheumatoid arthritis. Based on these data, the short-term use of ibuprofen as an analgesic/antipyretic should not be of concern regarding the development of liver disease.

Immune

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

Monitoring and Laboratory Tests

For Monitoring and Laboratory Tests related to the use of MOTRIN® Platinum Muscle & Body, see WARNINGS AND PRECAUTIONS, Fluid and Electrolyte Balance, Gastrointestinal, Hematologic, Hepatic, Renal and Special Populations: Geriatrics.

Pregnancy: If **MOTRIN® PLATINUM MUSCLE AND BODY** is administered in the middle

(approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women on **MOTRIN® PLATINUM MUSCLE AND BODY** be closely monitored for amniotic fluid volume since **MOTRIN® PLATINUM MUSCLE AND BODY** may result in reduction of amniotic fluid volume and even oligohydramnios (see Special Populations). **MOTRIN® PLATINUM MUSCLE AND BODY** is CONTRAINDICATED for use in the third trimester of pregnancy.

Neurologic

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

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

Ophthalmologic

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

Psychiatric

Some patients may experience depression with the use of ibuprofen.

Renal

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

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

Like other NSAIDs, ibuprofen inhibits renal prostaglandin synthesis, which may decrease renal

function and cause sodium retention. Renal blood flow and glomerular filtration rate decreased in patients with mild impairment of renal function who took 1200 mg/day of ibuprofen for one week. Renal papillary necrosis has been reported. A number of factors appear to increase the risk of renal toxicity. In comparative clinical trials involving 7624 ibuprofen-treated, 2822 ASA-treated and 2843 placebo-treated patients, adverse reactions involving renal function were reported by 0.6% of the ibuprofen group, 0.3% of the ASA group and 0.1% of the placebo group. The analysis included data from trials which employed doses greater than 1200 mg, used for longer periods than OTC recommendations and by patients being treated for serious conditions. Ibuprofen and its metabolites are eliminated primarily by the kidneys; therefore the drug should be used with great caution in patients with impaired renal function. In these cases, utilisation of lower doses of MOTRIN® Platinum Muscle & Body should be considered and patients carefully monitored.

Methocarbamol may also affect renal function if therapy lasts 5 days or more.

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

Fluid and Electrolyte Balance

Patients on MOTRIN® Platinum Muscle & Body should be cautioned to report to their physician any signs or symptoms of weight gain, or edema. MOTRIN® Platinum Muscle & Body should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

With nonsteroidal anti-inflammatory treatment there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with β -adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics. Serum electrolytes should be monitored periodically during long-term therapy, especially in patients who are at risk.

Sensitivity/Resistance

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

Skin

Ibuprofen may cause a severe allergic reaction, especially in patients allergic to acetylsalicylic acid. Symptoms may include hives, facial swelling, asthma (wheezing), shock, skin reddening, rash or blisters with or without pyrexia or erythema. If any of these symptoms occur, patients should stop use and seek medical help right away.

Serious skin reactions such as Erythema Multiforme (EM), Stevens - Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Acute Generalized Exanthematous Pustulosis (AGEP) have been reported very rarely in patients receiving ibuprofen.

7.1 Special Populations

Oligohydramnios/Neonatal Renal Impairment:

Use of NSAIDs, including **MOTRIN® PLATINUM MUSCLE AND BODY**, at approximately 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some more severe cases, neonatal respiratory, musculoskeletal and renal problems (see Non-Clinical Toxicology).

Published studies and post-marketing reports describe maternal NSAID use at approximately 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment, or failure. NSAIDs were shown to cause significant reduction in fetal urine production prior to reduction of amniotic fluid volume. There have also been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible, even after treatment discontinuation.

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If, after careful consideration of alternative treatment options for pain management, NSAID treatment is necessary anywhere from the middle (onset approximately 20 weeks) to the end of the second trimester of pregnancy, it is recommended that the use be limited to the lowest effective dose and shortest duration possible.

Consider ultrasound monitoring of fetal well-being, including of amniotic fluid volume assessment if **MOTRIN® PLATINUM MUSCLE AND BODY** treatment extends beyond 48 hours. It is recommended that NSAIDs treatment be discontinued if oligohydramnios occurs, followed by appropriate medical follow up.

Inform pregnant women not to use **MOTRIN® PLATINUM MUSCLE AND BODY** and other NSAIDs from the third trimester of pregnancy because of the risk of the premature closing of the fetal ductus arteriosus [see Contraindications]. If treatment with **MOTRIN® PLATINUM MUSCLE AND BODY** is needed for a pregnant woman anywhere from the middle (onset approximately 20 weeks gestation to the end of the second trimester of pregnancy), advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours.

7.1.1 Pregnant Women

There are no adequate data regarding use of methocarbamol/ibuprofen in pregnant women. Use during late pregnancy should be avoided.

Use of ibuprofen should be avoided during the last 3 months of pregnancy unless otherwise directed by a physician. When used within the third trimester of pregnancy, nonsteroidal anti-

inflammatory drugs, including ibuprofen, are associated with premature closure of the fetal ductus arteriosus, which may result in persistent pulmonary hypertension in the newborn infant. Caution should be exercised in prescribing MOTRIN® to women who are trying to conceive, during the first and second trimesters of pregnancy, or if nursing.

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. Because of the known effects of NSAIDs on the fetal cardiovascular system, use of ibuprofen during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of ibuprofen is not recommended during pregnancy.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo-fetal 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-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

7.1.2 Breast-feeding

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. One study showed an ibuprofen concentration of 13 ng/mL 30 minutes after ingesting 400 mg. The milk:plasma ratio was 1:126. This translates to an infant exposure of 0.0008% of the maternal dose. It is not known to what extent, if any, ibuprofen crosses the human placenta. No adverse effect has been detected in children 6 months of age who were administered ibuprofen.

7.1.3 Pediatrics

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

Caregivers should ask a physician before use if they believe that the child maybe dehydrated. Not drinking fluids, excessive fluid loss due to vomiting, diarrhea and high fevers may contribute to the risk of dehydration.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Patients older than 65 years and frail or debilitated patients are most susceptible to a variety of adverse reactions from NSAIDs: the incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal ulceration and bleeding. For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision.

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

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

8.5 Post-Market Adverse Reactions

Ibuprofen

The following adverse reactions have been noted in patients treated with doses (≥ 1200 mg/day).

Note: Reactions listed below under Causal Relationship Unknown are those which occurred under circumstances where a causal relationship could not be established. However, in these reported events, the possibility of a causal relationship to ibuprofen cannot be excluded.

Gastrointestinal

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

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

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

Incidence less than 1%: gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, hepatitis, jaundice, abnormal liver function AST, serum bilirubin and alkaline phosphatase, pancreatitis, oral discomfort (local burning sensation, irritation).

Allergic

Incidence less than 1%: anaphylaxis.

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

Central Nervous System

Incidence 3 to 9%: dizziness.

Incidence 1 to 3%: headache, nervousness, drowsiness/somnolence.

Incidence less than 1%: depression, insomnia.

Causal relationship unknown: paresthesias, hallucinations, dream abnormalities, psychomotor hyperactivity.

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

Dermatologic

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

Incidence 1 to 3%: pruritus.

Incidence less than 1%: vesiculobullous eruptions, urticaria, erythema, erythema multiforme.

Causal relationship unknown: alopecia, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), fixed eruption.

Cardiovascular

Incidence less than 1%: congestive heart failure in patients with marginal cardiac function, elevated blood pressure (hypertension), angioedema, myocardial infarction, stroke (cerebrovascular accident).

Causal relationship unknown: arrhythmias (sinus tachycardia, sinus bradycardia, palpitations), hemorrhage (non-GI), Kounis syndrome.

Special Senses

Incidence 1 to 3%: tinnitus, asthenia.

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

Causal relationship unknown: conjunctivitis, diplopia, optic neuritis.

Hematologic

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

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

Renal

Causal relationship unknown: decreased creatinine clearance, polyuria, azotemia, nephritis, nephrotic syndrome, renal failure.

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

Hepatic

Incidence less than 1%: hepatitis, jaundice, hepatotoxicity, abnormal liver function (transaminases increased, AST, serum bilirubin, and alkaline phosphatase), vanishing bile duct syndrome.

Endocrine

Causal relationship unknown: gynecomastia, hypoglycemic reaction.

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

Metabolic

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

Fluid retention generally responds to drug discontinuation.

Respiratory

Incidence less than 1%: asthma, bronchospasms

Methocarbamol

May cause drowsiness, dizziness, blurred vision, lightheadedness, somnolence, vertigo, anorexia, headache, fever, nausea, allergic reactions such as urticaria, pruritus, rash, skin eruptions, conjunctivitis with nasal congestion.

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.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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

Since methocarbamol may possess a general CNS depressant effect, patients taking MOTRIN® Platinum Muscle & Body should be cautioned about combined effects with alcohol and other CNS depressants.

9.4 Drug-Drug Interactions

Acetaminophen

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

Acetylsalicylic acid (ASA) or other NSAIDs

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

Antacids

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

magnesium hydroxide.

Anti-hypertensives

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

Prostaglandins are an important factor in cardiovascular homeostasis and inhibition of their synthesis by NSAIDs may interfere with circulatory control. NSAIDs may elevate blood pressure in patients receiving antihypertensive medication. Two meta analyses, 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 showed that ibuprofen 1600 mg/day for 14 days did not attenuate the antihypertensive effect of two β -adrenergic blockers. Houston et al showed no effect of three weeks' therapy with ibuprofen on the antihypertensive efficacy of verapamil, but it is not known whether this lack of interaction extends to other classes of calcium channel blockers.

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

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

Coumarin-type

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.

Digoxin

Ibuprofen has been shown to increase serum digoxin concentration. Increased monitoring and

dosage adjustments of digitalis glycoside may be necessary during concurrent ibuprofen therapy and following discontinuation of ibuprofen therapy.

Diuretics

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

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

H-2 antagonists

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

Hypoglycaemic Agents

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

Lithium

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

Methotrexate

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

Other drugs

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

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

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

10.1 Mechanism of Action

Methocarbamol

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

Ibuprofen

Ibuprofen, like all nonsteroidal anti-inflammatory drugs (NSAIDs), is an analgesic, antipyretic, and anti-inflammatory medication. 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.

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 sensitize 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 known as cyclooxygenase. There is significant evidence that the main

mechanism of analgesic/antipyretic action of NSAIDs is prostaglandin biosynthesis inhibition. 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.

10.3 Pharmacokinetics

Methocarbamol:

Absorption

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

Distribution:

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

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.

Elimination

Studies in humans dosed with radio-labelled (C14) methocarbamol indicated that 97-99% of the administered radioactivity was recovered in the urine over 3 days. Extremely small amounts of unchanged methocarbamol have also been recovered in the feces.

Ibuprofen:

Absorption

Ibuprofen is rapidly and almost completely absorbed. Peak serum concentration occurs within 1-2 hours in adults. 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.

Distribution:

The volume of distribution in adults after oral administration is 0.1 - 0.2 L/kg.

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

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

Metabolism:

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

Elimination

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

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

Special Populations and Conditions

- **Pregnancy and Breast-feeding**

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

Ibuprofen excretion in breast milk following ingestion of one 400 mg ibuprofen tablet every 6

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

11 STORAGE, STABILITY AND DISPOSAL

MOTRIN® Platinum Muscle & Body caplets should be stored in closed containers under room temperature (15°C to 30°C) (59°F to 86°F) conditions. Protect from moisture.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

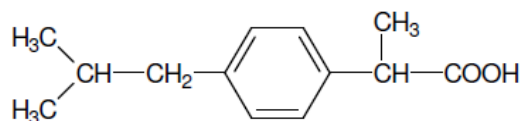
Drug Substance

Proper name: Ibuprofen

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

Molecular formula and molecular mass: C₁₃H₁₈O₂, 206.28 g/mol

Structural formula:



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

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

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

Melting Point: 75 – 77°C

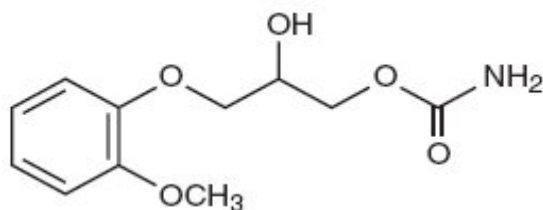
Drug Substance

Proper name: Methocarbamol

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

Molecular formula and molecular mass: C₁₁H₁₅NO₅, 241.25 g/mol

Structural formula:



Physicochemical properties: White powder or crystals

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

pH value: 1% solution in water approximate pH 6-8.

Melting Point: 92 – 94°C

14 CLINICAL TRIALS

14.3 Comparative Bioavailability Studies

MOTRIN® Platinum Muscle & Body Caplets

A blinded, randomized, two treatment, two sequence, two period, single oral dose, crossover bioequivalence study of MOTRIN® Platinum Muscle & Body caplets (containing ibuprofen 200 mg and methocarbamol 500 mg) manufactured by McNeil Consumer Healthcare, division of Johnson & Johnson Inc. (Canada) and ROBAX PLATINUM® caplets (containing ibuprofen 200 mg and methocarbamol 500 mg) manufactured by Wyeth Consumer Healthcare Inc. (Canada) was conducted in thirty-eight (38) healthy male and female subjects under fasting conditions.

A summary of the comparative bioavailability data is presented below:

Ibuprofen (1 x 200 mg ibuprofen/500 mg methocarbamol) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (µg·h/mL)	72.0 73.0 (17.8)	72.3 73.3 (17.5)	99.6	96.5 – 102.7
AUC _∞ (µg·h/mL)	73.6 74.7 (17.7)	73.9 75.0 (17.7)	99.6	96.6 – 102.8
C _{max} (µg/mL)	21.1 21.7 (22.1)	21.9 22.4 (19.2)	96.2	89.4 – 103.5
T _{max} § (h)	1.3 (0.3 – 6.0)	1.3 (0.5 – 4.0)		
T _½ € (h)	2.1 (10.0)	2.1 (12.6)		

*MOTRIN® Platinum Muscle & Body Caplets (containing ibuprofen 200 mg and methocarbamol 500 mg), McNeil Consumer Healthcare, division of Johnson & Johnson Inc. (Canada)

†ROBAX PLATINUM® Caplets (containing ibuprofen 200 mg and methocarbamol 500 mg), Wyeth Consumer Healthcare Inc. (Canada), purchased in Canada.

§ Expressed as median (range) only

€ Expressed as the arithmetic mean (CV%) only

Methocarbamol (1 x 200 mg ibuprofen/500 mg methocarbamol) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (µg·h/mL)	24.3 26.0 (40.8)	24.6 26.3 (39.6)	98.9	95.4 – 102.6
AUC _∞ (µg·h/mL)	24.9 26.6 (40.8)	25.2 26.7 (39.6)	98.9	95.4 – 102.5
C _{max} (µg/mL)	9.6 10.2 (35.8)	9.9 10.4 (31.5)	97.2	89.6 – 105.4
T _{max} § (h)	0.8 (0.3 – 3.0)	0.8 (0.5 – 2.5)		
T _{1/2} € (h)	1.5 (21.2)	1.4 (21.4)		

* MOTRIN® Platinum Muscle & Body Caplets (containing ibuprofen 200 mg and methocarbamol 500 mg), McNeil Consumer Healthcare, division of Johnson & Johnson Inc. (Canada)

† ROBAX PLATINUM® Caplets (containing ibuprofen 200 mg and methocarbamol 500 mg), Wyeth Consumer Healthcare Inc. (Canada), purchased in Canada.

§ Expressed as median (range) only

€ Expressed as the arithmetic mean (CV%) only

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

Parameter	Orally Administered Combination Drug Product	Orally Administered Single Drug
Methocarbamol mean t _{max}	0.72 ± 0.35 hours	1.01 ± 0.52 hours
Ibuprofen mean t _{max}	1.36 ± 1.04 hours	1.65 ± 0.96 hours
Methocarbamol mean t _{1/2}	1.30 ± 0.29 hours	1.25 ± 0.27 hours

Ibuprofen mean $t_{1/2}$	2.08 ± 0.37 hours	2.11 ± 0.43 hours
Methocarbamol mean C_{max}	8686.37 ± 2635.47 ng/ml	7698.73 ± 2657.59 ng/ml
Ibuprofen mean C_{max}	20376.2 ± 5592.44 ng/ml	18435.6 ± 4582.87 ng/ml
Methocarbamol $k_{el/hr}$	0.556 ± 0.116	0.579 ± 0.116
Ibuprofen $k_{el/hr}$	0.344 ± 0.065	0.342 ± 0.067

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

Published Literature

Methocarbamol has been studied in muscle relaxation models including tetanus therapy, muscle spasms, painful muscle conditions, and in combination with analgesics, with positive results. In gynecological postoperative patients, methocarbamol reduced the use of narcotics and other sedatives for pain and discomfort.

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

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

Ibuprofen has been studied in other pain models including dental, muscle contraction headache, soft tissue injury, post surgery, dysmenorrhea, and migraine, with equally effective pain relief results.

DETAILED PHARMACOLOGY

Methocarbamol

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

In a comparative bioavailability study, the 500 mg dose administered individually produced peak plasma level at about 1 hour and in about 45 minutes when administered in combination with ibuprofen. The C_{max} was 7698 ng/mL for methocarbamol when administered alone

relative to 8686 ng/mL when administered in combination. In about 6 hours the amount of methocarbamol level in plasma dropped to below 700 ng/mL for both individual and combination administrations.

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

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

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

Ibuprofen

Animal Pharmacology

After single oral doses of 20 to 150 mg/kg of C¹⁴ labelled ibuprofen in rats, the peak plasma level occurred at or before the earliest time examined (20 minutes in the 20 mg/kg group and 45 minutes in the 150 mg/kg group) and peak levels occurred with 45 minutes of dosing in nearly all tissues examined. The concentration in plasma and tissue decreased to very low levels by six hours after the 20 mg/kg dose and by 17 hours after the 150 mg/kg dose. Sixteen to 38% of the daily dose of ibuprofen was excreted in the urine.

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

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. The drug's protective action against fatal pulmonary embolism in rabbits injected intravenously with arachidonic acid may also relate to platelet inhibition. Various prostaglandins and thromboxane A₂ (TXA₂), are important factors in normal platelet aggregation. Cyclooxygenase inhibition reduces TXA₂ production and release, thereby reducing platelet aggregation. Ibuprofen may also reduce platelet membrane fluidity, which reduces aggregation, but it is not known to what extent TXA₂ synthesis inhibition is involved in this effect.

Human Pharmacology

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 as 2-4', (2-hydroxy-2-methylpropyl) phenylpropionic acid (metabolite A) and 2-4' (2-carboxpropyl) phenylpropionic acid (metabolite B). About 1/3 of the dose was excreted in the urine of patients as metabolite B, 1/10 as unchanged ibuprofen and 1/10 as metabolite A. The remainder of the dose could not be identified in the urine.

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

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

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

15 MICROBIOLOGY

Not applicable. No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Animal Toxicity

LD₅₀ was determined in rats with oral combined drugs (methocarbamol 2.5 and ibuprofen 1 w/w) and individually administered methocarbamol and ibuprofen as follows:

LD₅₀ (mg/kg)

Methocarbamol / ibuprofen (2.5/1)	2367.7
Methocarbamol	3576.2
Ibuprofen	762.9

The LD₅₀ of the combination drug was 2367.7 mg/kg. It contained 676.5 mg of ibuprofen and 1691.2 mg of methocarbamol. The ibuprofen component of the combination is close to the LD₅₀ of ibuprofen of 762.9 mg/kg. This suggests that ibuprofen was solely responsible for the toxicity/mortality of the animals dosed with the mixture. The results also indicate that the mixture of ibuprofen and methocarbamol (1:2.5 w/w) does not affect the acute oral toxicity of either constituent drug in rats.

Methocarbamol

Subacute Toxicity

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

Chronic Toxicity

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

Ibuprofen

Single Dose Toxicity Studies

Single dose toxicity studies have been conducted using mice, rats, and dogs.

The LD50 values for ibuprofen, expressed as mg/kg of body weight are as follows:

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

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

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

Multiple Dose Studies

The no-effect level was determined using groups of 10 male and 10 female rats which were dosed orally for 26 weeks with 180, 60, 20 or 7.5 mg/kg ibuprofen in 0.4% hydroxyethyl cellulose. The control group consisted of 20 males and 20 females which received 0.4% hydroxyethyl cellulose. Rats were weighed three times daily and blood samples were obtained in the final week of dosing. The rats were sacrificed the day after the last dose and the internal organs examined.

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

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

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

Since the highest dose of 180 mg/kg/day was only moderately toxic, an additional group of rats was dosed with 540 mg/kg/day. 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.

Carcinogenicity:

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.

Reproductive and Developmental Toxicology:

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 clycopia. The results of this experiment indicate that ibuprofen is not teratogenic when given in toxic doses to rabbits.

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.

Penetration into Animal Foetus

Rabbits and rats in late pregnancy were given ibuprofen single oral doses of 60 and 20 mg/kg respectively of C¹⁴ labelled ibuprofen. Rabbits were killed three hours after dosing and rats killed 1.5 hours after dosing when maternal and foetal blood was collected. Similar concentrations of radioactive ibuprofen were detected in both the mother and foetus indicating that the drug and its metabolites readily crossed the placental barrier into the foetal circulation.

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

17 SUPPORTING PRODUCT MONOGRAPHS

ROBAX Platinum (Methocarbamol and ibuprofen caplets, 500mg /200 mg), Control # 236559, Product Monograph. GlaxoSmithKline Consumer Healthcare Inc. Apr 03, 2020

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

MOTRIN® Platinum Muscle & Body

Ibuprofen 200 mg/Methocarbamol 500 mg Tablets

Read this carefully before you start taking **MOTRIN® Platinum Muscle & Body** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MOTRIN® Platinum Muscle & Body**.

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 (a disease affecting colon), 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.
- Talk to your doctor if you are trying to conceive, in your first or second trimester of pregnancy or if breastfeeding.

What is MOTRIN® Platinum Muscle & Body used for?

- For effective relief of pain associated with muscle spasm such as back pain, tense neck muscles, strains and sprains

How does MOTRIN® Platinum Muscle & Body work?

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.

What are the ingredients in MOTRIN® Platinum Muscle & Body?

Medicinal ingredients: Ibuprofen and methocarbamol.

Non-medicinal ingredients: Carnauba wax, colloidal silicon dioxide, FD&C yellow no. 6, hypromellose, microcrystalline cellulose, povidone, sodium lauryl sulphate, sodium starch glycolate, stearic acid, triacetin.

MOTRIN® Platinum Muscle & Body comes in the following dosage forms:

Tablet, ibuprofen 200 mg and methocarbamol 500 mg.

Do not use MOTRIN® Platinum Muscle & Body if:

- You are:
 - taking acetylsalicylic acid (ASA) or any other nonsteroidal anti-inflammatory medication including any other ibuprofen product.
 - allergic/hypersensitive to ibuprofen or other non-steroidal anti-inflammatory drugs (NSAIDs), ASA or other salicylates, methocarbamol or to any of the MOTRIN® Platinum Muscle & Body caplets ingredients (Refer to the inactive ingredients on outer carton or see Non-medicinal ingredients above) or any component of the container. Allergic reactions may appear as hives, difficulty breathing, shock, skin reddening, rash or blisters, swelling of the face or throat, or sudden collapse.
 - dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake.
 - in your third trimester of pregnancy.

- You have:
 - peptic ulcer disease or gastrointestinal bleeding or any other active inflammatory disease of the gastrointestinal tract (e.g. colitis, Crohn's disease).
 - nasal polyps (growth inside your nose), or allergic manifestations such as asthma, anaphylaxis (sudden severe life-threatening anaphylactic reactions), urticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms.
 - serious liver or kidney disease.
 - Systemic Lupus Erythematosus.
 - high potassium in the blood.

- You recently had or are about to have heart surgery.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MOTRIN® Platinum Muscle & Body. Talk about any health conditions or problems you may have, including if you:

- have diabetes, high blood pressure, heart or thyroid disease, asthma, mild to moderate kidney or liver disease, glaucoma, blood clotting disorder (such as hemophilia), or history of stomach bleeding or any other serious disease.
- are pregnant or breastfeeding
- are under a doctor's care for any serious condition
- are older than 65 years of age
- are taking any other drug, including over the counter drugs.

Other warnings you should know about:

- May cause drowsiness or dizziness. Exercise caution in operating machinery or motor vehicles.
- Avoid alcohol.
- Use with caution in the elderly.
- Long-term continuous use may increase the risk of heart attack or stroke.
- The use of NSAIDs, like MOTRIN® Platinum Muscle & Body, in the second trimester of pregnancy should be restricted to the lowest dose necessary for shortest possible duration.
- At 20 weeks or later in pregnancy, your use of NSAIDs may need to be monitored by a health care practitioner due to the rare risk of kidney problems in the unborn baby which may result in decreased amniotic fluid volume and other complications.

Stop use and ask a doctor if

- you show signs of stomach bleeding
- pain worsens or lasts more than 5 days
- you have chest pain
- any new or unusual symptoms appear
- you get a rash or itchy skin

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with MOTRIN® Platinum Muscle & Body:

- acetaminophen
- anticoagulants (blood thinners)
- ASA or other NSAIDs
- digoxin
- diuretics (water pills)
- lithium
- medications for high blood pressure
- methotrexate
- oral antidiabetic agents and insulin
- protein-bound drugs including probenecid, thyroxine, antibiotics, cyclosporine, phenytoin, corticosteroids or benzodiazepines

Do not use this product if you are taking ASA. Ibuprofen may interfere with the preventative benefits of ASA.

How to take MOTRIN® Platinum Muscle & Body:

Take with food or milk if upset stomach occurs.

Usual dose:

Adults and children over 12: Take 1 or 2 caplets every four to six hours as needed. Do not exceed 6 caplets in 24 hours, unless directed by a physician. Use the lowest effective dose for the shortest duration. Do not use longer than 5 days without consulting your physician.

Overdose:

If you think you, or a person you are caring for, have taken too much MOTRIN® Platinum Muscle & Body, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

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

What are possible side effects from using MOTRIN® Platinum Muscle & Body?

These are not all the possible side effects you may have when taking MOTRIN® Platinum Muscle & Body. If you experience any side effects not listed here, tell your healthcare professional.

MOTRIN® Platinum Muscle & Body may occasionally produce unwanted side effects, such as heartburn, constipation, nausea, bloating, sudden stomach pain or long-term stomach pain with the loss of appetite and/or new onset of itching, diarrhea, decreased appetite, headache, drowsiness, depression, tiredness, nervousness or sleeplessness, coloured urine, menstrual delays.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Symptoms of severe allergic reaction (anaphylaxis), including: rash, severe itching/redness, blisters, swelling, or trouble breathing, chest pain, Stevens-Johnson syndrome			✓
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			✓
Abdominal pain, vomiting, diarrhea		✓	
ringing or buzzing in the ears/dizziness		✓	
Change in vision, including: blurred or diminished vision		✓	
Fluid retention, decrease in white blood cells and hemoglobin		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at 15 to 30°C. Protect from moisture.

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

If you want more information about MOTRIN® Platinum Muscle & Body:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website www.motrin.ca, or by calling 1-888-6MOTRIN / 1-888-666-8746.

This leaflet was prepared by Kenvue Canada Inc.

Last Revised: February 26, 2026