PRODUCT MONOGRAPH

ADVIL BACK PAIN

500 mg Methocarbamol and 200 mg Ibuprofen Tablets

THERAPEUTIC CLASSIFICATION

Muscle Relaxant / Analgesic

GlaxoSmithKline Consumer Healthcare Inc.

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Control # 239840

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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.

Methocarbamol:

Methocarbamol is effective in reducing muscle spasm and pain in acute musculo-skeletal disorders secondary to trauma and inflammation.[17,70] Each drug of the combination of methocarbamol and aspirin contributed to the therapeutic effects against acute painful skeletal muscle problems of spasm, pain and tenderness.[69,18]

Orally administered methocarbamol is well absorbed from the gastrointestinal tract. Animal studies indicate that absorption occurs in the small intestine.[10] Studies in humans dosed with radio-labelled (C^{14}) methocarbamol indicated that 97-99% of the administered radioactivity was recovered in the urine over 3 days.[8] In a comparative bioavailability study, following oral administration peak plasma concentration was reached in approximately 45 minutes when methocarbamol was administered in combination with ibuprofen. The plasma half life of methocarbamol administered alone was 1.25 ± 0.27 hours and 1.30 ± 0.29 hours when administered in combination.

In a dose proportionality study of single doses of 500 mg, 1500 mg and 3000 mg, it was shown that kinetics of methocarbamol are not linear. However, rates of elimination suggest that no accumulation is expected with chronic dosing every 6 hours.[20]

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.

Extremely small amounts of unchanged methocarbamol have also been recovered in the feces.[8]

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

Ibuprofen:

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

Prostaglandins are naturally-occurring fatty acid derivatives that are widely distributed in the tissues. They are believed to be a common factor in the production of pain, fever, and inflammation. Prostaglandins are believed to sensitise tissues to pain- and inflammation-producing mediators such as histamine, 5-hydroxytryptamine, and kinins. The enzyme 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.[82] Other pharmacologic effects such as lysosome and plasma membrane stabilisation have been observed, but the potential relevance of these effects to ibuprofen-induced analgesia and antipyresis is unclear.

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

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

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

In humans, drug concentrations have been found in the synovial fluid of inflamed tissue approximately 5-12 hours after oral administration.[35, 37] In children (mean age 11 years), synovial fluid peak levels were reached within 5-6 hours of oral administration.[36]

Cytochrome P450 (CYP) 2C9 has been identified as the most important catalyst for formation of all oxidative metabolites of R-(-) and S-(+) ibuprofen.[9] Approximately 80% of a dose is recovered in urine, primarily as carboxymetabolites and conjugated hydroxymetabolites.[3] Ibuprofen does not appear to induce the formation of drug metabolising enzymes in the rat.[39]

There is no evidence of a differential metabolism or elimination of ibuprofen in the elderly. A pharmacokinetic evaluation of ibuprofen in geriatric subjects (65 to 78 years) compared with young adult subjects (22 to 35 years) found that there was no clinically significant difference in the kinetic profiles of ibuprofen for these age groups.[28]

Furthermore, there was no statistically significant difference between the two populations in the urinary excretion pattern of the drug and its major metabolites. [28]

Breast Milk and Placental Transport:

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

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

In a comparative bioavailability study in humans after a single dose of combination (methocarbamol 500mg and ibuprofen 200mg) drug product, and single-drug methocarbamol 500mg or ibuprofen 200mg, 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 $t_{½}$	1.30 ± 0.29 hours	1.25 ± 0.27 hours
Ibuprofen mean $t_{½}$	2.08 ± 0.37 hours	2.11 ± 0.43 hours
Methocarbamol mean C_{max}	8686.37 ± 2635.47 ng/ml	7698.73 ± 2657.59 ng/ml
Ibuprofen mean C_{max}	20376.2 ± 5592.44 ng/ml	18435.6 ± 4582.87 ng/ml
Methocarbamol k_{el}/hr.	0.556 ± 0.116	0.579 ± 0.116
Ibuprofen k_{el}/hr.	0.344 ± 0.065	0.342 ± 0.067

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

Indications:

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

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

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

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

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

Contraindications

The following are contraindications to the use of methocarbamol/ibuprofen combination drug product.

1. Known hypersensitivity to methocarbamol or ibuprofen. There is a potential for cross-reactivity between different NSAIDs and ibuprofen, and patients sensitive to other carbamate derivatives and methocarbamol.

2. Active peptic ulcer, a history of recurrent ulceration or active inflammatory disease of the G.I. system.[56]

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

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

5. 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.

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

Warnings:

Gastrointestinal (GI) System:

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

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

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

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

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

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

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

Aseptic Meningitis:

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.

Pregnancy:

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

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.

Renal function:

Long-term administration of nonsteroidal anti-inflammatory drugs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports

of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

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

Like other NSAIDs, ibuprofen inhibits renal prostaglandin synthesis, which may decrease renal function and cause sodium retention. Renal blood flow and glomerular filtration rate decreased in patients with mild impairment of renal function who took 1200 mg/day of ibuprofen for one week. Renal papillary necrosis has been reported. A number of factors appear to increase the risk of renal toxicity. In comparative clinical trials involving 7624 ibuprofen-treated, 2822 ASA-treated and 2843 placebo-treated patients, adverse reactions involving renal function were reported by 0.6% of the ibuprofen group, 0.3% of the ASA group and 0.1% of the placebo group. The analysis included data from trials which employed doses greater than 1200 mg, used for longer periods than OTC recommendations and by patients being treated for serious conditions.[83] Ibuprofen and its metabolites are eliminated primarily by the kidneys; therefore the drug should be used with great caution in patients with impaired renal function. In these cases, utilisation of lower doses of Advil Back Pain 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.

Genitourinary tract:

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.

Hepatic function:

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the

development of more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with nonsteroidal anti-inflammatory drugs.

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

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

The frequency of acute liver injury among 311,716 patients who were prescribed ibuprofen was 1.6/100,000. For NSAID users as a group, the only factors that had an independent effect on the occurrence of acute liver injury were the simultaneous use of hepatotoxic medication or the presence of rheumatoid arthritis.[24] Based on these data, the short-term use of ibuprofen as an analgesic/antipyretic should not be of concern regarding the development of liver disease.

Use in the Elderly:

Patients older than 65 years and frail or debilitated patients are most susceptible to a variety of adverse reactions from NSAIDs: the incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal ulceration and bleeding.[56]

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

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

Use in Children:

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, Advil Back Pain should not be administered to children in this age group.

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.

Precautions

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

Ophthalmology: 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.

Central nervous system: Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of this product. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

Anticoagulants: A study reported lack of change in hypoprothrombinemia caused by warfarin when administered with ibuprofen.[40] Other 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 hemostatis, and NSAIDs affect platelet function, concurrent therapy of Advil Back Pain with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary.[56]

Oral hypoglycemics: Ibuprofen may increase hypoglycemic effects of oral antidiabetic agents and insulin.[56]

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

CNS Depressants: 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 Advil Back Pain 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).

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.[33] One study showed an ibuprofen concentration of 13 ng/mL 30 minutes after ingesting 400 mg.[78] The milk:plasma ratio was 1:126. This translates to an infant exposure of 0.0008% of the maternal dose. It is not known to what extent, if any, ibuprofen crosses the human placenta. No adverse effect has been detected in children 6 months of age who were administered ibuprofen.

Hematology: 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 anemia and agranulocytosis) associated with the use of NSAIDs are rare, but could occur with severe consequences.[56]

Drug Interactions

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

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

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 aspirin given with NSAIDs including ibuprofen, yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-aspirin drug. Single dose bioavailability studies in normal volunteers have failed to show an effect of aspirin on ibuprofen blood levels. Correlation clinical studies have not been conducted.

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

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

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

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

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

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

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

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

Coumarin-type: [40, 15] Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding. Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function, concurrent therapy of ibuprofen with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary. 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.

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, steroids, antibiotics or benzodiazepines.

Adverse Reactions

Ibuprofen [56]

Gastrointestinal: The adverse reactions most frequently seen with prescribed ibuprofen therapy involve the gastrointestinal system. 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). 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: Less than 1%: anaphylaxis. Causal relationship unknown: fever, serum sickness, lupus erythematosus.

Central Nervous System: 3 to 9%: dizziness. 1 to 3%: headache, nervousness. 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: 3 to 9%: rash (including maculopapular type). 1 to 3%: pruritus. Less than 1%: vesiculobullous eruptions, urticaria, erythema multiforme. Causal relationship unknown: alopecia, Stevens-Johnson syndrome.

Cardiovascular: 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: 1 to 3%: tinnitus. 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: 1-20%: leukopenia and decreases in hemoglobin and hematocrit. Causal relationship unknown: hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes (e.g. purpura, epistaxis, hematuria, menorrhagia).

Renal : 3 to 9%: decreased creatinine clearance, polyuria, azotemia.

Hepatic: 3 to 9%: hepatitis, jaundice, abnormal liver function, AST, serum bilirubin, and alkaline phosphatase.

Endocrine: Causal relationship unknown: gynecomastia, hypoglycemic reaction. Menstrual delays of up to two weeks and dysfunctional uterine bleeding occurred in nine patients taking ibuprofen, 400 mg t.i.d., for three days before menses.

Metabolic: 1 to 3%: decreased appetite, edema, fluid retention. Fluid retention generally responds to drug discontinuation.

Methocarbamol: may cause drowsiness,[58] dizziness,[58] blurred vision,[74]

lightheadedness, somnolence,[58] vertigo,[58] anorexia, headache, fever, nausea, allergic reactions such as urticaria, pruritus, rash, skin eruptions, conjunctivitis with nasal congestion.[80]

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

Symptoms and Treatment of Overdose

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

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

Treatment of Overdose

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

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

For overdoses >200 mg/kg (ibuprofen), the patient should be referred to a medical facility and gastrointestinal decontamination with administration of activated charcoal (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.

Dosage and Administration

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.

Pharmaceutical Information

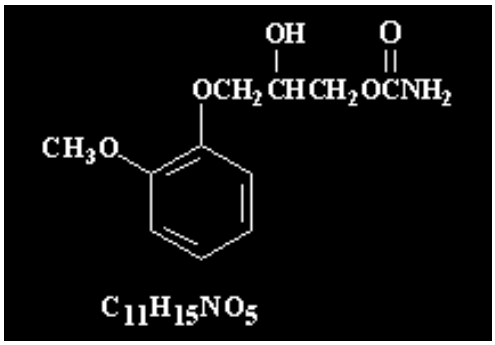
Drug Substances: Methocarbamol and Ibuprofen

Proper or Common Name: Methocarbamol

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

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

Structural Formula:



Molecular Formula:

Molecular Weight: 241.25

Physical Characteristics: White powder or crystals.

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

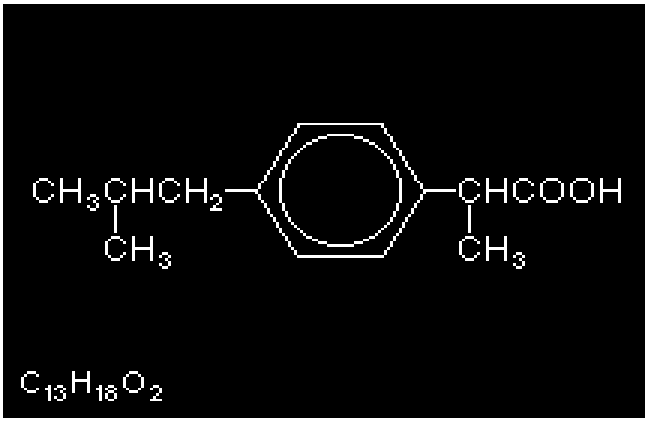
pKa and pH values: 1% solution in water approximate pH 6-8.

Melting Point: 92 - 94°C

Proper or common name*:* Ibuprofen

Chemical name: (±)-2-(p-isobutyl phenyl) propionic acid

Other names: (1) Benzene acetic acid, α-methyl-4-(2-methylpropyl), (±)



(2) (±)-p-isobutyl hydratropic acid

Structural formula

Molecular formula

Molecular weight 206.28

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^{0}C

Composition:

In addition to methocarbamol and ibuprofen, the caplets contain colloidal silicon dioxide, copovidone, FD&C Blue No.2, ferric oxide (red), hypromellose, methyl cellulose, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, stearic acid.

Stability and Storage

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

Availability of Dosage Forms

Each purple and white Advil Back Pain contains methocarbamol 500mg and ibuprofen 200mg.

Advil Back Pain are available in blisters of 18, and bottles of 40.

Information for the Consumer

Package Insert

Package Insert
Please Save This For Future Use

Advil Back Pain

Ibuprofen/Methocarbamol Caplets
Pain Reliever and Muscle Relaxant

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

Adult Dosage: 1 or 2 caplets every four to six hours, as needed. Do not exceed six caplets in 24 hours, unless directed by a physician.

_ **Caution: Keep out of reach of children.** This package contains enough medicine to seriously harm a child. Do not give to a child under 12, or exceed the recommended dose, unless directed by a physician. Do not take Advil Back Pain if taking acetylsalicylic acid (ASA) or ibuprofen, or if allergic to ASA, salicylates or anti-inflammatory drugs. Consult your physician before taking Advil Back Pain if you have peptic ulcers, high blood pressure, heart, kidney or liver disease, any other serious disease, or are taking any other drug. If pregnant or nursing, consult your physician before taking Advil Back Pain. If abdominal pain, heartburn, nausea or vomiting, bloating, diarrhea or constipation, ringing or buzzing in the ears, nervousness, sleeplessness, any change in vision, fluid retention, itching, skin rashes or any other side effect or unexplained symptom develops while taking Advil Back Pain, discontinue use immediately and contact a physician. In case of overdose, call a Poison Control Centre or a doctor at once, even if there are no symptoms.

Warning: May cause drowsiness or dizziness. Exercise caution in operating machinery or motor vehicles. Avoid alcohol. Consult your physician if symptoms persist for more than 5 days.

Product Monograph available to physicians and pharmacists upon request.

Medicinal Ingredients: Each caplet contains Methocarbamol 500mg, Ibuprofen 200mg.

Non-medicinal Ingredients: Colloidal silicon dioxide, copovidone, FD&C Blue No. 2, ferric oxide (red), hypromellose, methyl cellulose, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, stearic acid.

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

GlaxoSmithKline Consumer Healthcare Inc.
Mississauga, ON, Canada L5N 6L4

www.backrelief.com

Date of Revision: 06-July-2020

PHARMACOLOGY

Methocarbamol [8, 10, 27]

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

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

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

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

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

Ibuprofen

Animal

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

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

Inhibition of Platelet Aggregation in Animals

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

Human

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.[12]

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

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

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.

Toxicology

Advil Back Pain

Acute Animal Toxicity

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

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

The LD_{50} of the combination drug was 2367.7 mg/kg. It contained 676.5 mg of ibuprofen and 1691.2 mg of methocarbamol. The ibuprofen component of the combination is close to the LD_{50} of ibuprofen of 762.9 mg/kg. This suggests that ibuprofen was solely responsible for the toxicity/mortality of the animals dosed with the mixture. The results also indicate that the mixture of ibuprofen and methocarbamol (1:2.5 w/w) does not affect the acute oral toxicity of either constituent drug in rats.

Methocarbamol

Subacute Toxicity

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

Chronic Toxicity

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

Ibuprofen

Single Dose Toxicity Studies

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

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

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

Subcutaneous 1300 mg/kg

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

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

Multiple Dose Studies

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

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

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

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

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

The primary toxic effect of ibuprofen in rats is intestinal damage. Ibuprofen alters the organ to body weight ratio of certain organs, such as the liver, kidneys, gonads, and the secondary sex organs, although no histological abnormalities have occurred and the effect is reversible. The liver and kidney enlargement may be a reflection of work hypertrophy associated with the metabolism and excretion of the compound, whereas the significance of the effect on other organs is unknown. When administered in lethal doses, ibuprofen produces mild kidney lesions in addition to the intestinal damage.

Carcinogenic Potential

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

Teratology Study in Rabbits

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

Teratology Study in Rats

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

Penetration into Animal Foetus

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

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

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