

PRODUCT MONOGRAPH

Pr **MINT-INDOMETHACIN**

Indomethacin Capsules USP

25 mg and 50 mg Capsules

Non-Steroidal Anti-Inflammatory Drugs

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MINT-INDOMETHACIN

Indomethacin Capsules USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsules / 25 mg and 50 mg	Lactose Monohydrate <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

MINT-INDOMETHACIN (Indomethacin Capsules) is indicated for the relief of symptoms associated with selected cases of:

- Adult rheumatoid arthritis, not as a first choice because of the adverse reactions that may occur with its use.
- Ankylosing spondylitis
- Acute attacks of gout
- Severe osteoarthritis, including degenerative disease of the hip, which do not respond to treatment with other drugs

Indomethacin is not a simple analgesic, and its use should be limited to those conditions listed, above, particularly those cases not responding to conservative measures.

Through out this document, the term NSAIDs refers to both non-selective NSAIDs and selective COX-2 inhibitor NSAIDs, unless otherwise indicates.

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

Use of MINT-INDOMETHACIN should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for

cardiovascular or gastrointestinal adverse events (See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS)

MINT-INDOMETHACIN as a NSAID, does NOT treat clinical disease or prevent its progression.

MINT-INDOMETHACIN as a NSAID, only relieves symptoms and decreases inflammation for as long as the patient continues to take it.

Geriatrics (> 65 years of age):

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

Pediatrics (< 18 years of age):

Safety and Efficacy have not been established in the paediatric population. MINT-INDOMETHACIN is contraindicated in children and adolescents less than 18 years of age.

CONTRAINDICATIONS

MINT-INDOMETHACIN is contraindicated in:

- the peri-operative setting of coronary artery bypass graft surgery (CABG). Although indomethacin has NOT been studied in this patient population, a selective COX-2 inhibitor NSAID studied in such a setting has led to an increased incidence of cardiovascular/thromboembolic events, deep surgical infections and sternal wound complications.
- the third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus and prolonged parturition
- women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants
- severe uncontrolled heart failure
- known hypersensitivity to Indomethacin Capsules or to any of the components/excipients
- history of asthma, urticaria, or allergic-type reactions after taking ASA or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance - rhinosinusitis, urticaria/angioedema, nasal polyps, asthma). Fatal anaphylactoid reactions have occurred in such individuals. Individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction. The potential for cross-reactivity between different NSAIDs must be kept in mind (see **Warnings and Precautions – Hypersensitivity Reactions - Anaphylactoid Reactions**).
- active gastric / duodenal / peptic ulcer, active GI bleeding.
- cerebrovascular bleeding or other bleeding disorders
- inflammatory bowel disease
- severe liver impairment or active liver disease

- severe renal impairment (creatinine clearance <30 mL/min or 0.5 mL/sec) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored) (see **Warnings and Precautions - Renal**).
- known hyperkalemia (see **Warnings and Precautions - Renal - Fluid and Electrolyte Balance**).
- children and adolescents.

As with other anti-inflammatory agents, indomethacin may mask the signs and symptoms of peptic ulcer. Indomethacin itself may cause peptic ulceration or irritation of the gastrointestinal tract. For these reasons, it should not be given to patients with active peptic ulcer, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions.

MINT-INDOMETHACIN (Indomethacin Capsules) is contraindicated in patients who are hypersensitive to any component of this product, and in patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by acetylsalicylic acid (ASA) or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals.

The drug should not be prescribed for children because safe conditions for use have not been established. In a few cases of severe juvenile rheumatoid arthritis, where indomethacin was given along with other drugs, severe reactions, including fatalities, were reported.

WARNINGS AND PRECAUTIONS

Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV) (See Warnings and Precautions - Cardiovascular).

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

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

Use of NSAIDs, such as MINT-INDOMETHACIN can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure. (see also Warnings and Precautions - Renal - Fluid and Electrolyte Balance).

Randomized clinical trials with MINT-INDOMETHACIN have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing MINT-INDOMETHACIN.

Risk of Gastrointestinal (GI) Adverse Events (see Warnings and Precautions – *Gastrointestinal*).

Use of NSAIDs, such as MINT-INDOMETHACIN, is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction and gastrointestinal bleeding)

General

Frail or debilitated patients may tolerate side effects less well and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration.** As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

MINT-INDOMETHACIN is NOT recommended for use with other NSAIDs, with the exception of low-dose ASA for cardiovascular prophylaxis, because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. (See **Drug Interactions - *Drug/Drug Interactions - Acetylsalicylic acid (ASA) or other NSAIDs***).

Cardiovascular

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

Caution should be exercised in prescribing MINT-INDOMETHACIN to patients with risk factors for cardiovascular disease, cerebrovascular disease or renal disease, such as any of the following (NOT an exhaustive list)

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

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

Use of NSAIDs, such as MINT-INDOMETHACIN, can induce fluid retention and edema, and may exacerbate congestive heart failure, through a renally-mediated mechanism. (See **Warnings and Precautions - Renal - Fluid and Electrolyte Balance**).

For patients with a high risk of developing an adverse CV event, other management strategies that do NOT include the use of NSAIDs should be considered first. **To minimize the potential risk for an adverse CV event, the lowest effective dose should be used for the shortest possible duration.**

Central Nervous System

Headache may occur, usually early in treatment with indomethacin. If headache persists despite dosage reduction therapy with indomethacin should be discontinued. (Also, see WARNINGS AND PRECAUTIONS).

Patients who suffer from dizziness, lightheadedness, or feelings of detachment on indomethacin should be cautioned against operating motor vehicles or other machinery, climbing ladders, etc., if these symptoms are present.

Indomethacin should be used with caution in patients with psychiatric disturbances, epilepsy, or parkinsonism, since it may, in some instances, aggravate these conditions.

Endocrine and Metabolism

Corticosteroids:

MINT-INDOMETHACIN (Indomethacin Capsules) is NOT a substitute for corticosteroids. It does NOT treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids. (see **Drug Interactions - Drug-Drug Interactions – Glucocorticoids**).

Gastrointestinal (GI):

Serious GI toxicity (sometimes fatal), such as peptic / duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, such as MINT-INDOMETHACIN. Minor upper GI problems, such as dyspepsia, commonly occur at any time. Health care providers should remain alert for ulceration and bleeding in patients treated with MINT-INDOMETHACIN, even in the absence of previous GI tract symptoms. Most spontaneous

reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered. (see **Warnings and Precautions - Special Populations - Geriatrics**).

Patients should be informed about the signs and/or symptoms of serious GI toxicity and instructed to discontinue using MINT-INDOMETHACIN and seek emergency medical attention if they experience any such symptoms. The utility of periodic laboratory monitoring has NOT been demonstrated, nor has it been adequately assessed. Most patients who develop a serious upper GI adverse event on NSAID therapy have no symptoms. Upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. Even short-term therapy has its risks.

Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with non-steroidal anti-inflammatory drugs (NSAIDs) including Indomethacin Capsules.

MINT-INDOMETHACIN should be given under close medical supervision to patients prone to gastrointestinal tract irritation particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract. In these cases the physician must weigh the benefits of treatment against the possible hazards.

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

Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from NSAIDs. For such patients, consideration should be given to a starting dose lower than usual, with individual adjustment when necessary and under close supervision.

If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs MINT-INDOMETHACIN (Indomethacin Capsules) should be discontinued, an appropriate treatment instituted and patient closely monitored.

There is no definitive evidence that the concomitant administration of histamine H₂ antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of MINT-INDOMETHACIN therapy when and if these adverse reactions appear.

Indomethacin capsules should be used with caution because of the gastrointestinal reactions which may occur. The incidence of gastrointestinal effects may be decreased by giving the drug immediately after meals, with food or with antacids. The risk of continuing therapy with

indomethacin in the face of such symptoms must be weighed against the possible benefits to the individual patient. Indomethacin suppositories should be given with caution to patients with any anal or rectal pathology.

Studies in normal subjects with radioactive chromate-tagged red blood cells indicate that large doses of indomethacin (50 mg four times a day) produce less fecal blood loss than average doses of acetylsalicylic acid (600 mg four times a day). Notwithstanding, indomethacin may cause single or multiple ulceration of the stomach, duodenum, or small and large intestine. There have been reports of severe bleeding and of perforation with a few fatalities. Patients may also develop gastrointestinal bleeding with no obvious ulcer formation. If gastrointestinal bleeding occurs, discontinue using the drug. In many patients with peptic ulceration, a history of a previous ulcer was present or they were on concomitant steroids, salicylates or phenylbutazone. A possible potentiation of the ulcerogenic effect of these drugs cannot be ruled out at present. In some patients there was no history of a previous ulcer and other drugs were not being given. As a result of obvious or occult gastrointestinal bleeding some patients may manifest anemia. For this reason appropriate blood determinations are recommended periodically.

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

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

Genitourinary

Some NSAIDs are associated with persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with a NSAID. Should urinary symptoms occur, in the absence of an alternate explanation, treatment with MINT-INDOMETHACIN should be stopped to ascertain if symptoms disappear. This should be done before urological investigations or treatments are carried out.

Hematologic

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

Anti-coagulants:

Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of bleeding. Concurrent therapy of MINT-INDOMETHACIN with warfarin requires close monitoring of the international normalized ratio (INR).

Even with therapeutic INR monitoring, increased bleeding may occur.

Anti-platelet Effects:

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

MINT-INDOMETHACIN and other NSAIDs have no proven efficacy as antiplatelet agents and should NOT be used as a substitute for ASA or other antiplatelet agents for prophylaxis of cardiovascular thromboembolic diseases. Antiplatelet therapies (e.g. ASA) should NOT be discontinued. There is some evidence that use of NSAIDs with ASA can markedly attenuate the cardioprotective effects of ASA. (see **Drug Interactions - Drug-Drug Interactions - Acetylsalicylic Acid (ASA) or other NSAIDs**).

Concomitant administration of MINT-INDOMETHACIN with low dose ASA increases the risk of GI ulceration and associated complications.

Blood dyscrasias:

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

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

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed when MINT-INDOMETHACIN is administered.

Indomethacin Capsules, like other non-steroidal anti-inflammatory agents, can inhibit platelet aggregation. This effect is of shorter duration than that seen with acetylsalicylic acid and usually disappears within 24 hours after discontinuation of Indomethacin Capsules. Indomethacin has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this effect may be exaggerated in patients with underlying hemostatic defects, MINT-INDOMETHACIN should be used with caution in persons with coagulation defects.

Hepatic/Biliary/Pancreatic

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

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported with NSAIDs. ^{Ref. 50, page 11}

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

If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

Significant (3 times the upper limit of normal) elevations of SGPT (ALAT) or SGOT (ASAT) occurred in controlled clinical trials in less than 1% of patients receiving therapy with non-steroidal and-inflammatory drugs. 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 MINT-INDOMETHACIN.

Hypersensitivity Reactions:

Anaphylactoid Reactions:

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

ASA-Intolerance:

MINT-INDOMETHACIN should NOT be given to patients with complete or partial syndrome of ASA-intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps, asthma) in whom asthma, anaphylaxis, urticaria/angioedema, rhinitis or other allergic manifestations are precipitated by ASA or other NSAIDs. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction (see **Contraindications**).

Cross-sensitivity:

Patients sensitive to one NSAID may be sensitive to any of the other NSAIDs as well.

Serious skin reactions:

(See **Warnings and Precautions - Skin**)

Patients should be followed carefully to detect unusual manifestations of drug sensitivity, and since advancing years appear to increase the possibility of adverse reactions, indomethacin should be used with greater care in the elderly.

Immune

(See **Warnings and Precautions - Infection- Aseptic Meningitis**)

Infection:

MINT-INDOMETHACIN, in common with other NSAIDs, may mask signs and symptoms of an underlying infectious disease.

Aseptic Meningitis:

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

In common with other drugs which have anti-inflammatory, analgesic and antipyretic properties, indomethacin possesses the potential of masking the signs and symptoms which ordinarily accompany infectious disease. The physician must be alert to this possibility to avoid undue delay in initiating appropriate treatment of the infection.

Indomethacin should be used with caution in patients with existing, but controlled, infections.

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia or depression with the use of NSAIDs, such as MINT-INDOMETHACIN. If patients experience such adverse reaction(s), they should exercise caution in carrying out activities that require alertness.

Ophthalmologic

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

Corneal deposits and retinal disturbances, including those of the macula, have been reported in some patients with rheumatoid arthritis on prolonged therapy with indomethacin. Similar eye

changes have been observed in some patients with this disease who have not received indomethacin. Nevertheless, where therapy is prolonged, it is desirable to perform ophthalmological examinations at periodic intervals.

Peri-Operative Considerations

(See **Contraindications** - Coronary Artery Bypass Graft Surgery)

Psychiatric

(See **Warnings and Precautions** – *Neurologic*)

Renal

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

Renal insufficiency due to NSAID use is seen in patients with pre-renal conditions leading to reduction in renal blood flow or blood volume. Under these circumstances, renal prostaglandins help maintain renal perfusion and glomerular filtration rate (GFR). In these patients, administration of a NSAID may cause a reduction in prostaglandin synthesis leading to impaired renal function. Patients at greatest risk of this reaction are those with pre-existing renal insufficiency (GFR < 60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, taking angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, cyclosporin, diuretics, and those who are elderly. Serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short term therapy with NSAIDs. Even patients at risk who demonstrate the ability to tolerate a NSAID under stable conditions may decompensate during periods of added stress (e.g. dehydration due to gastroenteritis). Discontinuation of NSAIDs is usually followed by recovery to the pre-treatment state.

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

Advanced Renal Disease:

(See **Contraindications**)

Fluid and Electrolyte Balance:

Use of NSAIDs, such as MINT-INDOMETHACIN, can promote sodium retention in a dose-dependent manner, which can lead to fluid retention and edema, and consequences of increased blood pressure and exacerbation of congestive heart failure. Thus, caution should be exercised in prescribing MINT-INDOMETHACIN in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention (See **Warnings and Precautions - Cardiovascular**).

Fluid retention and peripheral edema have been observed in some patients taking indomethacin. Therefore, as with other non-steroidal anti-inflammatory drugs, MINT-INDOMETHACIN should be used with caution in patients with cardiac dysfunction, hypertension, or other conditions predisposing to fluid retention.

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

Use of NSAIDs, such as Indomethacin Capsules, can increase the risk of hyperkalemia, especially in patients with diabetes mellitus, renal failure, increased age, or those receiving concomitant therapy with adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, cyclosporin, or some diuretics. Electrolytes should be monitored periodically (see **Contraindications**).

As with other non-steroidal anti-inflammatory drugs, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome in patients receiving long-term administration of indomethacin.

In patients with reduced renal blood flow where renal prostaglandins play a major role in maintaining renal perfusion, administration of a non-steroidal anti-inflammatory agent may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with renal or hepatic dysfunction, diabetes mellitus, advanced age, extracellular volume depletion, congestive heart failure, sepsis, or concomitant use of any nephrotoxic drug. A non-steroidal anti-inflammatory drug should be given with caution and renal function should be monitored in any patient who may have reduced renal reserve. Discontinuation of non-steroidal anti-inflammatory therapy is usually followed by recovery to the pretreatment state.

Increases in serum potassium concentration, including hyperkalemia, have been reported, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic hypoaldosteronism state (see Drug Interactions).

Since MINT-INDOMETHACIN is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; a lower daily dosage should be used to avoid excessive drug accumulation.

Respiratory

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

Sexual Function/Reproduction

The use of MINT-INDOMETHACIN, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. Therefore, in women who have difficulties conceiving, or who are

undergoing investigation of infertility, withdrawal of MINT-INDOMETHACIN should be considered.

Skin

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

Special Populations

Pregnant Women:

MINT-INDOMETHACIN is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition.

Caution should be exercised in prescribing MINT-INDOMETHACIN during the first and second trimesters of pregnancy.

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

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

The safety of indomethacin for use in pregnancy has not been established.

Indomethacin has been found to delay parturition in rats. This effect has been described with other non-steroidal anti-inflammatory agents, which inhibit prostaglandin synthesis.

In rats, 4.0 mg/kg/day given during the last three days of gestation caused some maternal and fetal deaths. An increased incidence of neuronal necrosis in the diencephalon in the live-born fetuses was observed. At 2.0 mg/kg/day, no increase in neuronal necrosis was observed as compared to the control groups.

Nursing Women:

Indomethacin is excreted in the milk of lactating mothers. Indomethacin is not recommended for use in nursing mothers (See **Contraindications**).

Pediatrics:

(See **Contraindications**)

Geriatrics:

Patients older than 65 years (referred to in this document as older or elderly) and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs. The incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal injury including ulceration and bleeding. 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse reactions encountered with NSAIDs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred on occasion, particularly in the elderly.

Clinical Trial Adverse Drug Reactions

The adverse reactions for indomethacin capsules listed in the following table have been arranged into two groups: (1) incidence greater than 1%; and (2) incidence less than 1%. The incidence for group (1) was obtained from 33 double-blind controlled clinical trials reported in the literature (1,092 patients). The incidence for group (2) was based on reports in clinical trials, in the literature, and on voluntary reports since marketing. The probability of a causal relationship exists between indomethacin and these adverse reactions, some of which have been reported only rarely.

	<u>Incidence >1%</u>	<u>Incidence <1 %</u>
<u>GASTROINTESTINAL</u>		
Nausea ^x with or without vomiting	Anorexia	Gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.) development of ulcerative colitis and regional ileitis
Dyspepsia ^x (including indigestion, heartburn and epigastric pain)	Bloating (includes distention)	Ulcerative stomatitis
Diarrhea	Flatulence	Toxic hepatitis and jaundice (some fatal cases have been reported)
Abdominal distress or pain	Peptic ulcer	
Constipation	Gastroenteritis	
	Rectal Bleeding	
	Proctitis	
	Single and multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestines	
	Intestinal ulceration associated with stenosis and obstruction	
<u>CENTRAL NERVOUS SYSTEM</u>		
Headache	Anxiety (includes nervousness)	Lightheadedness
Dizziness ^x	Muscle weakness	Syncope
Vertigo	Involuntary muscle movements	Paresthesia
Somnolence	Insomnia	Aggravation of epilepsy and parkinsonism
Depression and fatigue (including malaise and listlessness)	Muzziness	Depersonalization
	Psychic disturbances including psychotic episode	Coma
	Mental confusion	Peripheral neuropathy
	Drowsiness	Convulsions
		Dysarthria
<u>DERMATOLOGIC</u>		
None	Pruritus	Exfoliative dermatitis
	Rash: urticaria	Erythema nodosum
	Petechiae or ecchymosis	Loss of hair
		Stevens-Johnson syndrome
		Erythema multiforme
		Toxic epidermal necrolysis
<u>CARDIOVASCULAR</u>		
None	Hypertension	Congestive heart failure
	Hypotension	Arrhythmia; palpitations
	Tachycardia	
	Chest pain	
^x Reactions occurring in 3% to 9% of patients treated with indomethacin (those reactions occurring in less than 3% of the patients are unmarked.)		

	<u>Incidence >1%</u>	<u>Incidence <1 %</u>
<u>SPECIAL SENSES</u>		
Tinnitus	Ocular -corneal deposits and retinal disturbances including those of the macula, have been reported in some patients on prolong therapy with indomethacin.	Blurred vision, diplopia Hearing disturbances, deafness
<u>HEMATOLOGIC</u>		
None	Leukopenia Bone marrow depression Anemia secondary to obvious or occult gastrointestinal bleeding	Aplastic anemia Hemolytic anemia Agranulocytosis Thrombocytopenic purpura Disseminated intravascular coagulation
<u>GENITOURINARY</u>		
None	Hematuria Vaginal bleeding Proteinuria Nephrotic syndrome Interstitial nephritis	BUN elevation Renal insufficiency, including renal failure
<u>HYPERSENSITIVITY</u>		
None	Acute anaphylaxis Acute respiratory distress Rapid fall in blood pressure resembling a shock-like state Angioedema	Dyspnea Asthma Purpura Angiitis Pulmonary edema
<u>METABOLIC</u>		
None	Edema Weight gain Fluid retention Flushing or sweating	Hyperglycemia Glycosuria Hyperkalemia
<u>MISCELLANEOUS</u>		
None	Epistaxis Breast changes including enlargement and tenderness. or gynecomastia	

Abnormal Hematologic and Clinical Chemistry Findings

The following additional side effects have been reported; however a causal relationship to therapy with indomethacin has not been established:

Cardiovascular

Thrombophlebitis

Hematologic

Although there have been several reports of leukemia, the supporting information is weak.

Genitourinary

Urinary frequency

DRUG INTERACTIONS

Drug-Drug Interactions

Acetylsalicylic acid (ASA) or other NSAIDs:

The use of MINT-INDOMETHACIN in addition to any other NSAID, including over-the-counter ones (such as ASA and ibuprofen) for analgesic and/or anti-inflammatory effects is NOT recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions.

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

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

The use of MINT-INDOMETHACIN in conjunction with acetylsalicylic acid or other salicylates is not recommended. Controlled clinical studies have shown that the combined use of indomethacin and acetylsalicylic acid does not produce any greater therapeutic effect than the use of indomethacin alone. Furthermore, in one of these clinical studies, the incidence of gastrointestinal side effects was significantly increased with combined therapy.

In a study in normal volunteers, it was found that chronic concurrent administration of 3.6 g of acetylsalicylic acid per day decreases indomethacin blood levels approximately 20%.

Anti-coagulants:

Controlled clinical studies have shown that indomethacin did not influence the hypoprothrombinemia produced by the use of anticoagulants in patients and in normal subjects. However, when any additional drug, including MINT-INDOMETHACIN is added to the treatment of patients on anticoagulant therapy, the patient should be observed closely for alterations of the prothrombin time. (See **Warnings and Precautions – Hematologic - Anti-coagulants**)

Anti-hypertensives:

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

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

Anti-platelet Agents (including ASA):

There is an increased risk of bleeding, via inhibition of platelet function, when anti-platelet agents are combined with NSAIDs, such as MINT-INDOMETHACIN (see **Warnings and Precautions – Hematologic – Antiplatelet Effects**).

Beta-adrenergic Receptor Blocking Agents

A decrease in the antihypertensive effect of beta-adrenergic receptor blocking agents by non-steroidal anti-inflammatory drugs including indomethacin has been reported. Therefore, when using a beta blocking agent to treat hypertension, patients should be observed carefully in order to confirm that the desired therapeutic effect has been obtained.

Diflunisal

The combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage. The coadministration of diflunisal and indomethacin results in an increase of about 30-35% in indomethacin plasma levels and a concomitant decrease in renal clearance of indomethacin and its conjugate. Therefore, MINT-INDOMETHACIN and diflunisal should not be used concomitantly.

Diuretics:

Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics.

In some patients, the administration of indomethacin can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when MINT-INDOMETHACIN and diuretics are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Indomethacin reduces basal plasma renin activity (PRA), as well as those elevations of PRA induced by furosemide administration, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients.

It has been reported that the addition of triamterene to a maintenance schedule of indomethacin resulted in reversible acute renal failure in two of four healthy volunteers. MINT-INDOMETHACIN and triamterene should not be administered together.

MINT-INDOMETHACIN and potassium-sparing diuretics each may be associated with increased serum potassium levels. The potential effects of MINT-INDOMETHACIN and potassium-sparing diuretics on potassium kinetics and renal function should be considered when these agents are administered concurrently.

Most of the above effects concerning diuretics have been attributed, at least in part, to mechanisms involving inhibition of prostaglandin synthesis by Indomethacin Capsules.

Glucocorticoids:

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

Lithium:

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

Indomethacin 50 mg t.i.d. produced a clinically relevant elevation of plasma lithium and reduction in renal lithium clearance in psychiatric patients and normal subjects with steady state plasma lithium concentrations. This effect has been attributed to inhibition of prostaglandin synthesis. As a consequence, when indomethacin and lithium are given concomitantly, the patient should be carefully observed for signs of lithium toxicity. (Read the Product Monograph for lithium preparation before use of such concomitant therapy.) In addition, the frequency of monitoring serum lithium concentration should be increased at the outset of such combination drug treatment.

Methotrexate:

Caution should be used if MINT-INDOMETHACIN is administered simultaneously with methotrexate. Indomethacin has been reported to decrease the tubular secretion of methotrexate and to potentiate toxicity.

Probenecid

When indomethacin is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased. Therefore, a lower total daily dosage of MINT-INDOMETHACIN may produce a therapeutic effect. When increases in the dose of MINT-INDOMETHACIN are made under these circumstances, they should be made cautiously and in small increments.

Selective Serotonin Reuptake Inhibitors (SSRIs):

Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see **Warnings and Precautions - Gastrointestinal**).

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

False-negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.

DOSAGE AND ADMINISTRATION

MINT-INDOMETHACIN (Indomethacin Capsules) is available as follows:

Capsules: 25 mg or 50 mg as standard capsules.

In chronic disorders, treatment should be started with a dosage of 25 mg two or three times a day. By starting therapy with low dosage, increased gradually when necessary, maximum benefit will be produced with fewer adverse reactions. Always give MINT-INDOMETHACIN with food immediately after meals or with antacids to reduce gastric irritation.

As with all drugs, the lowest possible effective dose should be utilized for each individual patient.

The drug should not be prescribed for children because safe conditions for use have not been established.

Since advancing years appear to increase the possibility of adverse reactions, MINT-INDOMETHACIN should be used with greater care in the elderly.

Adult Dosage Recommendations

1. Rheumatoid Arthritis and Ankylosing (Rheumatoid) Spondylitis.

Initial Dosage: 25 mg two or three times a day. If the response is not adequate, increase the daily dosage by 25 mg at about weekly intervals until a satisfactory response is obtained or a dosage of 150 to 200 mg a day is reached.

If a satisfactory response is not obtained with 200 mg a day, larger doses probably will not be effective.

If adverse reactions develop as the dosage is increased, reduce the dosage to a tolerated level and maintain this for 3 to 4 weeks. If an adequate response has not been obtained, gradually increase the daily dosage by 25 mg at about weekly intervals to 150 mg to 200 mg a day.

For patients with acute rheumatoid arthritis or with acute flares of chronic rheumatoid arthritis, increase the dosage daily by 25 mg until a satisfactory response is obtained or a total daily dosage of 150 to 200 mg is reached. If adverse effects develop as the dosage is increased, the dosage should be reduced to a tolerated level for 2 or 3 days, and then gradually increased by 25 mg every few days as tolerated. After the acute phase is under control, it is often possible to reduce the daily dosage gradually to 75 to 100 mg.

Reduction of Steroid Dosage: Use of indomethacin often will permit a gradual reduction of steroid dosage by 25 to 50 percent. In some patients steroids can be slowly discontinued over a

period of several weeks or months. The usual precautions should be observed in withdrawing steroids.

2. Severe Osteoarthritis and Degenerative Joint Disease of the Hip.

Initial Dosage: 25 mg two or three times a day. If the response is not adequate, increase the daily dosage by 25 mg at about weekly intervals until a satisfactory response is obtained or a dosage of 150 to 200 mg a day is reached. If a satisfactory response is not obtained with 200 mg a day, larger doses will probably not be effective.

If adverse reactions develop as the dosage is increased, reduce the dosage to a tolerated level and maintain this for 3 to 4 weeks. If an adequate response has not then been obtained, gradually increase the daily dosage by 25 mg at about weekly intervals to 150 to 200 mg a day.

3. Gout.

To Control Acute Attacks: 50 mg three times a day until all signs and symptoms subside. Definite relief of pain has been reported within 2 to 4 hours. Tenderness and heat usually subside in 24 to 36 hours, and swelling gradually disappears in 3 to 5 days.

Missed Dose

Patients who miss a dose of MINT-INDOMETHACIN and remember to take it within an hour or so, can take it right away. Patients can then go back to their regular dosing schedule.

Patients who do not remember until later, should not take the missed dose at all and should not double the next one. Instead, they should go back to their regular dosing schedule.

OVERDOSAGE

Relatively little experience is available recording overdosage with indomethacin. Nausea, vomiting, intense headache, dizziness, mental confusion, disorientation, or lethargy might be observed. There have been reports of paresthesias, numbness, and convulsions. Signs of gastrointestinal hemorrhage could appear but have not been reported following the acute ingestion of large amounts of indomethacin accidentally or intentionally.

Treatment of overdosage: Treatment is symptomatic and supportive. The stomach should be emptied as quickly as possible if the ingestion is recent. If vomiting has not occurred spontaneously, the patient should be induced to vomit with syrup of ipecac. If the patient is unable to vomit, gastric lavage should be performed. Once the stomach has been emptied, 25 or 50 g of activated charcoal may be given. Depending on the condition of the patient, close medical observation and nursing care may be required. The patient should be followed for several days because gastrointestinal ulceration and hemorrhage have been reported as adverse reactions of indomethacin. Use of antacids may be helpful.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Indomethacin is a non-steroidal drug that has anti-inflammatory, analgesic, and antipyretic activity. It has a unique chemical structure, which differentiates it from the salicylates, corticosteroids, phenylbutazone-like compounds and colchicine. Unlike corticosteroids, it has no effect on pituitary or adrenal function.

Indomethacin as certain other non-steroidal anti-inflammatory analgesics is an inhibitor of prostaglandin synthesis *in vitro*. Concentrations are reached during therapy, which have been demonstrated to have an effect *in vivo* as well.

Although indomethacin does not alter the course of the underlying disease, it has been found effective to relieve pain, reduce fever, swelling and tenderness, and increase mobility in patients with rheumatic disorders of the types listed.

Pharmacokinetics

In man, indomethacin is readily absorbed, attaining peak plasma concentrations of about 1 and 2 µg/mL at about 2 hours following single oral doses of 25 and 50 mg, respectively. 90 percent of the orally administered indomethacin is absorbed within 4 hours. Indomethacin is eliminated via renal excretion and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. The mean half-life of indomethacin is estimated to be about 4.5 hours. With a typical therapeutic regimen of 25 or 50 mg t.i.d., the steady state plasma concentrations of indomethacin are on average 1.4 times those following the first dose.

Indomethacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyl-desbenzoyl metabolites, all in the unconjugated form. About 60 percent of an oral dosage is recovered in urine as drug and metabolites (26 percent as indomethacin and its glucuronide), and 33 percent is recovered in feces (1.5 percent as indomethacin). About 90 percent of indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentration.

STORAGE AND STABILITY

Store between 15 and 30°C. Protect from moisture. Store in a tight container.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MINT-INDOMETHACIN Capsules contain indomethacin equivalent to 25 mg (opaque light green) and 50 mg (opaque light green).

Non-medicinal ingredients: Lactose monohydrate, sodium lauryl sulphate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate and empty gelatin capsules (FD&C Blue #1, D&C Yellow #10, titanium dioxide, gelatin and purified water) imprinted in black ink (shellac, propylene glycol, black iron oxide and potassium hydroxide).

Capsules 25 mg and 50 mg : MINT-INDOMETHACIN is available in bottles of 100.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

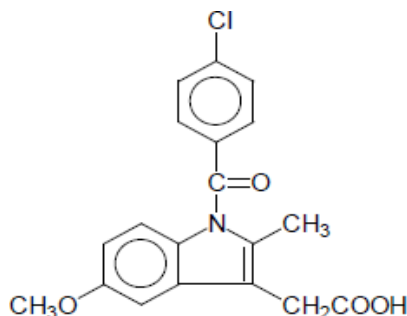
Drug Substance

Proper name: Indomethacin

Chemical name: 1H-Indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl

Molecular formula and molecular mass: C₁₉H₁₆ClNO₄ (Molecular weight 357.80)

Structural formula:



Physicochemical properties: Indomethacin occurs as a white to yellow powder with a melting point of about 158°C to 162°C. It is practically insoluble in water; sparingly soluble in alcohol, chloroform and ether.

CLINICAL TRIALS

Randomized clinical trials with MINT-INDOMETHACIN have NOT been designed to detect differences in cardiovascular adverse events in a chronic setting

Comparative Bioavailability Studies

A randomized, double blinded, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of ^{Pr}MINT-INDOMETHACIN 50 mg of Mint Pharmaceuticals Inc., and ^{Pr}NOVO-METHACIN (Indomethacin) 50 mg Capsules USP of Novopharm Ltd., in healthy adult, human subjects under fasting conditions (n=29).

Indomethacin (1 x 50 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (hr*µg/mL)	9.40 9.57 (19.65)	8.99 9.16 (18.55)	104.5	99.83 - 109.4
AUC _I (hr*µg/mL)	9.91 10.09 (19.63)	9.50 9.69 (18.52)	104.3	99.75 - 109.0
C _{MAX} (µg/mL)	3.44 3.62 (32.05)	3.47 3.64 (30.40)	99.17	89.47 - 109.9
T _{MAX} [§] (h)	1.25 (0.5 - 8.0)	2.0 (0.8 - 4.5)		
T _{1/2} ^ε (h)	6.13 (30.88)	6.35 (50.85)		

* MINT-INDOMETHACIN 50 mg capsules (Mint Pharmaceuticals Inc.)

† NOVO-METHACIN 50 mg capsules, Novopharm Ltd. (currently marketed by Teva Pharmaceuticals Inc.), purchased in Canada

§ Expressed as the median (range) only.

ε Expressed as the arithmetic mean (CV%) only.

DETAILED PHARMACOLOGY

Anti-Inflammatory Action

The anti-inflammatory activity of indomethacin was first demonstrated in animals, measuring the ability of the compound to inhibit either granuloma formation or edema induced by subplantar injection of carrageenin in rats. The latter appears to correlate well with anti-rheumatic activity in man. Assays of relative potency indicated that indomethacin was more potent than acetylsalicylic acid, phenylbutazone or hydrocortisone, the potency ratios varied with the test

employed. Good anti-inflammatory effect is exhibited in rats at 1/20th of the average human dose.

The inhibition of carrageenin-induced edema by indomethacin is specific; the compound failed to inhibit edema induced by a variety of agents other than carrageenin, nor did it reduce edema if the drug was administered after the edema had been established.

As with other anti-inflammatory agents, the mechanism of action of indomethacin is unknown. Indomethacin is fully active in the absence of the adrenals; and its activity is readily demonstrable by direct application of the compound to the site of action. Unlike anti-inflammatory steroids, indomethacin given to intact animals did not affect the size of the adrenals or the thymus, nor did it retard gain in body weight; these are sensitive indicators of adrenal activation. The anti-inflammatory activity of combinations of indomethacin and a steroid was greater than that of either drug alone in comparable doses.

Recent experiments have shown indomethacin to have a favorable effect upon adjuvant-induced polyarthritis in rats; it was more active than phenylbutazone or acetylsalicylic acid in suppressing the delayed manifestations of disseminated arthritis. This response is said to correlate well with clinical anti-arthritic activity.

Antipyretic Activity

The antipyretic activity of indomethacin has been demonstrated in rabbits and rats injected with bacterial pyrogen, and in the classical yeast-induced fever assay in rats. A direct comparison of peak antipyretic activity in the yeast fever test showed indomethacin to be about 9 times as potent as aminopyrine, 24 times as potent as phenylbutazone, and 43 times as potent as acetylsalicylic acid.

The antipyretic activity of indomethacin has been confirmed clinically by observations in patients with a variety of febrile conditions. However, indomethacin should not be used as an antipyretic agent.

Analgesic Activity

Laboratory tests designed to detect mild analgesic activity indicate that indomethacin is more potent than acetylsalicylic acid or aminopyrine. However, indomethacin should not be given as a simple analgesic.

TOXICOLOGY

Animal Toxicology

Indomethacin had been given to nine species of animals in short and long term studies. However, with the exception of pigs and chickens, the human dose is not tolerated. The main toxic signs exhibited are inflammation and/or ulceration of the gastrointestinal mucosa and diarrhea.

Reproduction and teratogenic studies in mice, rats and rabbits showed no effect on fetal development or the reproduction cycle. There was some decrease in fetal viability and some delay in the onset of parturition in the rat, as has been observed with other non-steroid anti-inflammatory agents. A similar delay in the onset of parturition was not observed in the rabbit. Studies in mice demonstrated that indomethacin crosses the placental barrier.

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PART III: CONSUMER INFORMATION

**PrMINT-INDOMETHACIN
Indomethacin Capsules USP**

Read this information each time you refill your prescription in case new information has been added.

This leaflet is a summary designed specifically for you to read. It will NOT tell you everything about MINT-INDOMETHACIN. See your health care provider and pharmacist regularly and ask them questions about your health and any medications you take.

ABOUT THIS MEDICATION

What the medication is used for:

Your health care provider has prescribed MINT-INDOMETHACIN, for you for one or more of the following medical conditions:

- treat the symptoms of certain types of arthritis, including gout.
- helps to relieve joint pain, swelling, stiffness and fever by reducing the production of certain substances (prostaglandins)
- help to control inflammation and other body reactions.

What it does:

MINT-INDOMETHACIN (Indomethacin Capsules), as a nonsteroidal anti-inflammatory drug (NSAID), can reduce the chemicals produced by your body which cause pain and swelling.

MINT-INDOMETHACIN, as a nonsteroidal anti-inflammatory drug (NSAID), does NOT cure your illness or prevent it from getting worse. MINT-INDOMETHACIN can only relieve pain and reduce swelling as long as you continue to take it.

When it should not be used:

DO NOT TAKE MINT-INDOMETHACIN if you have any of the following medical conditions:

- **Heart bypass surgery (planning to have or recently had)**
- **Severe, uncontrolled heart failure**
- **Bleeding in the brain or other bleeding disorders**
- **Current pregnancy (after 28 weeks of pregnancy) Currently breastfeeding (or planning to breastfeed)**
- **Allergy to ASA (Acetylsalicylic Acid) or other NSAIDs (Nonsteroidal Anti- Inflammatory Drugs)**
- **Ulcer (active)**
- **Bleeding from the stomach or gut (active)**
- **Inflammatory bowel disease (Crohn’s Disease or Ulcerative Colitis)**
- **Liver disease (active or severe)**
- **Kidney disease (severe or worsening)**
- **High potassium in the blood**

Patients who took a drug in the same class as MINT-INDOMETHACIN after a type of heart surgery (coronary

artery bypass grafting (CABG)) were more likely to have heart attacks, strokes, blood clots in the leg(s) or lung(s), and infections or other complications than those who did NOT take that drug.

MINT-INDOMETHACIN should NOT be used in children since the safety and effectiveness have NOT been established.

What the medicinal ingredient is:

Indomethacin

What the nonmedicinal ingredients are:

Non-medicinal ingredients: Lactose monohydrate, sodium lauryl sulphate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate and empty gelatin capsules (FD&C Blue #1, D&C Yellow #10, titanium dioxide, gelatin and purified water) imprinted in black ink (shellac, propylene glycol, black iron oxide and potassium hydroxide).

What dosage forms it comes in:

MINT-INDOMETHACIN (indomethacin) is available as follows:

Capsules: 25 mg or 50 mg.

WARNINGS AND PRECAUTIONS

If you have, or previously had, any of the following medical conditions, see your health care provider to discuss treatment options other than MINT-INDOMETHACIN:

- **Heart Attack or Angina**
- **Stroke or Mini-stroke**
- **Loss of Vision**
- **Current Pregnancy (less than 28 weeks)**
- **Congestive Heart Failure**

Before taking this medication, tell your health care provider if you have any of the following:

- High blood pressure
- High cholesterol
- Diabetes mellitus or on a low sugar diet
- Atherosclerosis
- Poor circulation to your extremities
- Smoker or ex-smoker
- Kidney disease or urine problems
- Previous ulcer or bleeding from the stomach or gut
- Previous bleeding in the brain
- Bleeding problems
- Family history of allergy to NSAIDs, such as acetylsalicylic acid (ASA), celecoxib, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, rofecoxib, sulindac, tenoxicam, tiaprofenic acid, tolmetin, or valdecoxib (NOT a complete list)
- Family history of asthma, nasal polyps, long-term swelling of the sinus (chronic sinusitis) or hives
- Family history of allergy to sulfonamide drugs
- A previous allergic reaction could increase the risk of

an allergic reaction to MINT-INDOMETHACIN.- if you ever had an ulcer with or without bleeding, of the stomach, duodenum, or any part of the digestive tract, liver or kidney diseases or any other medical problems.

Also, before taking this medication, tell your health care provider if you are planning to get pregnant.

Note also that MINT-INDOMETHACIN is not recommended for use during pregnancy and that one should not breast-feed while on MINT-INDOMETHACIN.

While taking this medication:

- tell any other doctor, dentist, pharmacist or other health care professional that you see, that you are taking this medication, especially if you are planning to have heart surgery;
- do NOT drink alcoholic beverages while taking this medication because you would be more likely to develop stomach problems;
- fertility may be decreased. The use of MINT-INDOMETHACIN is not recommended in women trying to get pregnant. In women who have difficulty conceiving, stopping MINT-INDOMETHACIN should be considered.
- be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or lightheaded after taking this medication;
- check with your physician if you are not getting any relief or if any problems develop;
- report any untoward reactions to your physician. This is very important as it will aid in the early detection and prevention of potential complications.
- your regular medical checkups are essential;
- if you require more information on this drug, consult your physician or pharmacist.
- keep this medication, and all others, out of the reach of children

- Cyclosporin
- Digoxin
- Diuretics e.g. furosemide, hydrochlorothiazide
- Lithium
- Methotrexate
- Oral contraceptives
- Oral hypoglycemics (diabetes medications)
- Tacrolimus

Do not take ASA (acetylsalicylic acid), ASA compounds or other drugs used to relieve symptoms of arthritis while taking MINT-INDOMETHACIN unless directed to do so by your physician.

If you are prescribed this medication for use over a long period of time, your physician will check your health during regular visits to assess your progress and to ensure that this medication is not causing unwanted effects.

Along with its beneficial effects, MINT-INDOMETHACIN like other NSAID drugs, may cause some undesirable reactions. Elderly, frail or debilitated patients often seem to experience more frequent or more severe side effects. Although not all of these side effects are common, when they do occur they may require medical attention. Check with physician immediately if any of the following are noted:

- bloody or black tarry stools.
- shortness of breath, wheezing, any trouble in breathing or tightness in the chest;
- skin rash, swelling, hives or itching;
- indigestion, nausea, vomiting, stomach pain or diarrhea;
- yellow discolouration of the skin or eyes, with or without fatigue;
- any changes in the amount or colour of your urine (such as dark, red or brown);
- swelling of the feet or lower legs;
- blurred vision or any visual disturbance;
- mental confusion, depression, dizziness, lightheadedness, hearing problems.

Your health care provider may prescribe low dose ASA (acetylsalicylic acid) as a blood thinner to reduce your risk of having a heart attack or stroke while you are taking MINT-INDOMETHACIN. Take only the amount of ASA prescribed by your health care provider. You are more likely to upset or damage your stomach if you take both MINT-INDOMETHACIN and ASA than if you took MINT-INDOMETHACIN alone.

INTERACTIONS WITH THIS MEDICATION

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

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

PROPER USE OF THIS MEDICATION

Usual dose:

In chronic disorders, treatment should be started with a dosage of 25 mg two or three times a day. By starting therapy with low dosage, increased gradually when necessary, maximum benefit will be produced with fewer adverse reactions. Always give MINT-INDOMETHACIN with food immediately after meals or with antacids to reduce gastric irritation.

As with all drugs, the lowest possible effective dose should be utilized for each individual patient.

HOW TO USE THIS MEDICINE

To lessen stomach upset, take this medicine immediately after a meal or with food or milk. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your physician.

PLEASE ADHERE TO THE DOSAGE AND ADMINISTRATION INSTRUCTIONS WHICH YOUR PHYSICIAN HAS GIVEN YOU

- Do not take more of it, do not take it more often, and do not take it for a longer period of time than your physician prescribed.

If you are taking MINT-INDOMETHACIN to relieve arthritis, you must take it regularly as prescribed by your physician. In some types of arthritis, up to 2 weeks may pass before you begin to feel better and up to 1 month may pass before you feel the full effects of this medicine.

Medical condition	Age group	Starting dose	Maximum dose (per day)	Maximum duration of Treatment (days)
Rheumatoid Arthritis and Ankylosing (Rheumatoid) Spondylitis	Adult	25 mg; 2 or 3 times daily	200 mg	2 to 3 weeks
Sever Osteoarthritis and Degenerative Joint Disease of the hip	Adult	25 mg; 2 or 3 times daily	200 mg	2 to 3 weeks
Gout	Adult	50 mg; three times daily	Not applicable	5 days

Take MINT-INDOMETHACIN only as directed by your health care provider. **Do NOT take more of it, do NOT take it more often and do NOT take it for a longer period of time than your health care provider recommended. If possible, you should take the lowest dose of this medication for the shortest time period.** Taking too much MINT-INDOMETHACIN may increase your chances of unwanted and sometimes dangerous side effects, especially if you are elderly, have other diseases or take other medications.

If you will be using MINT-INDOMETHACIN for more than 7 days, see your health care provider regularly to discuss whether this medicine is working for you and if it is causing you any unwanted effects.

This medication has been prescribed specifically for you. Do NOT give it to anyone else. It may harm them, even if their symptoms seem to be similar to yours.

MINT-INDOMETHACIN is NOT recommended for use in children since safety and effectiveness have NOT been established.

MINT-INDOMETHACIN must be taken with food.

Missed Dose:

If you miss a dose of MINT-INDOMETHACIN and remember within an hour or so, take it right away. Then go back to your regular dosing schedule.

But if you do not remember until later, do not take the missed dose at all and do not double the next one. Instead, go back to your regular dosing schedule.

Overdose:

If you take more than the prescribed dose, contact your health care provider immediately.

In case of accidental overdose, consult a physician immediately or contact your regional Poison Control Centre.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

MINT-INDOMETHACIN may cause some side effects, especially when used for a long time or in large doses. When these side effects occur, you may require medical attention. Report all symptoms or side effects to your health care provider.

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

MINT-INDOMETHACIN may cause you to become more sensitive to sunlight. Any exposure to sunlight or sunlamps may cause sunburn, skin blisters, skin rash, redness, itching or discoloration, or vision changes. If you have a reaction from the sun, check with your health care provider.

Check with your health care provider IMMEDIATELY if you develop chills, fever, muscle aches or pains, or other flu-like symptoms, especially if they occur before or together with a skin rash. These symptoms may be the first signs of a SERIOUS ALLERGIC REACTION to this medication.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Symptom	STOP taking MINT-INDOMETHACIN and get emergency medical attention immediately	STOP taking MINT-INDOMETHACIN and talk to your physician or pharmacist
Bloody or black tarry stools	√	
Shortness of breath, wheezing, and trouble breathing or chest tightness	√	
Skin rash, hives, swelling or itching	√	
Blurred vision, or any visual disturbance	√	
Any change in the amount or colour of your urine (red or brown)	√	
Any pain or difficulty experienced while Urinating		√
Swelling of the feet, lower legs; weight Gain		√
Vomiting or persistent indigestion, nausea, stomach pain or diarrhea		√
Yellow Discolouration of the skin or eyes, with or without itchy skin		√
Malaise, fatigue, loss of appetite		√
Headaches, stiff neck		√
Mental confusion, depression		√
Dizziness, lightheadedness		√
Hearing Problems		√

This is NOT a complete list of side effects. If you develop any other symptoms while taking MINT-INDOMETHACIN, see your health care provider.

HOW TO STORE IT

Store between 15 and 30°C. Protect from moisture. Store in a tight container.

Do NOT keep outdated medicine or medicine no longer needed. Any outdated or unused medicine should be returned to your pharmacist.

Keep out of reach and sight of children.

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

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
<http://www.mintpharmaceuticals.com>
 or by contacting the sponsor, Mint Pharmaceuticals Inc., at:
 1-877-398-9696

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