

**PRODUCT MONOGRAPH**

**Pr Auro-Indomethacin**

Indomethacin Capsules USP

50 mg

Non-Steroidal Anti-Inflammatory Drugs

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50 mg

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>All Non medicinal Ingredients</b>
Oral	Capsules / 50 mg	Lactose monohydrate, Magnesium Stearate and Talc. <b>Gelatin Capsule Shell contains:</b> Gelatin, FD & C Blue 1, D & C Red 28, and Titanium dioxide. <b>Black Ink contains:</b> Black Iron oxide and Potassium Hydroxide, Propylene Glycol and Shellac.

**INDICATIONS AND CLINICAL USE**

Auro-Indomethacin (indomethacin) is indicated for the following:

**For patients with an increased risk of developing CV and/or GI adverse events, other management strategies that do NOT include the use of NSAIDs should be considered first. (See Contraindications and Warnings and Precautions)**

**Use of Auro-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)**

Auro-Indomethacin as a NSAID, does NOT treat clinical disease or prevent its progression.

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

***Geriatrics:***

Evidence from clinical studies and postmarket experience suggests that use in the geriatric population is associated with differences in safety (See **Warnings and Precautions**).

***Pediatrics:***

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

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

Indomethacin has been found effective in the symptomatic treatment of: Selected cases of rheumatoid arthritis Ankylosing (rheumatoid) spondylitis Gout Selected cases of severe osteoarthritis, including degenerative disease of the hip.

In these conditions indomethacin may on occasion replace other commonly used agents such as corticosteroids, salicylates, phenylbutazone-like compounds and colchicine.

### **Rheumatoid Arthritis**

Auro-Indomethacin may be used singly or in combination with other agents. However, it should not be used as a drug of first choice because of the adverse reactions that may occur with its use.

Best results (relief of pain, tenderness, swelling and stiffness) have been obtained in the acute episodes of the disease. However, in many patients with chronic rheumatoid arthritis, indomethacin produces a significant lessening of pain and stiffness within 48 hours. In other patients, treatment must be continued longer before significant subjective relief or objective evidence of decreased joint swelling and tenderness occur. In some cases of chronic rheumatoid arthritis, it may be necessary to continue treatment for at least a month before concluding that it has not produced significant benefit. Use of Auro-Indomethacin may enable reduction of steroid dosage in patients receiving corticosteroids. In such instances, the steroid dosage should be reduced slowly.

### **Ankylosing (Rheumatoid) Spondylitis**

Auro-Indomethacin frequently produces marked relief of pain and improved motion of the spine within 3 to 10 days.

### **Osteoarthritis**

Auro-Indomethacin should be used in those cases of severe osteoarthritis which do not respond to treatment with such other drugs as the salicylates. In many cases prompt relief of pain is obtained.

### **Degenerative Joint Disease (Osteoarthritis) of the Hip**

Auro-Indomethacin has provided relief of pain and increased range of motion in patients with degenerative joint disease of the hip.

### **Gout**

In acute attacks of gout the response to Auro-Indomethacin is usually rapid and often dramatic. Marked reduction of pain may be obtained within 2 to 4 hours. Tenderness and heat subside within 24 to 36 hours, and swelling decreases over a 3 to 5 day period.

## CONTRAINDICATIONS

Auro-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 Auro-Indomethacin 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.

Auro-Indomethacin (indomethacin) 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 non-steroidal 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).**

**Auro-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 Auro-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 Auro-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 indomethacin have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing Auro-Indomethacin.**

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

**Use of NSAIDs, such as Auro-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.

Auro-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:***

**Auro-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 Auro-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 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 Auro-Indomethacin should hypertension either develop or worsen with its use.

Use of NSAIDs, such as 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:***

Auro-Indomethacin (indomethacin) 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 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 Auro-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 Auro-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.

Auro-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 Auro-Indomethacin (Indomethacin) should be discontinued, an appropriate treatment instituted and patient closely monitored.

There is no definitive evidence that the concomitant administration of histamine H<sub>2</sub> antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of Auro-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 Auro-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 Auro-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 anti-coagulants or suffering from haemophilia or platelet disorders should be carefully observed when Auro-Indomethacin is administered.

***Anti-coagulants:***

Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy of Auro-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.

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

Concomitant administration of Auro-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 Auro-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 Auro-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 Auro-Indomethacin is administered.

Indomethacin 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 Auro-Indomethacin. 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, Auro-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. <sup>Ref. 50, page 11</sup>

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 Auro-Indomethacin.

***Hypersensitivity Reactions:***

***Anaphylactoid Reactions:***

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to indomethacin. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving indomethacin. Auro-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:***

Auro-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:***

Auro-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 Auro-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 Auro-Indomethacin should be discontinued and an ophthalmologic examination performed. Ophthalmologic examination should be carried out at periodic intervals in any patient receiving Auro-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 Auro-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 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 Auro-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, Auro-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, 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 Auro-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 Auro-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 Auro-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:***

**Auro-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 Auro-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 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.



Incidence >1%		Incidence <1 %
<b>GASTROINTESTINAL</b>		
Nausea <sup>x</sup> with or without Vomiting Dyspepsia <sup>x</sup> (including indigestion, heartburn and epigastric pain) Diarrhea Abdominal distress or pain Constipation	Anorexia Bloating (includes distention) Flatulence Peptic ulcer 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	Gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.) development of ulcerative colitis and regional ileitis Ulcerative stomatitis Toxic hepatitis and jaundice (some fatal cases have been reported)
<b>CENTRAL NERVOUS SYSTEM</b>		
Headache Dizziness <sup>x</sup> Vertigo Somnolence Depression and fatigue (including malaise and listlessness)	Anxiety (includes nervousness) Muscle weakness Involuntary muscle movements Insomnia Muzziness Psychic disturbances including psychotic episode Mental confusion Drowsiness	Lightheadedness Syncope Paresthesia Aggravation of epilepsy and parkinsonism Depersonalization Coma Peripheral neuropathy Convulsions Dysarthria
<b>DERMATOLOGIC</b>		
None	Pruritus Rash: urticaria Petechiae or ecchymosis	Exfoliative dermatitis Erythema nodosum Loss of hair Stevens-Johnson syndrome Erythema multiforme Toxic epidermal necrolysis
<b>CARDIOVASCULAR</b>		
None	Hypertension Hypotension Tachycardia Chest pain	Congestive heart failure Arrhythmia; palpitations
<sup>x</sup> Reactions occurring in 3% to 9% of patients treated with indomethacin (those reactions occurring in less than 3% of the patients are unmarked.)		
<b>SPECIAL SENSES</b>		
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
<b>HEMATOLOGIC</b>		
None	Leukopenia Bone marrow depression Anemia secondary to obvious or occult gastrointestinal bleeding	Aplastic anemia Hemolytic anemia Agranulocytosis Thrombocytopenic purpura Disseminated intravascular coagulation

Incidence >1%		Incidence <1 %
<b>GENITOURINARY</b>		
None	Hematuria Vaginal bleeding Proteinuria Nephrotic syndrome Interstitial nephritis	BUN elevation Renal insufficiency, including renal failure
<b>HYPERSENSITIVITY</b>		
None	Acute anaphylaxis Acute respiratory distress Rapid fall in blood pressure resembling a shock-like state Angioedema	Dyspnea Asthma Purpura Angiitis Pulmonary edema
<b>METABOLIC</b>		
None	Edema Weight gain Fluid retention Flushing or sweating	Hyperglycemia Glycosuria Hyperkalemia
<b>MISCELLANEOUS</b>		
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 Auro-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 Auro-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 Auro-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 indomethacin (see **Warnings and Precautions – Hematologic - Anti-platelet 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, Auro-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 Auro-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. Auro-Indomethacin and triamterene should not be administered together.

Indomethacin and potassium-sparing diuretics each may be associated with increased serum potassium levels. The potential effects of Auro-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 Auro-Indomethacin.

***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 Auro-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 indomethacin may produce a therapeutic effect. When increases in the dose of Auro-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 Test 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**

Auro-Indomethacin (indomethacin) is available as follows:

Capsules: 50 mg as standard capsules.

## Dosing Considerations:

- **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.**
- **After observing the response to initial therapy with indomethacin, the dose and frequency should be adjusted to suit an individual patient's needs.**
- **Use of indomethacin should be limited to the lowest effective dose\* for the shortest possible duration of treatment consistent with individual patient treatment goals (see INDICATIONS AND CLINICAL USE).**
- **To maintain the integrity of the capsule, it should not be opened or chewed during ingestion.**
- **Auro-Indomethacin capsules should be swallowed whole with food or milk.**

\* Indomethacin capsules 25 mg is not available from Auro Pharma Inc. An alternative product should be considered since Auro-Indomethacin does not allow for administration of lower daily doses of indomethacin.

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, Auro-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.

**During the initial treatment of Rheumatoid Arthritis and Ankylosing (Rheumatoid) Spondylitis, an alternative product should be considered since Auro-Indomethacin does not allow for administration of 25 mg of indomethacin\*.**

**\*Indomethacin 25 mg is not available from Auro Pharma Inc.**

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 mg\* to 100 mg\*.

**\*An alternative product should be considered since Indomethacin 25 mg is not available from Auro Pharma Inc.**

**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.

**During the initial treatment of Severe Osteoarthritis and Degenerative Joint Disease of the Hip, an alternative product should be considered since Auro-Indomethacin does not allow for administration of 25 mg of indomethacin\*.**

\*Indomethacin capsules 25 mg is not available from Auro Pharma Inc.

## **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.

## **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 immediately.

## **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 in well-closed containers at room temperature (15° C to 30° C) protect from moisture.

Keep out of reach and sight of children.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

Auro-Indomethacin capsules contain indomethacin equivalent to 50 mg

<b>Dosage form</b>	<b>Capsules</b>
<b>Strength</b>	<b>50 mg</b>
<b>Description</b>	Blue Cap / White body, size '1' hard gelatin capsule shells, imprinted with 'IDN' on cap and '50' on body with black ink filled with White to off-white powder.
<b>Composition</b>	Lactose monohydrate, Talc, Magnesium Stearate. <b>Capsule Shell contains:</b> Gelatin, FD & C Blue 1, D & C Red 28, and Titanium dioxide. <b>Black Ink contains:</b> Black Iron oxide, Propylene Glycol, Potassium Hydroxide, and Shellac.
<b>Packaging</b>	HDPE bottles of 100, 500 and 1000 Capsules.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

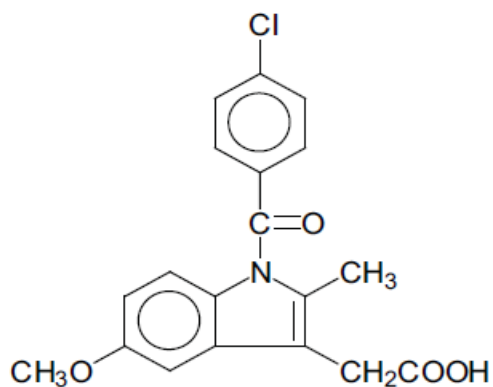
#### Drug Substance

Proper Name: Indomethacin

Chemical name: 1-(p-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid.

Molecular formula and molecular mass: C<sub>19</sub>H<sub>16</sub>ClNO<sub>4</sub> (molecular weight 357.80 g/mol).

Structural formula:



Physicochemical properties:

It is a white to yellow crystalline powder. It is practically insoluble in water (EP/USP) and sparingly soluble in alcohol (EP/USP) and in chloroform (USP).

## Comparative Bioavailability – Capsules

A double blind, randomized, two treatment, two sequence, two period, cross-over, single-dose oral bioequivalence study of Auro-Indomethacin Capsules 50 mg [Test; Aurobindo Pharma Limited, India manufactured for Auro Pharma Inc. (Canada)] versus Teva – Indomethacin (Indomethacin) Capsules 50 mg (Reference: Teva Canada Limited, Canada) was conducted in 42 healthy, adult, human subjects under fasting conditions. A summary of the bioavailability data of 39 subjects who completed the study is presented in the following table.

**Summary Table of the Comparative Bioavailability Data for Indomethacin**

<b>Indomethacin (1 X 50 mg) From measured data</b>				
<b>Geometric Mean Arithmetic Mean (CV %)</b>				
<b>Parameter</b>	<b>Test*</b>	<b>Reference<sup>†</sup></b>	<b>% Ratio of Geometric Means</b>	<b>90% Confidence Interval</b>
<b>AUC<sub>0→t</sub> (hr. µg/mL)</b>	8.9 9.1 (18.7)	8.9 9.0 (16.6)	101.2	97.8-104.0
<b>AUC<sub>0→∞</sub> (hr. µg/mL)</b>	9.3 9.5 (19.2)	9.2 9.3 (16.5)	100.8	98.1-104.3
<b>C<sub>max</sub> (µg/mL)</b>	3.7 3.8 (29.3)	3.2 3.4 (34.9)	113.2	102.3-125.3
<b>T<sub>max</sub><sup>§</sup> (hr)</b>	1.3 (0.5 – 3.5)	1.7 (0.5 – 4.0)		
<b>T<sub>1/2</sub><sup>§</sup> (hr)</b>	6.7 (37.8)	6.2 (32.6)		

\*Auro-Indomethacin (Indomethacin Capsules USP) 50 mg, by Auro Pharma Inc.

<sup>†</sup> Teva-Indomethacin (Indomethacin Capsules USP) 50 mg, of Teva Canada Limited were purchased from Canada.

<sup>§</sup> Expressed as the median (range) only.

<sup>§</sup> Expressed as 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**

**PrAuro-Indomethacin**

Indomethacin Capsules USP

50 mg

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

**ABOUT THIS MEDICATION**

**What the medication is used for:**

Your health care provider has prescribed Auro-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:**

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

Auro-Indomethacin, as a nonsteroidal anti-inflammatory drug (NSAID), does NOT cure your illness or prevent it from getting worse. Auro-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** Auro-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 Auro-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.**

Auro-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, Talc, Magnesium stearate and gelatin capsules.

Capsule Shell contains: Gelatin, FD & C Blue 1, D & C Red 28, and Titanium dioxide.

Black Ink contains: Shellac, Propylene Glycol, Black Iron oxide and Potassium Hydroxide.

**What dosage forms it comes in:**

Auro-Indomethacin (indomethacin) is available as follows:

Capsules: 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 Auro-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 Auro-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 Auro-Indomethacin is not recommended for use during pregnancy and that one should not breast-feed while on Auro-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 Auro-Indomethacin is not recommended in women trying to get pregnant. In women who have difficulty conceiving, stopping Auro-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 and sight of children

### **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. 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)

- 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
- 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 Auro-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, Auro-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 discoloration 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 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 Auro-Indomethacin and ASA than if you took Auro-Indomethacin alone.

**PROPER USE OF THIS MEDICATION**

**Usual Dose:**

Auro-Indomethacin is intended for use in patients 18 years of age or older for the shortest possible duration.

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 Auro-Indomethacin with food immediately after meals or with antacids to reduce gastric irritation.

\*Indomethacin capsules 25 mg are not available from Auro Pharma Inc. Your healthcare professional will start you on a different product. Once your dose has been increased to 50 mg, you can be switched to Auro-Indomethacin capsules 50 mg.

**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 HEALTHCARE PROVIDER 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 Auro-Indomethacin to relieve arthritis, you must take it regularly as prescribed by your healthcare provider. 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

\* Indomethacin 25 mg is not available by Auro Pharma Inc.

Take Auro-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 Auro-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 Auro-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.**

**Auro-Indomethacin is NOT recommended for use in children since safety and effectiveness have NOT been established.**

Auro-Indomethacin must be taken with food.

**Missed Dose:**

If you forgot to take a dose of Auro-Indomethacin and remember within an hour or so, take it right away. Then just carry on with the regular times you take your medication.

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 think you have taken too much Auro-Indomethacin, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

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

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Auro-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.

Auro-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 Auro-Indomethacin, do NOT drive or operate machinery.

Auro-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 discolouration, 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 Auro-Indomethacin and get emergency medical attention IMMEDIATELY	STOP taking Auro-indomethacin and talk to your health care professional
lightheadedness		
Hearing Problems		√

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

**HOW TO STORE IT**

Store in well-closed containers at room temperature (15° C to 30° C) protect from moisture.

**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.**

**SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Symptom	STOP taking Auro-Indomethacin and get emergency medical attention IMMEDIATELY	STOP taking Auro-indomethacin and talk to your health care professional
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 Discoloration of the skin or eyes, with or without itchy skin		√
Malaise, fatigue, loss of appetite		√
Headaches, stiff neck		√
Mental confusion, depression		√
Dizziness,		√

**Reporting Side Effects**

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

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: 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**

**If you want more information about Auro-Indomethacin:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](https://health-products.canada.ca/dpd-bdpp/index-eng.jsp) (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the manufacturer's website <http://www.auropharma.ca>, or by calling 1- 855-648-6681.

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