PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] SANDOZ INDOMETHACIN

Indomethacin Suppositories

Suppositories, 50 mg and 100 mg, For Rectal Use

Manufacturer's Standard

Anti-Inflammatory – Analgesic

ATC Code: M01AB01

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Date of Initial Authorization:
November 17, 1997

Date of Revision:
February 24, 2022

Submission Control Number: 255837

RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Sandoz Indomethacin (indomethacin suppositories) is indicated for the symptomatic treatment of:

- Selected cases of rheumatoid arthritis
- Ankylosing (rheumatoid) spondylitis
- Gout
- Selected cases of severe osteoarthritis, including degenerative disease of the hip

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.

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

Indomethacin suppositories are for those patients in whom rectal administration is preferred.

Rheumatoid Arthritis
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 indomethacin may enable reduction of steroid dosage in patients receiving corticosteroids. In such instances, the steroid dosage should be reduced slowly.

Ankylosing (Rheumatoid) Spondylitis
Indomethacin frequently produces marked relief of pain and improved motion of the spine within 3 to 10 days.

Osteoarthritis
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
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 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.

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 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS)

Use of SANDOZ 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 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS)

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

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

1.1 Pediatrics

Pediatrics (<15 years of age): The drug should not be prescribed for children because safe conditions for use have not been established in those 15 years and younger. **In a few cases of severe juvenile rheumatoid arthritis, where indomethacin was given along with other drugs, severe reactions, including fatalities, were reported. See 2 CONTRAINDICATIONS.**

1.2 Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. Since advancing years appear to increase the possibility of adverse reactions, indomethacin should be used with greater care in the elderly. See 7.1.4 Geriatrics and 4 DOSAGE AND ADMINISTRATION.

2 CONTRAINDICATIONS

Sandoz 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 breast-feeding, because of the potential for serious adverse reactions in nursing infants
- severe uncontrolled heart failure

- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- 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 7 WARNINGS AND PRECAUTIONS – Hypersensitivity Reactions - Anaphylactoid Reactions).
- active gastric / duodenal / peptic ulcer, active GI bleeding, a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system
- 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 7 WARNINGS AND PRECAUTIONS - Renal).
- known hyperkalemia (see 7 WARNINGS AND PRECAUTIONS - Renal - Fluid and Electrolyte Balance).
- children and adolescents less than 15 years of age
- For use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.
- In subjects with a recent history of rectal bleeding or proctitis.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

- **Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV)**
  (See 7 WARNINGS AND PRECAUTIONS - Cardiovascular).

SANDOZ 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 SANDOZ 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 SANDOZ 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 7 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 SANDOZ INDOMETHACIN.

- **Risk of Gastrointestinal (GI) Adverse Events**
  (see 7 WARNINGS AND PRECAUTIONS - Gastrointestinal)

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

- **Risk in Pregnancy:**

Caution should be exercised in prescribing SANDOZ INDOMETHACIN during the first and second trimesters of pregnancy. Use of NSAIDs at approximately 20 weeks of gestation or later may cause fetal renal dysfunction leading to oligohydramnios and neonatal renal impairment or failure (see 7 WARNINGS AND PRECAUTIONS). SANDOZ INDOMETHACIN is contraindicated for use during the third trimester because of risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition) (see 2 CONTRAINDICATIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing considerations

Carefully consider the potential benefits and risks of SANDOZ INDOMETHACIN and other treatment options before deciding to use SANDOZ INDOMETHACIN. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals.

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

Patient Monitoring Guidelines: Routine monitoring of liver function is recommended.

Indications for Discontinuing Treatment:

- If ulceration is suspected or confirmed or if GI bleeding occurs.
- Urinary symptoms (such as bladder pain, dysuria, urinary frequency), hematuria or cystitis.
- If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.)
- Blurred and/or diminished vision.
- If headache persists despite dosage reduction therapy.

4.2 Recommended Dose and Dosage Adjustment

Use of SANDOZ 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.

The recommended dosage of indomethacin suppositories is 100 to 200 mg daily and should be individually adjusted to the patient's response and tolerance. Daily doses of 100 mg can be given as 50 mg twice daily or as 100 mg at night. Doses higher than 100 mg must be given on a twice daily schedule.

Geriatrics (>65 years of age):
Consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision (see 7.1.4 Geriatrics).

Renal impairment:
A lower daily dose should be considered in patients with mild and moderate renal impairment (see 7 WARNINGS AND PRECAUTIONS - Renal - Fluid and Electrolyte Balance).

4.4 Administration

For combined administration of indomethacin capsules and suppositories, the total daily dose of indomethacin should not exceed 200 mg.

4.5 Missed Dose

If a dose of Sandoz Indomethacin suppositories is missed and remembered within an hour or so, it should be taken right away. Then go back to the regular dosing schedule.

5 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 paresthesia, 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: Symptomatic and supportive. Empty the stomach as quickly as possible by emesis or lavage if the ingestion is recent. Depending on the condition of the patients, 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. Indomethacin is not dialyzable.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Rectal	50 mg and 100 mg Suppository	Suppocire

Each white opaque suppository contains either 50 mg or 100 mg of indomethacin. Available in boxes of 30, individually wrapped in aluminum foil shells.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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.

SANDOZ 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 9 DRUG INTERACTIONS.

Cardiovascular
SANDOZ 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 SANDOZ 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 SANDOZ 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 SANDOZ INDOMETHACIN should hypertension either develop or worsen with its use.

Use of NSAIDs, such as SANDOZ INDOMETHACIN, can induce fluid retention and edema, and may exacerbate congestive heart failure, through a renally-mediated mechanism. (See 7 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.**

Endocrine and Metabolism
Corticosteroids: SANDOZ 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 9 DRUG INTERACTIONS

Fluid and Electrolyte Balance
See 7 WARNINGS AND PRECAUTIONS - Renal.

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 SANDOZ 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 SANDOZ 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 7 WARNINGS AND PRECAUTIONS -7.1 Special Populations – 7.1.4 Geriatrics).

Patients should be informed about the signs and/or symptoms of serious GI toxicity and instructed to discontinue using SANDOZ 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. The incidence of these complications increases with increasing dose.

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

Indomethacin suppositories should be given with caution to patients with any anal or rectal pathology. Caution should be taken if prescribing SANDOZ 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)

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 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.

Genitourinary Tract
Some NSAIDs are known to cause persistent urinary symptoms (bladder pain, dysuria, and urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with an NSAID. Some cases have become severe on continued treatment. Should urinary symptoms occur, treatment with indomethacin **must be stopped immediately** to obtain recovery. This should be done before any 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 SANDOZ 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 SANDOZ 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. This effect usually disappears within 24 hours after discontinuation of

indomethacin. Indomethacin has been shown to prolong bleeding time (but within the normal range) in normal subjects without underlying coagulation defects.

SANDOZ 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 9 DRUG INTERACTIONS - Drug-Drug Interactions - Acetylsalicylic Acid (ASA) or other NSAIDs)

Concomitant administration of SANDOZ 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 SANDOZ 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 SANDOZ INDOMETHACIN, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

Hepatic/Biliary/Pancreatic
As with other NSAIDs, borderline elevations of one or more liver function tests may occur in up to 15% of patients. Significant (3 times the upper limit of normal) elevations of ALT (SGPT) or AST (SGOT) occurred in controlled clinical trials in less than 1% of patients receiving therapy with NSAIDs. Liver function test abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported with nonsteroidal anti-inflammatory drugs.

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

Immune
In common with other anti-inflammatory drugs indomethacin may mask the usual signs of infection. 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.

Aseptic Meningitis*:*

In occasional cases, 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 tissues diseases, etc.) seem to be predisposed. Therefore, in such patients, the physician must be vigilant to the development of this complication.

Monitoring and Laboratory Tests

Cardiovascular: Patients on long-term treatment with SANDOZ INDOMETHACIN should have their blood pressure monitored regularly.

Hematology: Patients on long-term treatment with SANDOZ INDOMETHACIN, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. Concurrent therapy with warfarin requires close monitoring of the international normalized ratio (INR).

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

Ophthalmic: Ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for extended periods of time.

Pregnancy: If Sandoz Indomethacin is administered in the middle (approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women on Sandoz Indomethacin be closely monitored for amniotic fluid volume since Sandoz Indomethacin may result in reduction of amniotic fluid volume and even oligohydramnios (see Special Populations). Sandoz Indomethacin is contraindicated for use in the third trimester of pregnancy.

Renal: During long-term therapy, kidney function and serum electrolytes should be monitored periodically. See 7 WARNINGS AND PRECAUTIONS – Renal.

***Drug interactions*:** See 9 DRUG INTERACTIONS for other situations requiring monitoring.

Neurologic

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

Headache may occur, usually early in treatment with indomethacin. If headache persists despite dosage reduction therapy, indomethacin should be discontinued.

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

Geriatric patients are more likely to develop adverse CNS effects, especially confusion, while taking indomethacin.

Occupational Hazards

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

Ophthalmologic
Blurred and/or diminished vision has been reported with the use of indomethacin and other NSAIDs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed.

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.

Ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for extended periods of time.

Peri-Operative Considerations
See 2 CONTRAINDICATIONS.

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

See also 7 WARNINGS AND PRECAUTIONS – Neurologic.

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

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 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 SANDOZ 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.

Indomethacin and its metabolites are eliminated primarily by the kidneys; therefore the drug should be used with great caution in patients with impaired renal function. In these cases, utilisation of lower doses of indomethacin should be considered and patients carefully monitored. To avoid excessive drug accumulation, a lower daily dosage may be necessary.

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

Advanced Renal Disease: See 2 CONTRAINDICATIONS

Fluid and Electrolyte Balance: Use of NSAIDs, such as SANDOZ 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 SANDOZ INDOMETHACIN in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention.

Use of NSAIDs, such as SANDOZ 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 2 CONTRAINDICATIONS

Reproductive Health: Female and Male Potential

See 7.1.1 Pregnant Women.

Fertility: The use of SANDOZ 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 SANDOZ INDOMETHACIN should be considered.

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.

Sensitivity/Resistance

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.

Anaphylactoid Reactions: As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to SANDOZ INDOMETHACIN. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving indomethacin. SANDOZ 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 2 CONTRAINDICATIONS).

ASA-Intolerance: SANDOZ 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 2 CONTRAINDICATIONS).

Cross-sensitivity: Patients sensitive to one NSAID may be sensitive to any of the other NSAIDs as well.

Serious skin reactions: See 7 WARNINGS AND PRECAUTIONS - Skin

Skin

Serious skin reactions: Use of some NSAIDs, such as SANDOZ INDOMETHACIN, have been associated with rare post-market cases of serious, fatal or otherwise life-threatening skin reactions, including:

- drug reaction with eosinophilia and systemic symptoms (DRESS)
- Stevens-Johnson syndrome,
- toxic epidermal necrolysis,
- exfoliative dermatitis and
- erythema multiforme.

Patients appear to be at higher risk for these events early in the course of therapy, with the onset of cases usually occurring within the first month of treatment. These reactions may be reversible if the causative agent is discontinued, and appropriate treatment instituted. Patients should be advised that they should discontinue their NSAID at the first appearance of a skin rash, mucosal lesions or any other sign of hypersensitivity, and contact their physician immediately for assessment and advice, including which therapies to discontinue.

DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection, and eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident.

7.1 Special Populations

7.1.1 Pregnant Women

SANDOZ INDOMETHACIN is contraindicated for use during the third trimester of pregnancy because of risks of premature closure of the ductus arteriosus and the potential to prolong parturition (see 16 NON-CLINICAL TOXICOLOGY). Caution is recommended in prescribing SANDOZ INDOMETHACIN during the first and second trimesters of pregnancy, particularly from the middle to end of the second trimester of pregnancy (onset at approximately 20 weeks) due to possible fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment or failure.

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

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Complications of prolonged oligohydramnios may for example, include limb contractures and delayed lung maturation. In some post marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If after careful consideration of the benefit-risk, NSAID treatment is considered necessary to be administered anywhere from the middle (onset at approximately 20 weeks) to the end of the second trimester of pregnancy, the use should be limited to the lowest effective dose and shortest duration possible. It is also recommended that ultrasound monitoring of amniotic fluid be considered if SANDOZ INDOMETHACIN treatment extends beyond 48 hours and that NSAIDs treatment be discontinued if oligohydramnios occurs, followed by appropriate medical follow up.

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

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

7.1.2 Breast-feeding

Indomethacin is excreted in the milk of lactating mothers. Indomethacin is not recommended for use in nursing mothers. (See 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

The drug should not be prescribed for children because safe conditions for use have not been established in those 15 years and younger. In a few cases of severe juvenile rheumatoid arthritis, where indomethacin was given along with other drugs, severe reactions, including fatalities, were reported. (See 2 CONTRAINDICATIONS).

7.1.4 Geriatrics

Patients older than 65 years and frail or debilitated patients are most susceptible to a variety of adverse reactions from NSAIDs; the incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal

GI events are in this population. Older patients are also at risk of lower œsophageal 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 (see 7 WARNINGS AND PRECAUTIONS).

Geriatric patients are more likely to develop adverse CNS effects, especially confusion, while taking indomethacin.

8 ADVERSE REACTIONS

8.1 Adverse 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, particularly in the elderly.

The following local adverse reactions have been very commonly (> 10%) associated with the use of indomethacin suppositories:

- proctitis
- burning
- tenesmus
- rectal bleeding
- pain
- itching
- discomfort

8.2 Clinical Trial Adverse Reactions

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

The following table (Table 2) presents adverse reactions for indomethacin capsules. The incidence was obtained from 33 double-blind controlled clinical trials reported in the literature (1, 092 patients). The adverse reactions reported with indomethacin capsules may occur with the use of the suppositories.

Table 2: Most Common Clinical Trial Adverse Drug Reactions (3%-9% and >1%)

Body System	Incidence 3-9%	Incidence > 1%
Gastrointestinal	Nausea with or without vomiting. Dyspepsia, (including indigestion, heartburn and epigastric pain)	Diarrhea, abdominal distress or pain, constipation

Body System	Incidence 3-9%	Incidence > 1%
Central Nervous System	Dizziness	Headache, vertigo, somnolence, depression, and fatigue (including malaise and listlessness)
Special Senses	None	Tinnitus

8.3 Less Common Clinical Trial Adverse Reactions

Table 3: Less Common Clinical Trial Adverse Drug Reactions (<1%)

Body System	Incidence < 1%
Gastrointestinal	Anorexia, bloating (includes distention), flatulence, peptic ulcer, gastroenteritis, rectal bleeding, proctitis, single and multiple ulcerations (including perforation and hemorrhage of the œsophagus, stomach, duodenum, or small and large intestine), intestinal ulceration associated with stenosis and obstruction, gastrointestinal bleeding without obvious ulcer formation and perforation of preexisting sigmoid lesions (diverticulum, carcinoma, etc.), development of ulcerative colitis and regional ileitis, ulcerative stomatitis, toxic hepatitis and jaundice (some fatal cases have been reported).
Central Nervous System	Anxiety (includes nervousness), muscle weakness, involuntary muscle movements, insomnia, hebetude, psychic disturbances (including psychotic episode), mental confusion, drowsiness, lightheadedness, syncope, paresthesia, aggravation of epilepsy and parkinsonism, depersonalisation, coma, peripheral neuropathy, convulsions, dysarthria.
Dermatologic	Pruritus, rash; urticaria, petechiæ or ecchymosis, exfoliative dermatitis, erythema nodosum, loss of hair, Stevens Johnson syndrome, erythema multiforme, toxic epidermal necrolysis.
Cardiovascular	Hypertension, hypotension, tachycardia, chest pain, congestive heart failure, arrhythmia, palpitations
Special Senses	Ocular - corneal deposits and retinal disturbances including those of the macula have been reported in some patients on prolonged therapy with indomethacin, blurred vision, diplopia, hearing disturbances, deafness
Hematologic	Leukopenia, bone marrow depression, anemia secondary to obvious or occult gastrointestinal bleeding, aplastic anemia, hemolytic anemia, agranulocytosis, thrombocytopenic purpura, disseminated intravascular coagulation
Genitourinary	Hematuria, vaginal bleeding, proteinuria, nephrotic syndrome, interstitial nephritis, BUN elevation, renal insufficiency, including renal failure.
Hypersensitivity	Acute anaphylaxis, acute respiratory distress, rapid fall in blood pressure (resembling a shock-like state), angioedema, dyspnea, asthma, purpura, angiitis, pulmonary edema
Metabolic	Edema, weight gain, fluid retention, flushing or sweating, hyperglycemia, glycosuria, hyperkalemia
Miscellaneous	Epistaxis, breast changes (including enlargement and tenderness, or gynecomastia)

8.5 Post-Market Adverse Reactions

Additional reports of serious adverse events temporally associated with SANDOZ INDOMETHACIN during worldwide post-marketing experience are included below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or clearly establish a causal relationship to SANDOZ INDOMETHACIN exposure.

Local Adverse Reactions associated with the use of suppositories:	Rectal irritation, tenesmus, rectal bleeding, pain, itching, proctitis, burning, discomfort
Cardiovascular:	thrombophlebitis
Hematologic:	leukemia
Skin and Subcutaneous Tissue Disorders:	Photosensitivity reactions

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
The combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage. See 9.4 Drug-Drug Interactions.

9.3 Drug-Behaviour Interactions

Excess alcohol intake or smoking may increase the risk of gastrointestinal ulceration and bleeding. See 7 WARNINGS AND PRECAUTIONS, Gastrointestinal.

Patients on indomethacin, who suffer from dizziness, light-headedness, or feelings of detachment, should be cautioned against operating motor vehicles or other machinery, climbing ladders, etc., if these symptoms are present. See 7 WARNINGS AND PRECAUTIONS, Neurologic.

9.4 Drug-Drug Interactions

ASA or other NSAIDs: The use of indomethacin in addition to any other NSAID, including over-the-counter ones (such as ASA and ibuprofen) is not recommended due to the possibility of additive side effects and the absence of any evidence demonstrating synergistic benefits.

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 affects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1.

The use of indomethacin in conjunction with ASA or other salicylates is not recommended. Controlled clinical studies have shown that the combined use of indomethacin with ASA 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 ASA/day decreases indomethacin blood levels approximately 20%.

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 to 35% in indomethacin plasma levels and a concomitant decrease in renal clearance of indomethacin and its conjugate. Therefore, indomethacin and diflunisal should not be used concomitantly.

Acetaminophen: Prolonged concurrent use of acetaminophen with an NSAID may increase the risk of adverse renal effects. It is recommended that patients be under close medical supervision while receiving such combined therapy.

Alcohol: Concurrent use with an NSAID may increase the risk of gastrointestinal side effects, including ulceration or hemorrhage.

Aminoglycosides: Administration of indomethacin to neonates (see 2 CONTRAINDICATIONS) being treated for a patent ductus has decreased the renal clearance and increased the plasma concentration of concurrently administered aminoglycoside antibiotics. Although not documented, similar effects may occur in other patients, leading to increased risk of toxicity. Adjustment of aminoglycoside dosage may be required.

Anticoagulants and Thrombolytic Agents: Indomethacin has been reported to potentiate the effects of coumarin- or indanedione-derivative anticoagulants.

Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding.

Inhibition of platelet aggregation by NSAIDs, and the possibility of NSAID-induced gastrointestinal ulceration or bleeding, may be hazardous to patients receiving anticoagulant or thrombolytic therapy.

Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function, concurrent therapy of indomethacin with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary.

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 indomethacin is added to the treatment of patients on anticoagulant therapy, the patient should be observed closely for alterations of the prothrombin time.

Antidiabetic Agents and Insulin: NSAIDs may increase the hypoglycemic effect of these medications because prostaglandins are directly involved in regulatory mechanisms of glucose metabolism and possibly because of displacement of the oral antidiabetic from serum proteins. Decreased blood glucose concentrations have been reported. Dosage adjustments of the antidiabetic agent may be necessary.

Antihypertensive Agents and Diuretics: 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.

In some patients, the administration of indomethacin can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when 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.

Indomethacin may block the increase in plasma renin activity induced by butemide, furosemide and indapamide.

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. 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 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.

A decrease in the antihypertensive effect of beta-adrenergic receptor blocking agents by NSAIDs 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.

Bone Marrow Depressants: Leukopenic and/or thrombocytopenic effects of these medications may be increased with concurrent or recent therapy if an NSAID causes the same effects. Dosage adjustment of the bone marrow depressant, if necessary, should be based on blood counts.

Concomitant use of indomethacin and pemetrexed may increase the risk of pemetrexed-associated myelosupression, renal, and GI toxicity. In patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. Indomethacin should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed.

Colchicine: Concurrent use with an NSAID may increase the risk of gastrointestinal ulceration or hemorrhage.

Inhibition of platelet aggregation by NSAIDs, added to colchicine's effects on blood clotting mechanisms (colchicine may cause thrombocytopenia with chronic use and clotting defects, including disseminated intravascular coagulation, with overdose), may increase the risk of bleeding at sites other than the gastrointestinal tract.

Corticosteroids (Glucocorticoids & Prednisolone): Numerous studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals. However, concurrent use with a glucocorticoid or corticotropin in the treatment of arthritis may provide additional therapeutic benefit and permit reduction of glucocorticoid or corticotropin dosage.

Cyclosporine: Inhibition of renal prostaglandin activity by NSAIDs may increase the plasma concentration of cyclosporine and/or risk of cyclosporine-induced nephrotoxicity. Patients should be carefully monitored during concurrent use.

Digoxin: Indomethacin has been reported to increase digoxin concentrations in neonates being treated for patent ductus arteriosus. Presently, conflicting evidence exists for the clinical significance of digoxin-indomethacin interaction in man. While some studies have shown that indomethacin increases serum digoxin to levels high in the therapeutic range, others have shown that indomethacin did not alter the elimination half-life, systemic clearance or distribution of digoxin.

Increased monitoring is recommended when digoxin and NSAIDs are coadministered. Dosage adjustments of the digitalis glycoside may be necessary during and following concurrent NSAID therapy.

Lithium: 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 the appropriate 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 indomethacin is administered simultaneously with methotrexate. Indomethacin has been reported to decrease the tubular secretion of methotrexate and to potentiate toxicity.

Nephrotoxic Medications and Gold Compounds: The risk of adverse renal effects may also be increased when an NSAID is used concurrently with other nephrotoxic medications, possibly including gold compounds (although NSAIDs and gold compounds are commonly used concurrently in the treatment of arthritis).

Platelet Aggregation Inhibitors: Concurrent use with an NSAID may increase the risk of bleeding because of additive inhibition of platelet aggregation, as well as the potential for NSAID-induced gastrointestinal ulceration or hemorrhage.

Concurrent use of sulfinpyrazone with NSAIDs may also increase the risk of gastrointestinal ulceration or hemorrhage.

Potassium Supplements: Concurrent use with an NSAID may increase the risk of gastrointestinal side effects, including ulceration or hemorrhage.

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 indomethacin are made under these circumstances, they should be made cautiously and in small increments.

Protein-Bound Agents: Indomethacin, like other NSAIDs in general is highly protein-bound, and therefore the potential exists for drug interactions to occur when it is co-administered with other protein-bound agents.

The potential therefore exists for the displacement of a drug from its plasma protein binding sites by NSAIDs which are tightly protein-bound.

Competition for the same binding sites on plasma proteins may be at least partly responsible for some interactions of NSAIDs with other highly bound drugs. However, other mechanisms such as decreased metabolism or decreased urinary elimination may also be involved.

The clinical significance of these interactions is of greatest importance with drugs that have a small therapeutic window. For example, methotrexate may be displaced from its binding protein sites by NSAIDs.

Selective Serotonin Reuptake Inhibitors (SSRIs): Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see 7 WARNINGS AND PRECAUTIONS - Gastrointestinal).

Tacrolimus: Inhibition of renal prostaglandin activity by NSAIDs may increase the nephrotoxic effect of tacrolimus. Patients should be monitored for necessary dose adjustment and for signs of worsening renal function.

Quinolone anti-bacterials: There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs. Patients should be observed for adjustment of dose if required.

Valproic Acid: Valproic acid may cause hypoprothrombinemia and may inhibit platelet aggregation. Concurrent use with an NSAID may increase the risk of bleeding because of additive interferences with platelet function and/or the potential occurrence of NSAID-induced gastrointestinal ulceration or hemorrhage.

Zidovudine: Indomethacin may competitively inhibit hepatic glucuronidation and decrease the clearance of zidovudine, possibly leading to potentiation of zidovudine toxicity. Indomethacin toxicity may also be increased. Concurrent use of the two medications should be avoided.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

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.

False 5-HIAA concentration values may be measured via the Goldenberg modification of Underfriend's method because indomethacin metabolites are structurally similar to 5-HIAA.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Indomethacin is a nonsteroidal 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.

As with other nonsteroidal anti-inflammatory agents, the exact mechanism of action of indomethacin has not been fully elucidated but has been attributed to the inhibition of prostaglandin synthesis.

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.

10.2 Pharmacodynamics

Anti-Inflammatory Action

Two methods were used to demonstrate the anti-inflammatory activity of indomethacin – the inhibition of granuloma formation induced by subcutaneous implantation of cotton pellets into rats and the inhibition of edema induced by subplantar injection of carrageenan into rats.

Results of the inhibition of granuloma formation by orally administered drug indicate that indomethacin is approximately 85 times more potent than phenylbutazone and approximately 4 times more potent than hydrocortisone. Results of the inhibition of carrageenan-induced edema indicate the same order of potency, which is as follows:

indomethacin>hydrocortisone>phenylbutazone>aspirin

Indomethacin is effective in the absence of the adrenals. Administration of indomethacin did not affect the size of the adrenals or the thymus unlike anti-inflammatory steroids. Also, it did not slow down gain in body weight. The anti-inflammatory effect of combinations of indomethacin and a steroid was greater than comparable doses of either drug alone.

Results from an experiment on adjuvant-induced polyarthritis in rats indicate that indomethacin is more effective than phenylbutazone or acetylsalicylic acid in suppressing the delayed manifestations of disseminated arthritis.

Antipyretic Activity
The antipyretic activity of indomethacin was demonstrated in rats and rabbits in which fever was induced by injection of bacterial pyrogen. Results show that indomethacin is more potent than aminopyrine, aspirin, or phenylbutazone in preventing fever.

Clinical observations in patients with a variety of febrile conditions confirm the antipyretic activity of indomethacin. However, indomethacin should not be used simply as an antipyretic agent.

Analgesic Activity
The analgesic activity of indomethacin was demonstrated in laboratory tests designed to detect mild analgesic activity. Results indicate that indomethacin is more potent than acetylsalicylic acid or aminopyrine. However, indomethacin should not be used simply as an analgesic agent.

10.3 Pharmacokinetics

In man, indomethacin is readily absorbed, attaining peak plasma concentrations of about 1 and 2 mcg/mL at about 2 hours following single oral doses of 25 and 50 mg, respectively. Ninety 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.

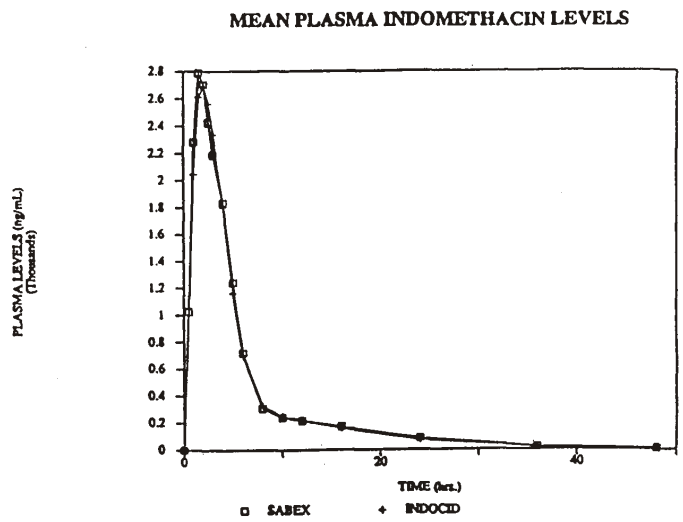
Indomethacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyldesbenzoyl metabolites, all in the unconjugated form. About 60% of an oral dosage is recovered in urine as drug and metabolites (26% as indomethacin and its glucuronide), and 33% is recovered in feces (1.5% as indomethacin).

About 90% of indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentration.

Following oral administration, bioavailability is virtually 100% with 90% of a single dose being absorbed within 4 hours. The bioavailability of the drug following rectal administration of suppositories has generally been reported to be comparable to or slightly less than that following oral administration of the drug. The bioavailability of the drug following rectal administration of suppositories has been reported to be about 80-90%.

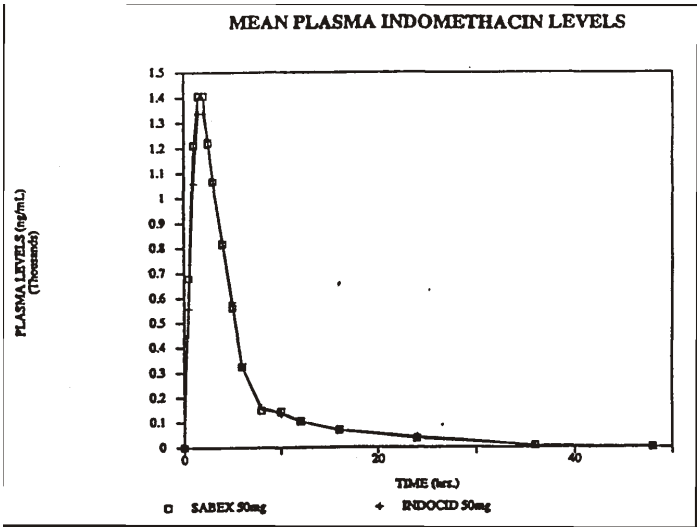
Bioavailability studies were performed using normal human volunteers on both the 50 mg and 100 mg indomethacin suppository formulations. Each formulation was measured and compared to either the 50 mg or 100 mg Indocid® suppository (Merck, Sharp & Dohme). The results are summarized as follows:

	Sandoz Indocid®		
50 mg Formulation	**1 x 50 mg**	**1 x 50 mg**	**Bioavailability**



$AUC_{(0\text{-}t)}$ (ng.hr/mL)	7251.75	7195.54	101.35%
$AUC_{(0\text{-infinity})}$ (ng.hr/mL)	7557.73	7454.65	102.06%
C_{max} (ng/mL)	1510.64	1473.45	102.24%
T_{max} (hours)	1.73	1.94	
$T_{½}$ (hours)	7.89	7.62	
K_{el} (hours-1)	0.103	0.099	

The mean plasma indomethacin levels (shown below) show that both 50 mg formulations have similar absorption and elimination patterns, which peak at approximately 2 hours.



Similar patterns can be seen for the 100 mg formulation (see below). Both the Sandoz 100 mg suppository and the Indocid® 100 mg suppository peak at approximately 2 hours and each have an apparent half-life of 8 hours.

The results of the comparison of the 100 mg Sandoz Indomethacin suppository and the 100 mg Indocid® suppository are as follows:

100 mg Formulation	Sabex 1 x 100 mg	Indocid® 1 x 100 mg	Bioavailability
$AUC_{(0-t)}$ (ng.hr/mL)	15127.42	14900.72	101.76%
$AUC_{(0-infinity)}$ (ng.hr/mL)	15536.53	15213.07	102.27%
C_{max} (ng/mL)	2988.25	2936.91	102.36%
T_{max} (hours)	1.88	1.94	
$T_{1/2}$ (hours)	8.13	7.54	
K_{el} ($hours^{-1}$)	0.091	0.097	

As can be seen from above, both the Sandoz 50 mg Sandoz Indomethacin suppository and the Sandoz 100 mg Sandoz Indomethacin suppository are bioequivalent to the corresponding 50 mg or 100 mg Indocid® suppository.

11 STORAGE, STABILITY AND DISPOSAL

Sandoz Indomethacin suppositories should be stored at room temperature, between 15 and 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

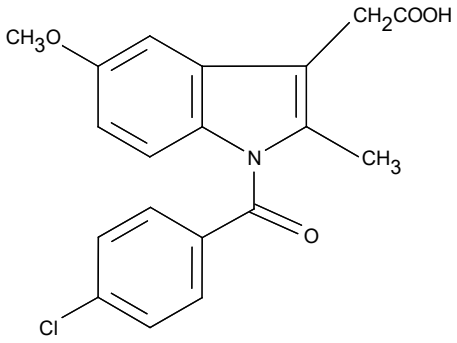
Drug Substance

Proper Name: indomethacin USP

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

Molecular Formula and molecular mass: C19H16C1NO4, 357.79g/mol

Structural Formula:



Physiochemical Properties: Indomethacin occurs as a pale yellow to yellow-tan crystalline powder, with a slight odour and is practically insoluble in water and sparingly soluble in alcohol. Indomethacin has a pKa of 4.5, a melting point of about 162□C and exhibits polymorphism. Indomethacin is sensitive to light and is unstable in alkaline solution.

14 CLINICAL TRIALS

14.3 Comparative Bioavailability Studies

Two bioavailability studies were performed using human volunteers. The rate and extent of absorption after a single rectal administration of Indocid® 50 mg suppositories and Sandoz Indomethacin 50 mg suppositories, and Indocid® 100 mg suppositories and Sandoz Indomethacin 100 mg suppositories, were measured and compared. The results can be summarized as follows:

Summary Tables of the Comparative Bioavailability Data

Indomethacin
(50 mg suppositories)
From measured data

Parameter	Geometric Mean Arithmetic Mean (CV %)		Ratio of Means (%) [A]
	Test	Reference*	Test/Reference
AUC_T (ng·hr/mL)	7044.48 7251.75 (24.15)	6974.39 7195.54 (27.91)	101%
AUC_I (ng·hr/mL)	7405.66 7557.73 (22.85)	7259.02 7454.65 (26.81)	102%
C_{max} (ng/mL)	1465.57 1510.64 (23.00)	1436.55 1473.45 (22.44)	102%
T_{max} (hours)**	1.73 (22.53)	1.94 (30.74)	---
$T_{1/2}$ (hours)**	7.89 (37.88)	7.62 (31.04)	---
K_{el} (hour $^{-1}$)**	0.103 (47.210)	0.099 (27.965)	---

* Reference: Indocid® 50 mg suppository (Merck, Sharp & Dohme, PQ, Canada)

** These are arithmetic means (CV %)

[A] Calculated using geometric means according to the formula: $e^{(Sabex(A)-Indocid®(B))} \times 100\%$

The T_{max} and T1/2 parameters are expressed as the arithmetic means (CV%) only.

Indomethacin

(100 mg suppositories)

From measured data

Parameter	Geometric Mean Arithmetic Mean (CV %)		Ratio of Means (%) [A]
	Test	Reference*	Test/Reference
AUC_T (ng·hr/mL)	14913.17 15127.42 (20.35)	14617.87 14900.72 (21.51)	102%
AUC_I (ng·hr/mL)	15214.44 15536.53 (20.29)	14913.17 15213.07 (20.94)	102%
C_{max} (ng/mL)	2921.93 2988.25 (23.02)	2864.07 2936.91 (21.96)	102%
T_{max} (hours)**	1.88 (43.96)	1.94 (28.79)	---
$T_{1/2}$ (hours)**	8.13 (25.27)	7.54 (24.16)	---
K_{el} (hour $^{-1}$)**	0.091 (26.978)	0.097 (24.824)	---

* Reference: Indocid® 100 mg suppository (Merck, Sharp & Dohme, PQ, Canada)

** These are arithmetic means (CV %)

[A] Calculated using geometric means according to the formula: $e^{(Sabex(A)-Indocid®(B))} \times 100\%$

The T_{max} and $T_{1/2}$ parameters are expressed as the arithmetic means (CV %) only.

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

Toxicity studies of indomethacin have been performed on many animal species including mice, rats, rabbits and dogs. The doses tolerated by man were higher than those tolerated by the experimental animals.

GI ulcerations, the main toxic effect of indomethacin, usually occurred within 2 weeks when more than 5 mg/kg/day were given. Other toxic effects reported were cellular infiltration of the kidney and liver in rats and renal amyloidosis and papillary necrosis in mice when 2-5 mg/kg/day were given.

Reproduction studies in rats and mice indicated that indomethacin is not teratogenic at doses up to 4 mg/kg/day. But, at higher doses of 5-15 mg/kg/day, maternal toxicity increased fetal resorption and fetal malformations were reported. In rats, indomethacin delays parturition.

The acute oral toxicity of indomethacin sustained-release pellets (LD50 = 912 mg/kg) is similar to that of indomethacin base compounds (LD50 = 849 mg/kg) in female mice based on 24-hour mortality. The LD50 of indomethacin base compounds based on a 14-day mortality in mice is 50 mg/kg.

Indomethacin has been found to delay parturition in rats. This effect has been described with other NSAIDs which inhibit prostaglandin synthesis.

In rats, 4 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 mg/kg/day no increase in neuronal necrosis was observed as compared to the control groups.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] SANDOZ INDOMETHACIN
Indomethacin Suppository

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

Serious Warnings and Precautions

Heart and blood vessel problems:

- Sandoz Indomethacin can cause heart and blood vessel problems like heart attacks, stroke, blood clots, high blood pressure and heart failure. These can lead to death.
- The risk of having heart problems is higher if you take Sandoz Indomethacin for long periods of time and/or at higher doses and/or in people who have heart disease.
- Tell your healthcare professional if you have or have had heart problems, high blood pressure or diabetes.

Gastrointestinal (stomach and intestine) problems:

- Sandoz Indomethacin can cause stomach and intestine problems like ulcers, inflammation, bleeding, holes/perforation, blockage or pain.

Talk to your healthcare professional about any medical conditions you have and drugs you are taking.

Pregnancy:

DO NOT take Sandoz Indomethacin if you are pregnant and in a later stage of pregnancy (28 weeks or later).

- If you are pregnant and in an earlier stage of pregnancy (less than 28 weeks) **only** Take Sandoz Indomethacin if you are told to do so by your healthcare professional.
- Medicines like Sandoz Indomethacin may cause harm to you and your baby. Your healthcare professional will need to closely monitor your health and that of your baby (including your amniotic fluid levels) if they prescribe Sandoz Indomethacin during this time.
- Tell your healthcare professional right away if you become pregnant, or think you may be pregnant or want to get pregnant during treatment with Sandoz Indomethacin

What is Sandoz Indomethacin used for?

Sandoz Indomethacin is used in adults and adolescents (15 years of age and older) to treat the symptoms of certain types of arthritis disorders, such as:

- Rheumatoid Arthritis. Sandoz Indomethacin may be taken alone or in combination with other medicines.
- Ankylosing (Rheumatoid) Spondylitis
- Osteoarthritis

- Severe osteoarthritis of the hip, when treatment with other medicines have not worked well
- Gout

How does Sandoz Indomethacin work?

Sandoz Indomethacin belongs to a group of medicines called nonsteroidal anti-inflammatory drug (NSAID). It works by reducing substances produced by your body which cause pain and swelling.

Sandoz Indomethacin does NOT cure your illness or prevent it from getting worse. It can only relieve pain and reduce inflammation as long as you continue to take it.

What are the ingredients in Sandoz Indomethacin?

Medicinal ingredients: indomethacin

Non-medicinal ingredients: suppocire

Sandoz Indomethacin comes in the following dosage forms:
Suppositories: 50 mg and 100 mg.

Do not use Sandoz Indomethacin if:

- you have heart bypass surgery (planning to have or recently had)
- you are pregnant and in a later stage of pregnancy (28 weeks or later)
- you are currently breastfeeding (or planning to breastfeed)
- you have severe, uncontrolled heart failure
- you have bleeding in the brain or other bleeding disorders
- you are allergic to indomethacin or any other ingredients in this medicine or the container
- have a history of asthma, hives, growths in your nose, sinus swelling or symptoms of an allergic reaction after taking Acetylsalicylic Acid (ASA) or other NSAIDs
- you have an active or a history of recurring stomach or intestine ulcers
- you have active bleeding from the stomach or gut
- you have inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis)
- you have liver disease (active or severe)
- you have kidney disease (severe or worsening)
- you have high potassium in the blood
- you are younger than 15 years of age
- You take other NSAIDs drugs used to relieve symptoms of arthritis.
- You have a recent history of bleeding or inflammation of the rectum

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Sandoz Indomethacin. Talk about any health conditions or problems you may have, including if you:

- have high blood pressure, high cholesterol or diabetes
- have or had heart attacks, chest pain, heart disease, stroke or heart failure
- have poor blood flow to your extremities (like your hands and feet)

- smoke or used to smoke
- drink a lot of alcohol
- have a stomach infection
- have liver or kidney problems, urine problems or are dehydrated
- have a history of ulcer or bleeding from the stomach or gut (small or large intestine)
- have other bleeding or blood problems
- have asthma
- have immune system problems
- have mental disturbance, convulsions, or Parkinsonism
- have urine abnormalities.

Other warnings you should know about:

Serious side effects: Sandoz Indomethacin can cause serious side effects, including:

- **Blood and bleeding problems:**
  Sandoz Indomethacin can cause blood problems, bleeding and prolonged bleeding.
  Taking Sandoz Indomethacin with the following drugs can increase the risk of bleeding:
    - Anticoagulants (prevents blood clots), corticosteroids (anti-inflammatory), or antidepressants like selective serotonin reuptake inhibitors (SSRIs).
- **Serious Skin Reactions:** In rare cases, serious, life-threatening allergic and skin reactions have been reported with some NSAIDs, such as Sandoz Indomethacin. These skin problems most often happen during the first month of treatment. Tell your healthcare professional immediately if you notice any changes in your skin both during and after treatment.

Sandoz Indomethacin might cause you to become more sensitive to sunlight. 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, talk to your healthcare professional.

Check-ups and testing: You will have regular visits with your healthcare professional during treatment with Sandoz Indomethacin. They will:

- Check your blood pressure.
- Check your eyes. Sandoz Indomethacin can cause blurred or reduced vision.
- Do blood and urine tests to check your liver, kidney and blood health.

Surgery: Tell any doctor, dentist, pharmacist or healthcare professional that you see, that you are taking this medicine. This is especially important if you are planning to have heart surgery.

Driving and using machinery: Sandoz Indomethacin may cause eye or nervous system problems. This includes tiredness, trouble sleeping, blurred vision, spinning or dizziness (vertigo), hearing problems or depression. Be careful about driving or doing activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking Sandoz Indomethacin, do NOT drive or operate machinery.

Fertility in Women: Sandoz Indomethacin may affect your fertility. This means that it may be difficult for you to have a child. If you have trouble having a child, you might need to stop taking Sandoz Indomethacin. Talk to your healthcare professional if you have any questions about this.

Adults (65 years or older): Side effects like gastrointestinal problems may happen more often. Your healthcare professional might have you start with a lower dose of Sandoz Indomethacin. They will monitor your health during and after treatment.

Serious Drug Interactions
Do not take Sandoz Indomethacin with diflunisal as it can cause fatal intestinal bleeding.

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

The following may interact with Sandoz Indomethacin:

- Acetylsalicylic Acid (ASA) or other NSAIDs, used to treat pain, fever and inflammation, like:
    - celecoxib, diclofenac, ibuprofen, naproxen
- Acetaminophen, used to treat reduce fever and relieve pain
- Medicines used as blood thinners or to prevent blood clots, like warfarin, ASA, clopidogrel
- Medicines used to treat diabetes, like sulphonylurea or other oral hypoglycemics
- Medicines used to lower extra fluid levels (diuretics), like furosemide, hydrochlorothiazide
- Medicines used to treat high blood pressure like enalapril, ramipril, candesartan, irbesartan, propranolol
- Medicines used to treat different cancers, like methotrexate and pemetrexed
- Medicines used to treat bacterial infections (antibiotics) like quinolones and aminoglycosides
- Oral birth control, used to prevent pregnancy
- Colchicine and Probenecid, used to prevent gout
- Corticosteroids (including glucocorticoids such as prednisone), used as an anti-inflammatory
- Medicines used to lower the risk of organ rejection, like tacrolimus and cyclosporin
- Digoxin, used to treat heart disorders
- Medicines used to treat depression (antidepressants) like citalopram, fluoxetine, paroxetine, sertraline, and lithium
- Gold Compounds
- Potassium Supplements
- Valproic Acid
- Zidovudine
- Alcohol

How to take Sandoz Indomethacin:

- Take Sandoz Indomethacin exactly as your healthcare professional tells you. They should recommend the lowest dose possible for your treatment for the shortest time needed.
- **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.**

- Sandoz Indomethacin suppositories are individually wrapped in aluminum foil shells. Make sure that the wrapping material is fully removed before inserting into the rectum.
- Do **not** take suppositories by mouth.

How to insert Sandoz Indomethacin:

1. If the bowel needs to be emptied, this should be done before inserting into rectum
2. For ease of insertion, lubricate the tapered end of the suppository with cold water.
3. Lie down on your side and use your finger to push the suppository as high as possible into the rectum.
4. If it is pushed out, wash it off in cold water and reinsert. If the suppository cannot be retained, do not use and consult a healthcare professional.

Usual dose:

Adolescents (15 years of age or older) and Adult Dosage: 100 to 200 mg per day.

- A daily dose of 100 mg can be given as 50 mg twice a day or 100 mg at night.
- Doses higher than 100 mg should be taken twice a day
- Your healthcare professional may adjusted your dose depending on how you respond or if you experience side effects

Overdose:

If you think you, or a person you are caring for, have taken too much Sandoz Indomethacin, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of Sandoz Indomethacin and remember within an hour or so, take it right away. Take your next dose at the usual time.
- If you do not remember until later, skip the missed dose. Take your next dose at the usual time.
- Do NOT double the dose to make up for the dose you have missed.

What are possible side effects from using Sandoz Indomethacin?

These are not all the possible side effects you may have when taking Sandoz Indomethacin. If you experience any side effects not listed here, tell your healthcare professional.

- Nausea, vomiting, diarrhea, constipation, stomach upset/abdominal pain, heartburn, indigestion, feeling gassy
- Headache, dizziness, light-headedness
- Feeling of burning/prickliness/numbing
- Confusion, hard to concentrate or think, short-term memory loss, nervousness
- Bruises
- Skin rash
- Taste disorder, thirst, dry mouth
- Muscle pain
- Mouth sores
- Hair loss

- Increased sweating
- Problems with your period (women)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Rectal problems related to the use of suppositories: inflamed, burning sensation, feeling that you need to pass stool, bleeding, pain, itching and discomfort	✓		
COMMON			
Gastrointestinal (GI) problems (bleeding, blockage, holes, ulcers or inflammation in your GI tract): blood in vomit, black tarry or bloody stool, dizziness, stomach pain, bloating, loss of appetite, weight loss, nausea, vomiting, constipation or diarrhea, chills or fever		✓	
Hypertension (high blood pressure): fatigue, dizziness or fainting, chest pain	✓		
UNCOMMON			
Anaphylaxis/hypersensitivity (severe allergic reactions): sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat, swelling or anaphylactic reaction/shock			✓
Aseptic meningitis (inflammation of the protective lining of the brain that is not caused by infection): Headaches, stiff neck, nausea and vomiting, fever or clouding of consciousness		✓	
Blood problems (low white and/or red blood cell or platelet count): feeling tired or weak, pale skin, bruising or bleeding for longer than usual if you hurt yourself, fever, chills		✓	
Congestive heart failure (heart does not pump blood as well as it should)**:** shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise			✓
Cystitis (bladder infection): increased need to urinate, pain in the pelvis or lower back, frequent urination during the night, cloudy urine that may contain blood, burning or pain urinating		✓	
Depression (sad mood that will not go away): difficulty sleeping or sleeping too much, changes		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
in appetite or weight, reduced sex drive and thoughts of death or suicide.			
Kidney disorder/problems (including kidney failure): nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, mental status changes (drowsiness, confusion, coma)		✓	
Liver problems (including hepatitis, liver failure, cholestasis): yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness		✓	
Lung problems, asthma: increased shortness of breath, wheezing, difficulty breathing, cough and chest tightness, irregular heartbeat			✓
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat.			✓
Stroke (bleeding or blood clot in the brain)**:** sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, sudden headache, blurry vision, difficulty swallowing or speaking, or lethargy, dizziness, fainting, vomiting, trouble understanding, trouble with walking and loss of balance			✓
Tinnitus (hearing problems): includes ringing, buzzing, clicking or hissing in ears, loss of hearing		✓	
Vertigo (a sense of severe spinning dizziness, lightheadedness)		✓	
RARE			
Serious Skin Reactions: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, swelling of face and/or legs, yellow skin or eyes, shortness of breath, dry			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine or dark urine, hives, red or dry itchy skin, purple or red spots on skin			

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

Reporting Side Effects

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

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

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

Storage:

- Sandoz Indomethacin suppositories should be stored at room temperature, between 15 and 30°C.
- Keep out of reach and sight of children.
- Do not keep outdated medicine or medicine no longer needed.

If you want more information about Sandoz 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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sandoz.ca or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

Last Revised: February 24, 2022

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