Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can lead to hospitalization and death. These increases were seen in clinical trials of several COX-2 selective and nonselective NSAIDs. While the risk may be greater with increasing doses of NSAIDs, it can occur at any dose. \( \text{CONTRAINDICATIONS AND WARNINGS} \)

\section*{Cardiovascular Disease Risk}

\textbf{Cardiovascular Thrombotic Events}

\begin{itemize}
  \item Increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can lead to hospitalization and death. These increases were seen in clinical trials of several COX-2 selective and nonselective NSAIDs. While the risk may be greater with increasing doses of NSAIDs, it can occur at any dose.
  \item Increased risk of hospitalization for new or worsening congestive heart failure.
  \item Increased cardiovascular mortality in trials involving patients with a history of cardiovascular disease.
\end{itemize}

\section*{Hypertension}

\begin{itemize}
  \item Increased blood pressure and symptoms of a worsening pre-existing hypertension may occur.
  \item Use in patients with a history of hypertension should be approached with caution.
\end{itemize}

\section*{Concomitant Use of Indomethacin and Aspirin}

\begin{itemize}
  \item The combination of indomethacin and aspirin should not be used in patients with documented aspirin hypersensitivity.
  \item History of or symptoms of aspirin-induced asthma are contraindications to the use of indomethacin.
\end{itemize}

\section*{Drug Interactions}

\begin{itemize}
  \item Increased risk of bleeding and other adverse events when used with warfarin and other anticoagulants.
  \item Use with NSAIDs, including indomethacin, should be avoided because it may cause premature closure of the ductus arteriosus in premature infants.
\end{itemize}

\section*{Skin Reactions}

\begin{itemize}
  \item Indomethacin extended-release capsules should not be used in patients with known hypersensitivity to indomethacin.
  \item Signs and symptoms of urticaria and angioedema may be part of an allergic hypersensitivity reaction.
\end{itemize}

\section*{Medication Guide for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)}

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

\begin{itemize}
  \item NSAIDs can cause serious side effects, including:
    \begin{itemize}
      \item Increased risk of a heart attack or stroke that can lead to death. This risk may happen early in treatment and may increase with longer use of NSAIDs.
      \item With increasing doses of NSAIDs.
      \item With longer use of NSAIDs.
    \end{itemize}
  \item Do not take NSAIDs right before or after a heart surgery called "coronary artery bypass graft (CABG) surgery.
\end{itemize}

Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach, and intestines:

\begin{itemize}
  \item Anytime during use
  \item Without warning symptoms
  \item That may cause death.
\end{itemize}

The risk of getting an ulcer or bleeding increases with:

\begin{itemize}
  \item Past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs.
  \item Taking medicines called "coxibs," "anticoagulants," "SSRIs," or "SNRIs.
\end{itemize}

NSAIDs should only be used:

\begin{itemize}
  \item At the lowest dose possible for your treatment
  \item For the shortest time needed.
\end{itemize}

What are NSAIDs?

NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?

\begin{itemize}
  \item Do not take NSAIDs:
    \begin{itemize}
      \item If you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
      \item Right before or after heart bypass surgery.
    \end{itemize}
  \item Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:
    \begin{itemize}
      \item Have liver or kidney problems
      \item Have high blood pressure
      \item Have asthma
      \item Are pregnant or plan to become pregnant.
      \item Are considering taking NSAIDs during pregnancy.
    \end{itemize}
  \item NSAIDs have been prescribed for you after 29 weeks of pregnancy.
  \item Are breastfeeding or plan to breast feed.
\end{itemize}

Tell your healthcare provider about all of the medicines you take, including prescriptions, over-the-counter medications, vitamins, or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. Do not start taking any new medicine while talking to your healthcare provider.

For Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

\begin{itemize}
  \item NSAIDs, including aspirin, can cause an increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach, and intestines:
    \begin{itemize}
      \item Anytime during use
      \item Without warning symptoms
      \item That may cause death.
    \end{itemize}
  \item NSAIDs can cause serious side effects, including:
    \begin{itemize}
      \item Increased risk of a heart attack or stroke that can lead to death. This risk may happen early in treatment and may increase with longer use of NSAIDs.
      \item With increasing doses of NSAIDs.
      \item With longer use of NSAIDs.
    \end{itemize}
\end{itemize}

Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:

\begin{itemize}
  \item Have liver or kidney problems
  \item Have high blood pressure
  \item Have asthma
  \item Are pregnant or plan to become pregnant.
  \item Are considering taking NSAIDs during pregnancy.
  \item NSAIDs have been prescribed for you after 29 weeks of pregnancy.
  \item Are breastfeeding or plan to breast feed.
\end{itemize}
Deaths due to indomethacin extended-release capsules have been observed in postmarketing experience. Deaths have occurred following both therapeutic and accidental overdosage of indomethacin extended-release capsules. The following symptoms may be observed following overdosage: vomiting, diarrhea, abdominal cramps, hypotension, shock, and circulatory failure. No specific treatment is known with indomethacin extended-release capsules. Tachycardia, hypotension, and circulatory failure may be treated with the usual support measures. Fluid and electrolyte balance must be maintained. Vasopressor drugs may be required to support blood pressure and perfusion. If hemodynamic parameters become unstable, monitor central venous pressure, arterial pressure, and urinary output. Indomethacin extended-release capsules 75 mg may be prescribed as one capsule daily in adults with the potential for serious reactions occurring in less than 2% of the patients treated with indomethacin extended-release capsules or in 1% of the patients treated with indomethacin extended-release capsules 75 mg. Patients should be observed for possible signs and symptoms of intolerance since the daily dosage is increased. Dosage adjustments should be made in the elderly as a result of age-related changes in pharmacokinetics. Dosage adjustments should also be made in patients with impaired renal function.

5. Patients should be informed of the warning signs and symptoms of potential serious skin reactions, including deaths. Patients should be apprised of the importance of this follow-up evaluation. Therapy should be discontinued if significant new skin symptoms occur.

See “What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?” before taking this medicine.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

• new or worse high blood pressure
• heart failure
• liver problems including liver failure
• kidney problems including kidney failure
• low red blood cells (anemia)
• life-threatening skin reactions
• life-threatening allergic reactions

Other side effects of NSAIDs include: stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get any of the following symptoms:

• shortness of breath or trouble breathing
• slurred speech
• chest pain
• swelling of the face or throat
• breaking out on one part or side of your body

Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:

• more tired or weaker than usual
• diarrhea
• nausea
• skin rash or blisters with fever
• flu-like symptoms
• liver problems including liver failure, including jaundice
• sudden weight gain
• rapid or pounding heartbeat
• sleepiness or unusual tiredness
• shortness of breath
• symptoms of bleeding in the stomach or intestines (such as stomach pain or bleeding after taking NSAIDs, peeling or black stools or vomiting dark blood), or
• unusual bleeding or bruising

• numbness, weakness, coldness, or pale color of the hands and feet
• severe headache
• fever or signs of a severe infection such as those listed in the section “What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?”

ADVERSE REACTIONS

The following adverse reactions have been observed in clinical trials with indomethacin extended-release capsules:

5. Patients should be informed of the warning signs and symptoms of potential serious skin reactions, including deaths. Patients should be apprised of the importance of this follow-up evaluation. Therapy should be discontinued if significant new skin symptoms occur.

Adverse reactions listed below may occur with indomethacin extended-release capsules. Patients may experience more than one side effect with this medication. Some side effects may occur more frequently than others. Some side effects may be more serious than others. Some side effects may not be apparent until the end of the treatment period. Some side effects may not be listed in this Medication Guide. The side effects listed below are not all of the possible side effects of this medication. Side effects other than those listed in this Medication Guide may occur while taking indomethacin extended-release capsules.