Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen, or if clinical signs and symptoms consistent with liver disease develop, or if jaundice, right upper quadrant tenderness, and "flu-like" symptoms occur. If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if jaundice, right upper quadrant tenderness, and "flu-like" symptoms occur, stop the drug and investigate for liver injury. If liver injury continues to progress, then the drug should be permanently withdrawn. This is a serious but rare condition, and patients should be closely monitored for evidence of liver injury for at least 30 days after starting ZIPSOR. The risk of liver injury may be increased in patients with the following risk factors: concomitant use of ZIPSOR and analgesic doses of aspirin, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.

Seek emergency help if an anaphylactic reaction occurs.

ZIPSOR is contraindicated in the setting of CABG surgery.

Concomitant use of ZIPSOR and analgesic doses of aspirin is not generally recommended.

ZIPSOR is contraindicated in the setting of CABG surgery.

The concomitant use of diclofenac with other NSAIDs or salicylates is not recommended.

Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)".

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

Increasing of bleeding, ulcers, and tears (perforation) of the esophagus (tubes leading from the mouth to the stomach), stomach ulcers:

- anytime during use
- without warning symptoms
- that may cause death

The risk of getting an ulcer or bleeding increases with:
- past heart attack, stroke, or blood clot in the lungs
- age
- high blood pressure
- high cholesterol or triglycerides
- receiving medicine for heart or blood vessels
- cigarette smoking
- diabetes
- kidney problems including kidney failure
- liver disease
- severe anemia
- vitamin B12 deficiency
- heart failure
- if you are a man over 60 years old
- if you are a woman over 65 years old
- if you have only one kidney
- if you are a smoker
- if you are an alcoholic

NSAIDs should only be used:
- as exactly as prescribed.

Avoid NSAIDs if you have had an asthma attack, fever, or other allergic reaction with aspirin or any other NSAID.

Avoid NSAIDs right before or after heart bypass surgery.

Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including:
- if you have heart or blood vessel disease
- if you have had a stroke
- if you have high blood pressure
- if you have asthma
- if you are pregnant or plan to become pregnant. Talk to your healthcare provider about the benefits and risks of taking NSAIDs during pregnancy. You should not take NSAIDs after 29 weeks of pregnancy.

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 some types of short-term pain.

Who should not take NSAIDs?

Do not take NSAIDs if you have:
- an allergy to NSAIDs
- asthma
- if you have had an asthma attack, fever, or other allergic reaction with aspirin or any other NSAID
- right before or after heart bypass surgery.

Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including:
- any drug or alcohol allergy
- if you have liver or kidney problems
- if you have high blood pressure
- if you have asthma
- if you are pregnant or plan to become pregnant.

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interact with each other and may have an adverse effect.

If you take NSAIDs, do not take any new medicine without telling your healthcare provider first.

NSAIDs can cause serious side effects, including:
- death
- hospitalization
- heart attack
- stroke
- blood clots in the lung
- ulcers or bleeding
- 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 diarrhea.

Potential emergency signs (Follow these signs immediately or call your healthcare provider as soon as possible):

- dizziness or fainting
- swelling of the face or throat
- weakness in one part of your body

Medication Guide for Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) — In this Medication Guide, we describe some of the problems called Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) that can cause serious side effects, including:
- increased risk of a heart attack or stroke that can lead to death
- other side effects of NSAIDs include: stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and diarrhea.
Diclofenac is metabolized by cytochrome P450 enzymes, predominantly by CYP2C9. A dosage adjustment may be warranted when diclofenac is administered with CYP2C9 inhibitors. 

4.1 Pharmacokinetics

Absorption

Diclofenac is 100% absorbed after oral administration compared to IV administration as measured by urine recovery. The extent of diclofenac absorption is not significantly affected when ZIPSOR is taken with food. However, the rate of absorption is increased.

Distribution

Diclofenac is 99% bound to plasma proteins, primarily to albumin. The apparent volume of distribution (V/F) of diclofenac potassium is 1.3 L/kg.

Metabolism

Diclofenac is metabolized by cytochrome P450 enzymes, predominantly by CYP2C9. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CPY2C8 may also play a role in diclofenac metabolism. Approximately 65% of the dose is excreted in the urine, and approximately 35% in the bile as conjugates of and metabolites. Because renal elimination is not a significant pathway of elimination for diclofenac, there is no need to adjust the dose in patients with renal impairment. A dose of 100 mg is recommended in patients with severe renal impairment (creatinine clearance <30 ml/min) beginning on the first day of treatment and is increased to 75 mg on the second day.

Excretion

The elimination half-life of diclofenac is approximately 1.5 hours.

5.10. Pregnancy

Advise females of reproductive potential who desire pregnancy that NSAIDs, including ZIPSOR, may be associated with adverse maternal or fetal outcomes when administered at usual therapeutic dosages. Patients should be informed that prolonged use of NSAIDs, including ZIPSOR, in pregnant women may result in premature closure of the ductus arteriosus.

6. FULLERTON, Calif. — Depomed, Inc. (Nasdaq: DPMI), today announced that the U.S. Food and Drug Administration (FDA) has approved ZIPSORTM (diclofenac potassium) delayed-release tablets for the management of osteoarthritis, rheumatoid arthritis, and distal symmetric polyarthritis.

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