**MITIgARe® (colchicine) Capsules**

### 5. WARNINGS AND PRECAUTIONS

- **•** Combination therapy with agents that inhibit both the P-glycoprotein (P-gp) efflux transporter and the CYP3A4 metabolic enzyme should be avoided in patients with renal or hepatic impairment. If avoidance is not possible, reduced daily dose should be considered and the patient should be monitored closely for colchicine toxicity.

### 7.4 Drug-Drug Interaction Studies

**7.2 P-glycoprotein**

- Gastrointestinal: abdominal pain, diarrhea, nausea and vomiting have been reported when colchicine is administered with inhibitors of CYP3A4 that may not be potent inhibitors of P-gp (e.g., erythromycin, clarithromycin).

**7.1 CYP3A4**

- Reflux: decreased incidence of relapse and reduced requirement for anti-reflux treatment

### 6. ADVERSE REACTIONS

- **•** Myotoxicity including rhabdomyolysis may occur, especially in combination with other drugs known to increase myotoxicity.

### 8. USE IN SPECIFIC POPULATIONS

- **•** Pregnancy: colchicine can cause serious side effects or death if MISIgARe® is too high in your body.

- **•** Taking certain medicines with MISIgARe® can cause your level of MISIgARe® to be too low, especially if you have kidney or liver problems.

- **•** Tell your healthcare provider about all your medical conditions, including if you have kidney or liver problems. Your dose of MISIgARe® may need to be changed.

- **•** Even medicines that you take for a short period of time, such as antibiotics, can interact with MISIgARe® and cause serious side effects or death.

- **•** MISIgARe® is a prescription medicine used to prevent gout flares in adults.

- **•** It is not known if MISIgARe® is safe and effective for the treatment of:

  - **acute gout flares**
  - **MISIgARe® is not a pain medicine and should not be taken to treat pain related to other conditions unless specifically for those conditions.**

- **•** It is not known if MISIgARe® is safe and effective in children.

### 4. CLINICAL PHARMACOLOGY

- **•** Using MISIgARe® with other drugs can result in life-threatening or fatal colchicine toxicity.

### 10. OVERDOSAGE

- **•** Do not take MISIgARe® if you have kidney or liver problems and you take certain other medicines. Serious side effects, including death, have been reported in these patients even when taken as directed. See "What is the most important information I should know about MISIgARe®?"

- **•** Do not take MISIgARe® if you have kidney or liver problems.

- **•** If you are pregnant or plan to become pregnant. MISIgARe® can pass into your breast milk and may harm your baby.

- **•** Tell your healthcare provider about the best way to feed your baby if you take MISIgARe®.

### 12. HOW SUPPLIED/STORAGE AND HANDLING

- **•** To report SUSPECTED ADVERSE REACTIONS, contact Hikma Americas, Inc. at 1-800-962-8364 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch or phone 1-800-332-1088.
How should I store MITIGARE®?

MITIGARE® can cause serious side effects or death. See "What is the most important information I should know about MITIGARE®?"

Get medical help right away if you have:

- unusual bleeding or bruising
- increased infections
- signs of liver or kidney problems
- muscle weakness or pain
- numbness or tingling in your fingers or toes
- pale or gray color to your lips, tongue, or pal of your hands
- serious diarrhea or vomiting

The most common side effects of MITIGARE® include abdominal pain, diarrhea, nausea, and vomiting. Tell your healthcare provider if any side effect bothers you or if it does not go away.

These are not all of the possible side effects of MITIGARE®. For more information ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store MITIGARE®?

Store MITIGARE® at room temperature between 68° to 77°F (20° to 25°C).

Keep MITIGARE® in a tightly closed container.

Keep MITIGARE® out of the light and away from moisture.

Keep MITIGARE® and all medicines out of the reach of children.

General information about the safe and effective use of MITIGARE®

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use MITIGARE® for other people unless your healthcare provider tells you it is safe for them.

Remember that your doctor has prescribed this medicine for you because he or she has judged that the benefits are greater than the risks. Many patients using this medicine do not have serious side effects.

This Medication Guide may not cover all possible interactions. Tell your healthcare provider if you are taking any other prescription or nonprescription (over-the-counter) medicines. Keep a list of all the medicines you take and show it to each healthcare provider you see.

References

2.1 DESCRIPTION

MITIGARE® capsules are supplied for oral administration. Each capsule contains 0.6 mg Colchicine and the following inactive ingredients: silicon dioxide, erythrosine, Brilliant Blue FCF and Quinoline Yellow.

5.2 Manufacturing

MITIGARE® capsules are filled by Hikma Americas Inc., Memphis, TN 38120.

Colchicine consists of pale yellow scales or powder; it darkens on exposure to light. Colchicine is soluble in water, freely soluble in alcohol, and slightly soluble in ether. Colchicine is a substrate of P-gp and P-gp efflux is postulated to play an important role in colchicine disposition. Elimination half-life in humans was found to be 31 h (range 21.7 to 49.9 h).

Colchicine has a mean apparent volume of distribution in healthy young volunteers of approximately 5 to 8 L/kg. Colchicine binding capacity is not saturable over the concentration range of 50 to 500 μg/mL. The mean volume of distribution ranges from 3 to 6 L/kg in patients with normal renal function.

Colchicine is metabolized in humans primarily by cytochrome P450 CYP3A4 to 2- and 3-O-demethylcolchicine (2-DMC and 3-DMC, respectively) by CYP3A4. Glucuronidation is also believed to be a metabolic pathway for colchicine. In a published study in healthy volunteers, 40 to 65% of the total absorbed dose of colchicine (1 mg administered orally) was recovered unchanged in urine. Enterohepatic recirculation and biliary excretion are also believed to play a role in colchicine elimination.

Colchicine is a substrate of P-gp and biliary excretion appears to play a role in biliary excretion of the parent drug and the metabolite 2-O-demethylcolchicine (2-DMC). The 2-DMC is also a substrate of P-gp in the liver. A human liver microsome study showed that about 16% of colchicine is metabolized to 2-O-demethylcolchicine (2-DMC). The 2-DMC is eliminated in the urine. Enterohepatic recirculation of the 2-DMC is also believed to occur. Colchicine and 2-DMC are substrates of organic cation transporters (OCT1 and OCT2). The OCTs may play a role in the reabsorption of colchicine and 2-DMC in the kidney. The OCTs are also believed to play a role in enterohepatic recycling of the parent drug and the metabolites.

Colchicine is a substrate of the active form of P-gp and, therefore, the co-administration of drugs that are substrates of P-gp may alter the pharmacokinetics of colchicine. Colchicine is also a substrate of ABCG2. Abcg2 may play a role in the intestinal absorption and biliary excretion of colchicine. Colchicine is a substrate of the human organic anion transporter 3 (hOAT3) which may play an important role in the renal clearance of colchicine. Colchicine is also a substrate of the human organic cation transporter 1 (hOCT1) which may play a role in the enterohepatic cycling of colchicine.

Colchicine is a substrate of OCT2. OCT2 may play a role in the renal excretion of colchicine.

The effects of other P-gp substrates on the pharmacokinetics of colchicine have not been evaluated.

Pharmacokinetic studies evaluating changes in systemic levels of colchicine when co-administered with CYP3A4 inhibitors in healthy volunteers using a modified single-dose self-administered oral dosing model have not been conducted. In a study conducted on human liver microsomes, increases in systemic levels of colchicine were observed following co-administration of colchicine with the CYP3A4 inhibitor ketoconazole. These findings may not be relevant to the systemic levels of colchicine in human subjects.

The effects of colchicine on labor and delivery are unknown. No dedicated pharmacokinetic study has been conducted using MITIGARE® in patients with varying degrees of renal impairment.

No dedicated pharmacokinetic study using MITIGARE® has been conducted in patients with varying degrees of hepatic impairment. These are not all of the possible side effects of MITIGARE®. For more information ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

In some subjects with mild to moderate cirrhosis, the clearance of colchicine is significantly reduced and plasma half-life prolonged.

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