Siklos® 100 mg hydroxyurea

Siklos® 1,000 mg hydroxyurea

DISSOLVING INSTRUCTIONS

FOR PATIENTS WHO CANNOT SWALLOW SIKLOS® TABLETS: INSTRUCTIONS FOR DISSOLVING TABLETS IN WATER

Please note that patients must take Siklos® once a day at the same time each day.

Siklos® is toxic to certain cells in the body. Therefore, anyone handling Siklos® tablets or bottles containing Siklos® tablets MUST follow these instructions at all times:

Before you get started, assemble the following items:

• Bottle of Siklos® tablets • Disposable gloves • Teaspoon and water to dissolve tablets • Paper towel
• Plastic bag or other closed disposable container • Detergent solution

Step 1

Wash your hands with soap and water.

Step 2

Put on disposable gloves. You must wear disposable gloves **AT ALL TIMES** when handling Siklos® tablets or bottles containing Siklos® tablets.

Step 3

Place prescribed dose of Siklos® on the teaspoon. Carefully add a small amount of water to the teaspoon. Tablet will dissolve within about 1 minute.

Step 4

Patient should swallow the dissolved tablet immediately.

Step 5

After swallowing dissolved tablet, patient should immediately drink a glass of water.

Please see Important Safety Information, including Boxed Warning, on following pages.

Step 6

IMPORTANT:
Immediately wipe up any powder spilled from Siklos® tablets with a damp disposable paper towel, using a detergent solution followed by clean water, and throw away the disposable paper towel in a closed container, such as a plastic bag. Remove disposable gloves only after administering Siklos®, cleaning up any spills and disposing of any items used to clean up spills. After removing gloves, wash hands again with soap and water.

In case of accidental contact with Siklos® tablets or powder from tablets:

Immediately wash any skin that comes into contact with a crushed or broken Siklos® tablet thoroughly with soap and water.

Immediately flush eyes thoroughly with water or isotonic eyewash for at least 15 minutes if contact with crushed or broken tablets happens in the eyes.

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Siklos® (hydroxyurea) tablets, for oral use

INDICATION

Siklos® is an antimetabolite indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients 2 years of age and older with sickle cell anemia with recurrent moderate to severe painful crises.

IMPORTANT SAFETY INFORMATION

WARNING: MYELOSUPPRESSION and MALIGNANCIES

See Full Prescribing Information for complete Boxed Warning.

- ***Myelosuppression:*** **Siklos® may cause severe myelosuppression. Do not give if bone marrow function is markedly depressed. Monitor blood counts at baseline and throughout treatment. Interrupt treatment and reduce dose as necessary.**
- ***Malignancies:*** **Hydroxyurea is carcinogenic. Advise sun protection and monitor patients for malignancies.**

CONTRAINDICATIONS

Siklos® is contraindicated in patients who have demonstrated a previous hypersensitivity to hydroxyurea or any other component of its formulation.

WARNINGS AND PRECAUTIONS

Myelosuppression

Hydroxyurea causes severe myelosuppression. Do not initiate treatment with hydroxyurea in patients if bone marrow function is markedly depressed. Bone marrow suppression may occur, and leukopenia is generally its first and most common manifestation. Thrombocytopenia and anemia occur less often, and are seldom seen without a preceding leukopenia.

Some patients, treated at the recommended initial dose of 20 mg/kg/day, have experienced severe or life-threatening myelosuppression. Due to the change in body weight requiring modification of daily dose, pediatric patients have an increased risk of myelosuppression at the time of dose adjustment.

Evaluate hematologic status prior to and during treatment with Siklos® Provide supportive care and modify dose or discontinue Siklos® as needed. Recovery from myelosuppression is usually observed within 15 days when therapy is interrupted. Resume therapy after interruption at a lower dose.

Malignancies

Hydroxyurea is a human carcinogen. In patients receiving long-term hydroxyurea for myeloproliferative disorders (a condition for which Siklos® is not approved), secondary leukemia has been reported. Skin cancer has also been reported in patients receiving long-term hydroxyurea. Advise protection from sun exposure and monitor for the development of secondary malignancies.

Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, Siklos® can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during and after treatment with Siklos® for at least 6 months after therapy. Advise males of reproductive potential to use effective contraception during and after treatment with Siklos® for at least 6 months after.

Vasculitic Toxicities (including Leg Ulcers)

Cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders during therapy with hydroxyurea. These vasculitic toxicities were reported most often in patients with a history of, or currently receiving, interferon therapy. Due to potentially severe clinical outcomes for the cutaneous vasculitic ulcers reported in patients with myeloproliferative disease (a condition for which Siklos® is not approved), treatment with Siklos® should be discontinued and/or its dose reduced if cutaneous vasculitic ulcerations develop. Rarely, ulcers are caused by leukocytoclastic vasculitis.

Avoid use of Siklos® in patients with wounds on the legs (leg ulcers).

Risks with Concomitant Use of Antiretroviral Drugs

Pancreatitis, hepatotoxicity, and peripheral neuropathy have occurred when hydroxyurea was administered concomitantly with antiretroviral drugs, including didanosine and stavudine.

Risks with Concomitant Use of Live Virus Vaccine

Avoid use of live virus vaccine in patients taking Siklos®. Concomitant use of hydroxyurea with a live virus vaccine may potentiate the replication of the vaccine virus and/or may increase the adverse reactions of the vaccine virus and result in severe infection. Patient's antibody response to vaccines may be decreased. Consider consultation with a specialist.

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Macrocytosis

Siklos® may cause macrocytosis, which is self-limiting, and is often seen early in the course of treatment. The morphologic change resembles pernicious anemia, but is not related to vitamin B12 or folic acid deficiency. This may mask the diagnosis of pernicious anemia. Prophylactic administration of folic acid is recommended.

Test Interference

Interference with Uric Acid, Urea, or Lactic Acid Assays is possible, rendering falsely elevated results of these in patients treated with hydroxyurea.

DOSAGE AND ADMINISTRATION

- **Do not split the Siklos® 100 mg tablets into smaller parts.**
- Siklos® is a cytotoxic drug. Ensure patients follow applicable special handling and disposal procedures.
- Siklos® dosing is based on patient's actual or ideal weight, whichever is less. Specific parameters (blood counts) must be monitored throughout treatment with Siklos® and dosing must be adjusted accordingly.
- Monitor the hematologic parameters closely in patients with renal impairments.

ADVERSE REACTIONS

- The most common adverse reactions to Siklos® (incidence > 10%) include infections and neutropenia. Other adverse reactions include skin and subcutaneous disorders (skin depigmentation/melanonychia, skin rash, alopecia), gastrointestinal disorders, vitamin D deficiency and headache.
- **Clinical Trial Experience:** The safety of Siklos® has been assessed in 405 pediatric patients with sickle cell disease from 2-18 years of age in the European Sickle Cell Disease prospective Cohort study ESCORT-HU. The most frequently reported adverse reactions in ESCORT-HU were infections and myelosuppression.

Other adverse reactions include skin and subcutaneous disorders (skin depigmentation/melanonychia, skin rash, alopecia), gastrointestinal disorders, vitamin D deficiency and headache.

At least one serious adverse reaction was reported in 32.6 % of the 405 pediatric patients with sickle cell disease in ESCORT-HU. The most frequent serious adverse reactions were infections (17.8 %), and blood and lymphatic system disorders (9.1 %). This included serious neutropenia (3.2%), thrombocytopenia (3.0%) and anemia (3.0%). Other reported serious adverse reactions were gastrointestinal disorders (3.2 %), fever (2.5 %) and nervous system disorders (4.0 %), including headache (2.7%).

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Siklos® can cause fetal harm based on findings from animal studies and the drug's mechanism of action. Advise pregnant women of the potential risk to a fetus.
- **Lactation:** It is not known whether Siklos® is excreted in human milk, the effects of Siklos® on the breastfed child, or the effects of Siklos® on milk production. Because of the potential for serious adverse reactions in a breastfed child from Siklos®, including carcinogenicity, advise patients not to breastfeed during treatment with Siklos®.
- **Females and Males of Reproductive Potential:** Advise patients to inform their healthcare provider of a known or suspected pregnancy. Advise females and males of reproductive potential to use contraception during and after treatment with Siklos® for at least 6 months after therapy. Based on findings in animals and humans, male fertility may be compromised by treatment with Siklos®. Prior to therapy, advise male patients about the possibility of sperm conservation.
- **Pediatric Use:** Continuous follow-up of the growth of treated children is recommended. Pediatric patients aged 2-16 years had a higher risk of neutropenia than patients more than 16 years old. The safety and effectiveness of Siklos® have not been established in pediatric patients less than 2 years of age.
- **Renal Impairment:** The exposure to Siklos® is higher in patients with creatinine clearance of less than 60 mL/min. Reduce dosage and closely monitor the hematologic parameters when Siklos® is to be administered to these patients
- **Hepatic Impairment:** Close monitoring of hematologic parameters is advised in patients with hepatic impairment receiving Siklos®.

OVERDOSAGE

Acute mucocutaneous toxicity has been reported in patients receiving hydroxyurea at doses several times above the therapeutic dose. Soreness, violet erythema, oedema on palms and soles followed by scaling of hand and feet, severe generalized hyperpigmentation of the skin and stomatitis have been observed.

To report suspected adverse reactions, contact Medunik USA at 1-844-884-5520 or medicalinfo@medunikusa.com.

Please read the Full Prescribing Information, including **Boxed Warning** at www.siklosusa.com.

Medunik USA