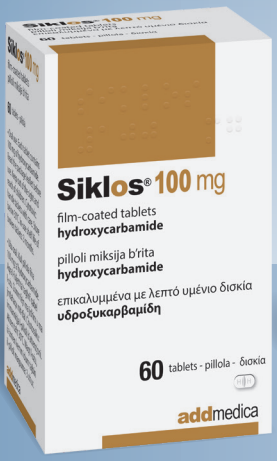
SICKLE CELL DISEASE

Siklos®
hydroxycarbamide

in SICKLE CELL DISEASE Physician Guide



Film-coated tablets hydroxycarbamide

Film-coated tablets hydroxycarbamide

Important recommendations for patient monitoring

addmedica

Introduction

Siklos® is indicated **in the prevention of painful, recurrent vaso-occlusive crises, including acute chest syndrome, in adults, adolescents and children over 2 years of age suffering from symptomatic sickle cell disease**.

Siklos® contains as active substance hydroxycarbamide, more commonly called hydroxyurea.

Siklos® should be administered under the supervision of a physician experienced in the treatment of sickle cell disease.

This guide is intended for all healthcare professionals involved in the management of patients requiring a treatment with Siklos®.
This educational material is essential to ensure the safe and effective use of the product and appropriate management of the important selected risks.

A patient guide is also available. You are requested to provide a copy of the patient guide to every patient/care giver when treatment with Siklos® is initiated.

Siklos® (hydroxycarbamide) is available in 2 strengths: 100 mg and 1000 mg.

PLEASE NOTE

Siklos® 100 mg

Off-white oblong-shaped, film-coated tablets **with 1 score line on both sides.**

Each half tablet is embossed “H” on one side.

Each tablet contains 100 mg hydroxycarbamide (active substance), and can be divided into 2 equal 50 mg parts.

Siklos® 100 mg is presented in a **plastic bottle containing 60 tablets.**

Siklos® 1000 mg

White, capsule shaped, film-coated tablets **with 3 score lines on both sides**.

Each tablet contains 1000 mg hydroxycarbamide and can be divided into **4 equal 250 mg parts**.
Each quarter of tablet is embossed “T” on one side.

Siklos® 1000 mg is presented in a **plastic bottle containing 30 tablets.**

1 Dosages and dose adjustment

The daily dose should be adjusted on the basis of the **patient's body weight, the biological and clinical response.**

- The starting dose is **15 mg per kg per day**.
- The usual maintenance dose is between **15 and 30 mg/kg/day**.
- In some exceptional cases, a maximum dose of 35 mg/kg/day may be justified and be administered under close monitoring of blood counts.

The daily dose of Siklos® can be adjusted in increments of 2.5 to 5 mg/kg/day using**:**

- either the Siklos® 100 mg tablet:
  - ½ tablet for a dose of **50 mg** hydroxycarbamide
  - A whole tablet for a dose of **100 mg** hydroxycarbamide

- or the Siklos® 1000 mg tablet:
  - ¼ tablet for a dose of **250 mg** hydroxycarbamide
  - ½ tablet for a dose of **500 mg** hydroxycarbamide
  - ¾ tablet for a dose of **750 mg** hydroxycarbamide
  - A whole tablet for a dose of **1000 mg** hydroxycarbamide.

Example:
Patient weighing 24 kg: Recommended initial dose of 15 mg/kg/day or 360 mg per day corresponding to:

Siklos® 100 mg: 1 tablet per day
+
Siklos® 1000 mg: 1 quarter of a tablet per day
or
Siklos® 100 mg: 3 tablets + ½ tablet per day

Whenever both strengths of Siklos® are prescribed simultaneously, make sure that the patient and/or the parents or legal representative understands the prescription in order to avoid any confusion between the two different strengths and prevent potential overdose or underdose.

Situations	**Recommended dosage and adjustment**
Adults	15-30 mg/kg/day
Children and adolescents (2-18 years of age)	15-30 mg/kg/day
In case of abnormality of blood cells count (see § 2.2)	Discontinue treatment until results return to normal (usually achieved within 2 weeks), then resume at a reduced dose and increase if necessary, under close supervision. A dose which caused haematological toxicity must not be tried more than twice.
In case of renal impairment	Creatinine clearance > 60 ml/min: 15-30 mg/kg per day. Creatinine clearance ≤ 60 ml/min, reduce starting dose by 50 %. Creatinine clearance < 30 ml/min, stop the treatment (see contraindication in SPC)
In case of leg ulcers	Consider dose reduction and/or discontinuation (see Special warnings and precautions for use in SPC)

Siklos® is taken once daily, preferably in the morning before breakfast.

For patients unable to swallow tablets, the tablets may be disintegrated immediately before administration, in a teaspoon with some water. Syrup may be added, or the content may be mixed with food, to mask any bitterness.

In any case, ensure that the patient is well informed about the **precautions for proper handling the tablets**.

- Wash hands before and after handling
- When the Siklos® tablet is broken, avoid touching the broken face. Handle the tablets away from food, on a surface such as a damp disposable towel which must be discarded after handling.

A warning recommending careful handling because of cytotoxicity was added to the package leaflet and is displayed on the immediate packaging bottle.

2 Warnings about the risks associated with using Siklos®

Hydroxycarbamide is also an antineoplastic agent and some risks have been observed for this pharmacotherapeutic group.

2.1 Teratogenicity and fertility

✔ **Women of childbearing potential/Contraception in males and females:** Hydroxycarbamide has been described as teratogenic in animals.
Appropriate contraception must be strongly advised to women of childbearing potential when treatment with Siklos® is initiated.

The need for contraception during treatment must be understood clearly by the patients.

If the male or female patient wishes to have children, the treatment must be discontinued, if possible, 3 to 6 months before the pregnancy.

If the patient is pregnant during treatment with Siklos®, she must be informed of the potential risk to the fœtus. Careful follow-up should be planned, including appropriate clinical examinations, laboratory tests and ultrasound scans.

Hydroxycarbamide is excreted in human milk. Because of the potential for adverse reactions in infants, breastfeeding must be discontinued while taking Siklos®.

✔ **Fertility in males:**

Sickle cell disease can affect sperm quality and quantity. Such cases with hydroxycarbamide have been reported with varying degrees of reversibility.

After providing the patient with information, the doctor may suggest sperm cryopreservation before starting the treatment.

2.2 Haematological toxicity

Bone marrow suppression is the most common adverse effect associated with hydroxycarbamide. It is accompanied most often by neutropenia, reticulocytopenia and macrocytosis. This is the reason why regular monitoring of blood counts is required during treatment with Siklos®.

Management of haematological toxicity:
Myelotoxicity may be characterized by the following blood test results:

- Neutrophils < 2,000 /mm^3
- Platelets < 80,000 /mm^3
- Haemoglobin < 4.5 g/dL
- Reticulocytes < 80,000 /mm^3 if the haemoglobin concentration is < 9 g/dl

- If blood counts are within the toxic range **Siklos® should be temporarily discontinued until blood counts recover**.
- Haematology recovery usually occurs within two weeks. Treatment may then be reinstituted at a reduced dose. The dose of Siklos® may then be increased again under close haematological monitoring.
- A dose producing haematological toxicity should not be attempted more than twice.

2.3 Leg ulcers

Leg ulcers are a common complication of sickle cell disease, but have also been reported in patients treated with hydroxycarbamide.

In patients with a **history of or an active leg ulcer**, Siklos® should be used with caution.

2.4 Long-term toxicity

Hydroxycarbamide is considered to be carcinogenic in various species. Some cases of acute concomitant leukaemia have been reported in patients receiving long-term treatment with hydroxycarbamide for myeloproliferative diseases or for the treatment of sickle cell disease. It is not clear whether this leukaemogenic effect is secondary to hydroxycarbamide or to the patient's condition.

3 Follow-up of patients treated with Siklos®

3.1 Haematological follow-up

The haematological toxicity of hydroxycarbamide requires close monitoring of haematological status.
Blood counts including a reticulocyte count must be carried out periodically:

- **Prior to treatment**
- **During treatment:**
  - every two weeks for the first 2 months,
  - every 2 months for patients who are stable on doses below 30 mg/kg. If the daily dosage of hydroxycarbamide reaches 35 mg/kg (exceptional dose), blood counts should be continued every two weeks.

3.2 Growth monitoring in children

Sickle cell disease may adversely affect height and weight gain in children and adolescents with the condition. Continuous monitoring of height and weight gain is recommended in children and adolescents treated with Siklos®.

3.3 Management of the adverse effects of treatment with Siklos®

The table below summarizes the adverse effects most frequently reported during treatment with Siklos®.
An assessment of the risks and benefits should be carried out whenever any adverse effect occurs.

✔ **Reporting of suspected adverse reactions:**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions :
HPRA Pharmacovigilance, Earlsfort Terrace IRL - Dublin 2 - Tel: +353 1 6764971 - Fax: +353 1 6762517 - Website: www.hpra.ie, e-mail: medsafety@hpra.ie.

Adverse events most frequently reported during treatment with Siklos®

Side effect	Frequency	Management
Bone marrow suppression including neutropenia (< 2.0 x 10^9/l), **Reticulocytopenia** (< 80 x 10^9/l)	Very common (10% below the maximum tolerated dose (MTD), 50% at MTD)	• Discontinuation until blood counts return to normal, then resume at reduced doses • Blood counts usually return to normal within two weeks of discontinuation of hydroxycarbamide • Treatment at a dose which caused haematological toxicity must not be re-attempted more than twice
Dizziness	Uncommon	• Check for a complication of sickle cell disease such as anaemia or ENT complication • Discuss discontinuation of treatment
Dry skin	Frequency not determined	• Topical care
Erythema, melanonychia, alopecia	Uncommon	• Discuss relationship with and discontinuation of treatment
Fever	Frequency not determined	• Must screen for infection
Headaches	Common	• Check for a complication of sickle cell disease such as anaemia or ENT complication
Leg ulcers	Rare	• Topical care • Prevention by local monitoring of the condition of the skin and avoidance of local injuries • Discuss dose reduction or discontinuation of treatment
Macrocytosis	Very common	• Administration of folic acid as a preventive measure
Oligospermia - azoospermia	Very common	• Consider a semen analysis for cryopreservation of sperm before starting treatment
Skin reactions (such as mouth, nail and skin pigmentation) and buccal mucositis.	Common	• Discuss discontinuation of treatment
Thrombocytopenia (< 80 x 10^9/l) **Anaemia** (haemoglobin < 4,5 g/dL)[3]	Common	• Discontinuation until blood counts return to normal, then resume at reduced doses • Treatment at a dose which caused haematological toxicity must not be re-attempted more than twice • Check for infection with parvovirus or splenic sequestration
Weight gain	Frequency not determined	• May be an effect of an improvement in the patient's general condition

4 ESCORT-HU postmarketing study

Addmedica has set up a prospective, observational European cohort study as part of the risk management plan for Siklos® and at the request of the European Medicines Agency (EMA). This study that has been ongoing since January 2009 aims at improving the knowledge of hydroxycarbamide in the population affected by sickle cell disease, notably in terms of long-term benefit. The inclusions of patients were closed in June 2017, the follow-up ended in January 2019.

For indications, contra-indications and side effects
please refer to the Summary of Product Characteristics at the end of this document.

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Any adverse event must be reported to ADDMEDICA

If you need additional hard copies of the educational materials, please fill the
on-line questionnaire available on our web site : www.addmedica.com

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