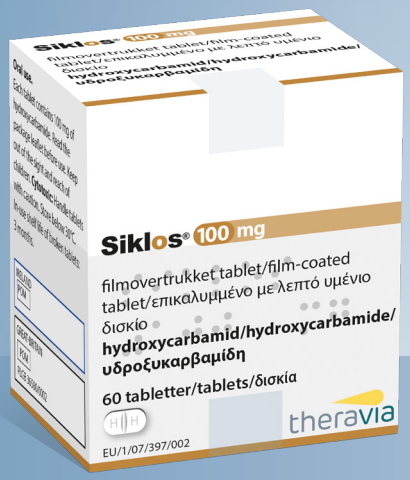
Siklos® hydroxycarbamide

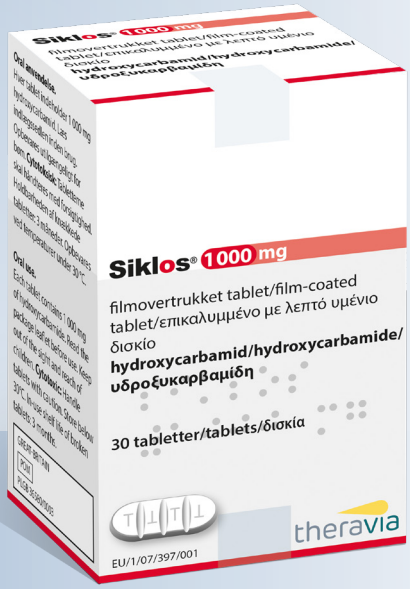
in SICKLE CELL DISEASE
Physician Guide

Siklos® 100 mg



Film-coated tablet
(bottle of 60 tablets)

Siklos® 1 000 mg



Film-coated tablet
(bottle of 30 tablets)

This educational material is key to ensure the safe and effective use of the product and appropriate management of the important selected risks. It should be read carefully before prescribing the product

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1 Indications and conditions of prescription

Siklos® (hydroxycarbamide) 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® should be administered under the supervision of a physician with experience in the treatment of sickle cell disease.

2 Administration

Siklos® should be taken **once daily** by oral route, preferably in the morning before breakfast.

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

Ensure that the patient or his carer is 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.

A guide for the patient is available displaying how to divide the tablets, how to manipulate the split tablet parts and how to administer the product.

Please provide a copy of this guide to every patient/caregiver when treatment with Siklos® is initiated.

3 Dose adjustment and combination of dose strengths

Siklos® is available in 2 strengths: 100 mg (box of 60 tablets) and 1 000 mg (box of 30 tablets):

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Siklos® 100 mg

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

Each half tablet is embossed **"H" for Hundred on one side**.

Each tablet contains 100 mg hydroxycarbamide and **can be divided into two 50 mg parts**.

Siklos® 1 000 mg

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

Each quarter of tablet is embossed **"T" for Thousand on one side.**

Each tablet contains 1 000 mg hydroxycarbamide and **can be divided into four 250 mg parts**.

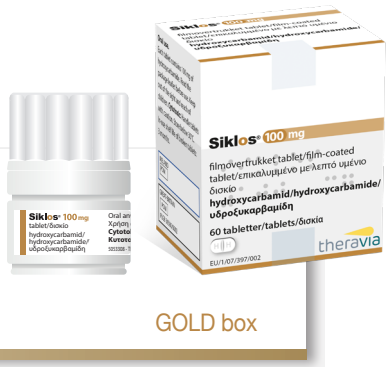
The daily dose of Siklos® can be adjusted in increments of 2.5 to 5 mg/kg/day using the 100 or the 1 000 mg tablet, or a combination of both strengths, if applicable.

A new "DOSING SHEET" has been developed and should be provided to all patients who are prescribed both strengths of Siklos simultaneously. The DOSING SHEET should be used to illustrate the prescription to the patient, to avoid any confusion between the two different strengths of Siklos and prevent accidental underdose or overdose. Please ensure that the patient/ carer understands the prescription and the differences between the two strengths. An extract from the DOSING SHEET is provided below.

Siklos® 100 mg

Each half-tablet is embossed "H" on one side

- ❑ **½** tablet: **50 mg** 
- ❑ .... entire tablet(s) of **100 mg** = ... mg 

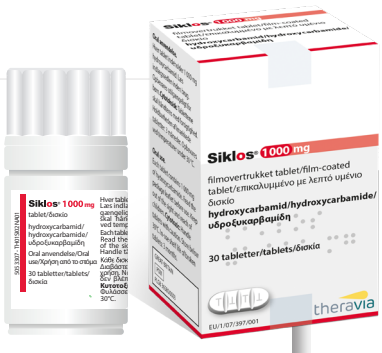


GOLD box

Siklos® 1 000 mg

Each quarter-tablet is embossed "T" on one side

- ❑ **¼** tablet: **250 mg** 
- ❑ **½** tablet: **500 mg** 
- ❑ **¾** tablet: **750 mg** 
- ❑ .... entire tablet(s) of **1 000 mg** = ... mg 



RED box

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4 Fertility - pregnancy & breastfeeding

Hydroxycarbamide is classified as antineoplastic agent and reproductive risks have been observed with this pharmacotherapeutic group.

4.1 Women of childbearing potential

Hydroxycarbamide has shown teratogenicity and embryo-toxicity in animals. Women of childbearing age receiving hydroxycarbamide should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur.

Effective contraception is strongly advised in women of childbearing potential when Siklos® is initiated.

If the patient wishes to have children, the treatment with Siklos® (in the male or the female patient) must be discontinued, if possible, 3 to 6 months before pregnancy.

If the patient or the patient's partner becomes pregnant during treatment with Siklos®:

- she must be informed of the potential risk to the foetus
- careful follow-up should be planned, including appropriate clinical examinations, laboratory tests and ultrasound scans.

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

4.2 Male fertility

Fertility in males might be affected by treatment. Sickle cell disease can affect sperm quality and quantity. Deleterious effects on sperm cells have also been reported with hydroxycarbamide, with varying degrees of reversibility (please refer to SmPC for further information).

After providing the patient with this information, sperm cryopreservation may be suggested before starting the treatment.

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5 Management of adverse drug reactions

The table below summarizes some recommendations for the management of adverse effects reported during treatment with Siklos®. An assessment of the risks and benefits should be carried out whenever adverse reactions occur.

Recommendations for the management of some adverse drug reactions with known frequency

Side effect	Frequency	Management
Bone marrow suppression including neutropenia (< 1.5 x 10^9/l), Reticulocytopenia (< 80 x 10^9/l)	Very common	• The effective dose may be the maximal tolerated dose • 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 attempted more than twice • In case of anaemia, check for infection with Parvovirus infection, splenic or hepatic sequestration, renal impairment
Thrombocytopenia (< 80 x 10^9/l) Anaemia (haemo-globin < 4.5 g/dl)	Common	
Dizziness	Uncommon	• Check for a complication of sickle cell disease such as anaemia or ENT complication • Discuss discontinuation of treatment
Erythema, melanonychia, alopecia	Uncommon	• Discuss relationship with the treatment and discontinuation of treatment
Headaches	Common	• Check for a complication of sickle cell disease such as anaemia or ENT complication
Leg ulcers	Rare	• In case of history of leg ulcer, initiate with caution • Topical care • Prevention by surveillance of skin condition 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 and cryopreservation before starting treatment
Skin reactions (such as mouth, nail and skin pigmentation) and buccal mucositis	Common	• Discuss discontinuation of treatment

For the full list of adverse reactions, please refer to the Summary of Product Characteristics available at the following address: https://siklos.eu/ir/ and on the EMA website: https://www.ema.europa.eu/documents/product-information/siklos-eparproduct-information_en.pdf.

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Reporting suspected adverse reactions after authorization 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 via the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

For further information, please contact:
Theravia
Tel.: +353(0)1 69 50 063
E-mail: pv-ie@theravia.com

If you need additional hard copies of the educational materials, please fill in the online questionnaire available on our web site:
https://siklos.eu/ir/

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