7.2 Concomitant Use of Live Virus Vaccine

Concomitant use of SIKLOS with a live virus vaccine may potentiate the replication of the vaccine virus and/or may increase the adverse reactions of the vaccine virus, because normal defense mechanisms may be suppressed by SIKLOS therapy. Vaccination with a live vaccine in a patient taking SIKLOS may result in severe infections. Generally, the patient's antibody response to vaccines may be decreased. Treatment with SIKLOS and concomitant immunization with live virus vaccines should only be performed if benefits clearly outweigh potential risks. Consider consultation with a specialist.

7.3 Test Interference

Interference with Uric Acid, Urea, or Lactic Acid Assays

Studies have shown that there is an analytical interference of SIKLOS with the enzymes (urease, uricase, and lactate dehydrogenase) used in the determination of urea, uric acid, and lactic acid, rendering falsely elevated results of these in patients treated with SIKLOS.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

SIKLOS can cause fetal harm based on findings from animal studies and the drug's mechanism of action *[see Clinical Pharmacology (12.1)]*. There are no studies with the use of SIKLOS in pregnant women, and limited available data on SIKLOS use during pregnancy are insufficient to inform drug-associated risks. Drugs which affect DNA synthesis, such as hydroxyurea, may be potential mutagenic agents. In animal reproduction studies, administration of hydroxyurea to pregnant rats and rabbits during organogenesis produced embryotoxic and teratogenic effects at doses 0.8 times and 0.3 times, respectively, the maximum recommended human daily dose on a mg/m^2 basis. In rats and rabbits, fetal malformations were observed with partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, and missing lumbar vertebrae. Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays *(see Data)*. Advise pregnant women of the potential risk to a fetus *(see Clinical Considerations).*

Background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Although the data on a limited number of exposed pregnancies indicate no adverse effects on pregnancy or on the health of the fetus/newborn, patients on SIKLOS should be made aware of the potential risks to the fetus.

Based on the limited amount of available information, in case of an exposure to SIKLOS of pregnant female patients or pregnant partners of male patients, treated by SIKLOS, a careful follow-up with adequate clinical, biological and ultrasonographic examinations should be considered.

Data

Human Data

According to a retrospective analysis of a cohort of 123 adult patients treated with hydroxyurea, twenty-three pregnancies have been reported from 15 women treated with hydroxyurea and partners of 3 men not using barrier contraception treated with hydroxyurea. Most (61%) had no adverse developmental

outcomes. In the other cases with known evolution, pregnancy had been interrupted either voluntarily or upon medical advice.

In retrospective cohorts of 352 children and adolescents with sickle cell disease older than 2 years treated with hydroxyurea for a period of up to 12 years, 3 pregnancies under hydroxyurea were reported with no adverse developmental outcomes.
From post-marketing data of SIKLOS, 3 pregnancies have been reported while the father was treated with SIKLOS and 16 pregnancies have been reported in 15 females treated with SIKLOS. Among the 13 cases with known evolution, 5 pregnancies had no adverse developmental outcomes, 4 led to premature birth, and 4 were early terminated.

Animal Data
Hydroxyurea has been demonstrated to be a potent teratogen in a wide variety of animal models, including mice, hamsters, cats, miniature swine, dogs, and monkeys at doses within 1-fold of the human dose given on a mg/m^2 basis. Hydroxyurea is embryotoxic and causes fetal malformations (partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, missing lumbar vertebrae) at 180 mg/kg/day (about 0.8 times the maximum recommended human daily dose on a mg/m^2 basis) in rats and at 30 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/m^2 basis) in rabbits. Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. Hydroxyurea crosses the placenta. Single doses of ≥375 mg/kg (about 1.7 times the maximum recommended human daily dose on a mg/m^2 basis) to rats caused growth retardation and impaired learning ability.

8.2 Lactation
Risk Summary
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.

8.3 Females and Males of Reproductive Potential
Pregnancy Testing
SIKLOS can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.
Verify the pregnancy status of females of reproductive potential prior to initiating SIKLOS therapy.

Contraception
Females

Advise females of reproductive potential to use effective contraception during and after treatment with SIKLOS for at least 6 months after therapy. Advise females to immediately report pregnancy.

Males
SIKLOS may damage spermatozoa and testicular tissue, resulting in possible genetic abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during and after treatment with SIKLOS for at least 6 months after therapy *[see Nonclinical Toxicology (13.1)]*.

Infertility
Males

Based on findings in animals and humans, male fertility may be compromised by treatment with SIKLOS. Azoospermia or oligospermia, sometimes reversible, has been observed in men. Before the start of

therapy, inform male patients about the possibility of sperm conservation *[see Adverse Reactions (6) and Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of SIKLOS have been established in pediatric patients aged 2-18 years with sickle cell anemia with recurrent moderate to severe painful crises. Use of SIKLOS in these age groups is supported by evidence from a non-interventional cohort study, the European Sickle Cell Disease prospective Cohort study, ESCORT-HU, in which 405 pediatric patients ages 2 to <18 were enrolled. Among the 405 pediatric patients treated with SIKLOS, 274 were children (2-11) and 108 were adolescents (12-16) *[see Clinical Studies (14)]*.

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.

8.6 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 *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Monitor hematologic parameters more frequently in patients with hepatic impairment receiving SIKLOS.

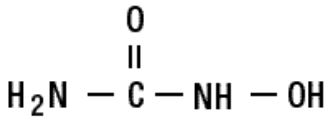
10 OVERDOSAGE

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. In patients with sickle cell anemia, neutropenia was reported in isolated cases of hydroxyurea overdose (1.43 times and 8.57 times of the maximum recommended dose of 35 mg/kg b.w./day). Monitor blood counts weekly until recovery. Treatment of overdose consists of gastric lavage, followed by symptomatic treatment and control of bone marrow function.

11 DESCRIPTION

SIKLOS (hydroxyurea) is an antimetabolite that is available for oral use as functionally scored 100 mg film-coated tablet and functionally triple-scored 1,000 mg film-coated tablet containing 100 and 1,000 mg of hydroxyurea, respectively. Inactive ingredients include silicified microcrystalline cellulose, sodium stearyl fumarate, and film-coating agent amino methacrylate copolymer.

Hydroxyurea is a white crystalline powder. It has a molecular weight of 76.05. Its structural formula is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which hydroxyurea produces its cytotoxic and cytoreductive effects is not known. However, various studies support the hypothesis that hydroxyurea causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or of protein.

The mechanisms by which SIKLOS produces its beneficial effects in patients with sickle cell Anemia (SCA) are uncertain. Known pharmacologic effects of SIKLOS that may contribute to its beneficial effects include increasing hemoglobin F levels in red blood cells (RBCs), decreasing neutrophils, increasing the water content of RBCs, increasing deformability of sickled cells, and altering the adhesion of RBCs to endothelium.

12.2 Pharmacodynamics

The correlation between hydroxyurea concentrations, reduction of crisis rate, and increase in HbF, is not known.

12.3 Pharmacokinetics

Mean peak plasma concentrations and AUCs increase more than proportionally with increase of dose. There is no drug accumulation upon once daily dosing of hydroxyurea.

Absorption

Following oral administration, hydroxyurea reaches peak plasma concentrations in 1 to 4 hours. The oral bioavailability of hydroxyurea was reported to be 85 -100%.

Effect of Food

There are no data on the effect of food on the absorption of hydroxyurea.

Distribution

Hydroxyurea distributes throughout the body with a volume of distribution approximating total body water. Hydroxyurea concentrates in leukocytes and erythrocytes.

Elimination

Half-life of hydroxyurea is about 2-4 hours.

Metabolism

Up to 60% of an oral dose undergoes conversion through saturable hepatic metabolism and a minor pathway of degradation by urease found in intestinal bacteria.

Excretion

The percentage of the dose excreted in urine was approximately 40% in pediatric patients with sickle cell anemia.

Specific Populations

Patients with Renal Impairment

The effect of renal impairment on the pharmacokinetics of hydroxyurea was assessed in adult patients with sickle cell anemia and renal impairment. Patients with normal renal function (creatinine clearance [CrCl] >80 mL/min), mild (CrCl 50-80 mL/min), moderate (CrCl =30-<50 mL/min), or severe (<30 mL/min) renal impairment received a single oral dose of 15 mg/kg hydroxyurea. Creatinine clearance values were obtained using 24-hour urine collections. Patients with ESRD received two doses of 15 mg/kg separated by 7 days; the first was given following a 4-hour hemodialysis session, the second prior to hemodialysis. The exposure to hydroxyurea (mean AUC) in patients with CrCl <60 mL/min and those with ESRD was 64% higher than in patients with normal renal function (CrCl >60 mL/min). Reduce the dose of SIKLOS when it is administered to patients with creatinine clearance of <60 mL/min or with ESRD following hemodialysis *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

Patients with Hepatic impairment

There are no data that support specific guidance for dose adjustment in patients with hepatic impairment.

Pediatric Patients

The pharmacokinetics of hydroxyurea is similar between children (4 to 17 years) and adults.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Conventional long-term studies to evaluate the carcinogenic potential of hydroxyurea have not been performed. However, hydroxyurea is presumed to be a transspecies carcinogen. Intraperitoneal administration of 125 to 250 mg/kg hydroxyurea (about 0.6-1.2 times the maximum recommended human oral daily dose on a mg/m^2 basis) thrice weekly for 6 months to female rats increased the incidence of mammary tumors in rats surviving to 18 months compared to control. Hydroxyurea is mutagenic *in vitro* to bacteria, fungi, protozoa, and mammalian cells. Hydroxyurea is clastogenic *in vitro* (hamster cells, human lymphoblasts) and *in vivo* (SCE assay in rodents, mouse micronucleus assay). Hydroxyurea causes the transformation of rodent embryo cells to a tumorigenic phenotype *[see Warnings and Precautions (5.2, 5.3)]*.

Hydroxyurea administered to male rats at 60 mg/kg /day (about 0.3 times the maximum recommended human daily dose on a mg/m^2 basis) produced testicular atrophy, decreased spermatogenesis and significantly reduced their ability to impregnate females *[see Use in Specific Populations (8.3)]*.

14 CLINICAL STUDIES

Pediatric Patients with Sickle Cell Disease

The efficacy of SIKLOS was assessed in the European Sickle Cell Disease Cohort study (ESCORT HU) [NCT02516579]. This is an open-label single-arm study of 405 pediatric patients with sickle cell disease from 2-18 years of age, of which 141 had not been previously treated with hydroxyurea prior to enrollment. Evaluable patients had at least 12 months follow-up (median [range] 23 months [12,80]). Median (range) hemoglobin F percentages were 5.6% (1.3, 15.0) at baseline and 12.8% (2.1, 37.2) at least 6 months (the value closest to 6 months collected between 5 and 14 months) after initiation of SIKLOS treatment, with median (range) change of 5.9% (-2.2, 34.7) in 47 patients. Median (range) hemoglobin levels were 8.2 g/dL (3.7, 14.2) at baseline, 8.8 g/dL (0.7, 13.1) at 6 months (the value closest to 6 months collected between 5 and 7 months), and 8.9 g/dL (5.5, 13.2) at 12 months (the value closest to 12 months collected between 10 and 14 months) after initiation of SIKLOS treatment. The median (range) change

was 0.5 g/dL (-4.6, 6.1) in 63 patients at 6 months (the post-baseline value closest to 6 months collected between 5 and 7 months) and 0.7 g/dL (-6.4, 6.0) in 83 patients at 12 months (the post-baseline value closest to 12 months collected between 10 and 14 months) after initiation of SIKLOS treatment.

Among pediatric patients not previously treated with hydroxyurea prior to enrollment and analyzable for efficacy (N=141), the percentage of patients with at least one vaso-occlusive episode, one episode of acute chest syndrome, one hospitalization due to SCD or one blood transfusion decreased after 12 months of SIKLOS treatment (Table 4).

Table 4: Comparison of SCD Events in the First Year of Treatment with SIKLOS with SCD Events in the 12 Months Prior to Enrollment – ESCORT HU Trial (N=141) in Pediatric Patients

SCD events	Patients under 18 years old previously not treated with hydroxyurea with at least 12 months follow-up data available for clinical efficacy (N=141)		
	In the 12 months prior to enrolment	After 12 months of Siklos® treatment	Change
Number of patients with at least one vaso-occlusive episode (in 120 evaluable patients)			
No	37 (31%)	69 (57.5%)	
Yes	83 (69%)	51 (42.5%)	
Number of vasoocclusive episodes over 12 months (in 113 evaluable patients)			
Median (range)	2 (0, 1)	0 (0.0, 7.0)	-1 (-10.0, 5.0)
Number of patients with at least one episode of acute chest syndrome (in 123 evaluable patients)			
No	94 (76%)	116 (94%)	
Yes	29 (24%)	7 (6%)	
Number of episodes of acute chest syndrome over 12 months (in 123 evaluable patients)			
Median (range)	0 (0.0, 2.0)	0 (0.0, 1.0)	0 (-2.0, 1.0)
Number of patients with at least one hospitalization related to SCD (in 110 evaluable patients)			
No	27 (25%)	64 (58%)	
Yes	83 (75%)	46 (42%)	
Number of hospitalizations related to SCD over 12 months (in 106 evaluable patients)			
Median (range)	2 (0.0, 6.0)	0 (0.0, 7.0)	-1 (-6.0, 6.0)
Number of days of hospitalizations related to SCD over 12 months (in 100 evaluable patients)			
Median (range)	8 (0.0, 58.0)	0 (0.0, 100.0)	-3 (-58.0, 86.0)
Number of patients with at least one blood transfusion (in 122 evaluable patients)			
No	66 (54%)	94 (77%)	
Yes	56 (46%)	28 (23%)	

Adult Patients with Sickle Cell Disease

In ESCORT-HU 1077 adult patients were included of which 436 patients were naïve to HU treatment. There were 370 evaluable patients who had at least 12 months follow-up (Median [range] 41 months [29, 54].

Median (range) hemoglobin F percentages were 5.2% (0.2, 30.9) at baseline and 14.2% (0.5, 41.5) at least 6 months (the value closest to 6 months collected between 5 and 14 months) after initiation of SIKLOS treatment, with a median (range) change of 8% (-8.0, 33.3) in 181 patients. Among adult patients previously not treated with hydroxyurea prior to enrollment and analyzable for efficacy (N=370), the incidence and number of vaso-occlusive events, hospitalizations, acute chest syndrome and blood transfusions in the 12 month period before treatment and after initiation of treatment decreased after 12 months of SIKLOS treatment. Table 5 provides the efficacy results for ESCORT-HU.

Table 5: Comparison of SCD Events in the First Year of Treatment with SIKLOS with SCD Events in the 12 Months Prior to Enrollment – ESCORT HU Trial (N=370) in Adult Patients

SCD events	Adult Patients previously not treated with hydroxyurea with at least 12 months follow-up data available for clinical efficacy (N=369)		
	In the 12 months prior to enrolment	After 12 months of Siklos® treatment	Change
Number of patients with at least one vaso-occlusive episode (in 367 evaluable patients)			
No	133 (36.2%)	226 (61.6%)	
Yes	234 (63.8%)	141 (38.4%)	
Number of vasoocclusive episodes over 12 months (in 343 evaluable patients)			
Median (range)	1.0 (0.0, 20.0)	0.0 (0.0, 30.0)	0.0 (-20.0, 24.0)
Number of patients with at least one episode of acute chest syndrome (in 365 evaluable patients)			
No	273 (74.8%)	338 (92.6%)	
Yes	92 (25.2%)	27 (7.4%)	
Number of episodes of acute chest syndrome over 12 months (in 364 evaluable patients)			
Median (range)	1.0 (0.0, 5.0)	0.0 (0.0, 3.0)	0.0 (-5.0 ; 2.0)
Number of patients with at least one hospitalization related to SCD (in 366 evaluable patients)			
No	152 (41.5%)	252 (68.9%)	
Yes	214 (58.5%)	114 (31.1%)	
Number of hospitalizations related to SCD over 12 months (in 360 evaluable patients)			
Median (range)	1 (0.0, 15.0)	0 (0.0, 10.0)	0 (-15.0, 8.0)
Number of days of hospitalizations related to SCD over 12 months (in 313 evaluable patients)			
Median (range)	2 (0.0, 90.0)	0 (0.0, 77.0)	0 (-90.0, 57.0)
Number of patients with at least one blood transfusion (in 365 evaluable patients)			
No	207 (56.7%)	296 (81.1%)	
Yes	158 (43.3%)	69 (18.9%)	

15 REFERENCES

OSHA Hazardous Drugs. OSHA.http://www.osha.gov/SLTC/hazardousdrugs/index.html.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

SIKLOS (hydroxyurea) film-coated tablet is supplied in high density polyethylene (HDPE) bottle with polypropylene child-resistant cap with a desiccant unit containing 30 (SIKLOS 1,000 mg) or 60 (SIKLOS 100 mg) film coated tablets. Each bottle containing SIKLOS 100 mg tablets or SIKLOS 1000 mg tablets is supplied in a carton.

SIKLOS is supplied in the following strengths:
- 100 mg off-white, capsule-shaped, film-coated, functionally scored tablet with scoring on both sides which can be divided into two equal parts, each part is debossed with “H” on one side.
- 1,000 mg off-white, capsule-shaped, film-coated, functionally triple-scored tablet with scoring on both sides which can be divided into four equal parts, each part is debossed with “T” on one side.

	Bottles of 30	Bottles of 60
100 mg	N/A	NDC 71770-105-60
1,000 mg	NDC 71770-120-30	N/A

16.2 Storage
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Keep tightly closed.
Broken tablets must be stored in the bottle and must be used within three months.

16.3 Handling and Disposal
SIKLOS is a cytotoxic drug. Follow applicable special handling and disposal procedures *[see References (15)]*.
To decrease the risk of contact, advise caregivers to wear disposable gloves when handling SIKLOS or bottles containing SIKLOS. Wash hands with soap and water before and after contact with the bottle or tablets when handling SIKLOS. Avoid exposure to crushed tablets. If contact with crushed tablets occurs on the skin, wash affected area immediately and thoroughly with soap and water. If contact with crushed tablets occurs on the eye(s), the affected area should be flushed thoroughly with water or isotonic eyewash designated for that purpose for at least 15 minutes.

Powder spilled from the broken tablet should be wiped up with a damp disposable towel which must be thrown away in a closed container such as a plastic bag to avoid ingestion of powder by other people. The spill areas should then be cleaned using a detergent solution followed by clean water.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Instructions for Use and Medication Guide).

- There is a risk of myelosuppression. Emphasize the importance of monitoring blood counts every two weeks throughout the duration of therapy to patients taking SIKLOS *[see Warnings and Precautions (5.1)]*. Advise patients to report signs and symptoms of infection or bleeding immediately.
- Advise patients that there is a risk of cutaneous vasculitic toxicities and secondary malignancies including leukemia. Advise use of sun protection *[see Warnings and Precautions (5.1)]*.
- Advise females of reproductive potential of the potential risk to a fetus should they become pregnant while taking SIKLOS. 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 *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)]*.
- Advise females to discontinue breastfeeding during treatment with SIKLOS *[see Use in Specific Populations (8.2)]*.
- Advise male patients of potential risk to fertility *[see Use in Specific Populations (8.3)]*.
- Advise patients with HIV infection to contact their physician for signs and symptoms of pancreatitis, hepatic events, and peripheral neuropathy *[see Warnings and Precautions (5.5)]*.
- Advise patients of the risk of hemolytic anemia. Advise patients that they will have blood tests to evaluate for this if they develop persistent anemia not related to sickle cell anemia *[see Warnings and Precautions (5.9)]*.
- Because SIKLOS tablets are scored, advise patients on how to take SIKLOS properly.

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Manufactured for Addmedica: 37 rue de Caumartin 75009 Paris France
Manufactured by: Delpharm Lille, 22 rue de Toufflers 59452 Lys Lez Lannoy France

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MEDICATION GUIDE

SIKLOS (See – k – los)

(hydroxyurea)

tablets

What is the most important information I should know about SIKLOS?

SIKLOS can cause serious side effects including:

- **Low blood cell counts are common with SIKLOS, including low red blood cells, white blood cells, and platelets, and can be severe and life-threatening. If your white blood cell count becomes very low, you are at increased risk for infection.** Your healthcare provider will check your blood cell counts before and every 2 weeks during treatment with SIKLOS. Your healthcare provider may change your dose or tell you to stop taking SIKLOS if you have low blood cell counts. Tell your healthcare provider right away if you get any of the following symptoms:
  - fever or chills
  - body aches
  - feeling very tired
  - shortness of breath
  - unusual headache
  - bleeding or unexplained bruising
- **Cancer.** Some people have developed cancer, such as leukemia and skin cancer, after taking SIKLOS for a long time. Your healthcare provider will check you for cancer. You should protect your skin from the sun using sunblock, hats, and sun-protective clothing.
- **SIKLOS can harm your unborn baby.**

  For females taking SIKLOS who can become pregnant:
  - You should talk with your healthcare provider about the risks of SIKLOS to your unborn baby.
  - You should use effective birth control during treatment with SIKLOS and for at least 6 months after treatment with SIKLOS.
  - Your healthcare provider will perform a pregnancy test before you start treatment with SIKLOS. Tell your healthcare provider right away if you become pregnant or think you may be pregnant.

  For males taking SIKLOS: SIKLOS can affect your sperm. If you have a female sexual partner who can become pregnant, you should use effective birth control during treatment with SIKLOS and for at least 6 months after treatment.

  SIKLOS may cause fertility problems in males. Talk to your healthcare provider if this is a concern for you.

See "**What are the possible side effects of SIKLOS?**" for more information about side effects.

What is SIKLOS?

SIKLOS is a prescription medicine that is used to reduce the frequency of painful crises and reduce the need for blood transfusions in adults and children, 2 years of age and older, with sickle cell anemia with recurrent moderate to severe painful crises.

It is not known if SIKLOS is safe and effective in children less than 2 years of age.

Do not take SIKLOS if you are allergic to hydroxyurea or any of the ingredients in SIKLOS. See the end of this Medication Guide for a list of the ingredients in SIKLOS.

Before taking SIKLOS, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems or are receiving hemodialysis
- have liver problems
- have human immunodeficiency virus (HIV) or take HIV medicines. **Taking SIKLOS with certain HIV medicines can cause serious reactions and may lead to death.**
- have increased levels of uric acid in your blood (hyperuricemia)
- have a history of receiving interferon therapy or are currently receiving interferon therapy
- have leg wounds or ulcers
- plan to receive any vaccinations. You should not receive "live vaccines" during treatment with SIKLOS.
- are pregnant or plan to become pregnant. See **"What is the most important information I should know about SIKLOS?**"
- are breastfeeding or plan to breastfeed. It is not known if SIKLOS can pass into your breast milk. Do not breastfeed during treatment with SIKLOS.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take SIKLOS?

Read the Instructions for Use at the end of this Medication Guide for step-by-step instructions on how to prepare a dose of SIKLOS. If you have any questions, talk to your healthcare provider or pharmacist.

- Take SIKLOS exactly as your healthcare provider tells you to take it.
- Take SIKLOS 1 time a day at the same time each day.

- Swallow the tablet(s) with a glass of water. If you are not able to swallow SIKLOS tablets, you can dissolve your prescribed dose in a small amount of water in a teaspoon and swallow right away.
- SIKLOS is supplied as 100 mg tablets and 1,000 mg tablets. The SIKLOS tablets have separation lines (score lines) and can be broken at these score lines to provide smaller doses.
  - Each 100 mg tablet can be divided into 2 equal parts (each part is 50 mg).
  - Each 1,000 mg tablet can be divided into 4 equal parts (each part is 250 mg).
- Your healthcare provider will tell you how many tablets or parts of a tablet you should take.
- SIKLOS tablets must be handled with care. To decrease the risk of exposure, you or your caregivers should do the following when handling SIKLOS:
  - Wear disposable gloves when handling SIKLOS or bottles containing SIKLOS. Wash your hands with soap and water before and after handling SIKLOS tablets or bottles containing SIKLOS.
  - Avoid contact with crushed tablets. If contact with crushed tablets happens on the skin, wash the skin area right away and thoroughly with soap and water. If contact with crushed tablets happens in the eyes, flush the eyes thoroughly with water or isotonic eyewash used for that purpose for at least 15 minutes.
  - Powder spilled from the broken tablet should be wiped up with a damp disposable towel which must be thrown away in a closed container such as a plastic bag to avoid ingestion of powder by other people. The spill areas should then be cleaned using a detergent solution followed by clean water.
- If you take too much SIKLOS, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of SIKLOS?

SIKLOS may cause serious side effects, including:

See "What is the most important information I should know about SIKLOS?"

- **Skin ulcers, including leg ulcers, and death of skin tissue (gangrene)** have happened in people who take SIKLOS. This has happened most often in people who receive interferon therapy or have a history of interferon therapy. Your healthcare provider will decrease your dose or stop treatment with SIKLOS if you develop any skin ulcers.
- **Enlarged red blood cells (macrocytosis)**. Macrocytosis is common in people who take SIKLOS and can make it difficult to detect a decrease of folic acid. Your healthcare provider may prescribe a folic acid supplement for you.
- **Hemolytic Anemia,** the fast breakdown of red blood cells, has happened in people who take SIKLOS. Tell your healthcare provider if you develop yellowing of your skin (jaundice) or blood in your urine. Your healthcare provider may do blood tests if you have persistent or worsening anemia not related to sickle cell anemia.

The most common side effects of SIKLOS in children include:

- infections
- low white blood cells

The most common side effects of SIKLOS in adults include:

- infections
- headache
- dry skin

These are not all the possible side effects of SIKLOS.

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 SIKLOS?

- Store SIKLOS at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the SIKLOS bottle tightly closed.
- Broken SIKLOS tablets must be stored in the bottle and must be used within three months.

Keep SIKLOS and all medicines out of the reach of children.

General information about the safe and effective use of SIKLOS.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SIKLOS for a condition for which it was not prescribed. Do not give SIKLOS to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about SIKLOS that is written for health professionals.

What are the ingredients of SIKLOS?

Active ingredient: hydroxyurea

Inactive ingredients: silicified microcrystalline cellulose, sodium stearyl fumarate, and film-coating agent amino methacrylate copolymer.

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Manufactured by: Delpharm Lille, 22 rue de Toufflers 59452 Lys Lez Lannoy France.

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