Summary of Risk Management Plan
For Siklos®

Active substance:	**Hydroxycarbamide**
Pharmaceutical form:	**scored film-coated tablets**
Version number of RMP summary:	**01**
Name of Marketing Authorisation Holder:	**iQone Healthcare Switzerland SA**
Date:	**23 May 2023**
Reference RMP:	**EU RMP version 01**

Disclaimer :

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Siklos® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Siklos® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. iQone Healthcare Switzerland SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of Siklos®.

Part VI: Summary of the risk management plan

Summary of risk management plan for Siklos® (hydroxycarbamide)

This is a summary of the risk management plan (RMP) for Siklos®. The RMP details important risks of Siklos®, how these risks can be minimised, and how more information will be obtained about Siklos®'s risks and uncertainties (missing information).

Siklos®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Siklos® should be used.

This summary of the RMP for Siklos® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Siklos®'s RMP.

I. The medicine and what it is used for

Siklos® is authorised for prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in adults, adolescents and children older than 2 years suffering from symptomatic Sickle Cell Syndrome. It contains hydroxycarbamide as the active substance and it is given by oral route.

Further information about the evaluation of Siklos®'s benefits can be found in Siklos®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage at the following address:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000689/human_med_001050.jsp&mid=WC0b01ac058001d124.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Siklos®, together with measures to minimise such risks and the proposed studies for learning more about Siklos®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Siklos®, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Siklos® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Siklos® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Siklos®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Summary of safety concerns	
Important identified risks	• Male fertility (spermatogenesis and spermatozoa function).
Important potential risks	• Skin ulceration and vasculitis • Effect on embryogenesis, teratogenic potential, breast-feeding and post-natal development of progeny • Malignancies (especially leukaemia) • Patients with underlying (SCD-related) hepatic or renal impairment • Handling of tablets • Medication error • Potential for off-label use • Interstitial lung disease in the SCD populations • Hyperkalemia in SCD population • Hyponatremia in SCD population
Important missing information	• Concomitant use of NARTI and other myelosuppressive agent or radiation therapy • Live vaccines

II.B Summary of important risks

Important identified risk: Male fertility	
Evidence for linking the risk to the medicine	In animal studies, hydroxycarbamide produced testicular atrophy, decreased spermatogenesis and significantly reduced their ability to impregnate females. In the academic HYDREP prospective study evaluating the effect of hydroxycarbamide (Hydrea®), on sperm count in 35 patients treated for 6 months (15-30 mg/kg/day), there was a statistical 5-fold decrease in total sperm count, with tenfold increase in the number of patients with azoospermia and cryptospermia. However, the underlying disease has also a negative impact on sperm parameters as 40% of the patients had abnormal value of total sperm count before introduction of hydroxycarbamide (Berthaut 2017). In Indian sickle-cell patients treated with low dose of hydroxycarbamide (10 mg/kg/d), 18% also developed oligospermia and 4% developed azoospermia (Sahoo 2017). However, the sperm count reverted back to normal after stoppage of hydroxycarbamide for 3 months in 73% of patients. In an Egyptian study on patients with thalassemia intermedia, there was

Important identified risk: Male fertility	
	statistically significant improvement of all sperm parameters at 6 months following discontinuation. In ESCORT-HU, 12 male patients treated with hydroxycarbamide have been able to father a child.
Risk factors and risk groups	Possibly depending on duration of treatment but less on the daily dose of hydroxycarbamide, with reversibility to be confirmed.
Risk minimisation measures	Routine risk minimisation measures: In SmPC ▪ Section 4.4 ▪ Section 4.6 ▪ Section 4.8 ▪ Section 5.3 In PL, section 4 Additional risk minimisation measures: Treatment guide for the patient and the prescriber
Additional pharmacovigilance activities	ESCORT-HU extension study

Important potential risk: Skin ulceration and vasculitis	
Evidence for linking the risk to the medicine	Case reports of leg ulcers have been reported in patients treated with non-proprietary hydroxycarbamide for sickle-cell disease. However, high grade evidence supports that hydroxycarbamide is not associated with the development of leg ulcers (Lanzkron 2008).
Risk factors and risk groups	In sickle-cell disease population, skin ulcerations had high prevalence with a wide geographical variability. In ESCORT-HU, which collected information from European population (France, Greece, Italy and Germany), In ESCORT-HU, incidence of skin ulceration (related or not to hydroxycarbamide) was 4.3% at enrolment and 4.5% during the study. The risk was lower in children than in adults (risk ratio 0.04). Incidence of skin ulceration with suspected relationship to Siklos® during the study was 1.7%, but the underlying disease could also explain the occurrence of skin ulceration in most cases.
Risk minimisation measures	Routine risk minimisation measures: In SmPC ▪ Section 4.4 ▪ Section 4.8 ▪ Section 4.9 In PL, section 2 and 4 Additional risk minimisation measures: None
Additional pharmacovigilance activities	ESCORT-HU extension study

Important potential risk: Effect on embryogenesis, teratogenic potential, breast-feeding and post-natal development of progeny

Evidence for linking the risk to the medicine	At high doses (> 500 mg/kg body weight) in rats hydroxycarbamide was embryotoxic and abnormalities were observed in the survivors (including anencephaly, cleft palate, and skeletal abnormalities). In human, The NTP-CERHR experts review (2008) concluded that there was insufficient evidence to conclude on developmental toxicity of hydroxycarbamide. In ESCORT-HU, live births were reported in 72% of the pregnancies with maternal exposure to Siklos® (excluding voluntary abortions).there was no statistical difference in the proportions of live birth in exposed and non-exposed females.
Risk factors and risk groups	Women of childbearing potential and breastfeeding women; female partners of males treated with hydroxycarbamide
Risk minimisation measures	Routine risk minimisation measures: In SmPC ▪ Section 4.3 ▪ Section 4.6 ▪ Section 5.3 In PL, section 2 and 4 A follow-up of any pregnancy in patient treated with hydroxycarbamide is carried out through pharmacovigilance activities; Additional risk minimisation measure: Treatment guide for patient and prescriber
Additional pharmacovigilance activities	ESCORT-HU extension study

Important potential risk: Malignancies (especially leukaemia)	
Evidence for linking the risk to the medicine	In patients treated with hydoxycarbamide for myeloproliferating disease, the available data do not allow concluding whether leukaemic transformation seen under hydroxycarbamide is due to a progression of the myeloproliferative process or hydroxycarbamide. In sickle-cell disease occurrence of secondary hematological /non-hematological second malignancies after hydroxycarbamide treatment in sickle-cell patients is controversial, with various results from one study to another. There is not enough evidence to support the concern of hydroxycarbamide induction of malignant disease and to estimate the risk of leukemia or other secondary malignancies in sickle-cell children. Incidence of malignancies in the ESCORT-HU study (0.7%) was comparable to previously reported literature data in adult SCD patients. One case of myelodysplastic syndrome after long-term exposure (18 years) was possibly related to Siklos®.
Risk factors and risk groups	There is a possible risk increased of some malignancies in patients with sickle cell disease especially leukaemia, lymphoma, and renal carcinoma disease according to some publications.
Risk minimisation measures	Routine risk minimisation measures: In SmPC ▪ Section 4.4 ▪ Section 4.8 ▪ Section 5.3 In PL, section 4 Additional risk minimisation measure: none
Additional pharmacovigilance activities	ESCORT-HU extension study

Important potential risk: Patients with underlying (SCD-related) hepatic or renal impairment	
Evidence for linking the risk to the medicine	In pharmacokinetic studies in sickle-cell patients with impaired renal function (creatinine clearance below 60 ml/min), retention of hydroxycarbamide was 51-64% higher than in patients with creatine clearance ≥ 60 ml/min due to an increase of its elimination rate. There is no evidence of increased toxicity in patients with sickle cell disease-related hepatic impairment.
Risk factors and risk groups	There is a potential risk of hydroxycarbamide accumulation in case of renal or hepatic impairment. Hydroxycarbamide is mainly excreted by renal pathway. Kidneys are particularly susceptible to hemoglobin S (Hb S) polymerization and red cell sickling, and chronic kidney disease, constitutes an independent risk factor for death in this population. The average age at which a patient develops renal failure is 40 years, but early manifestations of kidney damage, such as microalbuminuria, can be detected at an early age. Microalbuminuria occurs in ~42% of adult patients with HbSS SCD, although its prevalence can vary depending on age and SCD genotype. The use of hydroxycarbamide in this population is currently under investigation (SIKAMIC trial).
Risk minimisation measures	Routine risk minimisation measures: In SmPC ▪ Section 4.2 ▪ Section 4.3 ▪ Section 4.4 ▪ Section 4.8 ▪ Section 5.2: In PL, section 2 and 3 Additional risk minimisation measure: None
Additional pharmacovigilance activities	none

Important identified risk: Handling of tablets	
Evidence for linking the risk to the medicine	Siklos® is a cytotoxic medicine that must be handled with care. Any person, in particular pregnant women, who are not taking Siklos® should avoid direct contact with the parts when breaking a tablet.
Risk factors and risk groups	Patients, carers.
Risk minimisation measures	Routine risk minimisation measures: In SmPC ▪ Section 6.6 In PL, section 3 Additional risk minimisation measures: Treatment guide for the patient

Important identified risk: Medication error	
Evidence for linking the risk to the medicine	A few reports of confusion between Siklos® 100 mg and siklos® 1000 mg during administration or dispensation, in countries were both strengths are available, misunderstanding of the dosage regimen instructions, confusion between Siklos® and other non-proprietary hydroxycarbamide.

Risk factors and risk groups	Countries were both strengths are available
Risk minimisation measures	Routine risk minimisation measures: In SmPC ▪ Section 4.8 In PL, section 3 The two tablets are different in terms of colour, shape, embossing, size. Outer packaging are of different colour: Gold for Siklos® 100 mg film-coated tablets, red for Siklos® 1000 mg film-coated tablets. Additional risk minimisation measures: 1) Treatment guide for patient and prescriber 2) Dosing sheet (in countries where both strengths are available) for patients, prescribers and pharmacists 3)

Important identified risk: Potential for off label use	
Evidence for linking the risk to the medicine	Within the ESCORT-HU cohort, 21% of patients were treated with Siklos® for other subtypes or different severity grades of sickle-cell disease than the prevention of vaso-occlusive events. The most common indications were anemia, organopathy (e.g., renal impairment) and cerebrovascular disturbances. Most of these indications are supported by published clinical experience and some of them such as chronic severe anemia are recommended by US and European academic associations. Regarding the pediatric population < 2years in SCD indications, the Baby Hug trial (Wang 2011) had demonstrated a potential clinical benefit of HU on painful events, hemoglobin levels (Hb and HbF) with an acceptable safety profile.
Risk factors and risk groups	Patients with relevant condition.
Risk minimisation measures	Routine risk minimisation measures: In SmPC ▪ Section 4.1: ▪ Section 4.2: In PL, section 1 Additional risk minimisation measures: none
Additional pharmacovigilance activities	none

Important potential risk: Interstitial lung disease in SCD population	
Evidence for linking the risk to the medicine	Several cases of hydroxycarbamide-induced early-presenting acute pneumonitis (alveolitis and / or interstitial lung disease) late-onset lung disease (mostly fibrosis) reported in the medical and scientific literature in patients with various myeloproliferative disorders, although none in sickle-cell patients. The adverse effect is listed in the monographs of other hydroxycarbamide-containing products, e.g., Hydrea® indicated for myeloproliferative disorders.
Risk factors and risk groups	Not determined.
Risk minimisation measures	Routine risk minimisation measures: none Additional risk minimisation measures: none

Important potential risk: Hyperkalemia in SCD population	
Evidence for linking the risk to the medicine	A few cases reported in patients with myeloproliferative disorder in EMA pharmacovigilance database, although none in sickle-cell patients; risk included in monographs of other hydroxycarbamide-containing products, *e.g.*, Hydroxycarbamide MEDAC.
Risk factors and risk groups	Not determined
Risk minimisation measures	Routine risk minimisation measures: none Additional risk minimisation measures: none

Important potential risk: Hyponatremia in SCD population	
Evidence for linking the risk to the medicine	A few cases reported in patients with myeloproliferative disorders, glioma, rheumatoid arthritis or unknown indication, although none in sickle-cell patients.
Risk factors and risk groups	Not determined
Risk minimisation measures	Routine risk minimisation measures: none Additional risk minimisation measures: none

Missing information: Concomitant use of NARTI and other myelosuppressive agent or radiation therapy	
Risk minimisation measures	Routine risk minimisation measures: In SmPC ▪ Section 4.5 In PL, ▪ Section 4 Additional risk minimisation measure: none
Additional pharmacovigilance activities	none

Missing information: Live vaccines	
Risk minimisation measures	Routine risk minimisation measures: In SmPC ▪ Section 4.5 In PL, ▪ Section 4 Additional risk minimisation measure: none
Additional pharmacovigilance activities	none

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Siklos®.

II.C.2 Other studies in post-authorisation development plan

ESCORT-HU extension

As part of the Siklos® Risk Management Plan, a first study named ESCORT-HU evaluating the use of Siklos® in real-life conditions was completed and confirmed the safety profile of Siklos®. However, long-term follow-up data are lacking, especially on risks which are poorly documented or unknown. The ESCORT-HU Extension study aims at evaluating the long-term safety of Siklos® when used in current practice in adults and paediatric patients treated with Siklos® and followed for up to 5 years. The study population will include male or female patients, aged ≥2 years old, with symptomatic SCD, treated with Siklos®.