Product Name	Rydapt® (Midostaurin - PKC412)
Active substance	Rydapt® (Midostaurin - PKC412) soft gelatin capsules of 25 mg
Indication and conditions of use	Compassionate Use Program with Midostaurin for newly diagnosed FLT3 mutated acute myeloid leukemia patients eligible for standard induction and consolidation chemotherapy. Posology of Midostaurin 1) Induction (1-2 cycles; 28 day cycles): Midostaurin 50 mg (two 25 mg capsules) twice a day on days 8-21. 2.) Consolidation (4 cycles; 28 day cycles): Midostaurin 50 mg (two 25 mg capsules) twice a day on days 8-21. 3) Maintenance (12 cycles; 28 day cycles): 50 mg (two 25 mg capsules) by mouth twice a day, for 12 cycles or until relapse, unacceptable toxicity, or death
Conditions, delays and further rules for participation of patients	**Inclusion Criteria:** 1. Patient cannot be satisfactorily treated with the approved and commercially available alternative treatment options (including transplantation), in accordance with clinical guidelines. Patient is eligible for standard induction and consolidation therapy in accordance with clinical guidelines and therapeutic advantage with positive benefit/risk is expected in the judgment of the treating physician from adding midostaurin to standard induction therapy with cytarabine and daunorubicin (or idarubicin) followed by cytarabine consolidation. Patients who undergo SCT will be midostaurin discontinued prior to conditioning for transplantation, and will be removed from the treatment plan protocol 2. Patients must be 18 years of age or older; elderly patients must be fit to receive intensive induction and consolidation chemotherapy 3. Patients must have a documented unequivocal diagnosis of AML according to WHO 2008 classification (>20% blasts in the bone marrow and/or peripheral blood), excluding M3 (acute promyelocytic leukemia). Secondary AML patients are eligible, e.g. AML patients with antecedent history of treatment for a prior malignancy. 4. Patients must have a documented FLT3 mutation (ITD or TKD) using a validated test 5. Patients must have an ECOG Performance Status of ≤ 3 6. Patients requiring intrathecal chemotherapy must have a minimum washout of 48 hours prior to the first dose of midostaurin 7. AML patients with a history of antecedent treatment for myelodysplasia (MDS) remain eligible for treatment on Midostaurin CUP. (E.g. azacitidine or decitabine must have been discontinued for a period of at least 30 days or 5 half-lives of the drug, whichever is

longer, before Midostaurin can be administered).

8. Patients must have the following laboratory values:
   - Direct Bilirubin ≤ 2.5 x ULN
   - Serum Creatinine ≤ 2.5 x ULN
9. Patient is not eligible for any ongoing Midostaurin Clinical Study and/or a clinical trial running in the indication of this CUP
10. Patients must be able to swallow capsules
11. Patient must enroll prior to completion of cycle 2 of the consolidation chemotherapy

Exclusion Criteria:

1. History of hypersensitivity to any drugs (midostaurin, cytarabine, daunorubicin or idarubicin) or metabolites of similar chemical classes as the IMP or any other known contra-indication for cytarabine, daunorubicin (or idarubicin) treatment, according to the relevant SPC.
2. Prior therapy for AML with the following exceptions:
   - emergency leukapheresis
   - emergency treatment for hyperleukocytosis with hydroxyurea for ≤ 7 days
   - cranial RT for CNS leukostasis (one dose only)
   - growth factor/cytokine support
3. Patients with LVEF less than 45% (by echocardiogram or MUGA) or symptomatic congestive heart failure, Class III or IV according to New York Heart Association (NYHA) classification; patients myocardial infection or unstable angina within the past 6 months
4. Patients with any uncontrolled illness, including, but not limited to, acute or chronic pancreatitis or uncontrolled infection
5. QTc ≥470 msec on screening ECG.
6. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they are using two birth control methods during dosing and for 4 months after stopping medication. Women of child-bearing potential must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control – one highly effective method (e.g., IUD, hormonal, tubal ligation, or partner's vasectomy),and one additional effective method (e.g., latex condom, diaphragm, or cervical cap) - AT THE SAME TIME. Reliable contraception should be maintained throughout the period of treatment and for 3 months after treatment discontinuation.

   Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e age appropriate, history of vasomotor symptoms) or have had surgical bilateral

	oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. 7. Sexually active males unless they use a condom during intercourse while taking drug and for 4 months after stopping midostaurin medication. They should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. 8. Participation in a prior investigational study within 30 days prior to enrollment or within 5 half-lives of the investigational product, whichever is longer. 9. Not able to understand and to comply with treatment instructions and requirements. **Rules for participation** 1. For submission of a request, the following steps have to be taken: - An unsolicited request form to be completed by the treating physician for individual patient supply including a written motivation by the treating physician to enroll the patient within this program. - A signed physician declaration form including the request for an individual patient supply with a written motivation by the treating physician to enroll the patient within this program, and including the fact that the treating physician is personally responsible for the use of the compassionate use medication, that the patient will be informed in a clear and complete manner and sign the informed consent form accordingly and that the physician is committed to report (S)AEs as outlined in the protocol. - A signed protocol signature page to confirm that the physician is trained on the protocol by reading it carefully. - Treating Physician ICF Attestation Form: to be signed to confirm compliance with Novartis ICF requirements following enrollment of patient(s). 2. The unsolicited request form, the physician declaration form, the protocol signature page and the ICF attestation form have to be sent to Novartis Pharma Belgium (by fax on 02/246 18 73). 3. Internal evaluation of the request by Novartis Pharma Belgium The total duration between initial application and delivery of the medication will be approximately 7 working days due to the internal approval procedure. During this procedure, the responsible physician of the medical department of Novartis Belgium gives a reasoned advice on whether the patient can be included in this program. According to the internal Novartis procedures, the opinion of the medical director of Novartis Global responsible for Midostaurin is asked as well. Based on the reasoned advice of the responsible physician, the responsible of the program will make Midostaurin available for sending to the

	treating physician.
Duration of the program	Midostaurin will be provided free of charge by Novartis Pharma on an individual patient basis following the criteria stated in this program from the set-up of the Compassionate Use Program until the product will be commercially available in Belgium in the envisaged indication or until, in the clinical judgement of the treating physician, the patient is no longer benefiting from continuation of the treatment, whichever is sooner. . Novartis Pharma can end this program at any time. Inclusion in this program will end when drug reimbursement is obtained or when Novartis Pharma decides to discontinue this program in case of reimbursement refusal for this indication or in the light of newly emerged scientific data. Patients who are included in this program until that time and do not meet reimbursement criteria or in case when drug reimbursement is not obtained will be further treated with Midostaurin according to the protocol. The treating physician can also decide according to his clinical judgment to discontinue treatment, if the patient is no longer benefiting from continuation of the treatment. The patient can also decide at any time to end his participation.
Conditions of distribution	The medication is sent to the hospital pharmacy of the hospital of the treating physician.
Responsible of the program	**Responsible for the program** Dr. Wim Pluymers, PhD Therapeutic Area Head Hematology Medialaan 40 bus 1 B-1800 Vilvoorde Belgium Tel: +32 2 246 16 95 Wim.pluymers@novartis.com **Responsible physician for this program** Dr. Jan D'Haeyer, MD Medical Director Novartis Oncology Medialaan 40 bus 1 B-1800 Vilvoorde Belgium Tel: +32 (0)2 246 1611 jan.dhaeyer@novartis.com **Persons available for questions** Wim Pluymers Therapeutic Area Head Hematology Phone: +32 2 246 16 95 wim.pluymers@novartis.com

	and Karen Peeters Medical Advisor Hematology Phone: +32 2 246 17 28 karen.peeters@novartis.com Medialaan 40 bus 1 B-1800 Vilvoorde Belgium
Modalities for the disposal	Any unused medication needs to be returned to Novartis Pharma or destroyed in an appropriate facility as soon as possible after the patient's discontinuation from the Compassionate use program. The medication delivered for an individual patient request in the context of a Compassionate use program can only be used for that particular patient. The mention « CU-cannot be sold » will be present on the secondary packaging in the 3 national languages in addition to the requirements of annex 13 of the Good Manufacturing Practices Volume 4.
The information for registration of suspected unexpected serious adverse reactions	With the recommended sequential treatment schedule (where Midostaurin is started on day 8 after the completion of chemotherapy), AEs reported in ≥ 50% of patients included hematological AEs (thrombocytopenia, neutropenia, febrile neutropenia) and nausea, diarrhea, vomiting, pyrexia, hypokalemia, chills, and headache. The most frequent grade 3 and grade 4 AEs were hematological AEs (thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia). Grade 3 non-hematological AEs reported in >10% of patients were those associated with GI toxicity (nausea, vomiting), increases in liver function test results (ALT, AST, bilirubin), electrolyte imbalance (hypocalcemia, hypokalemia, hypophosphatemia), and pyrexia, hypoxia, and device-related infection. One on-treatment death was reported in the study. The patient died due to fungal infection associated with multi-organ failure that was not considered to be related to study drug by the Investigator. AEs that led to discontinuation were reported for 8.8% of patients (5% with 50 mg BID, and 14% with 100 mg BID).