FDA Approval Summary: Midostaurin for the Treatment of Advanced Systemic Mastocytosis

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Midostaurin • Systemic mastocytosis • Mast cell • Mast cell leukemia • KIT

ABSTRACT

In April 2017, the U.S. Food and Drug Administration granted regular approval to midostaurin for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL). Approval was based on results from CPKC412D2201, a single-arm trial of midostaurin (100 mg orally twice daily) in previously treated or untreated patients. For the patients with ASM and SM-AHN, efficacy was established on the basis of confirmed complete remission (CR) plus incomplete remission (ICR) by modified Valent criteria with six cycles of midostaurin. There were no CRs reported; ICR was achieved by 6 of 16 patients (38%; 95% confidence interval [CI]: 15%–65%) with ASM and by 9 of 57 patients (16%; 95% CI: 7%–28%) with SM-AHN. Within the follow-up period, the median duration of response was not reached for the patients with ASM (range, 12.1+ to 36.8+ months) or with SM-AHN (range, 6.6+ to 52.1+ months). For the patients with MCL, efficacy was established on the basis of confirmed CR using modified 2013 International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis criteria. Of 21 patients with MCL, 1 (5%) achieved a CR. Of 142 patients with SM evaluated for safety, 56% had dose modifications for toxicity, and 21% discontinued treatment due to toxicity. Over 50% reported nausea, vomiting, or diarrhea, and ≥30% reported edema, musculoskeletal pain, fatigue, abdominal pain, or upper respiratory tract infection. New or worsening grade ≥3 lymphopenia, anemia, thrombocytopenia, or neutropenia developed in ≥20%. Although midostaurin is an active drug for treatment of advanced SM, it is not clear that the optimal dose has been identified.

Implications for Practice: Midostaurin is the only U.S. Food and Drug Administration-approved therapy for patients with systemic mastocytosis with associated hematological neoplasm and mast cell leukemia and is the only therapy approved for patients with aggressive systemic mastocytosis regardless of KIT D816V mutation status. Based on response rate and duration, midostaurin has meaningful clinical activity in these rare, life-threatening diseases.

INTRODUCTION

Systemic mastocytosis (SM) is a rare, heterogeneous disease caused by the uncontrolled proliferation and accumulation of neoplastic mast cells. Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL) [1] are considered advanced forms of SM. In contrast to indolent variants of mastocytosis, the prognosis of advanced SM is poor, with an estimated median overall survival of 3.5 years with ASM, 2 years with SM-AHN, and <6 months with MCL [2–4]. Symptoms are caused both by the release of vasoactive mast cell mediators and by organ damage from mast cell infiltration. Clinical manifestations of organ infiltration (C-findings) include cytopenias, skeletal lesions, hepatomegaly with impaired liver function and/or portal hypertension, splenomegaly with hypersplenism, and weight loss due to gastrointestinal involvement [5–7]. Leukemic transformation can occur, with the observed risk ranging from 5% in ASM to 29% in SM that is associated with myelodysplastic syndrome (MDS) [2]. Imatinib mesylate, which is approved for the treatment of adult ASM without the D816V c-KIT mutation or...
with unknown c-Kit mutational status, is relevant for only approximately 10% of patients with ASM [8–11]. Somatic gain-of-function mutations in KIT, particularly the D816V mutation, occur in most adult cases of SM [10]. The KIT D816V mutation encodes a constitutively activated receptor tyrosine kinase that promotes mast cell differentiation and proliferation, driving the pathogenesis of SM [12]. This mutation is associated with resistance to several tyrosine kinase inhibitors including imatinib [13]. There have been no effective drug therapies for treatment of MCL [3].

Midostaurin is a small-molecule inhibitor of multiple receptor tyrosine kinases. In vitro, midostaurin or its active metabolites inhibit the activity of both wild-type and D816V mutant KIT [13, 14], as well as various other receptor tyrosine kinases including fms-related tyrosine kinase 3 (FLT3), platelet-derived growth factor receptor, vascular endothelial growth factor receptor 2, and members of the protein kinase C family [15]. In preclinical studies, midostaurin inhibited mast cell proliferation and suppressed histamine release [16]. In April 2017, the U.S. Food and Drug Administration (FDA) granted regular approval to midostaurin (Rydapt; Novartis Pharmaceuticals Corporation, Basel, Switzerland) for the treatment of adult patients with ASM, SM-AHN, or MCL. Midostaurin is the first approved therapy for SM-AHN and MCL and the second approved therapy for ASM. Herein, we summarize the FDA clinical review and rationale for regular approval of midostaurin for patients with ASM, SM-AHN, and MCL.

**Trial Design**

The primary basis of approval is a multicenter, single-arm, open-label phase II trial of midostaurin in 116 adults with previously treated or untreated ASM, SM-AHN, or MCL (CPKC412D221; NCT00233454) [17]. These diseases are collectively referred to as advanced SM. Eligible patients had a maximum of two prior regimens for SM and at least one measurable C-finding attributable to SM. The trial excluded patients with life-threatening AHN, serum creatinine >2 mg/dl, inadequate hepatic function, QTc >450 ms, cardiovascular disease, or any pulmonary infiltrate. Patients received midostaurin as a single agent, 100 mg orally twice daily with food in 28-day cycles until disease progression or intolerable toxicity.

The primary endpoint was confirmed overall response rate (ORR) with the first six cycles as determined by a study steering committee (SSC), with duration of response included as a secondary endpoint. The trial used modified Valent response criteria for advanced SM [18, 19] and, for transfusion-dependent cytopenias, revised International Working Group (IWG) criteria for MDS [20, 21], with confirmation of response required after 28 weeks. In the Valent criteria [18, 19], the status of C-findings is the foundation of response assessment. Major response requires normalization of at least one C-finding and is subcategorized (complete remission [CR], incomplete remission [ICR], pure clinical response) by the degree of reduction in mast cell infiltrates, serum tryptase levels, and SM-associated organomegaly. Partial response requires incomplete regression of at least one C-finding.

Supporting data came from a multicenter, single-arm phase II trial of midostaurin 100 mg twice daily in 26 adults with advanced SM (PKC412A2213; NCT00233454) [22, 23]. Eligibility criteria were similar to CPKC412D2201. The primary endpoint was investigator-assessed ORR in the first two cycles according to original Valent criteria.

**Results**

**Efficacy**

**Patient and Treatment Characteristics**

Table 1 summarizes the patient and treatment characteristics in Study CPKC412D2201. Of the 116 patients treated, 51 (44%) were age ≥65 years, and one third had an Eastern Cooperative Oncology Group performance status of 2 or 3. Approximately 40% had previous treatment for SM. Based on central review, 14% of patients had ASM, 63% SM-AHN, 18% MCL, and 6% an unconfirmed type of SM. Most patients (90%) had splenomegaly, 63% had documented bone lesions or hepatomegaly, 50% had ascites, and 29% had transfusion-dependent anemia. As is characteristic of adult SM, most patients (84%) had a documented KIT D816 mutation, mainly involving D816V. The median duration of study treatment was 11 months, with 49% receiving at least 1 year of midostaurin, 34% receiving at least 2 years, and 18% receiving at least 3 years of midostaurin (Table 1).

Of the 116 patients treated, the SSC identified 89 (77%) who had at least one measurable C-finding and were eligible for response assessment. These constituted the main efficacy population (Table 1). The other patients were excluded largely because they had unmeasurable C-findings only (e.g., ascites, skeletal lesions). For the main analysis, the study also considered patients on higher-dose corticosteroids (≥10 mg prednisone daily or equivalent during at least one cycle) to be un evaluable for response.

Of the 89 eligible patients, 36% had prior therapy for SM. The diagnosis was ASM in 16 patients, SM-AHN in 57, and MCL in 16. Notably, there was diagnostic uncertainty on central pathology review (Table 1). The most common measurable C-findings (≥20%) were thrombocytopenia (62%), anemia (31%), transfusion-dependent anemia (22%), hypoalbuminemia (54%), and hyperbilirubinemia (28%).

**Response by Modified Valenti Criteria**

Table 2 summarizes efficacy in the 89-patient subset according to modified Valent criteria and IWG MDS criteria for transfusions. The confirmed ORR (major + partial response) with six cycles was 75% (63% major response) in ASM, 58% (40% major) in SM-AHN, and 50% (44% major) in MCL. In the categories of major response, the ICR rate was 38% in ASM, 16% in SM-AHN, and 25% in MCL. No CRs were achieved by these criteria (Table 2).

Durable responses occurred in all subtypes (Table 2). With an estimated 30.5-month median follow-up in all patients, the estimated median duration of overall response was not reached in patients with ASM or MCL.

**Table 1:** Summary of Patient and Treatment Characteristics

| Characteristic                        | Frequency |
|--------------------------------------|-----------|
| Age (years)                          | 51 (44%)  |
| Performance Status (ECOG)            | 18% (3)   |
| Previous Treatment                   | 40%       |
| Central Pathology Review             | 89 (77%)  |
| Efficacy Population                  | 89 (77%)  |
|联合治疗科中主要疗效人群（Table 1）| 89 (77%)  |

**Table 2:** Summary of Efficacy Population

| Subtype   | Median Duration (months) | ORR (%) | CR (%) | ICR (%) |
|-----------|--------------------------|---------|--------|---------|
| ASM       | 11                       | 75      | 36     | 39      |
| SM-AHN    | 11                       | 58      | 36     | 22      |
| MCL       | 11                       | 50      | 36     | 25      |

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| Characteristic                              | Primary efficacy cohort, n = 89 | All treated patients, n = 116 |
|--------------------------------------------|----------------------------------|--------------------------------|
| **Baseline parameters, n (%)**             |                                  |                                |
| Age, years, median (range)                 | 64 (25–82)                       | 63 (25–82)                     |
| Sex, male                                  | 57 (64)                          | 76 (66)                        |
| Diagnosis on central review<sup>a</sup>     |                                  |                                |
| ASM<sup>b</sup>                            | 16 (18)                          | 16 (14)                        |
| SM with AHN                                | 57 (64)                          | 73 (63)                        |
| MCL<sup>b</sup>                            | 16 (18)                          | 21 (18)                        |
| Subtype not confirmed                      | 0(0)                             | 6 (5)                          |
| KIT D816 mutation status                   |                                  |                                |
| Mutated                                    | 77 (87)                          | 98 (84)                        |
| Known D816V mutation                       | 73 (82)                          | 94 (81)                        |
| Wild type                                  | 10 (11)                          | 13 (11)                        |
| Unknown                                    | 2 (2)                            | 5 (4)                          |
| Disease burden                             |                                  |                                |
| Splenomegaly                               | 82 (92)                          | 104 (90)                       |
| Bone lesions<sup>c</sup>                   | 56 (63)                          | 73 (63)                        |
| Hepatomegaly                               | 63 (71)                          | 73 (63)                        |
| Ascites                                    | 51 (57)                          | 58 (50)                        |
| G ≥2 LFT abnormalities                     | 39 (44)                          | 43 (37)                        |
| G ≥2 hypoalbuminemia                       | 15 (17)                          | 17 (15)                        |
| G ≥3 neutropenia                           | 9 (10)                           | 11 (9)                         |
| TD anemia<sup>d</sup>                      | 22 (25)                          | 22 (19)                        |
| TD thrombocytopenia<sup>d</sup>            | 4 (4)                            | 6 (5)                          |
| **No. of prior regimens for SM<sup>e</sup>**|                                  |                                |
| 0                                          | 57 (64)                          | 69 (59)                        |
| 1                                          | 19 (21)                          | 27 (23)                        |
| 2                                          | 11 (21)                          | 14 (12)                        |
| ≥3                                         | 2 (2)                            | 6 (5)                          |
| Prior regimens for SM                      |                                  |                                |
| Tyrosine kinase inhibitor                   | 15 (17)                          | 19 (16)                        |
| Cladribine                                 | 12 (13)                          | 17 (15)                        |
| Interferon                                 | 7 (8)                            | 11 (9)                         |
| Midostaurin exposure                       |                                  |                                |
| Exposure time, months                      | Median 11.3                      | 11.4                           |
|                                            | 25th, 75th percentile 4.5, 28.5 | 4.5, 30.3                      |
| Minimum treatment duration, n (%)          |                                  |                                |
| ≥6 months                                  | 59 (66)                          | 76 (66)                        |
| ≥12 months                                 | 42 (47)                          | 57 (49)                        |
| ≥24 months                                 | 28 (31)                          | 39 (34)                        |
| Relative dose intensity, %                 | Mean 91                          | 89                              |

<sup>a</sup>The protocol categorized the diagnoses as ASM or MCL with or without AHN. U.S. Food and Drug Administration review instead used the World Health Organization classification of SM with central pathology review, as presented here.

<sup>b</sup>On central pathology review, in the primary efficacy cohort, 25/89 cases (28%) were not assessable for MCL due to biopsy quality and were classified as ASM because of C-findings, and 11 cases with unconfirmed presence of AHN were classified as not having AHN. Overall, 31/116 cases (27%) were not assessable for MCL, and 15 cases with unconfirmed presence of AHN were classified as not having AHN.

<sup>c</sup>Missing data in three patients.

<sup>d</sup>Transfusion dependence was defined as ≥4 units transfused within preceding 8 weeks due to underlying disease.

<sup>e</sup>Excluding regimens for AHN.

Abbreviations: AHN, associated hematological neoplasm; ASM, aggressive systemic mastocytosis; G, grade; LFT, liver function test; MCL, mast cell leukemia; SM, systemic mastocytosis; TD, transfusion-dependent.
and was 12.7 months in SM-AHN. The estimated median duration of ICR was not reached in any subtype, with durations of ICR ranging from 6.6+ to 65.8+ months. The four ICRs in MCL persisted for 19.1+ to 65.8+ months (Table 2).

In the 89 patients combined, confirmed major or partial responses occurred in 46 of 73 patients (63%) with a documented KIT D816V mutation, 7 of 16 (44%) with wild-type or unknown status of KIT D816, and 21 of 32 (66%) having previous therapy for SM.

Efficacy results in Study PKC412A2213 based on investigator-assessed ORR were supportive.

**Response by Modified IWG-MRT-ECNM Criteria**

Recognized limitations of the Valent response criteria include the unclear minimum duration of response and the challenges in evaluating unmeasurable C-findings, distinguishing causes of organ damage and cytopenias, and assessing transfusion dependence [7]. The more recent IWG-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis (IWG-MRT-ECNM) consensus response criteria are more rigorous and overcome some of these limitations [7]. Responses require 12-week confirmation, and eligibility for response assessment requires at least one specific sign of organ damage [7].

CPKC412D2201 was initiated before the release of the IWG-MRT-ECNM criteria. FDA requested a post hoc exploratory analysis based on these criteria, given their stringency and utility for future clinical trials. The results are shown in Table 3 and include a CR among the 21 patients with MCL. Importantly, study data collection had not been tailored to these criteria, and information on response-evaluable organ damage was incomplete.

The Applicant applied modified eligibility criteria for organ damage (defined in Table 3) given these limitations and a computational algorithm for assessing response. In this analysis, use of corticosteroids did not preclude response assessment.

### Table 2. Response based on modified Valent criteria and International Working Group for myelodysplastic syndrome criteria for transfusion dependence

| Outcome per Study Steering Committeea | All subtypes, n = 89 | ASM, n = 16 | SM-AHN, n = 57 | MCL, n = 16 |
|--------------------------------------|----------------------|-------------|----------------|-------------|
| **Best response with six cycles, n (%)** |                      |             |                |             |
| MR                                   | 40 (45)              | 10 (63)     | 23 (40)        | 7 (44)      |
| CR                                   | 0 (0)                | 0 (0)       | 0 (0)          | 0 (0)       |
| ICR                                  | 19 (21)              | 6 (38)      | 9 (16)         | 4 (25)      |
| Pure clinical response                | 15 (17)              | 4 (25)      | 9 (16)         | 2 (13)      |
| Unspecified                          | 6 (7)                | 0 (0)       | 5 (9)          | 1 (6)       |
| PR                                   | 13 (15)              | 2 (13)      | 10 (18)        | 1 (6)       |
| Good PR                              | 11 (12)              | 1 (6)       | 10 (18)        | 0 (0)       |
| Minor response                       | 2 (2)                | 1 (6)       | 0 (0)          | 1 (6)       |
| Stable or progressive disease         | 21 (24)              | 2 (13)      | 13 (23)        | 6 (38)      |
| Not evaluable                        | 15 (17)              | 2 (13)      | 11 (19)        | 2 (13)      |
| **Overall response (major + partial)** |                      |             |                |             |
| ORR (MR + PR) with six cycles, n (%) | 53 (60)              | 12 (75)     | 33 (58)        | 8 (50)      |
| 95% CI                               | (49–70)              | (48–93)     | (44–71)        | (25–75)     |
| **DORb, months**                     |                      |             |                |             |
| Estimated median (95% CI)            | 31.4 (10.8–NE)       | NR (24.2–NE)| 12.7 (7.4–31.4)| NR (3.6–NE)|
| Range                                | 1.9+ to 66.9+        | 2.3+ to 66.9+| 1.9+ to 52.1+  | 3.6 to 65.8+|
| Responders censored                  | 22/53 (42)           | 2/12 (17)   | 18/33 (55)     | 2/8 (25)    |
| Months to response, median (range)   | 0.3 (0.1–3.7)        | 0.3 (0.1–1.9)| 0.5 (0.1–3.7)  | 0.3 (0.1–3.0)|
| **Complete + incomplete remission**  |                      |             |                |             |
| CR + ICR by six cyclesb, n (%)       | 19 (21)              | 6 (38)      | 9 (16)         | 4 (25)      |
| 95% CI                               | (13–31)              | (15–65)     | (7–28)         | (7–52)      |
| **Duration of CR + ICR, months**     |                      |             |                |             |
| Estimated median (95% CI)            | NR (24.1–NE)         | NR (24.1–NE)| NR (7.4–NE)    | NR (NE–NE)|
| Range                                | 6.6+ to 65.8+        | 12.1+ to 36.8+| 6.6+ to 52.1+  | 19.1+ to 65.8+|
| Months to CR + ICR, median (range)    | 0.5 (0.1–3.0)        | 0.7 (0.3–1.9)| 0.5 (0.1–3.0)  | 0.3 (0.1–0.5)|

aResponse confirmation after ≥8 weeks was required. Recipients of corticosteroids were considered unevaluable for these response assessments.

bThe estimated median follow-up for DOR was 30.5 months overall for MR + PR and 35.4 months for CR + ICR. A + sign indicates a censored value.

cAll are ICRs.

Abbreviations: ASM, aggressive systemic mastocytosis; CI, confidence interval; CR, complete remission; DOR, duration of response; ICR, incomplete remission; MCL, mast cell leukemia; MR, major response; NE, not estimable; NR, not reached; ORR, overall response rate; PR, partial response; SM-AHN, systemic mastocytosis with associated hematological neoplasm.

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Table 3. Efficacy per modified IWG-MRT-ECNM criteria using a retrospective, algorithmic approach (Study CPKC412D2201)

| Measure of efficacy | All subtypes, n = 115<sup>a,b</sup> | ASM, n = 16 | SM-AHN, n = 72<sup>c</sup> | MCL, n = 21 | Type not confirmed, n = 6 |
|---------------------|-------------------------------------|-------------|---------------------------|-------------|-------------------------|
| Best response with six cycles<sup>d</sup> | CR | 2 (2) | 1 (6) | 0 (0) | 1 (5) | 0 (0) |
| | PR | 17 (15) | 4 (25) | 8 (11) | 3 (14) | 2 (33) |
| | Clinical improvement | 20 (17) | 3 (19) | 13 (18) | 3 (14) | 1 (17) |
| | Stable or progressive disease | 63 (55) | 7 (44) | 42 (58) | 12 (57) | 2 (33) |
| | Not evaluable | 13 (11) | 1 (6) | 9 (13) | 2 (10) | 1 (17) |
| | CR + PR in six cycles | 19 (17) | 5 (31) | 8 (11) | 4 (19) | 2 (33) |
| | 95% CI | (10–25) | (11–59) | (5–21) | (5–42) | (4–78) |

Duration of CR + PR<sup>b</sup>, months

| Measure of efficacy | All subtypes, n = 89 | ASM, n = 16 | SM-AHN, n = 57 | MCL, n = 16 |
|---------------------|---------------------|-------------|----------------|-------------|
| Best response with six cycles | Complete remission | 1 (1) | 1 (6) | 0 (0) | 0 (0) |
| | Partial remission | 14 (16) | 4 (25) | 7 (12) | 3 (19) |
| | Clinical improvement | 17 (19) | 3 (19) | 12 (21) | 2 (13) |
| | Stable or progressive disease | 49 (55) | 7 (44) | 31 (54) | 10 (63) |
| | Not evaluable | 9 (10) | 1 (6) | 7 (12) | 1 (6) |
| | CR + PR with six cycles<sup>d</sup> | 15 (17) | 5 (31) | 7 (12) | 3 (19) |
| | 95% CI | (10–26) | (11–59) | (5–24) | (4–46) |

<sup>a</sup>Response criteria were not applied to one patient with SM-AHN.

<sup>b</sup>Median response duration was not reached in any subtype, with an estimated median follow-up of 35.0 months overall. A + sign indicates a censored value.

<sup>c</sup>Per applicant with 12 week continuation, IWG-MRT-ECNM criteria were modified with respect to eligible organ damage as follows: (a) Ascites was eligible, rather than grade ≥ 2 ascites; (b) Pleural effusions were not considered; (c) Splenomegaly by imaging, rather than symptomatic marked splenomegaly, was eligible; and (d) Transfusion-dependent anemia and thrombocytopenia in the preceding 8 weeks rather than 12 weeks were eligible, regardless of pretransfusion values.

<sup>d</sup>Corticosteroid use did not preclude response assessment according to these criteria.

Supportive Efficacy Data

Durable responses to midostaurin were also achieved in the supportive study, PKC412A2213 [22, 23]. Of the 26 patients treated, 23 had a confirmed subtype of SM. After two cycles of midostaurin, according to investigator-assessed original Valnet criteria, 10 of 17 patients with SM-AHN and 2 of 6 patients with MCL achieved a response that was sustained for at least 8 weeks [23]. The response durations ranged from 3.4+ to 79.2+ months in SM-AHN and 28.6+ to 32.1+ months in MCL [23].

Safety

The safety analysis combined the 142 patients on CPKC412D2201 and PKC412A2213 (median treatment duration, 11.4 months). The median age was 63 years, 46% had prior treatment for SM, and 37% had an Eastern Cooperative Oncology Group performance status of 2 or 3. Thirty-three patients (23%) had hepatic impairment at baseline (eight with moderate and two with severe impairment). Serious adverse reactions (ARs) were reported in 68% of patients, most commonly (≥20%) due to infections and gastrointestinal disorders. Sixteen patients (11%) died on-treatment from causes unrelated to the underlying malignancy, most often from infection (sepsis or pneumonia) followed by cardiac events.

Notably, 56% of patients had dose interruption or reduction due to ARs, with the most frequent causes (in >5%) being gastrointestinal symptoms, QT prolongation, neutropenia, pyrexia, thrombocytopenia, gastrointestinal hemorrhage, lipase increase, and fatigue. The median time to first dose modification for toxicity was 1.6 months, with 75% of dose modifications occurring or first occurring within 5 months (Fig. 1). Twenty-one percent of patients discontinued midostaurin due to ARs, most often due to infection, nausea or vomiting, QT prolongation, and hemorrhage.

Table 4 summarizes selected ARs and new or worsening laboratory abnormalities in patients with advanced SM. The most common all-grade ARs (reported in ≥20%), excluding laboratory terms, included nausea, vomiting, diarrhea, edema, musculoskeletal pain, abdominal pain, fatigue, upper
respiratory tract infection, constipation, pyrexia, headache, and dyspnea. Other common ARs (reported in \( \geq 10\% \)) included arthralgia (19%), cough (18%), urinary tract infection (16%), gastrointestinal hemorrhage (14%), pleural effusion (13%), dizziness (13%), epistaxis (12%), QT prolongation (11%), renal insufficiency (11%), insomnia (11%), pneumonia (10%), and herpesvirus infection (10%) [23].

The most common new or worsening grade \( \geq 3 \) laboratory abnormalities (reported in \( \geq 20\% \)) were lymphopenia, anemia, thrombocytopenia, and neutropenia (Table 4). More than 5% of patients developed grade 4 laboratory abnormalities involving thrombocytopenia (13%), hyperuricemia (11%), neutropenia (8%), anemia (6%), or lymphopenia (6%). The prescribing information provides dose modification guidelines for toxicity [23].

The prescribing information for midostaurin carries Warnings and Precautions for embryo-fetal toxicity and pulmonary toxicity, with the latter based on rare cases, some fatal, of interstitial lung disease and pneumonitis.

**Clinical Pharmacology**

In patients with advanced SM, the approved dose of midostaurin (100 mg twice daily as a single agent with food) is based on Study CPKC412D2201. Midostaurin exhibited time-dependent pharmacokinetics, with the maximum trough concentration (Cmin) by the end of the first week of dosing, followed by a decline to steady state by 4 weeks. The concentration of the active metabolite CGP62221 was similar to those of midostaurin, whereas the concentration of the other active metabolite, CGP52421, increased steadily following twice-daily dosing, reaching steady-state levels by 4 weeks. In addition, there was a lack of dose proportionality in exposure for midostaurin and its active metabolites after multiple dosing; the steady-state concentrations of midostaurin and its active metabolites were similar following doses of 50 mg twice daily and 100 mg twice daily. Food increased midostaurin exposure (22% with standard meal and 59% with high-fat meal). Midostaurin is administered with a meal mainly to reduce the

| Table 4. Selected adverse reactions and laboratory abnormalities in patients with advanced systemic mastocytosis |
|---------------------------------------------------------------|
| **Safety population, \( n = 142 \)**                          |
| **Adverse reaction or laboratory abnormality**               |
| All grades, %, Grade \( \geq 3, \% \)                        |
| Adverse reactions (incidence \( \geq 20\% \))                 |
| Nausea                                                        | 82 | 6 |
| Vomiting                                                      | 68 | 6 |
| Diarrhea                                                      | 54 | 8 |
| Edema                                                         | 40 | 7 |
| Musculoskeletal pain                                          | 35 | 4 |
| Fatigue                                                       | 34 | 9 |
| Abdominal pain                                                | 34 | 6 |
| Upper respiratory tract infection                             | 30 | 1 |
| Constipation                                                  | 29 | <1|
| Pyrexia                                                       | 27 | 4 |
| Headache                                                      | 26 | 1 |
| Dyspnea                                                       | 23 | 7 |
| Labs with \( \geq 5\% \) incidence of grade \( \geq 3 \)   |
| Hematology labs                                               |
| Lymphopenia                                                   | 66 | 42|
| Leukopenia                                                    | 61 | 19|
| Anemia                                                        | 60 | 38|
| Thrombocytopenia                                              | 50 | 27|
| Neutropenia                                                   | 49 | 22|
| Chemistries                                                   |
| Hyperglycemia                                                 | 80 | 18|
| Alkaline phosphatase increase                                 | 39 | 9 |
| Lipase increase                                               | 37 | 18|
| Hyperuricemia                                                 | 37 | 11|
| Gamma-glutamyl transferase increase                          | 35 | 9 |
| Hyponatremia                                                  | 34 | 5 |
| Hypokalemia                                                   | 25 | 6 |
| Amylase increase                                              | 20 | 7 |

*Toxicities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.

†Includes adverse reactions, with the exception of laboratory terms, reported up to 28 days after last midostaurin dose. Includes grouped preferred terms.

‡Represents laboratory abnormalities that are new or worsened from baseline grade.

§From 116 evaluable patients.

likelihood of gastrointestinal-related ARs, such as nausea and vomiting. The mean terminal elimination half-life (% coefficient of variation) was 19 hours (39%) for midostaurin, 32 hours (31%) for CGP62221, and 482 hours (25%) for CGP52421. Midostaurin is mainly excreted in feces with minimal urine excretion.

Drug interactions between midostaurin and strong inhibitors and inducers of CYP3A enzymes may be clinically
important. The coadministration of a strong CYP3A inhibitor (ketoconazole or itraconazole) increased midostaurin exposure by 10-fold following a single midostaurin dose and by twofold at steady state, and coadministration of a strong CYP3A inducer (rifampin) decreased midostaurin exposure by 90% after a single midostaurin dose. Product labeling recommends use of alternative therapies that do not inhibit CYP3A activity or monitoring patients for increased risk of ARs when coadministered with strong CYP3A4 inhibitors, especially during the first week of midostaurin therapy, and avoidance of strong CYP3A4 inhibitors may increase exposure to midostaurin and its active metabolites and thus increase the risk of ARs.

**Risks**
- Midostaurin has risks of embryo-fetal and pulmonary toxicity.
- Of 142 recipients of midostaurin for advanced SM, 66% had serious ARs (most often infections and gastrointestinal toxicity), 56% had dose modifications for ARs (most often from gastrointestinal toxicity, QT prolongation, and neutropenia), and 11% of patients died on-treatment for reasons other than disease progression.
- The most common (≥20%) all-grade ARs included gastrointestinal ARs, edema, musculoskeletal pain, fatigue, upper respiratory tract infection, pyrexia, headache, and dyspnea. The most common (≥20%) grade ≥3 laboratory abnormalities that developed were lymphopenia, anemia, thrombocytopenia, and neutropenia.
- Strong CYP3A4 inhibitors may increase exposure to midostaurin and its active metabolites and thus increase the risk of ARs.

**Uncertainties**
- The optimal dosage of midostaurin for SM is undetermined.
- A subset of ASM cases have diagnostic uncertainty on central review.
- Confidence intervals for response rates are broad due to sample size limitations.
- Efficacy according to original IWG-MRT-ECNM criteria is undefined.
- Safety data in patients with hepatic impairment are limited.

**Conclusions**
- Midostaurin has clinically meaningful activity in patients with advanced SM and an overall favorable benefit/risk balance.
- Given the high rate of dose modifications early in treatment, close monitoring for actionable toxicities is warranted especially during the first several months.
- Avoid concomitant use of strong CYP3A4 modulators.

**DISCUSSION**

Treatment of patients with ASM, SM-AHN, and MCL is generally palliative, with limited and largely unsatisfactory options [3, 9, 24]. Midostaurin has clinically meaningful activity in advanced SM based on response rate and duration, and it has an acceptable safety profile (Table 5). FDA granted regular approval of midostaurin for these rare diseases based on single-arm trial data, given the durability of response and the paucity or absence of available therapies. FDA granted this approval concurrently with the approval of midostaurin in newly diagnosed, FLT3-mutation-positive acute myeloid leukemia [25].

Imatinib mesylate received regular approval in 2006 for the treatment of adult ASM without the D816V c-Kit mutation or with c-Kit mutational status unknown. Of 28 patients with ASM, 8 (29%) achieved a complete hematologic response and 9 (32%) a partial hematologic response with imatinib mesylate, with response durations ranging from 1 to 30+ months [26]. The safety profile of imatinib mesylate was consistent with that described in other approved indications.

There were numerous challenges in evaluating the efficacy of midostaurin, as in any drug for advanced forms of SM. Response determination according to Valent and IWG-MRT-ECNM criteria is based on signs and symptoms that may not be measurable. Organ damage from SM can be difficult to quantify (e.g., ascites, effusions, bone lesions,

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**Table 5. Benefit-risk analysis for midostaurin for the treatment of advanced SM**

| Parameter | Summary |
|-----------|---------|
| **Unmet medical need** | - Advanced SM is rare and largely fatal.  
- No drugs were previously approved for SM-AHN or MCL. Imatinib, the only treatment approved previously for ASM, is irrelevant for most patients with ASM because of the D816V c-Kit mutation that confers imatinib resistance. |
| **Clinical benefit** | - In a single-arm trial of midostaurin (100 mg twice daily) in previously treated or untreated advanced SM (CPK412D2201), a treatment effect was demonstrated across disease subtypes.  
- By modified Valient criteria, among 89/116 patients assessed, the response rate with six cycles was 75% (63% major response) in ASM, 58% (40% major) in SM-AHN, and 50% (44% major) in MCL. The responses tended to be durable. The incomplete remission rate was 38% in ASM, 16% in SM-AHN, and 25% in MCL, with no CRs by these criteria.  
- Among 115 patients evaluated retrospectively using modified IWG-MRT-ECNM criteria, the CR + PR rate with six cycles was 17% (2% CR, 15% PR) overall. Of 21 patients with MCL, 1 achieved CR. |
| **Risks** | - Midostaurin has risks of embryo-fetal and pulmonary toxicity.  
- Of 142 recipients of midostaurin for advanced SM, 66% had serious ARs (most often infections and gastrointestinal toxicity), 56% had dose modifications for ARs (most often from gastrointestinal toxicity, QT prolongation, and neutropenia), and 11% of patients died on-treatment for reasons other than disease progression.  
- The most common (≥20%) all-grade ARs included gastrointestinal ARs, edema, musculoskeletal pain, fatigue, upper respiratory tract infection, pyrexia, headache, and dyspnea. The most common (≥20%) grade ≥3 laboratory abnormalities that developed were lymphopenia, anemia, thrombocytopenia, and neutropenia.  
- Strong CYP3A4 inhibitors may increase exposure to midostaurin and its active metabolites and thus increase the risk of ARs. |
| **Uncertainties** | - The optimal dosage of midostaurin for SM is undetermined.  
- A subset of ASM cases have diagnostic uncertainty on central review.  
- Confidence intervals for response rates are broad due to sample size limitations.  
- Efficacy according to original IWG-MRT-ECNM criteria is undefined.  
- Safety data in patients with hepatic impairment are limited. |
| **Conclusions** | - Midostaurin has clinically meaningful activity in patients with advanced SM and an overall favorable benefit/risk balance.  
- Given the high rate of dose modifications early in treatment, close monitoring for actionable toxicities is warranted especially during the first several months.  
- Avoid concomitant use of strong CYP3A4 modulators. |

**Abbreviations:** AR, adverse reaction; ASM, aggressive systemic mastocytosis; CR, complete remission; IWG-MRT-ECNM, International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis; MCL, mast cell leukemia; PR, partial response; SM, systemic mastocytosis; SM-AHN, systemic mastocytosis with associated hematological neoplasm.
gastrointestinal tract infiltration), making accurate and reproducible response assessment challenging. Therefore, in clinical trials of SM, it is especially important for case report forms to capture disease manifestations comprehensively. Organ dysfunction and cytopenias may be multifactorial (e.g., thrombocytopenia due to marrow infiltration by mast cells, hypersplenism, an AHN, or bleeding), and manifestations of SM and AHN can overlap. Further, the use of corticosteroids (as in >20% of patients on CPKC412D2201, most commonly for symptom palliation) potentially confounds the response assessment. For this marketing application, an additional limitation was the diagnostic uncertainty, by central review, in a significant subset of patients, in particular regarding the presence of AHN and MCL.

The response assessment using modified IWG-MRT-ECNM criteria (Table 3) has multiple limitations, as previously discussed. In addition, fewer patients would be eligible for response assessment according to the original criteria, due to lack of (or lack of documented) specific signs of hematologic or nonhematologic organ damage. Therefore, the response rate may be underestimated. With the available trial data, it is not possible to define efficacy according to the original consensus criteria as published, and no formal comparisons of outcome according to modified Valent versus IWG-MRT-ECNM consensus criteria are intended. Future clinical trials in advanced SM should include rigorous capture of data that permits response assessment according to the IWG-MRT-ECNM consensus criteria.

For a regulatory decision based on single-arm trial data, FDA considered what minimum level of improvement is a sufficiently robust indicator of clinical benefit. For responses assessed by modified Valent criteria, FDA’s decision was informed primarily by the CR + ICR categories of major response and their duration, rather than ORR. Other patients with major response had an unspecified type or had pure clinical response, which requires resolution of at least one C-finding but without significant changes in organ infiltration, organomegaly, or serum tryptase levels [18, 19]. The IWG-MRT-ECNM criteria define response as CR, partial remission, or clinical improvement [7]. Because the criteria for clinical improvement vary in stringency (e.g., ≥12-week resolution of transfusion-dependent anemia vs. of a grade 2 liver function abnormality caused by SM), the “clinical improvement” outcomes did not influence the regulatory decision. For all the criteria considered, the durability of response was a key determinant of efficacy.

Other kinase inhibitors are in clinical development for patients with aggressive or indolent forms of SM [27, 28]. Assessments of patient-reported outcomes are needed in trials of SM, given the substantial impact of disease-related symptoms on quality of life. Although some metrics of quality of life improved in Study CPKC412D2201, the assessments were hampered by missing data and by treatment-related ARs such as nausea and vomiting [25]. Therefore, the patient-reported outcome data were not sufficient to support a labeling claim for efficacy. Future trials in SM should incorporate comprehensive measures of quality of life.

Midostaurin is associated with frequent gastrointestinal side effects (most grade 1–2). To reduce this risk, prophylactic antiemetics are recommended, and midostaurin is recommended with food.

Notably, a dose-ranging study was not performed for the advanced SM indication. The dose for phase II study was based on the tolerability of a similar dose in patients with other malignancies and the report of a partial response in a single patient with MCL treated with 100 mg twice-daily on a compassionate use program. Using this dose in CPKC412D2201, there was a high rate of early dose modification for toxicity. Because the majority of dose modifications or first dose modifications occurred early (Fig. 1), more frequent monitoring is recommended during the first several months, and there remains uncertainty regarding whether the recommended dose of the midostaurin is optimal for treatment of advanced SM.

**CONCLUSION**

Based on response rate and duration, midostaurin has meaningful activity in advanced SM and a favorable benefit/risk balance for patients with these rare and largely fatal diseases.

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**DISCLOSURES**

The authors indicated no financial relationships.

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