ICLUSIG™

(ponatinib) tablets

45 mg, 15 mg

OBJECTION HANDLER

ARIAD Pharmaceuticals, Inc.

1 I DON'T UNDERSTAND YOUR INDICATION STATEMENT. WHERE CAN I USE ICLUSIG?

QUESTIONS TO CLARIFY

- Do you have a patient in mind for Iclusig?
  - What line of therapy?
  - What phase of disease?
  - Is the patient losing their response, or resistant or intolerant to their current TKI?
  - Does the patient have any comorbidities?
- Would you describe how you currently prescribe TKIs for your CML patients, and what factors you take into consideration when doing so?

APPROVED RESPONSES

- Iclusig is indicated for the:
  - Treatment of adult patients with CP, AP or BP CML or Ph+ ALL for whom no other TKI therapy is indicated
  - Treatment of adult patients with T315I-positive CML (CP, AP or BP) or T315I-positive Ph+ ALL
- Based on your patient's treatment objectives, comorbidities, risk factors, and other considerations, you can determine whether Iclusig is an appropriate treatment option for your patient as outlined in the indication.
- It is recommended that patient history and a benefit-risk assessment be used to determine if Iclusig is an appropriate treatment option for the patient.
- Iclusig is included in the NCCN Guidelines as an option for 3L or later in the appropriate CP-CML patient.

HANDLE TO RESOLVE: WHAT DATA TO USE

- USPI:
  - Indication statement
- NCCN Guidelines for CML
- Submit MIRF upon request for specific unsolicited information.

2 ALL OF MY CML PATIENTS ARE DOING FINE.

QUESTIONS TO CLARIFY

- What do you mean by “fine”?
- Tell me about your most difficult-to treat CML patient.
  - Line of therapy
  - Response to current treatment
  - Adverse events
  - Adherence
  - Patient support and lifestyle
- Iclusig is also indicated for Ph+ ALL. Do you have a patient with this diagnosis?
  - If yes, can you tell me about this patient?
- Is the patient meeting their milestones according to NCCN Guidelines?
- What are your treatment goals?
- What are your patient’s treatment goals?
- How often do you monitor response to TKI therapy, and what triggers a treatment change?

APPROVED RESPONSES

- As you know, monitoring TKI therapy is one of the key management strategies of CML.
- The goal of TKI therapy is to achieve a CCyR within 12 months of therapy initiation and to prevent disease progression to accelerated or blast phase.
- Routine monitoring of BCR-ABL transcripts, in conjunction with cytogenetic evaluation, provides important information about long term disease control in patients with CML.
  - Resistance to TKIs is the major reason for the failure of therapy in patients with Ph-positive disease.
- Let’s review the efficacy and safety data from the PACE trial, which enrolled difficult-to-treat resistant patients with and without mutations.

HANDLE TO RESOLVE: WHAT DATA TO USE

- NCCN Guidelines for CML
- Core Visual Aid
- PACE White Paper
- Submit MIRF upon request for specific unsolicited information.

3 NILOTINIB, DASATINIB AND IMATINIB ALL HAVE LONG-TERM DATA ON SAFETY AND EFFICACY, AND I TRUST THEM. WHY WOULD I USE AN AGENT WITH NO LONG-TERM EFFICACY DATA?

QUESTIONS TO CLARIFY

- What do you trust about these agents?
- What is your current treatment algorithm for resistant CP-CML?
- How do you determine whether to prescribe nilotinib or dasatinib first?
  - What is your starting dose?
  - Do you dose reduce for adverse events?
- What are your efficacy expectations for treatment in the 3L?
- What response rates have you seen when using these agents in resistant patients?
- How often do you monitor CP-CML patients for resistance or failure?
  - Do you monitor your patients for response at 3, 6, and 12 months based on NCCN guidelines recommendations?
  - Once the patient has achieved a CCyR, what is your monitoring strategy?
- At what point do you consider switching to an alternative TKI?

APPROVED RESPONSES

- Most patients in the PACE trial took all 3 of these drugs, yet enrolled in the trial because they grew intolerant or resistant to those therapies.
- PACE, Iclusig's pivotal trial, is ongoing, and the demographics included a heavily pre-treated, difficult-to-treat CML and Ph+ ALL patient population:
  - 93% of patients experienced failure of 2 or more prior TKIs
  - 88% of patients were resistant to prior TKI therapy
  - 55% of patients had one or more BCR-ABL kinase domain mutations at baseline
- Iclusig demonstrated efficacy in CP-CML patients in 3L or later with a 54% MCyR and 44% CCyR.
  - Of the 54% of CP-CML patients who achieved MCyR, 82% also achieved CCyR

APPROVED RESPONSES - Cont.

- At the time of PACE analysis, the median duration of follow-up was 10 months in patients with CP-CML and AP-CML, and 6 months in patients with BP-CML and Ph+ ALL.
- An individualized benefit-risk assessment can help determine whether Iclusig is an appropriate treatment option.
- Careful monitoring of TKI responses throughout the course of therapy is an important part of managing patients with CML.

HANDLE TO RESOLVE: WHAT DATA TO USE

- USPI:
  - Section 14, Clinical Studies
- Core Visual Aid
- Submit MIRF upon request for specific unsolicited information

4 I AM CONCERNED THAT THE OPTIMAL DOSE OF ICLUSIG HAS NOT BEEN DEFINED. WHAT IS THE DATA TO SUPPORT THE EFFICACY AND SAFETY OF ICLUSIG AT LOWER DOSES?

QUESTIONS TO CLARIFY

- What is your current starting dose for Iclusig?
- How does dose modification play into your treatment strategy for an Iclusig patient?
  - What are your thoughts on the recommendation to dose reduce Iclusig once a CP- or AP-CML patient achieves a MCyR?
- What are your thoughts about dose modification as a strategy to manage adverse reactions?
- To what extent, in general, do you dose modify when treating your oncology patients?
- In what situations would you dose reduce or dose modify other TKIs in the treatment of CML?

APPROVED RESPONSES

- The efficacy of lower Iclusig starting doses has not been investigated prospectively; however, one of the FDA's post-marketing requirements is a dose-ranging trial of Iclusig in resistant CP-CML, currently underway.
- The recommended starting dose for Iclusig is 45 mg once daily, taken with or without food.
- Consider dose reduction for CP-CML and AP-CML patients who achieve MCyR and for the management of adverse reactions (e.g., myelosuppression, hepatic toxicity, pancreatitis or elevations of lipase/amylase, and/or other nonhematologic adverse events).
- Actively monitor patients for response and signs of adverse reactions, and continue to treat at an appropriate dose.
- The median dose intensity in the PACE trial was 37 mg per day – 83% of the recommended 45 mg dose per day.
- The primary endpoint was met in the PACE trial with patients receiving 45 mg doses, and with frequent dose reductions to 30 mg and 15 mg:
  - 59% of patients in the PACE trial required dose reductions during therapy.

APPROVED RESPONSES - Cont.

  - 74% of patients required dose delays or dose reductions due to adverse reactions.
  - The PACE trial met its primary endpoints, with 54% achieving a MCyR and 44% achieving a CCyR in CP-CML patients.
- The recommended starting dose is 30mg once daily when administering Iclusig with strong CYP3A inhibitors.
- The recommended starting dose is 30mg once daily in patients with hepatic impairment.
- There are specific dosing modifications for myelosuppression, nonhematologic adverse reactions (hepatic toxicity, pancreatitis, and elevation of lipase), concomitant use with strong CYP3A inhibitors, and for use in patient with hepatic impairment.
- In the PACE trial, significant increases in grade ≥3 adverse reactions (hypertension, thrombocytopenia, pancreatitis, neutropenia, rash, ALT increase, AST increase, lipase increase, myelosuppression) were observed over the dose range of 15 to 45 mg once daily.
- In cell based assays, clinically achievable concentrations of ponatinib suppressed unmutated BCR-ABL and most mutant BCR-ABL clones at levels corresponding to once daily dosing of 15 or 30 mg.
- An ongoing benefit-risk assessment of each patient may help guide dose selection.

HANDLE TO RESOLVE: WHAT DATA TO USE

- USPI:
  - PI Highlights, Dosage and Administration
  - Section 2, Dosage and Administration
  - Section 12.2, Pharmacodynamics
- Dose Modification Guide
- Core Visual Aid
- Submit MIRF upon request for specific unsolicited information

5 I ONLY USE ICLUSIG IN PATIENTS WITH THE T315I MUTATION OR AFTER I'VE EXHAUSTED ALL OTHER TKI OPTIONS.

QUESTIONS TO CLARIFY

- Why?
- What is your treatment algorithm for CP-CML?
- What factors do you consider when selecting a treatment option for a patient who has failed multiple TKIs?
- What are you most concerned about in patients who have failed multiple TKIs?
- How would you characterize the level of disease risk in patients who have failed multiple TKIs?
- To what extent does the risk of disease progression impact your TKI selection?
- What are your efficacy expectations in a patient who has failed one TKI, two TKIs etc.?
- How often do you monitor response to TKI therapy, and what triggers a treatment change?
- Are you currently treating a patient who is losing their response to a TKI?
  - If so, tell me about the patient's disease and treatment history.
  - Does the patient have any comorbidities or risk factors?
  - Has the patient experienced recent events or side effects on their current therapy?
  - Is the patient adherent?
- At what point do you consider changing therapy if a patient does not achieve a response milestone per NCCN Guidelines? Do you conduct mutation analysis in these patients?

APPROVED RESPONSES

- Doctor, it's important to look at efficacy in conjunction with patient demographics and disease characteristics, as well as the overall benefit-risk to patients. Let me review the efficacy data for Iclusig with you.
- In the PACE trial, Iclusig demonstrated efficacy in CP-CML patients in 3L or later with a 54% MCyR and 44% CCyR.
  - Of the 54% of CP-CML patients who achieved MCyR, 82% also achieved CCyR.

APPROVED RESPONSES - Cont.

- In the PACE trial of CML and Ph+ ALL patients:
  - 93% of patients experienced failure of two or more prior TKIs.
  - 88% of patients were resistant to prior TKI therapy.
  - 55% of patients had one or more BCR-ABL kinase domain mutations at baseline.
- An individualized benefit-risk assessment can help determine whether Iclusig is an appropriate treatment option.
- Careful monitoring of TKI responses throughout the course of therapy is an important part of managing patients with CML.

HANDLE TO RESOLVE: WHAT DATA TO USE

- USPI:
  - PI Highlights, Indications and Usage
  - Section 1, Indications and Usage
  - Section 14, Clinical Studies
- Core Visual Aid
- Considerations for the Management of CP-CML Patients Resistant to Multiple TKIs (White Paper)
- A Review of the PACE Trial (White Paper)
- NCCN Guidelines for CML
- Submit MIRF for upon request for specific unsolicited information

6 I'M WORRIED ABOUT THE RATE OF CARDIOVASCULAR EVENTS WITH ICLUSIG, EVEN IN PATIENTS WITHOUT RISK FACTORS.

QUESTIONS TO CLARIFY

- Can you tell me a little more about what you've heard?
- Which adverse event causes you the most concern?
- Which comorbidities, risk factors, or other factors do you consider when prescribing Iclusig?
- How do you typically test, monitor and manage for CV events in CML patients?
- What has been your experience with CV events in CML patients?
- Do you have a particular patient in mind? If yes,
  - What is the patient's disease/treatment history?
  - Does the patient have any comorbidities or a history of CV disease?
- What Iclusig information is important to you as you weigh the benefit and risks of treatment selection in a resistant CML patient?
- When you are evaluating the potential benefits and risks of different treatment options, how do you factor in the risk of disease progression?
- What outcomes are important to you? To your patient?

APPROVED RESPONSES

- Let me review the breakdown of events in PACE by age and whether or not the patient had a prior history of cardiovascular risk factors.
- Although patients with and without cardiovascular risk factors, including patients aged 50 years or younger, experienced vascular occlusive events, they were more frequent with increasing age and in patients with prior history of ischemia, hypertension, and diabetes or hyperlipidemia.
- The median age of patients in the PACE trial was 59. In the age group 50-74, vascular occlusive adverse reactions occurred more frequently (33%) in patients with certain cardiovascular risk factors (i.e., ischemia, hypertension, diabetes, or hyperlipidemia) than those patients without these cardiovascular risk factors (18%).
- Allow me to review with you PACE's patient demographics, as well as the clinical trial response rates.

APPROVED RESPONSES - Cont.

- Treatment can be optimized by active management, monitoring, and follow-up of underlying conditions. The cardiovascular status of a patient should be assessed before starting treatment with Iclusig, and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored during treatment with Iclusig.
- It's advised that patients who are suspected of developing arterial or venous thrombotic events should interrupt or stop Iclusig treatment.
- Iclusig should not be used in patients with a history of myocardial infarction, prior revascularization or stroke, unless the benefit outweighs the risks.
- ARIAD is committed to understanding Iclusig-associated vascular occlusive events and is continuing to investigate how risk factors contribute to a patient's risk of experiencing these events. Because every patient is different, the benefit and risks of treatment with Iclusig should be considered carefully for each individual patient being considered for treatment.

HANDLE TO RESOLVE: WHAT DATA TO USE

- USPI:
  - PI Highlights, Boxed Warning
  - Section 5.1, Warnings & Precautions—Vascular Occlusion
  - Section 5.1, Table 4 (Vascular Occlusion Incidence According to Risk Categories)
  - Section 12.2, Pharmacodynamics
  - Section 14, Table 10 (Demographic and Disease Characteristics)
  - Section 14, Tables 11 & 12 (Efficacy CP-CML and R/I Advanced Disease)
- Safety Assessment Guide
- Core Visual Aid
- PACE White Paper
- Submit MIRF upon request for specific unsolicited information

7 I AM CONCERNED THAT THE INCIDENCE OF TREATMENT-EMERGENT HYPERTENSION WAS HIGH IN THE PACE TRIAL

QUESTIONS TO CLARIFY

- Are you considering Iclusig for a patient with hypertension?
  - If yes, is the patient's blood pressure controlled or uncontrolled?
- How do you typically manage CML patients with hypertension?

APPROVED RESPONSES

- Patients enrolled in PACE were heavily pretreated (56% were treated with 3 or more prior TKIs) and had a history of resistance or intolerance to other therapies. Therefore, patient demographics and disease characteristics should be taken into consideration when interpreting safety results.
- Patients were eligible for enrollment in PACE regardless of the presence of hypertension or increased blood pressure.
- Vascular occlusive events were more frequent with increasing age and in patients with a prior history of ischemia, hypertension, diabetes, or hyperlipidemia.
- The dose intensity-safety relationship indicates that there are significant increases in grade ≥3 hypertension events over the dose range of 15 to 45 mg once daily.
  - The median dose intensity in the PACE trial was 37 mg per day; 54% of CP-CML patients achieved a MCyR.
- When discussing Iclusig treatment with your patients, inform them of the possibility of new or worsening of existing hypertension, and instruct them to report hypertensive symptoms.
- During Iclusig treatment, blood pressure should be monitored and managed at each clinic visit, and hypertension should be treated to normalize blood pressure. Iclusig treatment should be temporarily interrupted if hypertension is not medically controlled.
- Interrupt, dose reduce, or stop Iclusig if hypertension is not medically controlled. In the event of significant worsening, labile or treatment-resistant hypertension, interrupt treatment and consider evaluating for renal artery stenosis.

HANDLE TO RESOLVE: WHAT DATA TO USE

- USPI:
  - Section 5.1, Table 4
  - Section 5.4, Hypertension
- Safety Assessment Guide
- PACE
- Submit MIRF upon request for specific unsolicited information

8 CAN I GIVE ICLUSIG TO PATIENTS WHO HAVE ALREADY HAD A CARDIOVASCULAR EVENT? CAN A PATIENT TAKE CONCOMITANT MEDICATIONS AS A PROPHYLACTIC MEASURE?

QUESTIONS TO CLARIFY

- Do you have a particular patient in mind for Iclusig?
  - What is the patient's disease/treatment history?
  - Does the patient have any comorbidities or a history of CV disease?
- How do you typically treat a CML patient with a history of CV disease?
- To what extent does the risk of disease progression impact your TKI selection?

APPROVED RESPONSES

- History of cardiovascular disease is not a contraindication for Iclusig therapy; however, Iclusig should not be used in patients with a history of myocardial infarction, or prior revascularization or stroke, unless the potential benefit of treatment outweighs the potential risk.
- Before starting treatment with Iclusig, the cardiovascular status of the patient should be assessed, including history and physical examination, and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored, and medical and supportive therapy for conditions that contribute to cardiovascular risk should be optimized during treatment with Iclusig.
- While hypertension, diabetes, and dyslipidemia should be properly managed in patients treated with Iclusig, there are no specific recommendations in the PI for prophylactic treatment of vascular events.

HANDLE TO RESOLVE: WHAT DATA TO USE

- USPI:
  - Section 5, Warning & Precautions
- Safety Assessment Guide
- Submit MIRF upon request for specific unsolicited information

9 I USE BOSULIF BEFORE ICLUSIG BECAUSE IT'S A SAFER DRUG.

QUESTIONS TO CLARIFY

- What specific concerns do you have about Iclusig's safety profile?
- Are you currently treating a patient with Bosulif?
  - If yes, at what dose, and has the patient achieved a MCyR?
  - Is the patient adherent?
- What is your preferred treatment algorithm for CML?
- What type of results do you expect to see with Bosulif in a patient who has failed multiple TKIs? To what extent do the development of resistance and the risk ~~ofdisease~~ progression impact your TKI selection in the 3L setting?
  - Are you concerned about progression to advanced phases of CML?
- How often do you monitor patients for response to TKI therapy?
- At what point do you consider changing therapy if a patient does not achieve a response milestone per NCCN Guidelines? Do you conduct mutation analysis in these patients?

APPROVED RESPONSES

- Doctor, there are no head-to-head comparison studies with Bosulif and Iclusig. However, let me review the efficacy and safety data for Iclusig with you.
- Doctor, it's important to look at efficacy in conjunction with patient demographics and disease characteristics, as well as the overall benefit-risk to patients. Let me review the efficacy data for Iclusig with you.
- Routine monitoring of TKI responses throughout the course of therapy is an important part of treating patients with CML.
- The NCCN Guidelines include Iclusig as an option for appropriate 3rd-line patients.
- An individualized benefit-risk assessment can help determine whether Iclusig is an appropriate treatment option.

HANDLE TO RESOLVE: WHAT DATA TO USE

- USPI
  - Section 14, Clinical Studies
- Core Visual Aid
  - Efficacy data
- NCCN Guidelines for CML
- Submit MIRF upon request for specific unsolicited information

10 WHAT IS THE INCIDENCE OF MYELOSUPPRESSION WITH ICLUSIG, AND HOW IS IT MANAGED?

QUESTIONS TO CLARIFY

- Are you currently treating a patient with Iclusig, or do you have a patient in mind who may be a candidate for Iclusig therapy?
  - What is the patient's treatment history?
- How do you typically manage myelosuppression in your CML patients?

APPROVED RESPONSES

- Myelosuppression was common in all patient populations. Severe (Grade 3 or 4) myelosuppression occurred in 48% of patients treated with Iclusig. The incidence of myelosuppression was greater in patients with AP-CML, BP-CML and Ph+ ALL than in CP-CML.
- Obtain complete blood counts every two weeks for the first 3 months, then monthly or as clinically indicated. Adjust the dose as recommended.
- Dose modifications (dose delays or dose reductions) due to adverse reactions occurred in 74% of patients in the PACE trial.
  - The trial still met its primary endpoints, with 54% of CP-CML patients achieving a MCyR and 44% of CP-CML patients achieving a CCyR.

HANDLE TO RESOLVE: WHAT DATA TO USE

- USPI
  - Section 2.2, Dose modification for myelosuppression
  - Section 5.11, Myelosuppression
  - Section 6, Table 7
- Dosing and Dose Modification Guide
- Safety Assessment Guide
- Submit MIRF upon request for specific unsolicited information

11 WHAT ARE THE GUIDELINES FOR MANAGING HEPATIC TOXICITY?

QUESTIONS TO CLARIFY

- Are you currently treating a patient with Iclusig, or do you have a patient in mind who may be a candidate for Iclusig therapy?
  - What is the patient's treatment history?
  - What is the patient's hepatic function?

APPROVED RESPONSES

- The most commonly reported treatment-emergent hepatic AEs in PACE were increased ALT (53% Any Grade, 8% Grade 3/4) and AST (41% Any Grade, 4% Grade 3/4).
- Management strategies include monitoring liver function tests at baseline, and then at least monthly or as clinically indicated thereafter.
- Interrupt, reduce or discontinue Iclusig as clinically indicated.

HANDLE TO RESOLVE: WHAT DATA TO USE

- USPI:
  - Section 2.3, Table 2
  - Section 5.3, Hepatotoxicity
- Dosing and Dose Modification Guide
- Safety Assessment Guide
- Submit MIRF upon request for specific unsolicited information

12 WHAT ARE THE GUIDELINES FOR MANAGING PANCREATITIS?

QUESTIONS TO CLARIFY

- Are you currently treating a patient with Iclusig, or do you have a patient in mind who may be a candidate for Iclusig therapy?
  - What is the patient's treatment history?
  - Does the patient have a history of pancreatitis or alcohol abuse?

APPROVED RESPONSES

- Clinical pancreatitis occurred in 6% of PACE patients:
  - 22 of the 28 cases of pancreatitis resolved within two weeks with dose interruption or reduction
  - The incidence of treatment-emergent lipase elevation was 41%
- Check serum lipase every 2 weeks for the first 2 months and then monthly thereafter or as clinically indicated.
- Consider additional serum lipase monitoring in patients with a history of pancreatitis or alcohol abuse.
- Interrupt or reduce dose according to PI recommendations.
- Interrupt treatment and evaluate patient for pancreatitis if lipase elevations are accompanied by abdominal symptoms.
- Do not consider restarting Iclusig until patients have complete resolution of symptoms and lipase levels are less than 1.5 x ULN.

HANDLE TO RESOLVE: WHAT DATA TO USE

- USPI:
  - Section 2.2, Table 3
  - Section 5.5, Pancreatitis
  - Dosing and Dose Modification Guide
- Safety Assessment Guide
- Submit MIRF upon request for specific unsolicited information

13 HOW MANY DEATHS OCCURRED IN THE PACE TRIAL? WHAT IS THE MEDIAN TIME TO A VASCULAR OCCLUSIVE EVENT?

QUESTIONS TO CLARIFY

- Do you currently have a patient on Iclusig? If yes:
  - What is the patient's disease/treatment history?
  - Does the patient have any comorbidities or a history of CV disease?
  - What is the patient's risk of disease progression?

APPROVED RESPONSES

- With a median follow-up of 24 months for all patients in PACE, 109/449 (24%) patients experienced a VOE. Of the patients who experienced a VOE, 5 patients died of a Grade 5 vascular event, and 5 additional patients died with vascular events possibly contributing to death.
- In the dose-escalation (Phase 1) clinical trial, the median time to onset of the first vascular occlusion event was 5 months.
- An individualized benefit-risk assessment can help determine whether Iclusig is an appropriate treatment option.

HANDLE TO RESOLVE: WHAT DATA TO USE

- USPI:
  - Section 5.1 Vascular Occlusion
- PACE publication
- Phase I publication
- Submit MIRF upon request for specific unsolicited information.

Ariad Pharmaceuticals, Inc.
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