POLICY NUMBER UM ONC_1241	SUBJECT Iclusig™ (ponatinib)		DEPT/PROGRAM UM Dept	PAGE 1 OF 4
DATES COMMITTEE REVIEWED 05/08/13, 07/24/14, 12/18/15, 12/21/16, 10/31/17, 11/08/17, 10/10/18, 09/11/19, 12/11/19	APPROVAL DATE December 11, 2019	EFFECTIVE DATE December 11, 2019	COMMITTEE APPROVAL DATES (latest version listed last) 05/08/13, 07/24/14, 12/18/15, 12/21/16, 10/31/17, 11/08/17, 10/10/18, 09/11/19, 12/11/19	
PRIMARY BUSINESS OWNER: UM APPROVED BY: Dr. Andrew Hertler		COMMITTEE/BOARD APPROVAL Utilization Management Committee		
URAC STANDARDS HUM 1		NCQA STANDARDS UM 2	ADDITIONAL AREAS OF IMPACT	
CMS REQUIREMENTS	STATE/FEDERAL REQUIREMENTS		APPLICABLE LINES OF BUSINESS All	

I. PURPOSE

To define and describe the accepted indications for Iclusig (ponatinib) usage in the treatment of cancer.

II. DEFINITIONS

Iclusig (ponatinib): is an oral multi-tyrosine kinase inhibitor (TKI). It works by inhibiting BCR-ABL and T315I mutant BCR-ABL in addition to other tyrosine kinase proteins (e.g., VEGFR, PDGFR, FGFR, EPH, Src family kinases, KIT, RET, FLT-3, and TIE-2) that promote the growth and development of cancer cells. The Philadelphia chromosome encodes for the BCR-ABL oncogene and is found in most chronic myelogenous leukemia cells. A common mutation occurs in the kinase domain caused by a substitution of a threonine residue with isoleucine at amino acid position 315 (T315I mutation). This mutation causes drug resistance to imatinib and some second generation TKI agents such as nilotinib and dasatinib. The T315I mutation prevents the formation of an important hydrogen bond between TKI agents and T315 of the BCR-ABL molecule. Ponatinib was designed to bind while allowing for the accommodation of the bulky isoleucine side chain. It also has activity against several other BCR-ABL mutations including the E255K, Y253H, and G250E mutations.

Iclusig (ponatinib) is FDA approved for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy. Treatment of adult patients with T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).

Iclusig (ponatinib) is available as 15 mg, 30 mg, and 45 mg tablets.

III. POLICY

New Century is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century may be deemed as not approvable and therefore not reimbursable.

Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must CMS Medicare Benefit Policy Manual Chapter 15. If references are not produced, delays may occur to the processing of such request.

Inclusion Criteria: Iclusig (ponatinib) may be considered medically necessary when any of the following selection criteria is met:

1. **Chronic Myelogenous Leukemia (CML)**
    a. The member has chronic, accelerated, or post-transplant relapse CML **AND**
    b. The member is Philadelphia chromosome positive **AND**

c. The member has failed to respond or has intolerance or contraindications to imatinib, nilotinib, dasatinib, and bosutunib **OR**

d. In member with T3151 mutation.

2. **Acute Lymphoblastic Leukemia (ALL)**

a. Iclusig (ponatinib) is being used for members with Philadelphia chromosome-positive ALL as **ONE** of the following:

i. Induction/consolidation therapy:

A. As a component of HyperCVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine) + TKI (ponatinib).

ii. Maintenance therapy:

A. In combination with vincristine and prednisone with or without methotrexate and mercaptopurine **AND**

B. Post-hematopoeitic stem cell transplant

iii. Relapsed/refractory therapy:

A. The member has failed to respond or has intolerance or contraindications to at least 2 tyrosine kinase inhibitors (i.e., imatinib, nilotinib, or dasatinib) **OR**

B. In combination with an induction regimen not previously given **OR**

C. In members with T3151 mutations

Exclusion Criteria: Iclusig (ponatinib) is not considered medically necessary when any of the following selection criteria is met:

1. Disease progression while taking Iclusig (ponatinib).
2. Concurrent use with other tyrosine kinase inhibitors.
3. Dosing exceeds single dose limit of Iclusig (ponatinib) 45 mg.
4. Treatment exceeds the maximum limit of 30 (45 mg) tablets/month or 90 (15 mg) tablets/month.
5. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.

IV. PROCEDURE

Requests for Iclusig (ponatinib) shall be reviewed for appropriateness per FDA approved product labeling, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical guidelines, or CMS approved compendia.

1. **Dosage and Administration:** 45 mg orally one daily.
2. **Dosage Adjustments:**

a. Concomitant use of strong CYP3A inhibitor: reduce ponatinib dose to 30 mg orally once daily.

b. Hepatic impairment (Child-Pugh class A, B, or C): Initial, 30 mg orally once daily

c. Hepatic toxicity (liver transaminase more than 3 times ULN): interrupt therapy, monitor hepatic function, resume dosing after recovery of liver transaminase to less than 3 times

ULN; for occurrence on 45 mg, resume at 30 mg; for occurrence on 30 mg, resume at 15 mg; for occurrence at 15 mg, discontinue therapy.

d. Hepatic toxicity (elevation of AST or ALT to 3 times or higher ULN with a concurrent elevation of bilirubin to more than 2 times ULN and alkaline phosphatase less than 2 times ULN): discontinue therapy.

e. Cardiovascular, slow or rapid heart rate: Interrupt therapy

f. Cardiovascular, serious arterial or venous occlusive reaction: Modify, interrupt, or discontinue therapy; do not restart unless benefit outweighs risk and no other treatment options are available.

g. Fluid retention: Interrupt therapy, reduce dosage, or discontinue treatment

h. Hemorrhage, serious or severe: Interrupt therapy.

i. Hypertension: Interrupt therapy, reduce dosage, or discontinue for uncontrolled hypertension.

j. Major surgery: Interrupt therapy for at least 1 week prior to surgery and resume when clinically assessed for adequate wound heal.

k. Myelosuppression (ANC less than 1 x 10(9)/L or platelet count less than 50 x 10(9)/L): interrupt therapy, resume after recovery of ANC to 1.5 x 10(9)/L or greater and platelet count to 75 x 10(9)/L or greater; for first occurrence, resume at 45 mg; for second occurrence, resume at 30 mg; for third occurrence, resume at 15 mg.

l. Pancreatitis (asymptomatic grade 1 or 2 serum lipase increase): consider interrupting therapy or reducing the ponatinib dose.

m. Pancreatitis (asymptomatic grade 3 or 4 serum lipase increase (more than 2 times ULN) or asymptomatic radiologic pancreatitis (grade 2)): interrupt therapy and resume after recovery to grade 1 or less (less than 1.5 times ULN); for occurrence on 45 mg, resume at 30 mg; for occurrence on 30 mg, resume at 15 mg; for occurrence at 15 mg, discontinue therapy.

n. Pancreatitis (symptomatic grade 3): interrupt therapy and resume after complete resolution of symptoms and recovery of lipase elevation to grade 1 or less; for occurrence on 45 mg, resume at 30 mg; for occurrence on 30 mg, resume at 15 mg; for occurrence at 15 mg, discontinue therapy.

o. Pancreatitis (grade 4): discontinue ponatinib therapy.

p. Serious ischemic reaction: modify or interrupt therapy; do not restart unless benefit outweighs risk and no other treatment options are available.

q. Serious nonhematologic nonischemic reaction: modify or interrupt therapy, do not restart unless benefit outweighs risk.

3. **Monitoring:**

a. Cytogenetic response and/or hematologic response are an indication of efficacy.

b. CBC; every 2 weeks during the first 3 months, and monthly thereafter, or as clinically indicated; include differential.

c. Hypertension; regularly throughout therapy.

d. Lipase; every 2 weeks during the first 2 months, and monthly thereafter, or as clinically indicated; additional monitoring may be necessary in patients with a history of pancreatitis or alcohol abuse.

e. Liver function tests; at baseline and monthly thereafter or as clinically indicated.

f. Signs of congestive heart failure; regularly throughout therapy.

g. Signs of fluid retention; regularly throughout therapy.

h. Vascular Occlusion: Arterial and venous thrombosis and occlusions have occurred in at least 35% of ponatinib hydrochloride-treated patients, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events.

i. Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or stop ponatinib hydrochloride immediately for vascular occlusion. A benefit-risk consideration should guide a decision to restart ponatinib hydrochloride therapy.

V. APPROVAL AUTHORITY

1. Review – UM Department
2. Final Approval – UM Committee

VI. ATTACHMENTS

None

VII. REFERENCES

1. Iclusig prescribing information. Ariad Pharmaceuticals, Cambridge, MA. 2019.
2. Clinical Pharmacology Elsevier Gold Standard. 2019.
3. Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, Co. 2019.
4. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium. 2019.
5. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD. 2019