Drug Monograph

Drug/Drug Class:	**Tibsovo® (ivosidenib) 250mg tablet / Antineoplastic Agent**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Tibsovo® is available as a 250 mg film coated immediate release tablet. Distributed by: Agios Pharmaceuticals, Inc. Cambridge, MA 02139.
Summary of Findings:	Tibsovo® is currently the only FDA approved therapy for RR AML with an IDM1 mutation. Based on the medications risk of differentiation syndrome, QTc interval prolongation and drug interactions, special care should be held when dosing and monitoring patients taking Tibsovo®. Efficacy of Tibsovo® was demonstrated in an open label, single arm, multicenter, clinical trial. Efficacy was defined as rate of complete remission (CR) plus complete remission with partial hematologic recovery (CRh), the duration of CR+CRh and the rate of conversion from transfusion dependence to transfusion independence. 56 out of 174 (32.8%) of patients achieved CR and CRh in a median time period of 2 months. 41% of patients achieved transfusion independence at some point in the 56 days post baseline.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ Fiscal Edit
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Non-Preferred Agent ☒ Appropriate Indications ☐ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2]

Acute myeloid leukemia (AML), sometimes known as acute myelocytic leukemia, is a type of cancer originating in the bone marrow and can quickly spread to blood and other parts of the body including lymph nodes, liver and central nervous system. Because of the progression and presentation of AML, it is not staged in the manner of most cancers. Instead we utilize lab tests to determine the subtype of AML and other factors, a person's age for instance, to better predict outcomes. In regard to prognosis, the different subtypes of AML can also help doctors determine the intensity of treatment and risk of the leukemia returning after treatment. The majority of AML subtypes are centered around abnormalities. These abnormalities can be traced back to chromosome alterations, gene mutations, certain protein markers, age, or infection to name a few. By utilizing subtype treatment options, we can produce more specific and targeted therapy regimens that can lead to increased responses. This is important because better initial responses have been linked with improved long-term outcomes.

Dosage Form [1,3]

Tibsovo® is available as a film-coated 250 mg tablet.

Manufacturer [1]

Distributed by: Agios Pharmaceutical, Inc. Cambridge, MA 02139.

Indication(s) [1,3]

Tibsovo® is FDA approved for the treatment of adults with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test.

Clinical Efficacy [1] (mechanism of action/pharmacology, comparative efficacy)

Tibsovo® (ivosidenib) is an inhibitor of isocitrate dehdrogenase-1 (IDH1) enzyme. These IDH1 mutations can lead to increased levels of 2-hydroxyglutarate (2-HG) in leukemia cells and impaired hematopoietic differentiation. Ivosidenib decreased intracellular 2-HG, reduced blast counts and induced differentiation in IDH1 mutated AML blood samples.

Pharmacokinetics:

	Tibsovo®
Protein Binding	92 – 96% in vitro
Volume of Distribution	234 L
Metabolism	Hepatic, Primarily CYP3A4

Excretion (Renal)	Urine, 17% (10% Unchanged drug) Feces, 77% (67% Unchanged drug)
Half-life	~93 hours

Efficacy of Tibsovo® in patients with Relapsed or Refractory AML

STUDY DESIGN	Open-label, single-arm, multicenter, clinical trial (N=174).
INCLUSION CRITERIA	Adult patients, over 18 years old, with RR AML with an IDH1 mutation as defined by an FDA-approved diagnostic test and confirmed retrospectively using the Abbott Real*Time*™ IDH1 Assay. The most common IDH1 mutation types were R132C and R132H.
EXCLUSION CRITERIA	Patients not identified as having RR AML with an IDH1 mutation, which is the requirement for treatment with Tibsovo®.
TREATMENT REGIMEN	Patients received Tibsovo® 500 mg (n=174) once daily until disease progression, development of unacceptable toxicity, or undergoing hematopoietic stem cell transplantation.
RESULTS	Efficacy was defined as rate of complete remission (CR) plus complete remission with partial hematologic recovery (CRh), the duration of CR+CRh and the rate of conversion from transfusion dependence to transfusion independence. Of the patients that achieved a CR or CRh, the median time to this point was 2 months. Of the 57 patients who achieved this response, all achieved a CR or CRh within 6 months of starting Tibsovo®. There were 100 patients that were transfusion dependent at baseline, 41 became independent at some point 56-day post-baseline and 38 of 64 who were independent at baseline remained independent. 21 patients (12%) went on stem cell transplant following Tibsovo® treatment.

Contraindications (1)

- There are no contraindications listed per the manufacturer labeling.

Warnings and Precautions (1,3)

- Differentiation Syndrome: 19% of Tibsovo® treated patients experienced differentiation syndrome. This is associated with a potential life threatening or fatal rapid proliferation and differentiation of myeloid cells if not treated. Symptoms include leukocytosis, peripheral edema, dyspnea, hypotension, pleural effusion, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome and

creatinine increase.

- QTc Interval Prolongation: Patients can develop QT prolongation and ventricular arrhythmias while on Tibsovo® which may be increased with concomitant use with other known QTc prolonging medications. Appropriate monitoring should be done while on Tibsovo® and treatment should be stopped if QTc increases to greater than 480 msec and less than 500 msec, stopped and reduced if greater than 500 msec and discontinued if signs/symptoms of life-threatening arrhythmia.
- Guillain-Barré Syndrome: While only occurring in <1% of patients taking Tibsovo®, patients should be monitored for onset of new signs/symptoms of motor and/or sensory neuropathy. Tibsovo® should be discontinued in patients who are diagnosed with Guillain-Barré syndrome.

Adverse Effects (1)

The most common adverse reactions (≥ 20%) with Tibsovo® were fatigue, leukocytosis, arthralgia, diarrhea, dyspnea, edema, nausea, mucositis, electrocardiogram QT prolonged, rash, pyrexia, cough and constipation. The most common reactions leading to stopping therapy were electrocardiogram QT prolonged (17%), differentiation syndrome (3%), leukocytosis (3%) and dyspnea (3%).

Most Common (≥10%) or ≥5% (Grade ≥3) New or Worsening Lab Abnormalities Reported

	Tibsovo® 500mg Daily N=179	**Tibsovo® 500mg Daily N=179**
Parameter	**All Grades (n) %**	**≥ Grade 3 (n) %**
Hemoglobin decreased	108 (60)	83 (46)
Sodium decreased	69 (39)	8(4)
Magnesium decreased	68 (38)	0
Uric acid decreased	57 (32)	11(6)
Potassium decreased	55 (31)	11 (6)
Alkaline phosphatase increased	49 (27)	1 (1)
Aspartate aminotransferase increased	49 (27)	1 (1)
Phosphate decreased	45 (25)	15 (8)
Creatinine increased	42 (23)	2 (1)
Alanine aminotransferase increased	26 (15)	2 (1)
Bilirubin increased	28 (16)	1 (1)

*Lab abnormality is defined as new/worsened by at least 1 grade from baseline.

Drug Interactions [1]

- Strong and Moderate CYP3A4 Inhibitors
- QTc Prolongation Drugs
- Tibsovo® can induce CYP2C9

Dosage and Administration [1,3]

The FDA recommended dose is 500 mg (2 tablets) by mouth once daily until disease progression or unacceptable toxicity. Tibsovo® can be given with or without food however should not be administered with a high-fat meal as this can lead to an increase in ivosidenib concentration. Tibsovo® should not be split or crushed and should be given at or around the same time each day. If a dose is missed, the dose should be taken as soon as possible and at least 12 hours before the next scheduled dose.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost/Month
Ivosidenib	**Tibsovo®**	Agios Pharmaceuticals	250 mg Tablet	$

* Wholesale Acquisition Cost

** Maximum Allowable Cost

Conclusion

Tibsovo® is indicated for adult patients with relapsed or refractory AML with a susceptible isocitrate dehydrogenase-1 (IDH1) mutations. There is estimated to be less than 1100 adult patients in the United States eligible for Tibsovo®, causing this medication to be designated as an Orphan Drug by the FDA. Each year the US sees around 20,000 new AML cases with less than 10% having the IDH1 mutation.

In a clinical trial looking at the efficacy of Tibsovo® in patients with RR AML with an IDM1 mutation, Tibsovo® showed promise in getting patients to reach an end-point of complete remission, complete remission with partial hematologic recovery and independence from transfusions. The most common reasons to stop Tibsovo® therapy were QT prolongation, leukocytosis, differentiation syndrome and dyspnea.

Recommendation

The Division recommends adding this drug to the current 15 day quantity limitation Oral Oncology Fiscal Edit.

References

1) Product Information: Tibsovo® (ivosidenib) Agios Pharmaceuticals, Inc Cambridge, MA 2018.
2) Falco, Miriam, Alteri, Rick MD et al. Acute Myeloid Leukemia (AML) Subtypes and Prognostic Factors, American Cancer Society August 21st, 2018.

3) Ivosidenib (Lexi-Drugs) Wolters Kluwer Clinical Drug Information Inc 8/27/2018

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