ティブソボ錠250mg
に関する資料

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ティブソボ錠 250mg

医薬品製造販売承認申請書添付資料

第 1 部（モジュール 1）

1.5　起原又は発見の経緯及び開発の経緯

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1.　起原又は発見の経緯及び開発の経緯

急性骨髄性白血病（AML）は急速に進行する造血器悪性腫瘍であり、適切な治療がなされない場合は感染症や出血によって短期間で死に至る。未治療 AML 患者に対する初回治療の目標は、強力な寛解導入療法によって完全寛解を目指すことであるが、高齢の患者、重大な併存症を有する患者及び全身状態が不良な患者に対して強力な寛解導入療法を適応することは困難であり、治療選択肢は限られる。

AML でみられる遺伝子変異の 1 つに、イソクエン酸脱水素酵素 1（IDH1）に関する遺伝子変異がある。*IDH1* 遺伝子変異によって発現する変異型 IDH1 は、細胞の分化を阻害する代謝物である 2-ヒドロキシグルタル酸（2-HG）を過剰に産生させ、腫瘍形成を促進させる。

イボシデニブ（ティブソボ®、本剤）は IDH1 に対する低分子の強力な選択的阻害剤であり、経口投与により活性を示す。本剤は変異型 IDH1 を直接的に阻害することにより、2-HG の産生を阻害し、細胞分化を回復させ、腫瘍形成を抑制する。

本剤は AML の治療薬として 2018 年 7 月に米国で承認されて以降、2024 年 4 月時点で *IDH1* 遺伝子変異陽性の AML、胆管癌又は骨髄異形成症候群の治療薬として 35 カ国以上で承認されている。本邦では、第 IV 回医療上の必要性の高い未承認薬・適応外薬の要望募集において日本血液学会より要望書が提出されており、20[redacted]年[redacted]月より、強力な寛解導入療法の適応とならない未治療の *IDH1* 遺伝子変異を有する AML 患者を対象とした国際共同第 III 相試験（AG120-C-009 試験）が開始された。

IDH1 の変異に特異的な治療薬は本邦では承認されていないことから、本剤は本邦での AML 治療におけるアンメットメディカルニーズに応え、強力な寛解導入療法の適応とならない *IDH1* 遺伝子変異陽性の未治療 AML 患者に対する新しい治療選択肢を与えるものと期待される。

なお、本剤は本邦において「*IDH1* 遺伝子変異陽性の急性骨髄性白血病」を予定される効能又は効果として希少疾病用医薬品に指定されており、米国及び欧州においては、急性骨髄性白血病の治療に対して希少疾病用医薬品の指定を受けている。

1.1　開発の経緯

本剤の開発の経緯図を図 1.1:1 に示す。

1.1.1　品質

モジュール 2.3 に示す。

1.1.2　非臨床試験

モジュール 2.4 に示す。

1.1.3　臨床試験

モジュール 2.5 第 1.5 項に示す。

1.1.4　申請効能・効果に対する本剤の有用性

本剤は、図 1.1:1 に示した試験結果を踏まえ、その有効性及び安全性が確認され、*IDH1* 遺伝子変異陽性の急性骨髄性白血病に対して有用であると結論付けることができる。

詳細はモジュール 2.5 第 6 項に示す。

試験項目		[redacted]
品質	品質に関する試験	
薬理	効力を裏付ける試験	
	副次的薬理試験	
	安全性薬理試験	
薬物動態	分析法及びバリデーション報告書	
	吸収	
	分布	
	代謝	
	排泄	
	薬物動態学的薬物相互作用	
毒性試験	単回投与毒性試験	
	反復投与毒性試験	
	遺伝毒性試験	
	生殖発生毒性試験	
	不純物の毒性試験	
	その他の試験	

図 1.1:1　開発の経緯図

試験項目		開始日	終了日	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
第 I 相	海外、健康成人（AG120-C-006）	2017 年 3 月	2017 年 9 月									―							
	海外、進行性血液悪性腫瘍患者（AG120-C-001）	2014 年 3 月	継続中						―	―	―	―	―	―	―	―	―	―	―
第 Ib/II 相	海外、AML 患者（AG-221-AML-005）	2016 年 6 月	継続中								―	―	―	―	―	―	―	―	―
第 III 相	国際共同、AML 患者（AG120-C-009）	20[redacted]年[redacted]月	継続中	[redacted]															
臨床薬理	海外、食事の影響（AG120-C-004）	2015 年[redacted]月	2016 年 6 月																
	海外、マスバランス（AG120-C-003）	2015 年 6 月	20[redacted]年[redacted]月																
	海外、肝機能障害（AG120-C-012）	2017 年 9 月	2018 年[redacted]月																
	海外、薬物相互作用（AG120-C-007）	2016 年[redacted]月	20[redacted]年 [redacted]月																
その他第 I 相	海外、進行性悪性固形腫瘍患者（AG120-C-002）	2014 年 3 月	継続中						―	―	―	―	―	―	―	―	―	―	―

図 1.1:1　開発の経緯図（続き）

ティブソボ錠 250mg

医薬品製造販売承認申請書添付資料

第 1 部（モジュール 1）

1.6　外国における使用状況等に関する資料

日本セルヴィエ株式会社

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1.　外国における使用状況等

2024 年 11 月 30 日時点において、本剤は米国、英国、ドイツ、フランス、カナダ、オーストラリアを含む 42 カ国で承認されている（急性骨髄性白血病 41 カ国、胆管癌 40 カ国、骨髄異形成症候群 3 カ国）。

米国及び EU における販売名、剤形、含量、効能・効果、用法・用量及び承認日を表 1:1 に示す。

表 1:1　　米国及び EU の販売名、剤形、含量、効能・効果、用法・用量及び承認日

国名	米国	EU
販売名	TIBSOVO	Tibsovo
剤形	錠剤	錠剤
含量	250 mg	250 mg
効能・効果	**未治療の急性骨髄性白血病** 本剤はアザシチジンとの併用投与又は単剤投与において、FDA に承認された検査により感受性イソクエン酸脱水素酵素 1（IDH1）変異が検出された、75 歳以上又は寛解導入療法の適応とならない併存症を有する未治療の成人の急性骨髄性白血病（AML）患者の治療を適応とする。［用法及び用量（2.1）、臨床薬理試験（12.1）及び臨床成績（14.1）を参照］ **再発又は難治性の急性骨髄性白血病** 本剤は、FDA に承認された検査により感受性イソクエン酸脱水素酵素 1（IDH1）変異が検出された、再発又は難治性の成人の急性骨髄性白血病（AML）患者の治療を適応とする。［用法及び用量（2.1）、臨床薬理試験（12.1）及び臨床成績（14.2）を参照］ **再発又は難治性の骨髄異形成症候群** 本剤は、FDA に承認された検査により感受性イソクエン酸脱水素酵素 1（IDH1）変異が検出された、再発又は難治性の成人の骨髄異形成症候群（MDS）患者の治療を適応とする。［用法及び用量（2.1）、臨床薬理試験（12.1）及び臨床成績（14.3）を参照］ **局所進行性又は転移性の胆管癌** 本剤は、FDA に承認された検査により感受性イソクエン酸脱水素酵素 1（IDH1）変異が検出された、前治療歴のある成人の局所進行性又は転移性の胆管癌患者の治療を適応とする。［用法及び用量（2.1）、臨床薬理試験（12.1）及び臨床成績（14.4）を参照］	本剤とアザシチジンの併用投与は、標準的な寛解導入療法の適応とならないイソクエン酸脱水素酵素 1（IDH1）R132 変異陽性の未治療の成人の急性骨髄性白血病（AML）患者の治療を適応とする（5.1 項を参照）。 本剤の単剤投与は、少なくとも 1 ライン以上の全身療法の治療歴があり、IDH1 R132 変異陽性の局所進行性又は転移性の成人の胆管癌患者の治療を適応とする（5.1 項を参照）。
用法・用量	**患者選択** IDH1 変異の発現を確認し、本剤による治療の対象患者を選択す	抗悪性腫瘍剤の使用経験がある医師の監督のもとで治療を開始する。

	る。［臨床成績（14.1、14.2、14.3、14.4）を参照］ AML、MDS 及び胆管癌患者を対象とした FDA に承認された IDH1 変異検出検査に関する情報は次のとおりである： http://www.fda.gov/CompanionDiagnostics. **推奨用量** 本剤の推奨用量は、疾患進行又は許容できない毒性の発現まで 1 日 1 回 500 mg の経口投与である。［臨床成績（14.1、14.2、14.3、14.4）を参照］ 疾患進行又は許容できない毒性が発現しない AML 患者又は MDS 患者には、臨床効果を確認するため 6 カ月以上は本剤の投与を継続する。 ・ 食事の有無にかかわらず本剤は投与可能である。 ・ 高脂肪食とともに本剤を投与しない。［警告及び使用上の注意（5.2）及び臨床薬理試験（12.3）を参照］ ・ 錠剤を分割、粉砕又は噛み砕いて服用しない。 ・ 毎日所定の時刻に本剤を経口投与する。 ・ 本剤を嘔吐した場合、再投与せず次回の投与時刻まで待つ。 ・ 本剤を飲み忘れた場合又は所定の時刻に服用しなかった場合、次回投与の 12 時間以上前であれば気づいた時点で直ちに服用し忘れた分を投与する。翌日から所定の時刻に投与する。12 時間以内に 2 回投与しない。 未治療の AML（併用療法レジメン） 本剤はサイクル 1 の 1 日目に投与開始し、併用薬であるアザシチジンは 28 日サイクルの 1～7 日目（又は 1～5 日目と 8、9 日目）に 1 日 1 回 75 mg/m^2 で皮下投与又は点滴静注する。［臨床成績（14.1）を参照］アザシチジンの用法及び用量の情報について、詳しくは添付文書を参照する。 **副作用に対するモニタリング及び用量調節** 治療開始前に心電図（ECG）を測定する。治療開始後 3 週間は週 1 回以上、その後の治療期間中は月 1 回以上 ECG をモニタリング	本剤を投与する前に適切な診断検査により IDH1 R132 の変異の有無を確認する必要がある。 用法及び用量 急性骨髄性白血病 本剤の推奨用量はイボシデニブ 500 mg（250 mg 錠×2）の 1 日 1 回経口投与である。本剤はサイクル 1 の 1 日目に投与開始し、併用薬であるアザシチジンは 28 日サイクルの 1～7 日目に 1 日 1 回 75 mg/m^2（体表面積）で点滴静注又は皮下投与する。アザシチジンはサイクル 1 では投与量のうち全量投与する。最低 6 サイクルの治療が推奨される。 アザシチジンの用法及び用量については、アザシチジンの製品情報全文を参照。 疾患進行が認められるか患者に許容できない毒性が確認されるまで治療を継続する。 胆管癌 本剤の推奨用量はイボシデニブ 500 mg（250 mg 錠×2）の 1 日 1 回経口投与である。 疾患進行が認められるか患者に許容できない毒性が確認されるまで治療を継続する。 飲み忘れ又は服用のタイミングが遅れた場合 本剤の飲み忘れや、所定の時刻に服用されなかった場合、本来服用すべき時点から 12 時間以内であれば気づいた時点で直ちに服用し忘れた分を服用する。12 時間以内に 2 回服用しない。翌日から所定の時刻に服用する。 本剤を嘔吐した場合、再度服用せず、翌日から所定の時刻に服用する。 投与前の注意及びモニタリング 治療開始前に心電図（ECG）を測定する。治療開始前に心拍数で補正した QT 間隔（QTc）は 450 msec 未満である。QT の異常が認められた場合、本剤を開始することのベネフィット／リスクを

する。［警告及び使用上の注意（5.2）を参照］異常が認められた場合は速やかに管理する。
毒性が認められた場合は休薬又は減量する。用量調節のガイドラインについては表 1 を参照する。

表 1：推奨される本剤の用量調節

副作用	推奨される対応
・ 分化症候群［警告及び使用上の注意（5.1）を参照］	・ 分化症候群が疑われる場合、全身性コルチコステロイドを投与し、血行動態モニタリングを 3 日以上かつ症状が消失するまで継続する。 ・ 全身性コルチコステロイド投与開始後 48 時間以降も重度の徴候及び／又は症状が続いた場合、本剤を休薬する。 ・ 徴候及び症状が Grade 2*以下に改善した場合、本剤の投与を再開する。
・ 非感染性の白血球増加症（白血球数が 25×10^9/L 超又は総白血球数の絶対数がベースラインより 15×10^9/L 超増加）	・ 医療機関ごとの基準に従いヒドロキシウレアによる治療を開始し、臨床上必要ならば白血球アフェレーシスを実施する。 ・ 白血球増加症が改善又は消失した後に限りヒドロキシウレアを漸減する。 ・ ヒドロキシウレア投与により白血球増加症が改善しない場合、本剤を休薬し、白血球増加症が消失した場合、本剤を 1 日 1 回 500 mg で再開する。
・ QTc 間隔が 480 msec 超 500 msec 以下［警告及び使用上の注意（5.2）及び薬物相互作用（7.1）を参照］	・ 電解質濃度をモニタリングし、臨床上必要に応じて電解質を補給する。 ・ QTc 間隔延長を起こすことが知られている併用薬を確認し調節する。 ・ 本剤を休薬する。 ・ QTc 間隔が 480 msec 以下に回復した後、本剤を 500 mg1 日 1 回で再開する。 ・ QTc 延長の消失後 2 週間は週に 1 回以上 ECG をモニタリングする。
・ QTc 間隔が 500 msec 超［警告及び使用上の注意（5.2）及び	・ 電解質濃度をモニタリングし、臨床上必要に応じて電解質を補給する。 ・ QTc 間隔延長を起こすことが知られている併用薬を確認し調節する。

医師が十分に再評価する。QTc 間隔延長が 480 msec から 500 msec の場合、本剤による治療を開始することは例外的なケースとし、治療を開始した場合は密にモニタリングする。
治療開始前、治療開始後 3 週間は週 1 回以上、その後は月 1 回 ECG を測定し、QTc 間隔が 480 msec 以下であるか確認する。QTc 間隔の異常が認められた場合は速やかに処置を行う（表 1 及び 4.4 項を参照）。徴候が示唆された場合、臨床上必要に応じて ECG を測定する。
QTc 間隔延長を起こすことが知られている薬剤又は中程度若しくは強い CYP3A4 阻害剤と本剤とを併用投与すると、QTc 間隔延長のリスクが上昇する可能性があるため、本剤の治療期間中は可能な限り併用投与を避ける。適切な代替薬を使用できない場合、慎重に投与し、QTc 間隔延長について密にモニタリングする。併用投与開始前、投与開始後少なくとも 3 週間は週 1 回、その後は臨床上必要に応じて ECG を測定する（4.4、4.5 及び 4.8 項を参照）。
全血球数及び血液生化学の評価は、本剤による治療開始前、治療開始の 1 カ月目は週 1 回以上、2 カ月目は隔週 1 回、治療期間中は来院時に臨床上必要に応じて実施する。

<u>中程度又は強い CYP3A4 阻害剤を併用投与した場合の用量調節</u>
中程度又は強い CYP3A4 阻害剤の投与が避けられない場合、本剤の推奨用量を 1 日 1 回 250 mg（250 mg 錠×1）に減量する。中程度又は強い CYP3A4 阻害剤の投与を中止する場合、CYP3A4 阻害剤の 5 半減期以上経過後に本剤の用量を 500 mg に増量する（上記、4.4 及び 4.5 項を参照）。

<u>副作用に対する用量調節及び推奨される管理</u>
表 1 - 副作用に対する推奨される用量調節

副作用	推奨される対応
分化症候群（4.4 及び 4.8 項を参照）	・ 分化症候群が疑われる場合、全身性コルチコステロイドを 3 日以上投与し、症状が消失した後に限り漸減する。早期投与中止により、症状再発の可能性がある。 ・ 3 日以上かつ症状が消失するまで血行動態モニタリングを実施する。

薬物相互作用（7.1）を参照］	・ 本剤を休薬する。 ・ QTc 間隔がベースライン時の 30 msec 以内又は 480 msec 以下に回復した後、本剤を 1 日 1 回 250 mg に減量し再開する。 ・ QTc 延長の消失後 2 週間は週に 1 回以上 ECG をモニタリングする。 ・ QTc 延長に他の原因が特定された場合、本剤の用量を 1 日 1 回 500 mg に再度増量することを考慮する。
・ 生命を脅かす不整脈の徴候／症状を伴う QTc 間隔延長［警告及び使用上の注意（5.2）を参照］	・ 本剤を中止する。
・ ギラン・バレー症候群［警告及び使用上の注意（5.3）を参照］	・ 本剤を中止する。
・ その他の Grade 3*の副作用	AML 及び MDS での単剤療法： ・ 副作用が Grade 2*以下に回復するまで本剤を休薬する。 ・ 本剤を 1 日 1 回 250 mg で再開し、副作用が Grade 1*以下に回復後は 1 日 1 回 500 mg に増量してもよい。 ・ Grade 3*以上の副作用が再発した場合、本剤を中止する。 胆管癌、又は AML におけるアザシチジンとの併用療法： ・ 副作用が Grade 1*以下又はベースラインに回復するまで本剤を休薬し、その後本剤を 1 日 1 回 500 mg（Grade 3 の副作用）又は 1 日 1 回 250 mg（Grade 4 の副作用）で再開する。 ・ Grade 3 の副作用が再発した場合（2 回目）、本剤を 1 日 1 回 250 mg に減量し、副作用が消失してから 1 日 1 回 500 mg で再開する。 ・ Grade 3 の副作用が再発した場合（3 回目）、又は Grade 4 の副作用が再発した場合、本剤を中止する。

*Grade 1 は軽症、Grade 2 は中等症、Grade 3 は重症、Grade 4 は生命を脅かす副作用。Grade は有害事象共通用語規準（CTCAE）version 4.03 に基づく。

	・ 全身性コルチコステロイド投与開始後 48 時間以降も重度の徴候／症状が続いた場合、本剤を休薬する。 ・ 徴候／症状が中等度又は軽度に回復し、臨床状態に改善がみられた場合、本剤を 1 日 1 回 500 mg で再開する。
白血球増加症（白血球数が 25×10^9/L 超又は総白血球数の絶対数がベースラインより 15×10^9/L 超増加、4.4 及び 4.8 項を参照）	・ 医療機関ごとの治療基準に従いヒドロキシカルバミドによる治療を開始し、臨床上必要に応じて白血球アフェレーシスを実施する。 ・ 白血球増加症が改善又は消失した後に限りヒドロキシカルバミドを漸減する。早期投与中止により再発の可能性がある。 ・ ヒドロキシカルバミドによる治療を開始後白血球増加症が改善しなかった場合、本剤を休薬する。 ・ 白血球増加症が消失した場合、本剤を 1 日 1 回 500 mg で再開する。
QTc 間隔延長 480 msec 超 500 msec 以下（Grade 2；4.4、4.5 及び 4.8 項を参照）	・ 電解質濃度をモニタリングし、臨床上必要に応じて電解質を補給する。 ・ QTc 間隔延長を起こすことが知られている併用薬を確認し調節する（4.5 項を参照）。 ・ QTc 間隔が 480 msec 以下に回復するまで本剤を休薬する。 ・ QTc 間隔が 480 msec 以下に回復した後、本剤を 1 日 1 回 500 mg で再開する。 ・ QTc 間隔が 480 msec 以下に回復した後は、投与再開後 3 週間は週 1 回以上及び臨床上必要に応じて ECG をモニタリングする。
QTc 間隔延長 500 msec 超（Grade 3；4.4、4.5 及び 4.8 項を参照）	・ 電解質濃度をモニタリングし、臨床上必要に応じて電解質を補給する。 ・ QTc 間隔延長を起こすことが知られている併用薬を確認し調節する（4.5 項を参照）。 ・ 本剤を休薬し、QTc 間隔がベースライン時の 30 msec 以内又は 480 msec 以下に回復するまで 24 時間ごとに ECG をモニタリングする。 ・ QTc 間隔延長が 550 msec 超の場合、予定されていた本剤の休薬に加えて QTc 間隔が 500 msec 未満に回復するまで連続的な心電図モニタリングの実施を検討する。 ・ QTc 間隔がベースライン時の 30 msec 以内又は 480 msec 以下に回復した後、本剤を 1 日 1 回 250 mg で再開する。 ・ QTc 間隔がベースライン時の 30 msec 以内又は 480 msec 以

AML 患者又は MDS 患者

血球数及び血液生化学の評価を、本剤の投与開始前、投与開始の 1 カ月目は週 1 回以上、2 カ月目は隔週 1 回、治療期間中は月 1 回実施する。

治療開始後 1 カ月は週 1 回、血中クレアチンホスホキナーゼをモニタリングする。

強い CYP3A4 阻害剤投与時の用量調節

強い CYP3A4 阻害剤を併用投与する場合、本剤を 1 日 1 回 250 mg に減量する。強い CYP3A4 阻害剤の投与を中止したときは（強い CYP3A4 阻害剤の 5 半減期以上経過後）、本剤を推奨用量である 1 日 1 回 500 mg に増量する。

	下に回復した後は、投与再開後 3 週間は週 1 回以上及び臨床上必要に応じて ECG をモニタリングする。 ・ QTc 間隔延長に他の原因が特定された場合、本剤の用量を 1 日 1 回 500 mg に増量してもよい。
生命を脅かす心室性不整脈の徴候／症状を伴う QTc 間隔延長（Grade 4；4.4、4.5 及び 4.8 項を参照）	・ 本剤を中止する。
その他の Grade 3 以上の副作用	・ 副作用が Grade 1 以下又はベースラインに回復するまで本剤を休薬し、その後本剤を 1 日 1 回 500 mg（Grade 3 の副作用）又は 1 日 1 回 250 mg（Grade 4 の副作用）で再開する。 ・ Grade 3 の副作用が再発した場合（2 回目）、本剤の用量を 1 日 1 回 250 mg に減量し、副作用が消失してから 1 日 1 回 500 mg で再開する。 ・ Grade 3 の副作用が再発した場合（3 回目）、又は Grade 4 の副作用が再発した場合、本剤を中止する。

Grade 1 は軽症、Grade 2 は中等症、Grade 3 は重症、Grade 4 は生命を脅かす副作用。

特定の集団

高齢者

高齢患者での本剤の用量調節は不要である（65 歳以上、4.8 及び 5.2 項を参照）。85 歳以上の患者を対象としたデータはない。

腎機能障害

軽度（eGFR ≥60～<90 mL/min/1.73 m^2）又は中等度（eGFR ≥30～<60 mL/min/1.73 m^2）の腎機能障害患者での用量調節は不要である。重度（eGFR <30 mL/min/1.73 m^2）の腎機能障害患者に対する推奨用量は決定されていない。重度の腎機能障害患者には慎重に本剤を投与し密にモニタリングする（4.4 及び 5.2 項を参照）。

		肝機能障害 軽度の肝機能障害（Child-Pugh 分類 A）患者での本剤の用量調節は不要である。中等度及び重度の肝機能障害（Child-Pugh 分類 B 及び C）患者に対する推奨用量は決定されていない。中等度及び重度の肝機能障害患者には慎重に本剤を投与し密にモニタリングする（4.4 及び 5.2 項を参照）。 小児等 18 歳未満の小児及び青少年の患者における本剤の安全性及び有効性は確立されていない。入手可能なデータはない。 投与方法 本剤は経口投与用である。 錠剤は毎日所定の時刻に 1 日 1 回投与する。錠剤服用前 2 時間から服用後 1 時間は食事を摂らない（5.2 項を参照）。錠剤は水とともにそのまま服用する。 治療中はグレープフルーツ及びグレープフルーツジュースの摂取を避けるよう指導する（4.5 項を参照）。錠剤の容器に入っているシリカゲル乾燥剤の誤飲を避けるよう指導する（6.5 項を参照）。
承認日	2018 年 7 月 20 日（再発又は難治性の急性骨髄性白血病） 2019 年 5 月 2 日（未治療の急性骨髄性白血病（単剤療法）） 2021 年 8 月 25 日（局所進行性又は転移性の胆管癌） 2022 年 5 月 25 日（未治療の急性骨髄性白血病（アザシチジンとの併用療法）） 2023 年 10 月 24 日（再発又は難治性の骨髄異形成症候群）	2023 年 5 月 4 日

このほかの主要国の承認日は、オーストラリアは 2023 年 4 月 5 日（胆管癌）及び 2023 年 9 月 20 日（急性骨髄性白血病）、英国は 2023 年 7 月 5 日（急性骨髄性白血病及び胆管癌）、カナダは 2024 年 7 月 19 日（急性骨髄性白血病及び胆管癌）である。

2.　外国の添付文書等の概要

最新の米国添付文書及び欧州製品概要の写しと和訳、並びに CCDS の写しを添付する。

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TIBSOVO safely and effectively. See full prescribing information for TIBSOVO.

TIBSOVO® (ivosidenib tablets), for oral use
Initial U.S. Approval: 2018

WARNING: DIFFERENTIATION SYNDROME IN AML AND MDS
See full prescribing information for complete boxed warning.

Patients treated with TIBSOVO have experienced symptoms of differentiation syndrome, which can be fatal. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution (5.1, 6.1).

----------RECENT MAJOR CHANGES----------

Indications and Usage, Relapsed or Refractory MDS (1.3)	10/2023
Dosage and Administration, Patient Selection (2.1)	10/2023
Dosage and Administration, Recommended Dosage (2.2)	10/2023

----------INDICATIONS AND USAGE----------

TIBSOVO is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for patients with a susceptible IDH1 mutation as detected by an FDA-approved test with:

Newly Diagnosed Acute Myeloid Leukemia (AML)
- In combination with azacitidine or as monotherapy for the treatment of newly diagnosed AML in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy (1.1).

Relapsed or refractory AML
- For the treatment of adult patients with relapsed or refractory AML (1.2).

Relapsed or refractory Myelodysplastic Syndromes (MDS)
- For the treatment of adult patients with relapsed or refractory myelodysplastic syndromes (1.3).

Locally Advanced or Metastatic Cholangiocarcinoma
- For the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma who have been previously treated (1.4).

----------DOSAGE AND ADMINISTRATION----------

500 mg orally once daily with or without food until disease progression or unacceptable toxicity (2.2). Avoid a high-fat meal.

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 250 mg (3).

----------CONTRAINDICATIONS----------

None (4).

----------WARNINGS AND PRECAUTIONS----------

- QTc Interval Prolongation: Monitor electrocardiograms and electrolytes. If QTc interval prolongation occurs, dose reduce or withhold, then resume dose or permanently discontinue TIBSOVO (2.3, 5.2).
- Guillain-Barré Syndrome: Monitor patients for signs and symptoms of new motor and/or sensory findings. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome (2.3, 5.3).

----------ADVERSE REACTIONS----------

The most common adverse reactions including laboratory abnormalities (≥ 25%) in patients with AML are leukocytes decreased, diarrhea, hemoglobin decreased, platelets decreased, glucose increased, fatigue, alkaline phosphatase increased, edema, potassium decreased, nausea, vomiting, phosphate decreased, decreased appetite, sodium decreased, leukocytosis, magnesium decreased, aspartate aminotransferase increased, arthralgia, dyspnea, uric acid increased, abdominal pain, creatinine increased, mucositis, rash, electrocardiogram QT prolonged, differentiation syndrome, calcium decreased, neutrophils decreased, and myalgia (6.1).

The most common adverse reactions including laboratory abnormalities (≥ 25%) in patients with relapsed or refractory MDS are creatinine increased, hemoglobin decrease, arthralgia, albumin decreased, aspartate aminotransferase increased, fatigue, diarrhea, cough, sodium decreased, mucositis, decreased appetite, myalgia, phosphate decreased, pruritus, and rash (6.1).

The most common adverse reactions (≥ 15%) in patients with cholangiocarcinoma are fatigue, nausea, abdominal pain, diarrhea, cough, decreased appetite, ascites, vomiting, anemia, and rash (6.1).

The most common laboratory abnormalities (≥ 10%) in patients with cholangiocarcinoma are hemoglobin decreased, aspartate aminotransferase increased, and bilirubin increased (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Servier Pharmaceuticals at 1-800-807-6124 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong or Moderate CYP3A4 Inhibitors: Reduce TIBSOVO dose with strong CYP3A4 inhibitors. Monitor patients for increased risk of QTc interval prolongation (2.4, 5.2, 7.1, 12.3).
- Strong CYP3A4 Inducers: Avoid concomitant use with TIBSOVO (7.1, 12.3).
- Sensitive CYP3A4 substrates: Avoid concomitant use with TIBSOVO (7.2, 12.3).
- QTc Prolonging Drugs: Avoid concomitant use with TIBSOVO. If co-administration is unavoidable, monitor patients for increased risk of QTc interval prolongation (5.2, 7.1).

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise women not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: DIFFERENTIATION SYNDROME IN AML AND MDS

Patients treated with TIBSOVO have experienced symptoms of differentiation syndrome, which can be fatal. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

1.1 Newly Diagnosed Acute Myeloid Leukemia

TIBSOVO is indicated in combination with azacitidine or as monotherapy for the treatment of newly diagnosed acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy *[see Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.1)]*.

1.2 Relapsed or Refractory Acute Myeloid Leukemia

TIBSOVO is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test *[see Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.2)]*.

1.3 Relapsed or Refractory Myelodysplastic Syndromes

TIBSOVO is indicated for the treatment of adult patients with relapsed or refractory myelodysplastic syndromes (MDS) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test *[see Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.3)]*.

1.4 Locally Advanced or Metastatic Cholangiocarcinoma

TIBSOVO is indicated for the treatment of adult patients with previously treated, locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test *[see Dosage and Administration (2.1), Clinical Pharmacology (12.1), and Clinical Studies (14.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment with TIBSOVO based on the presence of IDH1 mutations *[see Clinical Studies (14.1, 14.2, 14.3, 14.4)]*.

Information on FDA-approved tests for the detection of IDH1 mutations in AML, MDS, and cholangiocarcinoma is available at http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage

The recommended dosage of TIBSOVO is 500 mg taken orally once daily until disease progression or unacceptable toxicity *[see Clinical Studies (14.1, 14.2, 14.3, 14.4)]*.

For patients with AML or MDS without disease progression or unacceptable toxicity, continue TIBSOVO for a minimum of 6 months to allow time for clinical response.

- Administer TIBSOVO with or without food.
- Do not administer TIBSOVO with a high-fat meal *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.
- Do not split, crush, or chew TIBSOVO tablets.
- Administer TIBSOVO tablets orally about the same time each day.
- If a dose of TIBSOVO is vomited, do not administer a replacement dose; wait until the next scheduled dose is due.
- If a dose of TIBSOVO is missed or not taken at the usual time, administer the dose as soon as possible and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours.

Newly Diagnosed AML (Combination Regimen)
Start TIBSOVO administration on Cycle 1 Day 1 in combination with azacitidine 75 mg/m^2 subcutaneously or intravenously once daily on Days 1-7 (or Days 1-5 and 8-9) of each 28-day cycle *[see Clinical Studies (14.1)]*. Refer to the Prescribing Information for azacitidine for additional dosing information.

2.3 Monitoring and Dosage Modifications for Toxicities

Obtain an electrocardiogram (ECG) prior to treatment initiation. Monitor ECGs at least once weekly for the first 3 weeks of therapy and then at least once monthly for the duration of therapy *[see Warnings and Precautions (5.2)]*. Manage any abnormalities promptly.

Interrupt dosing or reduce dose for toxicities. See Table 1 for dosage modification guidelines.

Table 1: Recommended Dosage Modifications for TIBSOVO

Adverse Reactions	Recommended Action
• Differentiation syndrome *[see Warnings and Precautions (5.1)]*	• If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution and for a minimum of 3 days. • Interrupt TIBSOVO if severe signs and/or symptoms persist for more than 48 hours after initiation of systemic corticosteroids. • Resume TIBSOVO when signs and symptoms improve to Grade 2* or lower.

Table 1: Recommended Dosage Modifications for TIBSOVO

• Noninfectious leukocytosis (white blood cell [WBC] count greater than 25 x 10^9/L or an absolute increase in total WBC of greater than 15 x 10^9/L from baseline)	• Initiate treatment with hydroxyurea, as per standard institutional practices, and leukapheresis if clinically indicated. • Taper hydroxyurea only after leukocytosis improves or resolves. • Interrupt TIBSOVO if leukocytosis is not improved with hydroxyurea, and then resume TIBSOVO at 500 mg daily when leukocytosis has resolved.
• QTc interval greater than 480 msec to 500 msec *[see Warnings and Precautions (5.2) and Drug Interactions (7.1)]*	• Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medications with known QTc interval-prolonging effects. • Interrupt TIBSOVO. • Restart TIBSOVO at 500 mg once daily after the QTc interval returns to less than or equal to 480 msec. • Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation.
• QTc interval greater than 500 msec *[see Warnings and Precautions (5.2) and Drug Interactions (7.1)]*	• Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medications with known QTc interval-prolonging effects. • Interrupt TIBSOVO. • Resume TIBSOVO at a reduced dose of 250 mg once daily when QTc interval returns to within 30 msec of baseline or less than or equal to 480 msec. • Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation. • Consider re-escalating the dose of TIBSOVO to 500 mg daily if an alternative etiology for QTc prolongation can be identified.
• QTc interval prolongation with signs/symptoms of life-threatening arrhythmia *[see Warnings and Precautions (5.2)]*	• Discontinue TIBSOVO permanently.
• Guillain-Barré syndrome *[see Warnings and Precautions (5.3)]*	• Discontinue TIBSOVO permanently.

Table 1: Recommended Dosage Modifications for TIBSOVO

• Other Grade 3* adverse reactions	*As monotherapy in AML and MDS*: • Interrupt TIBSOVO until toxicity resolves to Grade 2* or lower. • Resume TIBSOVO at 250 mg once daily; may increase to 500 mg once daily if toxicities resolve to Grade 1* or lower. • If Grade 3* or higher toxicity recurs, discontinue TIBSOVO. *In cholangiocarcinoma, or in AML in combination with azacitidine*: • Interrupt TIBSOVO until toxicity resolves to Grade 1* or lower, or baseline, then resume at 500 mg daily (Grade 3 toxicity) or 250 mg daily (Grade 4 toxicity). • If Grade 3 toxicity recurs (a second time), reduce TIBSOVO dose to 250 mg daily until the toxicity resolves, then resume 500 mg daily. • If Grade 3 toxicity recurs (a third time), or Grade 4 toxicity recurs, discontinue TIBSOVO.

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening; grading based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Patients with AML or MDS

Assess blood counts and blood chemistries prior to the initiation of TIBSOVO, at least once weekly for the first month, once every other week for the second month, and once monthly for the duration of therapy.

Monitor blood creatine phosphokinase weekly for the first month of therapy.

2.4 Dosage Modification for Use with Strong CYP3A4 Inhibitors

If a strong CYP3A4 inhibitor must be coadministered, reduce the TIBSOVO dose to 250 mg once daily. If the strong inhibitor is discontinued, increase the TIBSOVO dose (after at least 5 half-lives of the strong CYP3A4 inhibitor) to the recommended dose of 500 mg once daily.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 250 mg as a blue oval-shaped film-coated tablet debossed “IVO” on one side and “250” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Differentiation Syndrome in AML and MDS

Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal.

Symptoms of differentiation syndrome in patients treated with TIBSOVO included noninfectious leukocytosis, peripheral edema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome and creatinine increased.

In the combination study AG120-C-009, 15% (11/71) patients with newly diagnosed AML treated with TIBSOVO plus azacitidine experienced differentiation syndrome *[see Adverse Reactions (6.1)]*. Of the 11 patients with newly diagnosed AML who experienced differentiation syndrome with TIBSOVO plus azacitidine 8 (73%) recovered. Differentiation syndrome occurred as early as 3 days after start of therapy and during the first month on treatment.

In the monotherapy clinical trial AG120-C-001, 25% (7/28) of patients with newly diagnosed AML and 19% (34/179) of patients with relapsed or refractory AML treated with TIBSOVO experienced differentiation syndrome *[see Adverse Reactions (6.1)]*. Of the 7 patients with newly diagnosed AML who experienced differentiation syndrome, 6 (86%) patients recovered. Of the 34 patients with relapsed or refractory AML who experienced differentiation syndrome, 27 (79%) patients recovered after treatment or after dose interruption of TIBSOVO. Differentiation syndrome occurred as early as 1 day and up to 3 months after TIBSOVO initiation and has been observed with or without concomitant leukocytosis.

In the monotherapy clinical trial AG120-C-001, 11% (2/19) of patients with relapsed or refractory MDS treated with TIBSOVO experienced differentiation syndrome *[see Adverse Reactions (6.1)]*. Of the 2 patients who experienced differentiation syndrome, both recovered after treatment or after dose interruption of TIBSOVO. Differentiation syndrome occurred as early as 1 day and up to 3 months after TIBSOVO initiation and has been observed with or without concomitant leukocytosis.

If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement *[see Dosage and Administration (2.3)]*. If concomitant noninfectious leukocytosis is observed, initiate treatment with hydroxyurea or leukapheresis, as clinically indicated. Taper corticosteroids and hydroxyurea after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxyurea treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt TIBSOVO until signs and symptoms are no longer severe *[see Dosage and Administration (2.3)]*.

5.2 QTc Interval Prolongation

Patients treated with TIBSOVO can develop QT (QTc) prolongation and ventricular arrhythmias *[see Clinical Pharmacology (12.2)]*.

Of the 71 patients with newly diagnosed AML treated with TIBSOVO in combination with azacitidine in the clinical trial (Study AG120-C-009), 10 (14%) were found to have a heart-rate corrected QT interval (using Fridericia's method) (QTcF) greater than 500 msec and 15 out of 69 (22%) had an increase from baseline QTcF greater than 60 msec *[see Adverse Reactions (6.1)]*. The clinical trial excluded patients with a QTcF $\geq$ 470 msec or other factors that increased the risk of QT prolongation or arrhythmic events (e.g. NYHA Class III or IV congestive heart failure, hypokalemia, family history of long QT interval syndrome).

Of the 265 patients with hematological malignancies, including patients with AML and MDS, treated with TIBSOVO monotherapy in the clinical trial (AG120-C-001), 9% were found to have a QTc interval greater than 500 msec and 14% of patients had an increase from baseline QTc greater than 60 msec *[see Adverse Reactions (6.1)]*. One patient developed ventricular fibrillation attributed to TIBSOVO. The clinical trial excluded patients with baseline QTc of ≥ 450 msec (unless the QTc ≥ 450 msec was due to a pre-existing bundle branch block) or with a history of long QT syndrome or uncontrolled or significant cardiovascular disease.

Of the 123 patients with cholangiocarcinoma treated with TIBSOVO in the clinical trial (Study AG120-C-005), 2% were found to have a QTc interval greater than 500 msec and 5% of patients had an increase from baseline QTc greater than 60 msec *[see Adverse Reactions (6.1)]*. The clinical trial excluded patients with a heart-rate corrected QT interval (using Fridericia's formula) (QTcF) ≥ 450 msec or other factors that increased the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome).

Concomitant use of TIBSOVO with drugs known to prolong the QTc interval (e.g., anti-arrhythmic medicines, fluoroquinolones, triazole anti-fungals, 5-HT_3 receptor antagonists) and CYP3A4 inhibitors may increase the risk of QTc interval prolongation *[see Drug Interactions (7.1), Clinical Pharmacology (12.2)].* Conduct monitoring of electrocardiograms (ECGs) and electrolytes *[see Dosage and Administration (2.3)]*.

In patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval, more frequent monitoring may be necessary.

Interrupt TIBSOVO if QTc increases to greater than 480 msec and less than 500 msec. Interrupt and reduce TIBSOVO if QTc increases to greater than 500 msec. Permanently discontinue TIBSOVO in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia *[See Dosage and Administration (2.3)]*.

5.3 Guillain-Barré Syndrome

Guillain-Barré syndrome can develop in patients treated with TIBSOVO. Guillain-Barré syndrome occurred in 0.8% (2/265) of patients treated with TIBSOVO in study AG120-C-001 *[see Adverse Reactions (6.1)]*.

Monitor patients taking TIBSOVO for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome *[see Dosage and Administration (2.3)].*

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Differentiation Syndrome in AML and MDS *[see Warnings and Precautions (5.1)]*
- QTc Interval Prolongation *[see Warnings and Precautions (5.2)]*
- Guillain-Barré Syndrome *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Acute Myeloid Leukemia

In AML, the safety population reflects exposure to TIBSOVO at 500 mg daily in combination with azacitidine or as monotherapy in patients in Studies AG120-C-009 (N=71) and AG120-C-001 (N=213), respectively *[see Clinical Studies (14.1 and 14.2)]*. In this safety population, the most common adverse reactions including laboratory abnormalities (≥ 25% in either trial) were leukocytes decreased, diarrhea, hemoglobin decreased, platelets decreased, glucose increased, fatigue, alkaline phosphatase increased, edema, potassium decreased, nausea, vomiting, phosphatase decreased, decreased appetite, sodium decreased, leukocytosis, magnesium decreased, aspartate aminotransferase increased, arthralgia, dyspnea, uric acid increased, abdominal pain, creatinine increased, mucositis, rash, electrocardiogram QT prolonged, differentiation syndrome, calcium decreased, neutrophils decreased, and myalgia.

Newly Diagnosed AML

TIBSOVO in Combination with Azacitidine

The safety of TIBSOVO was evaluated in AML patients treated in combination with azacitidine, in Study AG120-C-009 *[see Clinical Studies (14.1)]*. Patients received at least one dose of either TIBSOVO 500 mg daily (N=71) or placebo (N=73). Among patients who received TIBSOVO in combination with azacitidine, the median duration of exposure to TIBSOVO was 6 months (range 0 to 33 months). Thirty-four patients (48%) were exposed to TIBSOVO for at least 6 months and 22 patients (31%) were exposed for at least 1 year.

Common (≥ 5%) serious adverse reactions in patients who received TIBSOVO in combination with azacitidine included differentiation syndrome (8%).

Fatal adverse reactions occurred in 4% of patients who received TIBSOVO in combination with azacitidine, due to differentiation syndrome (3%) and one case of cerebral ischemia.

Adverse reactions leading to discontinuation of TIBSOVO in ≥ 2% of patients were differentiation syndrome (3%) and pulmonary embolism (3%).

The most common (> 5%) adverse reactions leading to dose interruption of TIBSOVO were neutropenia (25%), electrocardiogram QT prolonged (7%), and thrombocytopenia (7%).

Adverse reactions leading to dose reduction of TIBSOVO included electrocardiogram QT prolonged (8%), neutropenia (8%), and thrombocytopenia (1%).

The most common adverse reactions and laboratory abnormalities observed in Study AG120-C-009 are shown in Tables 2 and 3.

Table 2: Adverse Reactions (≥ 10%) in Patients with AML Who Received TIBSOVO azacitidine with a Difference Between Arms of ≥ 2% Compared with Placebo + azacitidine in AG120-C-009

	TIBSOVO + Azacitidine N=71		Placebo + Azacitidine N=73	
Body System Adverse Reaction	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Gastrointestinal disorders				
Nausea	30 (42)	2 (3)	28 (38)	3 (4)
Vomiting[1]	29 (41)	0	20 (27)	1 (1)
Investigations				
Electrocardiogram QT prolonged	14 (20)	7 (10)	5 (7)	2 (3)
Psychiatric Disorders				
Insomnia	13 (18)	1 (1)	9 (12)	0
Blood system and lymphatic system disorders				
Differentiation Syndrome[2]	11 (15)	7 (10)	6 (8)	6 (8)
Leukocytosis[3]	9 (13)	0	1 (1)	0
Vascular disorders				
Hematoma[4]	11 (15)	0	3 (4)	0
Hypertension[5]	9 (13)	3 (4)	6 (8)	4 (5)
Musculoskeletal and connective tissue disorders				
Arthralgia[6]	21 (30)	3 (4)	6 (8)	1 (1)
Respiratory, thoracic and mediastinal disorders				
Dyspnea[7]	14 (20)	2 (3)	11 (15)	4 (5)
Nervous system disorders				
Headache	8 (11)	0	2 (3)	0

[1] Grouped term includes vomiting and retching.
[2] Differentiation syndrome can be associated with other commonly reported events such as peripheral edema, leukocytosis, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonia, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased.
[3] Grouped term includes leukocytosis, white blood cell count increased.
[4] Grouped term includes hematoma, eye hematoma, catheter site hematoma, oral mucosa hematoma, spontaneous hematoma, application site hematoma, injection site hematoma, periorbital hematoma.
[5] Grouped term includes blood pressure increased, essential hypertension, and hypertension.
[6] Grouped term includes pain in extremity, arthralgia, back pain, musculoskeletal stiffness, cancer pain, and neck pain.
[7] Grouped term includes dyspnea, dyspnea exertional, hypoxia, respiration failure.

Table 3: Select Laboratory Abnormalities[1, 2] (≥ 10%) That Worsened from Baseline in Patients with AML Who Received TIBSOVO + azacitidine in AG120-C-009

	TIBSOVO + Azacitidine N=71		Placebo + Azacitidine N=73	
Parameter	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Hematology Parameters				
Leukocytes decreased	46 (65)	39 (55)	47 (64)	42 (58)
Platelets decreased	41 (58)	30 (42)	52 (71)	42 (58)
Hemoglobin decreased	40 (56)	33 (46)	48 (66)	42 (58)
Neutrophils decreased	18 (25)	16 (23)	25 (35)	23 (32)
Lymphocytes increased	17 (24)	1 (1)	7 (10)	1 (1)
Chemistry Parameters				
Glucose increased	40 (56)	9 (13)	34 (47)	8 (11)
Phosphate decreased	29 (41)	7 (10)	25 (34)	9 (12)
Aspartate Aminotransferase increased	26 (37)	0	17 (23)	0
Magnesium decreased	25 (35)	0	19 (26)	0
Alkaline Phosphatase increased	23 (32)	0	21 (29)	0
Potassium increased	17 (24)	2 (3)	9 (12)	1 (1)

[1] Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or if baseline is unknown.
[2] The denominator used to calculate percentages is the number of treated subjects who can be evaluated for CTCAE criteria for each parameter in each arm.

TIBSOVO Monotherapy

The safety profile of single-agent TIBSOVO was studied in 28 adults with newly diagnosed AML treated with 500 mg daily *[see Clinical Studies (14.1)]*. The median duration of exposure to TIBSOVO was 4.3 months (range 0.3 to 40.9 months). Ten patients (36%) were exposed to TIBSOVO for at least 6 months and 6 patients (21%) were exposed for at least 1 year.

Common (≥ 5%) serious adverse reactions included differentiation syndrome (18%), electrocardiogram QT prolonged (7%), and fatigue (7%). There was one case of posterior reversible encephalopathy syndrome (PRES).

Common (≥ 10%) adverse reactions leading to dose interruption included electrocardiogram QT prolonged (14%) and differentiation syndrome (11%). Two (7%) patients required a dose reduction due to electrocardiogram QT prolonged. One patient each required permanent discontinuation due to diarrhea and PRES.

The most common adverse reactions reported in the trial are shown in Table 4.

Table 4: Adverse Reactions Reported in ≥ 10% (Any Grade) or ≥ 5% (Grade ≥ 3) of Patients with Newly Diagnosed AML in AG120-C-001

	TIBSOVO (500 mg daily) N=28	
Body System Adverse Reaction	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Gastrointestinal disorders		
Diarrhea	17 (61)	2 (7)
Nausea	10 (36)	2 (7)
Abdominal pain[1]	8 (29)	1 (4)
Constipation	6 (21)	1 (4)
Vomiting	6 (21)	1 (4)
Mucositis[2]	6 (21)	0
Dyspepsia	3 (11)	0
General disorders and administration site conditions		
Fatigue[3]	14 (50)	4 (14)
Edema[4]	12 (43)	0
Metabolism and nutrition disorders		
Decreased appetite	11 (39)	1 (4)
Blood system and lymphatic system disorders		
Leukocytosis[5]	10 (36)	2 (7)
Differentiation Syndrome[6]	7 (25)	3 (11)
Musculoskeletal and connective tissue disorders		
Arthralgia[7]	9 (32)	1 (4)
Myalgia[8]	7 (25)	1 (4)
Respiratory, thoracic, and mediastinal disorders		
Dyspnea[9]	8 (29)	1 (4)
Cough[10]	4 (14)	0
Investigations		
Electrocardiogram QT prolonged	6 (21)	3 (11)
Weight decreased	3 (11)	0
Nervous system disorders		
Dizziness	6 (21)	0
Neuropathy[11]	4 (14)	0
Headache	3 (11)	0
Skin and subcutaneous tissue disorders		
Pruritus	4 (14)	1 (4)
Rash[12]	4 (14)	1 (4)

[1] Grouped term includes abdominal pain, upper abdominal pain, abdominal discomfort, and abdominal tenderness.
[2] Grouped term includes aphthous ulcer, esophageal pain, esophagitis, gingival pain, gingivitis, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal pain, proctalgia, and stomatitis.
[3] Grouped term includes asthenia and fatigue.
[4] Grouped term includes edema, face edema, fluid overload, fluid retention, hypervolemia, peripheral edema, and swelling face.
[5] Grouped term includes leukocytosis, hyperleukocytosis, and increased white blood cell count.
[6] Differentiation syndrome can be associated with other commonly reported events such as peripheral edema, leukocytosis, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonia, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased.
[7] Grouped term includes arthralgia, back pain, musculoskeletal stiffness, neck pain, and pain in extremity.
[8] Grouped term includes myalgia, muscular weakness, musculoskeletal pain, musculoskeletal chest pain, musculoskeletal discomfort, and myalgia intercostal.
[9] Grouped term includes dyspnea, dyspnea exertional, hypoxia, and respiratory failure.
[10] Grouped term includes cough, productive cough, and upper airway cough syndrome.
[11] Grouped term includes burning sensation, lumbosacral plexopathy, neuropathy peripheral, paresthesia, and peripheral motor neuropathy.
[12] Grouped term includes dermatitis acneiform, dermatitis, rash, rash maculo-papular, urticaria, rash erythematous, rash macular, rash pruritic, rash generalized, rash papular, skin exfoliation, and skin ulcer.

Changes in selected post-baseline laboratory values that were observed in patients with newly diagnosed AML are shown in Table 5.

Table 5: Most Common (≥ 10%) or ≥ 5% (Grade ≥ 3) New or Worsening Laboratory Abnormalities Reported in Patients with Newly Diagnosed AML[1] in AG120-C-001

	TIBSOVO (500 mg daily) N=28	
Parameter	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Hemoglobin decreased	15 (54)	12 (43)
Alkaline phosphatase increased	13 (46)	0
Potassium decreased	12 (43)	3 (11)
Sodium decreased	11 (39)	1 (4)
Uric acid increased	8 (29)	1 (4)
Aspartate aminotransferase increased	8 (29)	1 (4)
Creatinine increased	8 (29)	0
Magnesium decreased	7 (25)	0
Calcium decreased	7 (25)	1 (4)
Phosphate decreased	6 (21)	2 (7)
Alanine aminotransferase increased	4 (14)	1 (4)

[1] Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or if baseline is unknown.

Relapsed or Refractory AML

The safety profile of single-agent TIBSOVO was studied in 179 adults with relapsed or refractory AML treated with 500 mg daily *[see Clinical Studies (14.2)]*.

The median duration of exposure to TIBSOVO was 3.9 months (range 0.1 to 39.5 months). Sixty-five patients (36%) were exposed to TIBSOVO for at least 6 months and 16 patients (9%) were exposed for at least 1 year.

Serious adverse reactions (≥ 5%) were differentiation syndrome (10%), leukocytosis (10%), and electrocardiogram QT prolonged (7%). There was one case of progressive multifocal leukoencephalopathy (PML).

The most common adverse reactions leading to dose interruption were electrocardiogram QT prolonged (7%), differentiation syndrome (3%), leukocytosis (3%) and dyspnea (3%). Five out of 179 patients (3%) required a dose reduction due to an adverse reaction.

Adverse reactions leading to a dose reduction included electrocardiogram QT prolonged (1%), diarrhea (1%), nausea (1%), decreased hemoglobin (1%), and increased transaminases (1%).

Adverse reactions leading to permanent discontinuation included Guillain-Barré syndrome (1%), rash (1%), stomatitis (1%), and creatinine increased (1%).

The most common adverse reactions reported in the trial are shown in Table 6.

Table 6: Adverse Reactions Reported in ≥ 10% (Any Grade) or ≥ 5% (Grade ≥ 3) of Patients with Relapsed or Refractory AML

	TIBSOVO (500 mg daily) N=179	
Body System Adverse Reaction	**All Grades n (%)**	**Grade ≥ 3 n (%)**
General disorders and administration site conditions		
Fatigue[1]	69 (39)	6 (3)
Edema[2]	57 (32)	2 (1)
Pyrexia	41 (23)	2 (1)
Chest pain[3]	29 (16)	5 (3)
Blood system and lymphatic system disorders		
Leukocytosis[4]	68 (38)	15 (8)
Differentiation Syndrome[5]	34 (19)	23 (13)
Musculoskeletal and connective tissue disorders		
Arthralgia[6]	64 (36)	8 (4)
Myalgia[7]	33 (18)	1 (1)
Gastrointestinal disorders		
Diarrhea	60 (34)	4 (2)
Nausea	56 (31)	1 (1)
Mucositis[8]	51 (28)	6 (3)
Constipation	35 (20)	1 (1)
Vomiting[9]	32 (18)	2 (1)
Abdominal pain[10]	29 (16)	2 (1)
Respiratory, thoracic, and mediastinal disorders		
Dyspnea[11]	59 (33)	16 (9)
Cough[12]	40 (22)	1 (< 1)
Pleural effusion	23 (13)	5 (3)
Investigations		
Electrocardiogram QT prolonged	46 (26)	18 (10)
Skin and subcutaneous tissue disorders		
Rash[13]	46 (26)	4 (2)
Metabolism and nutrition disorders		
Decreased appetite	33 (18)	3 (2)
Tumor lysis syndrome	14 (8)	11 (6)
Nervous system disorders		
Headache	28 (16)	0
Neuropathy[14]	21 (12)	2 (1)
Vascular disorders		
Hypotension[15]	22 (12)	7 (4)

[1] Grouped term includes asthenia and fatigue.
[2] Grouped term includes peripheral edema, edema, fluid overload, fluid retention, and face edema.
[3] Grouped term includes angina pectoris, chest pain, chest discomfort, and non-cardiac chest pain.
[4] Grouped term includes leukocytosis, hyperleukocytosis, and increased white blood cell count.
[5] Differentiation syndrome can be associated with other commonly reported events such as peripheral edema, leukocytosis, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonia, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased.
[6] Grouped term includes arthralgia, back pain, musculoskeletal stiffness, neck pain, and pain in extremity.
[7] Grouped term includes myalgia, muscular weakness, musculoskeletal pain, musculoskeletal chest pain, musculoskeletal discomfort, and myalgia intercostal.
[8] Grouped term includes aphthous ulcer, esophageal pain, esophagitis, gingival pain, gingivitis, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal pain, proctalgia, and stomatitis.
[9] Grouped term includes vomiting and retching.
[10] Grouped term includes abdominal pain, upper abdominal pain, abdominal discomfort, and abdominal tenderness.
[11] Grouped term includes dyspnea, respiratory failure, hypoxia, and dyspnea exertional.

[12] Grouped term includes cough, productive cough, and upper airway cough syndrome.
[13] Grouped term includes dermatitis acneiform, dermatitis, rash, rash maculo-papular, urticaria, rash erythematous, rash macular, rash pruritic, rash generalized, rash papular, skin exfoliation, and skin ulcer.
[14] Grouped term includes ataxia, burning sensation, gait disturbance, Guillain-Barré syndrome, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, peripheral motor neuropathy, and sensory disturbance.
[15] Grouped term includes hypotension and orthostatic hypotension.

Changes in selected post-baseline laboratory values that were observed in patients with relapsed or refractory AML are shown in Table 7.

Table 7: Most Common (≥ 10%) or ≥ 5% (Grade ≥ 3) New or Worsening Laboratory Abnormalities Reported in Patients with Relapsed or Refractory AML[1]

	TIBSOVO (500 mg 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 increased	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)

[1] Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or if baseline is unknown.

Relapsed or Refractory Myelodysplastic Syndromes

The safety of TIBSOVO was evaluated in 19 adults with relapsed or refractory MDS treated with 500 mg daily in AG120-C-001 *[see Clinical Studies (14.3)]*. The median duration of exposure to TIBSOVO was 9.3 months (range 3.3 to 78.8 months). Fourteen patients (74%) were exposed to TIBSOVO for at least 6 months and 8 patients (42%) were exposed for at least 1 year.

Serious adverse reactions in ≥ 5% included differentiation syndrome (11%), fatigue (5%), and rash (5%).

Permanent discontinuation of TIBSOVO due to an adverse reaction occurred in 5% of patients. The adverse reaction which resulted in permanent discontinuation of TIBSOVO was fatigue.

Adverse reactions leading to dosage interruption of TIBSOVO occurred in 16% of patients. Adverse reactions which required dosage interruption in ≥ 5% were differentiation syndrome, leukocytosis, and rash.

Dose reductions of TIBSOVO due to an adverse reaction occurred in 16% of patients. Adverse reactions which required a dose reduction in ≥ 5% included differentiation syndrome, fatigue, and rash.

The most common (≥ 25%) adverse reactions, including laboratory abnormalities, were creatinine increased, hemoglobin decrease, arthralgia, albumin decreased, aspartate aminotransferase increased, fatigue, diarrhea, cough, sodium decreased, mucositis, decreased appetite, myalgia, phosphate decreased, pruritus, and rash.

Table 8 summarizes the adverse reactions in AG120-C-001.

Table 8: Adverse Reactions ≥ 10% in Patients with Relapsed or Refractory MDS in AG120-C-001

	TIBSOVO (500 mg daily) N=19	
Body System Adverse Reaction	**All Grades %**	**Grade 3 or 4 %**
Musculoskeletal and connective tissue disorders		
Arthralgia[1]	42	16
Myalgia[2]	26	0
General disorders and administration site conditions		
Fatigue[3]	37	11
Respiratory, thoracic, and mediastinal disorders		
Cough	32	0
Dyspnea[4]	21	0
Gastrointestinal disorders		
Diarrhea	32	0
Mucositis[5]	26	5
Constipation	16	0
Nausea	16	0
Skin and subcutaneous tissue disorders		
Pruritus	26	0
Rash[6]	26	0
Metabolism and nutrition disorders		
Decreased appetite	26	0
Blood system and lymphatic system disorders		
Leukocytosis[7]	16	5
Differentiation Syndrome	11	0
Nervous system disorders		
Headache	16	0
Vascular disorders		
Hypertension	16	16
Investigations		
Electrocardiogram QT prolonged	11	0

[1] Grouped term includes arthralgia, back pain, pain in extremity, flank pain, joint swelling, and neck pain.
[2] Grouped term includes myalgia, muscle spasms, muscle discomfort, and musculoskeletal chest pain.
[3] Grouped term includes fatigue and asthenia.
[4] Grouped term includes dyspnea and dyspnea exertional.
[5] Grouped term includes oropharyngeal pain, gingivitis, mouth ulceration, stomatitis.
[6] Grouped term includes rash, catheter site erythema, and urticaria.
[7] Grouped term includes leukocytosis, hyperleukocytosis, and white blood cell count increased.

Table 9 summarizes laboratory abnormalities in AG120-C-001.

Table 9: Select Laboratory Abnormalities (≥ 15%) That Worsened from Baseline in Patients with Relapsed or Refractory MDS in AG120-C-001

	TIBSOVO[1] N=19	
Laboratory Abnormality	**All Grades %**	**Grade 3 or 4 %**
Creatinine increased	95	5
Hemoglobin decreased	42	32
Albumin decreased	37	0
Aspartate Aminotransferase increased	37	5
Sodium decreased	32	5
Phosphate decreased	26	5
Alanine Aminotransferase increased	21	5
Bilirubin increased	21	0
Magnesium decreased	21	0
Alkaline Phosphatase increased	16	0
Potassium increased	16	0

[1] Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or if baseline is unknown.

Locally Advanced or Metastatic Cholangiocarcinoma

The safety of TIBSOVO was studied in patients with previously treated, locally advanced or metastatic cholangiocarcinoma in Study AG120-C-005 *[see Clinical Studies (14.4)]*. Patients received at least one dose of either TIBSOVO 500 mg daily (N=123) or placebo (N=59). The median duration of treatment was 2.8 months (range 0.1 to 34.4 months) with TIBSOVO.

Serious adverse reactions occurred in 34% of patients receiving TIBSOVO. Serious adverse reactions in ≥ 2% of patients in the TIBSOVO arm were pneumonia, ascites, hyperbilirubinemia, and jaundice cholestatic.

Fatal adverse reactions occurred in 4.9% of patients receiving TIBSOVO, including sepsis (1.6%) and pneumonia, intestinal obstruction, pulmonary embolism, and hepatic encephalopathy (each 0.8%).

TIBSOVO was permanently discontinued in 7% of patients. The most common adverse reactions leading to permanent discontinuation was acute kidney injury (1.6%).

Dose interruptions due to adverse reactions occurred in 29% of patients treated with TIBSOVO. The most common (>2%) adverse reactions leading to dose interruption were hyperbilirubinemia, alanine aminotransferase increased, aspartate aminotransferase increased, ascites, and fatigue.

Dose reductions of TIBSOVO due to an adverse reaction occurred in 4.1% of patients. Adverse reactions leading to dose reduction were electrocardiogram QT prolonged (3.3%) and neuropathy peripheral (0.8%).

The most common adverse reactions (≥15%) were fatigue, nausea, abdominal pain, diarrhea, cough, decreased appetite, ascites, vomiting, anemia, and rash.

Adverse reactions and laboratory abnormalities observed in Study AG120-C-005 are shown in Tables 10 and 11.

Table 10: Adverse Reactions Occurring in ≥ 10% of Patients Receiving TIBSOVO in Study AG120-C-005

	TIBSOVO (500 mg daily) N=123		Placebo N=59	
Body System Adverse Reaction	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**
General disorders and administration site conditions				
Fatigue[1]	53 (43)	4 (3)	18 (31)	3 (5)
Gastrointestinal disorders				
Nausea	51 (41)	3 (2)	17 (29)	1 (2)
Diarrhea	43 (35)	0	10 (17)	0
Abdominal pain[2]	43 (35)	3 (2)	13 (22)	2 (3)
Ascites	28 (23)	11 (9)	9 (15)	4 (7)
Vomiting[3]	28 (23)	3 (2)	12 (20)	0
Respiratory, thoracic, and mediastinal disorders				
Cough[4]	33 (27)	0	5 (9)	0
Metabolism and nutrition disorders				
Decreased appetite	30 (24)	2 (2)	11 (19)	0
Blood and lymphatic system disorders				
Anemia	22 (18)	8 (7)	3 (5)	0
Skin and subcutaneous tissue disorders				
Rash[5]	19 (15)	1 (1)	4 (7)	0
Nervous system disorders				
Headache	16 (13)	0	4 (7)	0
Neuropathy peripheral[6]	13 (11)	0	0	0
Investigations				
Electrocardiogram QT prolonged	12 (10)	2 (2)	2 (3)	0

[1] Grouped term includes asthenia and fatigue.
[2] Grouped term includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, epigastric discomfort, abdominal tenderness, and gastrointestinal pain.
[3] Grouped term includes vomiting and retching.
[4] Grouped term includes cough and productive cough.
[5] Grouped term includes rash, rash maculo-papular, erythema, rash macular, dermatitis exfoliative generalized, drug eruption, and drug hypersensitivity.
[6] Grouped term includes neuropathy peripheral, peripheral sensory neuropathy, and paresthesia.

Table 11: Selected Laboratory Abnormalities Occurring in ≥ 10% of Patients Receiving TIBSOVO in Study AG120-C-005[1]

	TIBSOVO (500 mg daily) N=123		Placebo N=59	
Parameter	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**
AST increased	41 (34)	5 (4)	14 (24)	1 (2)
Bilirubin increased	36 (30)	15 (13)	11 (19)	2 (3)
Hemoglobin decreased	48 (40)	8 (7)	14 (25)	0

[1] Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or baseline is unknown.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Ivosidenib

Strong or Moderate CYP3A4 Inhibitors	
Clinical Impact	• Co-administration of TIBSOVO with strong or moderate CYP3A4 inhibitors increased ivosidenib plasma concentrations *[see Clinical Pharmacology (12.3)]*. • Increased ivosidenib plasma concentrations may increase the risk of QTc interval prolongation *[see Warnings and Precautions (5.2)]*.
Prevention or Management	• Consider alternative therapies that are not strong or moderate CYP3A4 inhibitors during treatment with TIBSOVO. • If co-administration of a strong CYP3A4 inhibitor is unavoidable, reduce TIBSOVO to 250 mg once daily *[see Dosage and Administration (2.3)]*. • Monitor patients for increased risk of QTc interval prolongation *[see Warnings and Precautions (5.2)]*.
Strong CYP3A4 Inducers	
Clinical Impact	• Co-administration of TIBSOVO with strong CYP3A4 inducers decreased ivosidenib plasma concentrations *[see Clinical Pharmacology (12.3)]*.
Prevention or Management	• Avoid co-administration of strong CYP3A4 inducers with TIBSOVO.
QTc Prolonging Drugs	
Clinical Impact	• Co-administration of TIBSOVO with QTc prolonging drugs may increase the risk of QTc interval prolongation *[see Warnings and Precautions (5.2)]*.
Prevention or Management	• Avoid co-administration of QTc prolonging drugs with TIBSOVO or replace with alternative therapies. • If co-administration of a QTc prolonging drug is unavoidable, monitor patients for increased risk of QTc interval prolongation [*see Warnings and Precautions (5.2)]*.

7.2 Effect of Ivosidenib on Other Drugs

Ivosidenib induces CYP3A4 and may induce CYP2C9. Co-administration will decrease concentrations of drugs that are sensitive CYP3A4 substrates and may decrease concentrations of drugs that are sensitive CYP2C9 substrates *[see Clinical Pharmacology (12.3)]*. Use alternative therapies that are not sensitive substrates of CYP3A4 and CYP2C9 during TIBSOVO treatment. If co-administration of TIBSOVO with sensitive CYP3A4 substrates or CYP2C9 substrates is unavoidable, monitor patients for loss of therapeutic effect of these drugs.

Do not administer TIBSOVO with anti-fungal agents that are substrates of CYP3A4 due to expected loss of antifungal efficacy.

Co-administration of TIBSOVO may decrease the concentrations of hormonal contraceptives, consider alternative methods of contraception in patients receiving TIBSOVO.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal embryo-fetal toxicity studies, TIBSOVO may cause fetal harm when administered to a pregnant woman. There are no available data on TIBSOVO use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal embryo-fetal toxicity studies, oral administration of ivosidenib to pregnant rats and rabbits during organogenesis was associated with embryo-fetal mortality and alterations to growth starting at 2 times the steady state clinical exposure based on the AUC at the recommended human dose *(see Data).* If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data
Ivosidenib administered to pregnant rats at a dose of 500 mg/kg/day during organogenesis (gestation days 6-17) was associated with adverse embryo-fetal effects including lower fetal weights, and skeletal variations. These effects occurred in rats at approximately 2 times the human exposure at the recommended dose of 500 mg daily.

In pregnant rabbits treated during organogenesis (gestation days 7-20), ivosidenib was maternally toxic at doses of 180 mg/kg/day (exposure approximately 3.9 times the human exposure at the recommended dose of 500 mg daily) and caused spontaneous abortions as well as decreased fetal weights, skeletal variations, and visceral variations.

8.2 Lactation

Risk Summary

There are no data on the presence of ivosidenib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed children, advise women not to breastfeed during treatment with TIBSOVO and for 1 month after the last dose.

8.4 Pediatric Use

The safety and effectiveness of TIBSOVO in pediatric patients have not been established.

8.5 Geriatric Use

Of the 304 patients who received TIBSOVO in the clinical studies for AML and MDS, 75% were 65 years of age or older and 35% were 75 years or older.

Of the 124 patients with cholangiocarcinoma treated with TIBSOVO in Study AG120-C-005, 37% were 65 years of age or older and 11% were 75 years or older.

No overall differences in effectiveness or safety were observed between patients who were 65 years and older compared to younger patients.

8.6 Renal Impairment

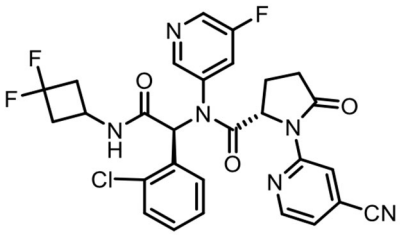
No modification of the starting dose is recommended for patients with mild or moderate renal impairment (eGFR ≥ 30 mL/min/1.73m^2, MDRD). The pharmacokinetics and safety of ivosidenib in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2, MDRD) or renal impairment requiring dialysis are unknown *[see Clinical Pharmacology (12.3)]*. For patients with pre-existing severe renal impairment or who are requiring dialysis, consider the risks and potential benefits before initiating treatment with TIBSOVO.

8.7 Hepatic Impairment

No modification of the starting dose is recommended for patients with mild or moderate (Child-Pugh A or B) hepatic impairment *[see Clinical Pharmacology (12.3)]*. The pharmacokinetics and safety of ivosidenib in patients with severe hepatic impairment (Child-Pugh C) are unknown. For patients with pre-existing severe hepatic impairment, consider the risks and potential benefits before initiating treatment with TIBSOVO.

11 DESCRIPTION

TIBSOVO (ivosidenib) is an inhibitor of isocitrate dehydrogenase 1 (IDH1) enzyme. The chemical name is (2*S*)-*N*-{(1*S*)-1-(2-chlorophenyl)-2-[(3,3-difluorocyclobutyl)-amino]-2-oxoethyl}-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide. The chemical structure is:



The molecular formula is $C_{28}H_{22}ClF_3N_6O_3$ and the molecular weight is 583.0 g/mol. Ivosidenib is practically insoluble in aqueous solutions between pH 1.2 and 7.4.

TIBSOVO (ivosidenib) is available as a film-coated 250 mg tablet for oral administration. Each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet coating includes FD&C blue #2, hypromellose, lactose monohydrate, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ivosidenib is a small molecule inhibitor that targets the mutant isocitrate dehydrogenase 1 (IDH1) enzyme. In patients with AML, susceptible IDH1 mutations are defined as those leading to increased levels of 2-hydroxyglutarate (2-HG) in the leukemia cells and where efficacy is predicted by 1) clinically meaningful remissions with the recommended dose of ivosidenib and/or 2) inhibition of mutant IDH1 enzymatic activity at concentrations of ivosidenib sustainable at the recommended dosage according to validated methods. The most common of such mutations in patients with AML are R132H and R132C substitutions.

Ivosidenib was shown to inhibit selected IDH1 R132 mutants at much lower concentrations than wild-type IDH1 in vitro. Inhibition of the mutant IDH1 enzyme by ivosidenib led to decreased 2-HG levels and induced myeloid differentiation in vitro and in vivo in mouse xenograft models of IDH1-mutated AML. In blood samples from patients with AML with mutated IDH1, ivosidenib decreased 2-HG levels ex-vivo, reduced blast counts, and increased percentages of mature myeloid cells.

In a patient-derived xenograft intra-hepatic cholangiocarcinoma mouse model with IDH1 R132C, ivosidenib reduced 2-HG levels.

12.2 Pharmacodynamics

Multiple doses of ivosidenib 500 mg daily were observed to decrease plasma 2-HG concentrations in patients with hematological malignancies and cholangiocarcinoma to levels similar to those observed at baseline in healthy subjects. In bone marrow of patients with hematological malignancies and in tumor biopsy of patients with cholangiocarcinoma, the mean [% coefficient of variation (%CV)] reduction in 2-HG concentrations were 93.1% (11.1%) and 82.2% (32.4%), respectively.

Cardiac Electrophysiology

The mean increase in QTc was 17 msec (UCI: 20 msec) following administration of TIBSOVO 500 mg in patients with newly diagnosed AML and patients with relapsed or refractory AML. The increase in QTc interval was concentration-dependent *[see Warnings and Precautions (5.2)]*. A similar mean increase following administration of TIBSOVO 500 mg daily was observed in patients with relapsed or refractory MDS and in patients with solid tumors, including patients with cholangiocarcinoma. Co-administration with moderate or strong CYP3A inhibitors is expected to further increase QTc interval prolongation from baseline.

12.3 Pharmacokinetics

The AUC and C_{max} of ivosidenib increase in a less than dose-proportional manner from 200 mg to 1,200 mg daily (0.4 to 2.4 times the approved recommended dosage). The following ivosidenib pharmacokinetic parameters (Table 12) were observed following administration of ivosidenib 500 mg as a single dose or daily dose (for steady state), unless otherwise specified. The steady-state pharmacokinetics of ivosidenib 500 mg were comparable between patients with newly diagnosed AML, relapsed or refractory AML, and relapsed or refractory MDS, and were lower in patients with cholangiocarcinoma.

Table 12: Pharmacokinetics of ivosidenib

	Newly diagnosed AML treated with a combination of TIBSOVO and azacitidine	Relapsed or refractory AML treated with TIBSOVO	Relapsed or refractory MDS treated with TIBSOVO	Cholangiocarcinoma treated with TIBSOVO
PK parameters				
Single dose C_{max} (ng/mL)[a]	4,820 (39%)	4,503 (38%)	4,020 (31%)	4,060 (45%)
Steady state C_{max} (ng/mL)[a]	6,145 (34%)	6,551 (44%)	5,820 (37%)	4,799 (33%)
Steady state AUC (ng·hr/mL)[a]	106,326 (41%)	117,348 (50%)	103,770 (40%)	86,382 (34%)
Steady state PK	Within 14 days			
Accumulation				
C_{max}	1.2	1.5	1.4	1.2
AUC	1.6	1.9	2	1.5
Absorption				
Median T_{max} (hr)	2	3	3	2
Effect of Food[b] C_{max} AUC	1.98-fold (90% CI: 1.79, 2.19) 1.24-fold (90% CI: 1.16, 1.33)			
Distribution				
In vitro protein binding	92 to 96%			
Apparent volume of distribution at steady state (L)[a]	504 (22%)	403 (35%)	552 (26%)	706 (45%)
Elimination				
Apparent clearance at steady state (L/hr)[a]	4.6 (35%)	5.6 (35%)	5.1 (35%)	6.1 (31%)
Terminal half-life at steady state (hr)[a]	98 (42%)	58 (42%)	96 (43%)	129 (102%)
Metabolism				
Plasma[c]	>92% of total radioactivity as ivosidenib			
Metabolic pathways				
Major	CYP3A4			
Minor	N-dealkylation and hydrolytic pathways			
Excretion[c]				
Urine	17% (10% as unchanged ivosidenib)			
Feces	77% (67% as unchanged ivosidenib)			

[a] PK parameters expressed as mean (%CV).
[b] Following administration of a single dose in healthy subjects, a high-fat meal (approximately 900 to 1,000 calories, 500 to 600 fat calories, 250 carbohydrate calories and 150 protein calories).
[c] Data from a single radiolabeled ivosidenib dose in healthy subjects.

Specific Populations

No clinically significant effects on the pharmacokinetics of ivosidenib were observed based on age (18 years to 89 years), sex, race (White, Asian, Black or African American), body weight (38 to 150 kg), ECOG performance status, mild or moderate hepatic impairment (Child-Pugh A or B) or mild or moderate renal impairment (eGFR ≥ 30 mL/min/1.73m^2, MDRD). The pharmacokinetics of ivosidenib in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2, MDRD) or renal impairment requiring dialysis or severe hepatic impairment (Child-Pugh C) is unknown.

Drug Interaction Studies

Clinical Studies and Model-Based Approaches

Effect of Strong or Moderate CYP3A4 Inhibitors on Ivosidenib

Co-administration of 250 mg ivosidenib with a strong CYP3A4 inhibitor (200 mg itraconazole once daily for 18 days) increased ivosidenib single-dose AUC by 269% (90% CI: 245%, 295%) with no change in C_{max} in healthy subjects. Co-administration of 500 mg ivosidenib with the moderate CYP3A4 inhibitor fluconazole (dosed to steady-state) increases ivosidenib single-dose AUC by 173% with no change in C_{max}. Co-administration of fluconazole following multiple daily ivosidenib doses is predicted to increase ivosidenib steady-state C_{max} by 152% and AUC by 190%.

Effect of Strong CYP3A4 Inducers on Ivosidenib

Co-administration of ivosidenib with a strong CYP3A4 inducer (600 mg rifampin once daily for 15 days) is predicted to decrease ivosidenib steady-state AUC by 33%.

Effect of Ivosidenib on CYP3A4 Substrates

Ivosidenib induces CYP3A4, including its own metabolism. Co-administration of ivosidenib with CYP3A4 substrates, including certain azole anti-fungal agents, is expected to decrease CYP3A4 substrate steady-state AUC.

Effect of Gastric Acid Reducing Agents on Ivosidenib

No clinically significant ivosidenib pharmacokinetic differences were observed following co-administration with gastric acid reducing agents (e.g., proton pump inhibitors, H2-receptor antagonists, antacids).

In vitro Studies

Metabolic Pathways

Ivosidenib may induce CYP2B6, CYP2C8, and CYP2C9.

Drug Transporter Systems

Ivosidenib is a substrate for P-glycoprotein (P-gp). Ivosidenib is not a substrate for BCRP or hepatic transporters OATP1B1 and OATP1B3.

Ivosidenib is an inhibitor of OAT3 and P-gp. Ivosidenib does not inhibit BCRP, OATP1B1, OATP1B3, OAT1, and OCT2.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ivosidenib. Ivosidenib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay. Ivosidenib was not clastogenic in an in vitro human lymphocyte micronucleus assay, or in an in vivo rat bone marrow micronucleus assay. Fertility studies in animals have not been conducted with ivosidenib. In repeat-dose toxicity studies up to 90 days in duration with twice daily oral administration of ivosidenib in rats, uterine atrophy was reported in females at non-tolerated dose levels.

14 CLINICAL STUDIES

14.1 Newly Diagnosed AML

Newly Diagnosed AML in Combination with Azacitidine

The efficacy of TIBSOVO was evaluated in a randomized (1:1), multicenter, double-blind, placebo-controlled clinical trial (Study AG120-C-009, NCT03173248) of 146 adult patients with newly-diagnosed AML with an IDH1 mutation who were 75 years or older, or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin > 1.5 times the upper limit of normal, creatinine clearance < 45 mL/min, or other comorbidity. IDH1 mutations were confirmed centrally using the Abbott RealTi*m*e™ IDH1 Assay. Local diagnostic tests were permitted for screening and randomization provided a bone marrow or peripheral blood sample was sent for central confirmation. Gene mutation analysis to document IDH1 mutated disease from a bone marrow or peripheral blood sample was conducted for all patients. Patients were randomized to receive either TIBSOVO 500 mg or matched placebo orally once daily on Days 1-28 in combination with azacitidine 75 mg/m^2/day either subcutaneously or intravenously on Days 1-7 or Days 1-5 and 8-9 of each 28-day cycle beginning on Cycle 1 Day 1. Patients were treated for a minimum of 6 cycles unless they experienced disease progression, unacceptable toxicity or undergoing hematopoietic stem cell transplantation. Baseline demographic and disease characteristics are shown in Table 13.

Table 13: Baseline Demographic and Disease Characteristics in Patients with Newly Diagnosed AML (Study AG120-C-009)

Demographic and Disease Characteristics	**TIBSOVO + azacitidine (500 mg daily) N=72**	**Placebo + azacitidine N=74**
Demographics		
Age (Years) Median (Min, Max)	76 (58, 84)	76 (45, 94)
Age Categories, n (%)		
< 65 years	4 (6)	4 (5)
≥ 65 years to < 75 years	29 (40)	27 (36)
≥ 75 years	39 (54)	43 (58)
Sex, n (%)		
Male	42 (58)	38 (51)
Female	30 (42)	36 (49)

Table 13: Baseline Demographic and Disease Characteristics in Patients with Newly Diagnosed AML (Study AG120-C-009)

Demographic and Disease Characteristics	TIBSOVO + azacitidine (500 mg daily) N=72	Placebo + azacitidine N=74
Race, n (%)		
Asian	15 (21)	19 (26)
White	12 (17)	12 (16)
Black or African American	0	2 (3)
Other	1 (1)	1 (1)
Not provided	44 (61)	40 (54)
Disease Characteristics		
ECOG PS, n (%)		
0	14 (19)	10 (14)
1	32 (44)	40 (54)
2	26 (36)	24 (32)
IDH1 Mutation, n (%)[1]		
R132C	45 (63)	51 (69)
R132H	14 (19)	12 (16)
R132G	6 (8)	4 (5)
R132L	3 (4)	0
R132S	2 (3)	6 (8)
Wild type	1 (1)	0
Missing	1 (1)	1 (1)
Cytogenetic risk status[2] n (%)		
Favorable	3 (4)	7 (9)
Intermediate	48 (67)	44 (59)
Poor	16 (22)	20 (27)
Other	3 (4)	1 (1)
Missing	2 (3)	2 (3)
Transfusion Dependent at Baseline[3], n (%)	39 (54)	40 (54)
Type of AML, n (%)		
De novo AML	54 (75)	53 (72)
Secondary AML	18 (25)	21 (28)
Therapy-related AML	2 (3)	1 (1)
MDS related	10 (14)	12 (16)
MPN related	4 (6)	8 (11)

ECOG PS: Eastern Cooperative Oncology Group Performance Status; MPN = Myeloproliferative Neoplasm; MDS = Myelodysplastic syndrome

[1] Using confirmatory Abbott RealTi*m*e IDH1 assay testing results.

[2] Cytogenetic risk status: National Comprehensive Cancer Network (NCCN) guidelines.

[3] Patients were defined as transfusion dependent at baseline if they received any red blood cell or platelet transfusion within 56 days prior to the first dose of TIBSOVO.

Efficacy was established on the basis of event-free survival (EFS), overall survival (OS), and rate and duration of complete remission (CR). EFS was defined as the time from randomization until treatment failure, relapse from remission, or death from any cause, whichever occurred first. Treatment failure was defined as failure to achieve CR by 24 weeks. The efficacy results are shown in Table 14 and Figure 1.

Table 14: Efficacy Results in Patients with Newly Diagnosed AML (Study AG120-C-009)

Endpoint	TIBSOVO (500 mg daily) + azacitidine N=72	Placebo + azacitidine N=74
EFS, events (%)	47 (65)	62 (84)
Treatment Failure	43 (60)	59 (80)
Relapse	3 (4)	2 (3)
Death	1 (1)	1 (1)
Hazard ratio[1] (95% CI)	0.35 (0.17, 0.72)	
p-value[2]	0.0038	
OS events (%)	28 (39)	46 (62)
Median OS (95% CI) months	24.0 (11.3, 34.1)	7.9 (4.1, 11.3)
Hazard ratio[1] (95% CI)	0.44 (0.27, 0.73)	
p-value[2]	0.0010	
CR, n (%)	34 (47)	11 (15)
95% CI[3]	(35, 59)	(8, 25)
Risk difference[4] (95% CI), (%)	31 (17, 46)	
p-value[5]	< 0.0001	
Median duration of CR (95% CI), months	NE (13.0, NE)	11.2 (3.2, NE)
CR +CRh, n (%)	37 (51)	13 (18)
95% CI[3]	(39, 63)	(10, 28)
Risk difference[4] (95% CI), (%)	33 (18, 47)	
p-value[5]	< 0.0001	
Median duration of CR + CRh (95% CI), months	NE (13.0, NE)	9.2 (5.8, NE)

Abbreviations: EFS = Event free survival; CI: confidence interval; OS = Overall survival; CR = Complete remission; CRh = Complete remission with partial hematologic recovery; NE = Not estimable.

The 2-sided p-value boundaries for EFS, OS, CR, and CR+CRh are 0.0095, 0.0034, 0.0174, and 0.0174, respectively.

[1] Hazard ratio is estimated using a Cox's proportional hazards model stratified by the randomization stratification factors (AML status and geographic region) with Placebo + azacitidine as the denominator.

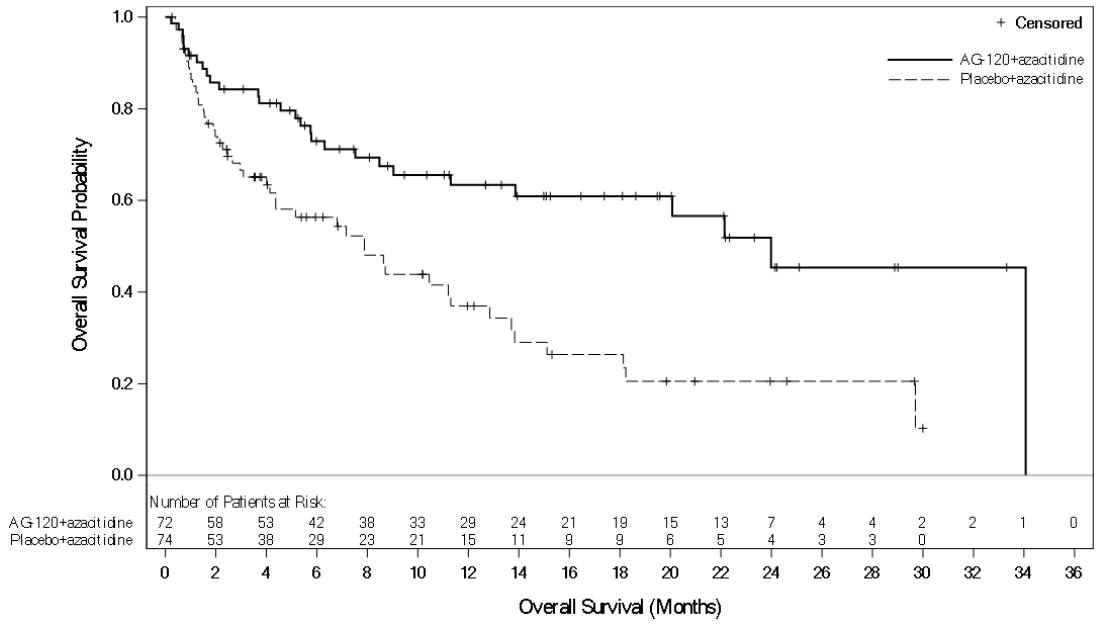
[2] Two-sided p-value is calculated from the log-rank test stratified by the randomization stratification factors (AML status and geographic region).

[3] CI of percentage is calculated with the Clopper and Pearson (exact Binomial) method.

[4] Mantel-Haenszel estimate of risk difference in percentage between TIBSOVO + azacitidine and Placebo + azacitidine is calculated.

[5] Two-sided p-value is calculated from the Cochran-Mantel-Haenszel test stratified by the randomization stratification factors (AML status and geographic region).

Figure 1: Kaplan-Meier Curve for Overall Survival in AG120-C-009



The median time to first CR for TIBSOVO with azacitidine was 4 months (range, 1.7 to 11.9 months).

The median time to first CR + CRh for TIBSOVO with azacitidine was 4 months (range, 1.7 to 11.9 months).

Monotherapy in Newly Diagnosed AML

The efficacy of TIBSOVO was evaluated in an open-label, single-arm, multicenter clinical trial (Study AG120-C-001, NCT02074839) that included 28 adult patients with newly diagnosed AML with an IDH1 mutation. IDH1 mutations were identified by a local or central diagnostic test and confirmed retrospectively using the Abbott RealTi*m*e™ IDH1 Assay. The cohort included patients who were age 75 years or older or who had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline ECOG performance status of ≥ 2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin > 1.5 times the upper limit of normal, or creatinine clearance < 45 mL/min. TIBSOVO was given orally at a starting dose of 500 mg daily until disease progression, development of unacceptable toxicity, or undergoing hematopoietic stem cell transplantation. Two (7%) of the 28 patients went on to stem cell transplantation following TIBSOVO treatment.

The baseline demographic and disease characteristics are shown in Table 15.

Table 15: Baseline Demographic and Disease Characteristics in Patients with Newly Diagnosed AML (Study AG120-C-001)

Demographic and Disease Characteristics	TIBSOVO (500 mg daily) N=28
Demographics	
Age (Years) Median (Min, Max)	77 (64, 87)
Age Categories, n (%)	
< 65 years	1 (4)
≥ 65 years to < 75 years	8 (29)
≥ 75 years	19 (68)
Sex, n (%)	
Male	15 (54)
Female	13 (46)
Race, n (%)	
White	24 (86)
Black or African American	2 (7)
Asian	0
Native Hawaiian/Other Pacific Islander	0
Other/Not provided	2 (7)
Disease Characteristics	
ECOG PS, n (%)	
0	6 (21)
1	16 (57)
2	5 (18)
3	1 (4)
IDH1 Mutation, n (%)[1]	
R132C	24 (86)
R132H	2 (7)
R132G	1 (4)
R132L	1 (4)
R132S	0
ELN Risk Category, n (%)	
Favorable	0
Intermediate	9 (32)
Adverse	19 (68)
Transfusion Dependent at Baseline[2], n (%)	17 (61)
Type of AML, n (%)	
De novo AML	6 (21)
AML-MRC[3]	19 (68)
Therapy-related AML	3 (11)
Prior Hypomethylating Agent for Antecedent Hematologic Disorder	13 (46)

ECOG PS: Eastern Cooperative Oncology Group Performance Status. ELN: European Leukemia Net

[1] Using confirmatory Abbott RealTi*m*e IDH1 assay testing results.

[2] Patients were defined as transfusion dependent at baseline if they received any transfusion occurring within 56 days prior to the first dose of TIBSOVO.

[3] AML with myelodysplasia-related changes.

Efficacy was established on the basis of the rate of complete remission (CR) or complete remission with partial hematologic recovery (CRh), the duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. The efficacy results are shown in Table 16. The median follow-up was 8.1 months (range, 0.6 to 40.9 months) and median treatment duration was 4.3 months (range, 0.3 to 40.9 months).

Table 16: Efficacy Results in Patients with Newly Diagnosed AML (Study AG120-C-001)

Endpoint	TIBSOVO (500 mg daily) N=28
CR[1] n (%)	8 (28.6)
95% CI	(13.2, 48.7)
Median DOCR[2] (months)	NE[3]
95% CI	(4.2, NE)
CRh[4] n (%)	4 (14.3)
95% CI	(4.0, 32.7)
Observed DOCRh[2] (months)	2.8, 4.6, 8.3, 15.7+
CR+CRh n (%)	12 (42.9)
95% CI	(24.5, 62.8)
Median DOCR+CRh[2] (months)	NE[3]
95% CI	(4.2, NE)

CI: confidence interval, NE: not estimable

[1] CR (complete remission) was defined as < 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and absolute neutrophil counts [ANC] >1,000/microliter).

[2] DOCR (duration of CR), DOCRh (duration of CRh), and DOCR+CRh (duration of CR+CRh) was defined as time since first response of CR, CRh or CR/CRh, respectively, to relapse or death, whichever is earlier. + indicates censored observation.

[3] The median durations of CR and CR+CRh were not estimable, with 5 patients (41.7%) who achieved CR or CRh remaining on TIBSOVO treatment (treatment duration range: 20.3 to 40.9 months).

[4] CRh (complete remission with partial hematological recovery) was defined as < 5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).

For patients who achieved a CR or CRh, the median time to CR or CRh was 2.8 months (range, 1.9 to 12.9 months). Of the 12 patients who achieved a best response of CR or CRh, 11 (92%) achieved a first response of CR or CRh within 6 months of initiating TIBSOVO.

Among the 17 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 7 (41.2%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 11 patients who were independent of both RBC and platelet transfusions at baseline, 6 (54.5%) remained transfusion independent during any 56-day post-baseline period.

14.2 Relapsed or Refractory AML

The efficacy of TIBSOVO was evaluated in an open-label, single-arm, multicenter clinical trial (Study AG120-C-001, NCT02074839) of 174 adult patients with relapsed or refractory AML with an IDH1 mutation. IDH1 mutations were identified by a local or central diagnostic test and confirmed retrospectively using the Abbott RealTi*me*™ IDH1 Assay. TIBSOVO was given orally at a starting dose of 500 mg daily until disease progression, development of unacceptable toxicity, or undergoing hematopoietic stem cell transplantation. Twenty-one (12%) of the 174 patients went on to stem cell transplantation following TIBSOVO treatment.

The baseline demographic and disease characteristics are shown in Table 17.

Table 17: Baseline Demographic and Disease Characteristics in Patients with Relapsed or Refractory AML (Study AG120-C-001)

Demographic and Disease Characteristics	**TIBSOVO (500 mg daily) N=174**
Demographics	
Age (Years) Median (Min, Max)	67 (18, 87)
Age Categories, n (%)	
< 65 years	63 (36)
≥ 65 years to < 75 years	71 (41)
≥ 75 years	40 (23)
Sex, n (%)	
Male	88 (51)
Female	86 (49)
Race, n (%)	
White	108 (62)
Black or African American	10 (6)
Asian	6 (3)
Native Hawaiian/Other Pacific Islander	1 (1)
Other/Not provided	49 (28)
Disease Characteristics	
ECOG PS, n (%)	
0	36 (21)
1	97 (56)
2	39 (22)
3	2 (1)
IDH1 Mutation, n (%)[1]	
R132C	102 (59)
R132H	43 (25)
R132G	12 (7)
R132S	10 (6)
R132L	7 (4)
Cytogenetic Risk Status, n (%)	
Intermediate	104 (60)
Poor	47 (27)
Missing/Unknown	23 (13)

Table 17: Baseline Demographic and Disease Characteristics in Patients with Relapsed or Refractory AML (Study AG120-C-001)

Relapse Type	
Primary refractory	64 (37)
Refractory relapse	45 (26)
Untreated relapse	65 (37)
Relapse Number	
0	64 (37)
1	83 (48)
2	21 (12)
≥ 3	6 (3)
Prior Stem Cell Transplantation for AML, n (%)	40 (23)
Transfusion Dependent at Baseline[2], n (%)	110 (63)
Median Number of Prior Therapies (Min, Max)	2 (1, 6)
Type of AML, n (%)	
De novo AML	116 (67)
Secondary AML	58 (33)

ECOG PS: Eastern Cooperative Oncology Group Performance Status.

[1] Using confirmatory Abbott RealTi*m*e IDH1 assay testing results.

[2] Patients were defined as transfusion dependent at baseline if they received any transfusion occurring within 56 days prior to the first dose of TIBSOVO.

Efficacy was established on the basis of the 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. The efficacy results are shown in Table 18. The median follow-up was 8.3 months (range, 0.2 to 39.5 months) and median treatment duration was 4.1 months (range, 0.1 to 39.5 months).

Table 18: Efficacy Results in Patients with Relapsed or Refractory AML (Study AG120-C-001)

Endpoint	**TIBSOVO (500 mg daily) N=174**
CR[1] n (%)	43 (24.7)
95% CI	(18.5, 31.8)
Median DOCR[2] (months)	10.1
95% CI	(6.5, 22.2)
CRh[3] n (%)	14 (8.0)
95% CI	(4.5, 13.1)
Median DOCRh[2] (months)	3.6
95% CI	(1, 5.5)
CR+CRh[4] n (%)	57 (32.8)
95% CI	(25.8, 40.3)
Median DOCR+CRh[2] (months)	8.2
95% CI	(5.6, 12)

CI: confidence interval

[1] CR (complete remission) was defined as < 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and absolute neutrophil counts [ANC] >1,000/microliter).

[2] DOCR (duration of CR), DOCRh (duration of CRh), and DOCR+CRh (duration of CR+CRh) was defined as time since first response of CR, CRh or CR/CRh, respectively, to relapse or death, whichever is earlier.

[3] CRh (complete remission with partial hematological recovery) was defined as < 5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/ microliter and ANC > 500/microliter).

[4] CR+CRh rate appeared to be consistent across all baseline demographic and baseline disease characteristics with the exception of number of prior regimens.

For patients who achieved a CR or CRh, the median time to CR or CRh was 2 months (range, 0.9 to 5.6 months). Of the 57 patients who achieved a best response of CR or CRh, all achieved a first response of CR or CRh within 6 months of initiating TIBSOVO.

Among the 110 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 41 (37.3%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 64 patients who were independent of both RBC and platelet transfusions at baseline, 38 (59.4%) remained transfusion independent during any 56-day post-baseline period.

14.3 Relapsed or Refractory MDS

The efficacy of TIBSOVO was evaluated in an open-label, single-arm, multicenter study (study AG120-C-001, NCT02074839) of 18 adult patients with relapsed or refractory MDS with an IDH1 mutation. IDH1 mutations were detected in peripheral blood or bone marrow by a local or central diagnostic test and confirmed retrospectively using the Abbott RealTi*m*e™ IDH1 Assay. TIBSOVO was given orally at a starting dose of 500 mg daily continuous for 28-day cycles until disease progression, development of unacceptable toxicity, or undergoing hematopoietic stem cell transplantation. One (6%) of the 18 patients went on to stem cell transplantation following TIBSOVO treatment.

The baseline demographic and disease characteristics are shown in Table 19.

Table 19: Baseline Demographic and Disease Characteristics in Patients with Relapsed or Refractory MDS (Study AG120-C-001)

Demographic and Disease Characteristics	TIBSOVO (500 mg daily) N=18
Demographics	
Age (Years) Median (Min, Max)	74 (61, 82)
Age Categories, n (%)	
< 65 years	3 (17)
≥ 65 years to < 75 years	7 (39)
≥ 75 years	8 (44)
Sex, n (%)	
Male	14 (78)
Female	4 (22)
Race, n (%)	
White	14 (78)
Black or African American	1 (6)
Not Reported	3 (17)
Disease Characteristics	
ECOG PS, n (%)	
0	5 (28)
1	10 (56)
2	3 (17)
IDH1 Mutation, n (%)[1]	
R132C	9 (50)
R132H	5 (28)
R132G	2 (11)
R132L	1 (6)
R132S	1 (6)

Table 19: Baseline Demographic and Disease Characteristics in Patients with Relapsed or Refractory MDS (Study AG120-C-001)

Demographic and Disease Characteristics	TIBSOVO (500 mg daily) N=18
Cytogenetic Risk Status, n (%)	
Good	4 (22)
Intermediate	8 (44)
Poor	5 (28)
Missing	1 (6)
Baseline Bone Marrow Blasts, n (%)	
< 5%	7 (39)
≥ 5%	11 (61)
Prior Therapies	
Intensive chemotherapy	3 (17)
Non-intensive chemotherapy	15 (83)
1 line of HMA-based therapy	14 (78)
2 lines of HMA-based therapy	1 (6)

ECOG PS: Eastern Cooperative Oncology Group Performance Status.
[1] Using confirmatory Abbott RealTime IDH1 assay testing results.

Efficacy was established on the basis of the rate of complete remission (CR) or partial remission (PR) as per the 2006 International Working Group response criteria for MDS, the duration of CR+PR, and the rate of conversion from transfusion dependence to transfusion independence. All observed responses were CRs. The efficacy results are shown in Table 20. The median follow-up was 27.1 months (range 3.7 to 88.7 months) and median duration of exposure to TIBSOVO was 8.3 months (range 3.3 to 78.8 months).

Table 20: Efficacy Results in Patients with Relapsed or Refractory MDS (Study AG120-C-001)

Endpoint	TIBSOVO (500 mg daily) N=18
CR[1] n (%)	7 (38.9)
95% CI	(17.3, 64.3)
DOCR[2] (months) median (range)	NE (1.9, 80.8+[3])

CI: confidence interval, CR: complete remission, NE: not estimable, derived based on Kaplan-Meier method.
[1] CR responders with baseline bone marrow blast < 5% was 43% (3/7).
[2] Duration of CR (DOCR) = date of first documented CR (lasted at least 4 weeks) to date of first documented confirmed relapse or death, whichever is earlier.
[3] + indicates censored observation.

For patients who achieved a CR, the median time to CR was 1.9 months (range, 1.0 to 5.6 months).

Among the 9 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 6 (67%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 9 patients who were independent of both RBC and platelet transfusions at baseline, 7 (78%) remained transfusion independent during any 56-day post-baseline period.

14.4 Locally Advanced or Metastatic Cholangiocarcinoma

The efficacy of TIBSOVO was evaluated in a randomized (2:1), multicenter, double-blind, placebo-controlled clinical trial (Study AG120-C-005, NCT02989857) of 185 adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation whose disease had progressed following at least 1 but not more than 2 prior regimens, including at least one gemcitabine- or 5-FU-containing regimen. Patients were randomized to receive either TIBSOVO 500 mg orally once daily or matched placebo until disease progression or unacceptable toxicity. Randomization was stratified by number of prior therapies (1 or 2). Eligible patients who were randomized to placebo were allowed to cross over to receive TIBSOVO after documented radiographic disease progression. Patients with IDH1 mutations were selected using a central diagnostic next generation sequencing assay. Tumor imaging assessments were performed every 6 weeks for the first 8 assessments and every 8 weeks thereafter.

The major efficacy outcome measure was Progression Free Survival (PFS) as determined by independent review committee (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

The median age was 62 years (range: 33 to 83); 63% were female; 57% were White, 12% Asian, 1.1% Black, 0.5% Native Hawaiian/Other Pacific Islander, 0.5% American Indian or Alaska Native, 28% race missing/not reported; and 37% had an ECOG performance status of 0 (37%) or 1 (62%). All patients received at least 1 prior line of systemic therapy and 47% received two prior lines. Most patients had intrahepatic cholangiocarcinoma (91%) at diagnosis and 92% had metastatic disease. Across both arms, 70% patients had an R132C mutation, 15% had an R132L mutation, 12% had an R132G mutation, 1.1% had an R132H mutation, and 1.6% had an R132S mutation.

The efficacy results are shown in Table 21 and Figure 2. The study demonstrated a statistically significant improvement in PFS.

Table 21: Efficacy Results in Patients with Locally Advanced or Metastatic Cholangiocarcinoma in AG120-C-005

Endpoint	TIBSOVO (500 mg daily)	Placebo
Progression-Free Survival by IRC Assessment	**N=124**	**N=61**
Events, n (%) Progressive Disease Death	76 (61) 64 (52) 12 (10)	50 (82) 44 (72) 6 (10)
Hazard ratio (95% CI)[1]	0.37 (0.25, 0.54)	
p-value[2]	< 0.0001	
Objective Response Rate, n (%)	3 (2.4)	0
Overall Survival[3]	**N=126**	**N=61**
Deaths, n (%)	100 (79)	50 (82)
Hazard ratio (95% CI)[1]	0.79 (0.56, 1.12)	
p-value[2]	0.093	

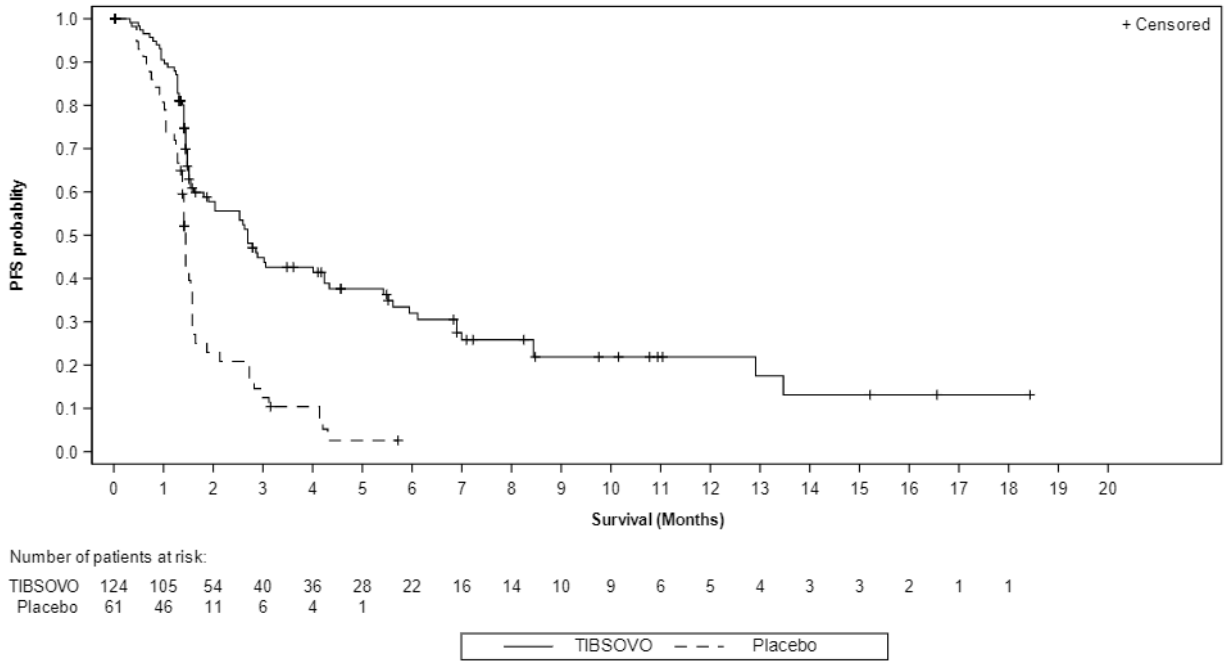
IRC: Independent Review Committee; CI: Confidence Interval

[1] Hazard ratio is calculated from stratified Cox regression model. Stratified by number of prior lines of therapy.

[2] P-value is calculated from the one-sided stratified log-rank test. Stratified by number of prior lines of therapy.

[3] OS results are based on the final analysis of OS (based on 150 deaths) which occurred 16 months after the final analysis of PFS. The median OS (95% CI) for TIBSOVO was 10.3 (7.8, 12.4) months; and placebo was 7.5 (4.8, 11.1) months without adjusting for crossover. In the analysis of OS, 70% of the patients randomized to placebo had crossed over to receive TIBSOVO after radiographic disease progression.

Figure 2: Kaplan-Meier Plot of Progression-Free Survival per Independent Review Committee - Before Crossover (ITT)



16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

250 mg tablet: Blue oval-shaped film-coated tablet debossed “IVO” on one side and “250” on the other side.

- 60-count bottles of 250 mg tablets with a desiccant canister (NDC 72694-617-60).

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Differentiation Syndrome in AML and MDS

Advise patients being treated with TIBSOVO of the risks of developing differentiation syndrome as early as 1 day after start of therapy and during the first 3 months on treatment. Ask patients to immediately report any symptoms suggestive of differentiation syndrome, such as fever, cough or difficulty breathing, rash, decreased urinary output, low blood pressure, rapid weight gain, or swelling of their arms or legs, to their healthcare provider for further evaluation *[see Boxed Warning and Warnings and Precautions (5.1)]*.

QTc Interval Prolongation

Inform patients of symptoms that may be indicative of significant QTc interval prolongation including dizziness, lightheadedness, and fainting. Advise patients to report these symptoms and the use of all medications to their healthcare provider *[see Warnings and Precautions (5.2)]*.

Guillain-Barré Syndrome

Inform patients of symptoms that may be indicative of Guillain-Barré syndrome, including new signs or symptoms of motor and/or sensory neuropathy, such as weakness or tingling sensation in the legs, arms, or upper body, numbness and pain on one side or both sides of the body, changes to any sensory function, or burning or prickling sensation, or difficulty breathing. Advise patients to report these symptoms to their healthcare provider *[see Warnings and Precautions (5.3)]*.

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications, vitamins, and herbal products *[see Drug Interactions (7)]*.

Tumor Lysis Syndrome

Advise patients on the risks of developing tumor lysis syndrome. Advise patients on the importance of maintaining high fluid intake, and the need for frequent monitoring of blood chemistry values *[see Adverse Reactions (6.1)]*.

Gastrointestinal Adverse Reactions

Advise patients on the risks of experiencing gastrointestinal reactions such as diarrhea, nausea, mucositis, constipation, vomiting, decreased appetite, ascites and abdominal pain. Ask patients to report these events to their healthcare provider and advise patients how to manage them *[see Adverse Reactions (6.1)]*.

Lactation

Advise women not to breastfeed during treatment with TIBSOVO and for 1 month after the last dose *[see Use in Specific Populations (8.2)]*.

Dosing and Storage Instructions

- Advise patients to swallow tablets whole and to not split, crush, or chew TIBSOVO tablets.
- Advise patients to avoid taking TIBSOVO with a high-fat meal.
- Instruct patients that if a dose of TIBSOVO is vomited, not to take an additional dose, and wait until the next scheduled dose is due. If a dose of TIBSOVO is missed or not taken at the usual time, instruct patients to take the dose as soon as possible unless the next dose is due within 12 hours. Patients can return to the normal schedule the following day.
- Store TIBSOVO at room temperature from 20°C to 25°C (68°F to 77°F).
- Advise patients not to remove the desiccant canister from the bottle.

Manufactured for Servier Pharmaceuticals LLC, Boston, MA 02210

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AG-PI-006

MEDICATION GUIDE

TIBSOVO® (tib-SOH-voh)

(ivosidenib tablets)

What is the most important information I should know about TIBSOVO?

TIBSOVO may cause serious side effects, including:

Differentiation Syndrome. Differentiation syndrome is a common condition that affects your blood cells and may be life-threatening or lead to death. Differentiation syndrome in adults with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) has happened as early as 1 day and up to 3 months after starting TIBSOVO. Call your healthcare provider or go to the nearest hospital emergency room right away if you develop any of the following symptoms of differentiation syndrome during treatment with TIBSOVO:

- fever
- cough
- trouble breathing
- rash
- decreased urination
- dizziness or lightheadedness
- rapid weight gain
- swelling of your arms or legs

If you develop signs and symptoms of differentiation syndrome, your healthcare provider may treat you with a corticosteroid medicine or a medicine called hydroxyurea and may monitor you in the hospital.

See **"What are the possible side effects of TIBSOVO?"** for more information about side effects.

What is TIBSOVO?

TIBSOVO is a prescription medicine used to treat adults with an isocitrate dehydrogenase-1 (IDH1) mutation with:

- acute myeloid leukemia (AML):
  - with newly diagnosed AML treated in combination with azacitidine, or alone, who are 75 years or older or who have health problems that prevent the use of certain chemotherapy treatments.
  - when the disease has come back or has not improved after previous treatment(s).
- myelodysplastic syndrome (MDS):
  - when the disease has come back or has not improved after previous treatment(s).
- bile duct cancer (cholangiocarcinoma):
  - with bile duct cancer that has spread and
  - who have already received previous treatment(s).

Your healthcare provider will perform a test to make sure that TIBSOVO is right for you.

It is not known if TIBSOVO is safe and effective in children.

Before taking TIBSOVO, tell your healthcare provider about all of your medical conditions, including if you:

- have any heart problems, including a condition called long QT syndrome.
- have problems with abnormal electrolytes, such as sodium, potassium, calcium or magnesium levels.
- have nervous system problems.
- have problems with your kidneys or are on dialysis.
- have any liver disorders, including cirrhosis.
- are pregnant or plan to become pregnant. TIBSOVO may cause harm to your unborn baby. You should avoid becoming pregnant during treatment with TIBSOVO. Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with TIBSOVO.
- are breastfeeding or plan to breastfeed. It is not known if TIBSOVO passes into your breast milk. Do not breastfeed during your treatment with TIBSOVO and for 1 month after your last dose of TIBSOVO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you take hormonal contraceptives. TIBSOVO may affect how hormonal contraceptives work and may cause them to not work as well.

How should I take TIBSOVO?

- Take TIBSOVO exactly as your healthcare provider tells you to.
- Do not change your dose or stop taking TIBSOVO without talking to your healthcare provider.
- Take TIBSOVO 1 time a day about the same time each day.
- Swallow TIBSOVO tablets whole. Do not split, crush, or chew the tablet.
- TIBSOVO can be taken with or without food.
- Do not take TIBSOVO with a high-fat meal. An example of a high-fat meal includes 2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with 1 slice of cheese, and 8 ounces of whole milk (approximately 1,000 calories and 58 grams of fat).
- If you vomit after taking a dose of TIBSOVO, do not take an additional dose. Take your next dose at your usual time.
- If you miss a dose of TIBSOVO or did not take it at the usual time, take your dose as soon as possible and at least 12 hours before your next dose. Return to your normal schedule the following day. **Do not** take 2 doses of TIBSOVO within 12 hours.

What are the possible side effects of TIBSOVO?

TIBSOVO may cause serious side effects, including:

- See **"What is the most important information I should know about TIBSOVO?"**
- Changes in the electrical activity of your heart called **QTc prolongation. QTc prolongation can cause irregular heartbeats that can be life-threatening.** Your healthcare provider will check the electrical activity of your heart with a test called an electrocardiogram (ECG) before and during treatment with TIBSOVO. Tell your healthcare provider right away if you feel dizzy, lightheaded, or faint.
- **Guillain-Barré syndrome** has happened in people treated with TIBSOVO. Your healthcare provider will monitor you for nervous system problems and will permanently stop your treatment with TIBSOVO if you develop Guillain-Barré syndrome. Tell your healthcare provider right away if you develop any signs or symptoms of Guillain-Barré syndrome, including:
  - weakness or tingling feeling in your legs, arms, or upper body
  - numbness and pain on one side or both sides of your body
  - any changes in your ability to see, touch, hear, or taste
  - burning or prickling sensation
  - difficulty breathing

The most common side effects of TIBSOVO when used in combination with azacitidine or alone in adults with AML include:

- changes in certain blood cell counts
- diarrhea
- increased blood sugar
- fatigue
- changes in certain liver function tests
- swelling of arms or legs
- decreased levels of electrolytes in the blood
- nausea
- vomiting
- decreased appetite
- joint pain
- shortness of breath
- uric acid increased
- stomach (abdominal) pain
- changes in certain kidney function tests
- pain or sores in your mouth or throat
- rash
- irregular heart rhythm or heartbeat (QTc prolongation)
- differentiation syndrome
- muscle pain

The most common side effects of TIBSOVO when used in adults with Myelodysplastic Syndromes (MDS) include:

- changes in certain kidney function tests
- changes in certain blood cell counts
- joint pain, back pain, or neck pain
- decreased levels of albumin in the blood
- changes in liver function tests
- fatigue
- diarrhea
- cough
- decreased levels of sodium in the blood
- pain or sores in your mouth or throat
- decreased appetite
- muscle pain
- decreased levels of phosphorus in the blood
- itchy skin
- rash

The most common side effects of TIBSOVO when used in adults with Cholangiocarcinoma include:

- fatigue
- fluid and swelling in your stomach area

- nausea
- abdominal pain
- diarrhea
- cough
- decreased appetite
- vomiting
- hemoglobin decreased (anemia)
- rash
- changes in liver function tests

Your healthcare provider will do blood tests before you start and during treatment with TIBSOVO. Your healthcare provider may decrease, temporarily hold, or permanently stop your treatment with TIBSOVO if you develop certain side effects.

TIBSOVO may cause fertility problems in females and males, which may affect your ability to have children. Talk to your healthcare provider if you have concerns about fertility. These are not all of the possible side effects of TIBSOVO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TIBSOVO?

- Store TIBSOVO at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not remove the desiccant canister from the bottle.

Keep TIBSOVO and all medicines out of the reach of children.

General information about the safe and effective use of TIBSOVO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take TIBSOVO for conditions for which it was not prescribed. Do not give TIBSOVO to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TIBSOVO that is written for healthcare professionals.

What are the ingredients in TIBSOVO?

Active ingredient: ivosidenib

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet coating includes FD&C blue #2, hypromellose, lactose monohydrate, titanium dioxide, and triacetin.

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For more information go to www.TIBSOVO.com or call 1-800-807-6124.

AG-MG-006

2.2　米国添付文書日本語訳

米国添付文書の和訳を以下に示す。

警告：AML 及び MDS における分化症候群
本剤を投与した患者において分化症候群の症状が認められており、死亡に至る可能性がある。症状には、発熱、呼吸困難、低酸素症、肺湿潤、胸水又は心嚢液貯留、急激な体重増加又は末梢性浮腫、低血圧、並びに肝機能障害、腎機能障害又は多臓器障害が挙げられる。分化症候群が疑われる場合、コルチコステロイド療法及び血行動態モニタリングを開始し、症状が消失するまで継続する。*［警告及び使用上の注意（5.1）及び副作用（6.1）を参照］*

1.　効能又は効果

1.1　未治療の急性骨髄性白血病

本剤はアザシチジンとの併用投与又は単剤投与において、FDA に承認された検査により感受性イソクエン酸脱水素酵素 1（IDH1）変異が検出された、75 歳以上又は寛解導入療法の適応とならない併存症を有する未治療の成人の急性骨髄性白血病（AML）患者の治療を適応とする。*［用法及び用量（2.1）、臨床薬理試験（12.1）及び臨床成績（14.1）を参照］*

1.2　再発又は難治性の急性骨髄性白血病

本剤は、FDA に承認された検査により感受性イソクエン酸脱水素酵素 1（IDH1）変異が検出された、再発又は難治性の成人の急性骨髄性白血病（AML）患者の治療を適応とする。*［用法及び用量（2.1）、臨床薬理試験（12.1）及び臨床成績（14.2）を参照］*

1.3　再発又は難治性の骨髄異形成症候群

本剤は、FDA に承認された検査により感受性イソクエン酸脱水素酵素 1（IDH1）変異が検出された、再発又は難治性の成人の骨髄異形成症候群（MDS）患者の治療を適応とする。*［用法及び用量（2.1）、臨床薬理試験（12.1）及び臨床成績（14.3）を参照］*

1.4　局所進行性又は転移性の胆管癌

本剤は、FDA に承認された検査により感受性イソクエン酸脱水素酵素 1（IDH1）変異が検出された、前治療歴のある成人の局所進行性又は転移性の胆管癌患者の治療を適応とする。*［用法及び用量（2.1）、臨床薬理試験（12.1）及び臨床成績（14.4）を参照］*

2.　用法及び用量

2.1　患者選択

IDH1 変異の発現を確認し、本剤による治療の対象患者を選択する。*［臨床成績（14.1、14.2、14.3、14.4）を参照］*

AML、MDS 及び胆管癌患者を対象とした FDA に承認された IDH1 変異検出検査に関する情報は次のとおりである：http://www.fda.gov/CompanionDiagnostics.

2.2　推奨用量

本剤の推奨用量は、疾患進行又は許容できない毒性の発現まで 1 日 1 回 500mg の経口投与である。*［臨床成績（14.1、14.2、14.3、14.4）を参照］*

疾患進行又は許容できない毒性が発現しない AML 患者又は MDS 患者には、臨床効果を確認するため 6 カ月以上は本剤の投与を継続する。

- 食事の有無にかかわらず本剤は投与可能である。
- 高脂肪食とともに本剤を投与しない。*［警告及び使用上の注意（5.2）及び臨床薬理試験（12.3）を参照］*
- 錠剤を分割、粉砕又は噛み砕いて服用しない。
- 毎日所定の時刻に本剤を経口投与する。
- 本剤を嘔吐した場合、再投与せず次回の投与時刻まで待つ。
- 本剤を飲み忘れた場合又は所定の時刻に服用しなかった場合、次回投与の 12 時間以上前であれば気づいた時点で直ちに服用し忘れた分を投与する。翌日から所定の時刻に投与する。12 時間以内に 2 回投与しない。

未治療の AML（併用療法レジメン）

本剤はサイクル 1 の 1 日目に投与開始し、併用薬であるアザシチジンは 28 日サイクルの 1～7 日目（又は 1～5 日目と 8、9 日目）に 1 日 1 回 75 mg/m^2 で皮下投与又は点滴静注する。*［臨床成績（14.1）を参照］*アザシチジンの用法及び用量の情報について、詳しくは添付文書を参照する。

2.3　副作用に対するモニタリング及び用量調節

治療開始前に心電図（ECG）を測定する。治療開始後 3 週間は週 1 回以上、その後の治療期間中は月 1 回以上 ECG をモニタリングする。［*警告及び使用上の注意（5.2）を参照］*異常が認められた場合は速やかに管理する。

毒性が認められた場合は休薬又は減量する。用量調節のガイドラインについては表 1 を参照する。

表 1：推奨される本剤の用量調節

副作用	推奨される対応
• *分化症候群［警告及び使用上の注意（5.1）を参照］*	• 分化症候群が疑われる場合、全身性コルチコステロイドを投与し、血行動態モニタリングを3日以上かつ症状が消失するまで継続する。 • 全身性コルチコステロイド投与開始後48時間以降も重度の徴候及び／又は症状が続いた場合、本剤を休薬する。 • 徴候及び症状がGrade 2*以下に改善した場合、本剤の投与を再開する。
• 非感染性の白血球増加症（白血球数が25×10^9/L超又は総白血球数の絶対数がベースラインより15×10^9/L超増加）	• 医療機関ごとの基準に従いヒドロキシウレアによる治療を開始し、臨床上必要ならば白血球アフェレーシスを実施する。 • 白血球増加症が改善又は消失した後に限りヒドロキシウレアを漸減する。 • ヒドロキシウレア投与により白血球増加症が改善しない場合、本剤を休薬し、白血球増加症が消失した場合、本剤を1日1回500 mgで再開する。
• QTc間隔が480 msec超500 msec以下*［警告及び使用上の注意（5.2）及び薬物相互作用（7.1）を参照］*	• 電解質濃度をモニタリングし、臨床上必要に応じて電解質を補給する。 • QTc間隔延長を起こすことが知られている併用薬を確認し調節する。 • 本剤を休薬する。 • QTc間隔が480 msec以下に回復した後、本剤を500 mg1日1回で再開する。 • QTc延長の消失後2週間は週に1回以上ECGをモニタリングする。
• QTc間隔が500 msec超*［警告及び使用上の注意（5.2）及び薬物相互作用（7.1）を参照］*	• 電解質濃度をモニタリングし、臨床上必要に応じて電解質を補給する。 • QTc間隔延長を起こすことが知られている併用薬を確認し調節する。 • 本剤を休薬する。 • QTc間隔がベースライン時の30 msec以内又は480 msec以下に回復した後、本剤を1日1回250 mgに減量し再開する。 • QTc延長の消失後2週間は週に1回以上ECGをモニタリングする。 • QTc延長に他の原因が特定された場合、本剤の用量を1日1回500 mgに再度増量することを考慮する。

副作用	推奨される対応
● 生命を脅かす不整脈の徴候／症状を伴うQTc間隔延長*［警告及び使用上の注意（5.2）を参照］*	• 本剤を中止する。
● ギラン・バレー症候群*［警告及び使用上の注意（5.3）を参照］*	• 本剤を中止する。
● その他のGrade 3*の副作用	AML及びMDSでの単剤療法： • 副作用がGrade 2*以下に回復するまで本剤を休薬する。 • 本剤を1日1回250 mgで再開し、副作用がGrade 1*以下に回復後は1日1回500 mgに増量してもよい。 • Grade 3*以上の副作用が再発した場合、本剤を中止する。 胆管癌、又はAMLにおけるアザシチジンとの併用療法： • 副作用がGrade 1*以下又はベースラインに回復するまで本剤を休薬し、その後本剤を1日1回500 mg（Grade 3の副作用）又は1日1回250 mg（Grade 4の副作用）で再開する。 • Grade 3の副作用が再発した場合（2回目）、本剤を1日1回250 mgに減量し、副作用が消失してから1日1回500 mgで再開する。 • Grade 3の副作用が再発した場合（3回目）、又はGrade 4の副作用が再発した場合、本剤を中止する。

*Grade 1 は軽症、Grade 2 は中等症、Grade 3 は重症、Grade 4 は生命を脅かす副作用。Grade は有害事象共通用語規準（CTCAE）version 4.03 に基づく。

AML 患者又は MDS 患者

血球数及び血液生化学の評価を、本剤の投与開始前、投与開始の 1 カ月目は週 1 回以上、2 カ月目は隔週 1 回、治療期間中は月 1 回実施する。

治療開始後 1 カ月は週 1 回、血中クレアチンホスホキナーゼをモニタリングする。

2.4　強い CYP3A4 阻害剤投与時の用量調節

強い CYP3A4 阻害剤を併用投与する場合、本剤を 1 日 1 回 250 mg に減量する。強い CYP3A4 阻害剤の投与を中止したときは（強い CYP3A4 阻害剤の 5 半減期以上経過後）、本剤を推奨用量である 1 日 1 回 500 mg に増量する。

3.　剤形及び含量

錠剤：楕円形の青色フィルムコーティング錠（250 mg）であり、錠剤の片面に「IVO」、反対面に「250」と刻印されている。

4.　禁忌

該当せず。

5.　警告及び使用上の注意

5.1　AML 及び MDS における分化症候群

分化症候群は骨髄系細胞の急激な増殖及び分化に関連し、生命を脅かす又は死亡に至る可能性がある。

本剤を投与した患者にみられる分化症候群の症状は、非感染性の白血球増加症、末梢性浮腫、発熱、呼吸困難、胸水、低血圧、低酸素症、肺水腫、肺臓炎、心嚢液貯留、発疹、水分過負荷、腫瘍崩壊症候群及びクレアチニン増加である。

併用療法を検討した AG120-C-009 試験では、本剤とアザシチジンを投与した未治療 AML 患者の 15%（11/71 例）に分化症候群が認められた。*［副作用（6.1）を参照］*本剤とアザシチジンの投与後に分化症候群が認められた未治療 AML 患者 11 例のうち 8 例（73%）が回復した。分化症候群は、早い患者で治療開始 3 日後から 1 カ月間に発症した。

単剤療法を検討した AG120-C-001 試験では、本剤を投与した未治療 AML 患者の 25%（7/28 例）、再発又は難治性 AML 患者の 19%（34/179 例）に分化症候群が認められた。*［副作用（6.1）を参照］*分化症候群が認められた未治療 AML 患者の 7 例のうち 6 例（86%）が回復した。分化症候群が認められた再発又は難治性 AML 患者の 34 例のうち、治療後又は本剤の休薬後に 27 例（79%）が回復した。分化症候群は、白血球増加症の併発にかかわらず、早い患者で本剤の投与 1 日後から最長 3 カ月後までに発症した。

単剤療法を検討した AG120-C-001 試験では、本剤を投与した再発又は難治性 MDS 患者の 11%（2/19 例）に分化症候群が認められた。*［副作用（6.1）を参照］*分化症候群が認められた 2 例は治療後又は本剤の休薬後にともに回復した。分化症候群は、白血球増加症の併発にかかわらず、早い患者で本剤の投与 1 日後から最長 3 カ月後までに発症した。

分化症候群が疑われる場合、デキサメタゾン 10 mg を 12 時間ごとに点滴静注（又は同等量の代替コルチコステロイドを経口投与若しくは点滴静注）及び血行動態モニタリングを開始し、症状が消失するまで継続する。*［用法及び用量（2.3）を参照］*非感染性の白血球増加症を併発している場合、臨床上必要に応じてヒドロキシウレアの投与又は白血球アフェレーシスを開始する。症状

消失後はコルチコステロイド及びヒドロキシウレアを漸減するが、コルチコステロイドは 3 日以上投与する。コルチコステロイド及び／又はヒドロキシウレアの投与を早期に中止すると、分化症候群の症状が再発することがある。コルチコステロイド投与開始後 48 時間以降も重度の徴候及び／又は症状が続いた場合、重度の徴候及び／又は症状が回復するまで本剤を休薬する。*［用法及び用量（2.3）を参照］*

5.2　　QTc 間隔延長

本剤の投与により QT（QTc）延長及び心室性不整脈があらわれることがある。*［臨床薬理試験（12.2）を参照］*

臨床試験（AG120-C-009 試験）において本剤とアザシチジンを併用投与した未治療 AML 患者 71 例のうち、10 例（14%）で心拍数で補正した QT 間隔（Fridericia 法を使用）（QTcF）が 500 msec 超であり、69 例のうち 15 例（22%）の QTcF はベースライン時よりも 60 msec 超延長した。*［副作用（6.1）を参照］*本試験では、QTcF が 470 msec 以上並びに QT 延長又は不整脈のリスクが上昇する他の要因（NYHA クラス III 又は IV のうっ血性心不全、低カリウム血症、QT 延長症候群の家族歴など）を有する患者を除外した。

臨床試験（AG120-C-001 試験）において本剤を単剤投与した AML 及び MDS を含む血液悪性腫瘍患者 265 例のうち、9%の QTc 間隔は 500 msec 超であり、14%はベースライン時よりも QTc が 60 msec 超延長した。*［副作用（6.1）を参照］*1 例で本剤に関連する心室細動が認められた。本試験では、QTc が 450 msec 以上の患者（従来認められていた脚ブロックにより QTc が 450 msec 以上であった患者を除く）並びに QT 延長症候群の既往歴を有する患者又は管理不能若しくは重要な心血管疾患を有する患者を除外した。

臨床試験（AG120-C-005 試験）において本剤を投与した胆管癌患者 123 例のうち、2%は QTc 間隔が 500 msec 超であり、5%では QTc がベースライン時よりも 60 msec 超延長した。*［副作用（6.1）を参照］*本試験では、心拍数で補正した QT 間隔（Fridericia 法を使用）（QTcF）が 450 msec 以上の患者並びに QT 延長又は不整脈のリスクが上昇する他の要因（心不全、低カリウム血症、QT 延長症候群の家族歴など）を有する患者を除外した。

QTc 間隔延長を起こすことが知られている薬剤（抗不整脈薬、フルオロキノロン、トリアゾール系抗真菌薬、5-HT_3 受容体拮抗薬など）及び CYP3A4 阻害剤と本剤とを併用投与すると、QTc 間隔延長のリスクが上昇する可能性がある。*［薬物相互作用（7.1）、臨床薬理試験（12.2）を参照］*心電図及び電解質をモニタリングする。*［用法及び用量（2.3）を参照］*

先天性 QTc 延長症候群、うっ血性心不全、電解質異常を有する患者又は QTc 間隔延長を起こすことが知られている薬剤を服用している患者には、頻回のモニタリングが必要となる可能性がある。

QTc 間隔が 480 msec 超 500 msec 以下に延長した場合は本剤を休薬する。QTc 間隔が 500 msec 超に延長した場合、本剤を休薬及び減量する。生命を脅かす不整脈の徴候又は症状を伴う QTc 間隔延長が認められた場合、本剤を中止する。*［用法及び用量（2.3）を参照］*

5.3　ギラン・バレー症候群

本剤の投与によりギラン・バレー症候群が発症する可能性がある。AG120-C-001 試験において本剤を投与した患者の 0.8%（2/265 例）にギラン・バレー症候群が認められた。*［副作用（6.1）を参照］*

本剤を服用している患者に対して、片側又は両側の筋力低下、感覚の変化、錯感覚、呼吸困難などの運動性及び／又は感覚性ニューロパチーの新たな徴候と症状についてモニタリングする。ギラン・バレー症候群と診断された場合、本剤を中止する。*［用法及び用量（2.3）を参照］*

6.　副作用

以下の重大な副作用は添付文書の他の項に記載する。

- AML及びMDSにおける分化症候群 *［警告及び使用上の注意（5.1）を参照］*
- QTc間隔延長 *［警告及び使用上の注意（5.2）を参照］*
- ギラン・バレー症候群 *［警告及び使用上の注意（5.3）を参照］*

6.1　臨床試験成績

臨床試験は多様な条件下で実施されるため、ある被験薬の臨床試験で認められた副作用の発現率を別の被験薬による臨床試験で認められた発現率と直接比較することはできない。また、実臨床での発現率が反映されない可能性がある。

<u>急性骨髄性白血病</u>

AMLの安全性解析対象集団は、AG120-C-009試験（N=71）及びAG120-C-001試験（N=213）でそれぞれ本剤1日1回500 mgとアザシチジンとの併用投与及び本剤を単剤投与した患者である。*［臨床成績（14.1及び14.2）を参照］*この安全性解析対象集団で、最もよくみられた臨床検査値異常を含む副作用（各試験25%以上）は、白血球数減少、下痢、ヘモグロビン減少、血小板減少、ブドウ糖増加、疲労、アルカリホスファターゼ増加、浮腫、カリウム減少、悪心、嘔吐、ホスファターゼ減少、食欲減退、ナトリウム減少、白血球増加症、マグネシウム減少、アスパラギン酸アミノトランスフェラーゼ増加、関節痛、呼吸困難、尿酸増加、腹痛、クレアチニン増加、粘膜炎、発疹、心電図QT延長、分化症候群、カルシウム減少、好中球数減少及び筋肉痛であった。

未治療のAML

本剤とアザシチジンの併用療法

AG120-C-009試験ではAML患者を対象とし本剤とアザシチジンを併用投与したときの本剤の安全性を評価した。*［臨床成績（14.1）を参照］*本剤1日1回500 mg（N=71）又はプラセボ（N=73）を少なくとも1回投与した。本剤とアザシチジンを併用投与した患者では、本剤の曝露期間の中央値は6カ月であった（範囲0～33カ月）。曝露期間は、34例（48%）は少なくとも6カ月以上、22例（31%）は少なくとも1年以上であった。

本剤とアザシチジンの併用投与例でよくみられた重篤な副作用（5%以上）は分化症候群（8%）であった。

本剤とアザシチジンの併用投与例の4%で致死的な副作用である分化症候群（3%）及び脳虚血（1例）が認められた。

患者の2%以上に認められた本剤の中止に至った副作用は、分化症候群（3%）及び肺塞栓症（3%）であった。

最もよくみられた本剤の休薬に至った副作用（5%超）は、好中球減少症（25%）、心電図QT延長（7%）及び血小板減少症（7%）であった。

本剤の減量に至った副作用は心電図QT延長（8%）、好中球減少症（8%）及び血小板減少症（1%）であった。

AG120-C-009試験で最もよくみられた副作用及び臨床検査値異常を表2及び表3に示す。

表2：AG120-C-009試験でプラセボ+アザシチジン群と比較して本剤+アザシチジン併用療法を受けたAML患者の発現割合の差が2%以上であった副作用（10%以上）

	本剤+アザシチジン N=71		プラセボ+アザシチジン N=73	
器官分類 副作用	**全Grade** **n（%）**	**Grade 3以上** **n（%）**	**全Grade** **n（%）**	**Grade 3以上** **n（%）**
胃腸障害				
悪心	30 (42)	2 (3)	28 (38)	3 (4)
嘔吐[1]	29 (41)	0	20 (27)	1 (1)
臨床検査				
心電図QT延長	14 (20)	7 (10)	5 (7)	2 (3)
精神障害				
不眠症	13 (18)	1 (1)	9 (12)	0
血液およびリンパ系障害				
分化症候群[2]	11 (15)	7 (10)	6 (8)	6 (8)
白血球増加症[3]	9 (13)	0	1 (1)	0
血管障害				

	本剤+アザシチジン N=71		プラセボ+アザシチジン N=73	
器官分類 副作用	**全Grade** **n（%）**	**Grade 3以上** **n（%）**	**全Grade** **n（%）**	**Grade 3以上** **n（%）**
血腫[4]	11 (15)	0	3 (4)	0
高血圧[5]	9 (13)	3 (4)	6 (8)	4 (5)
筋骨格系および結合組織障害				
関節痛[6]	21 (30)	3 (4)	6 (8)	1 (1)
呼吸器、胸郭および縦隔障害				
呼吸困難[7]	14 (20)	2 (3)	11 (15)	4 (5)
神経系障害				
頭痛	8 (11)	0	2 (3)	0

1 グループ化した用語：嘔吐及びレッチング
2 分化症候群は、末梢性浮腫、白血球増加症、発熱、呼吸困難、胸水、低血圧、低酸素症、肺水腫、肺炎、心嚢液貯留、発疹、水分過負荷、腫瘍崩壊症候群及びクレアチニン増加など、よく報告される他の事象と関連することがある。
3 グループ化した用語：白血球増加症及び白血球数増加
4 グループ化した用語：血腫、眼血腫、カテーテル留置部位血腫、口腔粘膜血腫、特発性血腫、適用部位血腫、注射部位血腫及び眼窩周囲血腫
5 グループ化した用語：血圧上昇、本態性高血圧症及び高血圧
6 グループ化した用語：四肢痛、関節痛、背部痛、筋骨格硬直、癌疼痛及び頚部痛
7 グループ化した用語：呼吸困難、労作性呼吸困難、低酸素症及び呼吸不全

表 3：AG120-C-009 試験で本剤+アザシチジン併用療法を受けた AML 患者においてベースラインから悪化した臨床検査値異常[1、2]の一部（10%以上）

	本剤+アザシチジン N=71		プラセボ+アザシチジン N=73	
臨床検査値異常	**全Grade** **n（%）**	**Grade 3以上** **n（%）**	**全Grade** **n（%）**	**Grade 3以上** **n（%）**
血液学的検査値異常				
白血球数減少	46 (65)	39 (55)	47 (64)	42 (58)
血小板減少	41 (58)	30 (42)	52 (71)	42 (58)
ヘモグロビン減少	40 (56)	33 (46)	48 (66)	42 (58)
好中球数減少	18 (25)	16 (23)	25 (35)	23 (32)
リンパ球数増加	17 (24)	1 (1)	7 (10)	1 (1)
生化学的検査値異常				
ブドウ糖増加	40 (56)	9 (13)	34 (47)	8 (11)
リン酸塩減少	29 (41)	7 (10)	25 (34)	9 (12)
アスパラギン酸アミノトランスフェラーゼ増加	26 (37)	0	17 (23)	0
マグネシウム減少	25 (35)	0	19 (26)	0
アルカリホスファターゼ増加	23 (32)	0	21 (29)	0
カリウム増加	17 (24)	2 (3)	9 (12)	1 (1)

1 臨床検査値異常は、新規若しくはベースライン時より1グレード以上悪化した場合、又はベースライン時の値が不明な場合と定義した。
2 割合の算出に使用した分母は、各群の各パラメータについてCTCAE規準で評価可能な、薬剤を投与した被験者の数である。

本剤の単剤療法

本剤を1日1回500 mg投与した未治療の成人AML患者28例において単剤の安全性プロファイル

を検討した。*［臨床成績（14.1）を参照］*本剤の曝露期間の中央値は4.3カ月（範囲0.3～40.9カ月）であった。曝露期間は、10例（36%）は少なくとも6カ月以上、6例（21%）は少なくとも1年以上であった。

よくみられた重篤な副作用（5%以上）は分化症候群（18%）、心電図QT延長（7%）及び疲労（7%）であった。可逆性後白質脳症症候群（PRES）が1例で発現した。

本剤の休薬に至ったよくみられた副作用（10%以上）は心電図QT延長（14%）及び分化症候群（11%）であった。2例（7%）で心電図QT延長により本剤の減量を要した。1例は下痢、他の1例はPRESにより本剤を中止した。

AG120-C-001試験における最もよくみられた副作用を表4に示す。

表4：AG120-C-001試験で未治療のAML患者の10%以上（全Grade）又は5%以上（Grade 3以上）に報告された副作用

	本剤（500 mg1日1回） N=28	
器官分類 副作用	**全Grade n（%）**	**Grade 3以上 n（%）**
胃腸障害		
下痢	17 (61)	2 (7)
悪心	10 (36)	2 (7)
腹痛[1]	8 (29)	1 (4)
便秘	6 (21)	1 (4)
嘔吐	6 (21)	1 (4)
粘膜炎[2]	6 (21)	0
消化不良	3 (11)	0
一般・全身障害および投与部位の状態		
疲労[3]	14 (50)	4 (14)
浮腫[4]	12 (43)	0
代謝および栄養障害		
食欲減退	11 (39)	1 (4)
血液およびリンパ系障害		
白血球増加症[5]	10 (36)	2 (7)
分化症候群[6]	7 (25)	3 (11)
筋骨格系および結合組織障害		
関節痛[7]	9 (32)	1 (4)
筋肉痛[8]	7 (25)	1 (4)
呼吸器、胸郭および縦隔障害		
呼吸困難[9]	8 (29)	1 (4)
咳嗽[10]	4 (14)	0
臨床検査		
心電図QT延長	6 (21)	3 (11)
体重減少	3 (11)	0
神経系障害		
浮動性めまい	6 (21)	0

	本剤（500 mg1日1回） N=28	
器官分類 副作用	**全Grade** **n（%）**	**Grade 3以上** **n（%）**
ニューロパチー[11]	4 (14)	0
頭痛	3 (11)	0
皮膚および皮下組織障害		
そう痒症	4 (14)	1 (4)
発疹[12]	4 (14)	1 (4)

1 グループ化した用語：腹痛、上腹部痛、腹部不快感及び腹部圧痛
2 グループ化した用語：アフタ性潰瘍、食道痛、食道炎、歯肉痛、歯肉炎、口腔内潰瘍形成、粘膜の炎症、口腔内痛、口腔咽頭痛、肛門周囲痛及び口内炎
3 グループ化した用語：無力症及び疲労
4 グループ化した用語：浮腫、顔面浮腫、水分過負荷、体液貯留、血液量増加症、末梢性浮腫及び顔面腫脹
5 グループ化した用語：白血球増加症、著明な白血球増多及び白血球数増加
6 分化症候群は、末梢性浮腫、白血球増加症、発熱、呼吸困難、胸水、低血圧、低酸素症、肺水腫、肺炎、心嚢液貯留、発疹、水分過負荷、腫瘍崩壊症候群及びクレアチニン増加など、よく報告される他の事象と関連することがある。
7 グループ化した用語：関節痛、背部痛、筋骨格硬直、頚部痛及び四肢痛
8 グループ化した用語：筋肉痛、筋力低下、筋骨格痛、筋骨格系胸痛、筋骨格不快感及び肋間筋肉痛
9 グループ化した用語：呼吸困難、労作性呼吸困難、低酸素症及び呼吸不全
10 グループ化した用語：咳嗽、湿性咳嗽及び上気道咳症候群
11 グループ化した用語：灼熱感、腰仙部神経叢障害、末梢性ニューロパチー、錯感覚及び末梢性運動ニューロパチー
12 グループ化した用語：ざ瘡様皮膚炎、皮膚炎、発疹、斑状丘疹状皮疹、蕁麻疹、紅斑性皮疹、斑状皮疹、そう痒性皮疹、全身性皮疹、丘疹性皮疹、皮膚剥脱及び皮膚潰瘍

未治療AML患者に認められたベースライン後の臨床検査値の変化（一部）を表5に示す。

表5：AG120-C-001試験で未治療AML[1]患者に最もよく（10%以上）又は5%以上（Grade 3以上）に報告された新規の又は悪化した臨床検査値異常

	本剤（500 mg1日1回） N=28	
臨床検査値異常	**全Grade** **n（%）**	**Grade 3以上** **n（%）**
ヘモグロビン減少	15 (54)	12 (43)
アルカリホスファターゼ増加	13 (46)	0
カリウム減少	12 (43)	3 (11)
ナトリウム減少	11 (39)	1 (4)
尿酸増加	8 (29)	1 (4)
アスパラギン酸アミノトランスフェラーゼ増加	8 (29)	1 (4)
クレアチニン増加	8 (29)	0
マグネシウム減少	7 (25)	0
カルシウム減少	7 (25)	1 (4)
リン酸塩減少	6 (21)	2 (7)
アラニンアミノトランスフェラーゼ増加	4 (14)	1 (4)

1 臨床検査値異常は、新規若しくはベースライン時より1グレード以上悪化した場合、又はベースライン時の値が不明な場合と定義した。

再発又は難治性のAML

本剤を1日1回500 mg投与した再発又は難治性の成人AML患者179例において単剤の安全性プロファイルを検討した。*［臨床成績（14.2）を参照］*

本剤の曝露期間の中央値は3.9カ月（範囲0.1～39.5カ月）であった。曝露期間は、65例（36%）は少なくとも6カ月以上、16例（9%）は少なくとも1年以上であった。

重篤な副作用（5%以上）は分化症候群（10%）、白血球増加症（10%）及び心電図QT延長（7%）であった。進行性多巣性白質脳症（PML）が1例で認められた。

本剤の休薬に至った最もよくみられた副作用は心電図QT延長（7%）、分化症候群（3%）、白血球増加症（3%）及び呼吸困難（3%）であった。179例のうち5例（3%）が副作用により減量を要した。

本剤の減量に至った副作用は心電図QT延長（1%）、下痢（1%）、悪心（1%）、ヘモグロビン減少（1%）及びトランスアミナーゼ上昇（1%）であった。

本剤の中止に至った副作用はギラン・バレー症候群（1%）、発疹（1%）、口内炎（1%）及びクレアチニン増加（1%）であった。

AG120-C-001試験で最もよくみられた副作用を表6に示す。

表6：再発又は難治性のAML患者の10%以上（全Grade）又は5%以上（Grade 3以上）に報告された副作用

	本剤（500 mg1日1回）N=179	
器官分類 副作用	**全Grade** **n（%）**	**Grade 3以上** **n（%）**
一般・全身障害および投与部位の状態		
疲労[1]	69 (39)	6 (3)
浮腫[2]	57 (32)	2 (1)
発熱	41 (23)	2 (1)
胸痛[3]	29 (16)	5 (3)
血液およびリンパ系障害		
白血球増加症[4]	68 (38)	15 (8)
分化症候群[5]	34 (19)	23 (13)
筋骨格系および結合組織障害		
関節痛[6]	64 (36)	8 (4)
筋肉痛[7]	33 (18)	1 (1)
胃腸障害		
下痢	60 (34)	4 (2)
悪心	56 (31)	1 (1)
粘膜炎[8]	51 (28)	6 (3)

	本剤（500 mg1日1回） N=179	
器官分類 副作用	**全Grade** **n（%）**	**Grade 3以上** **n（%）**
便秘	35 (20)	1 (1)
嘔吐[9]	32 (18)	2 (1)
腹痛[10]	29 (16)	2 (1)
呼吸器、胸郭および縦隔障害		
呼吸困難[11]	59 (33)	16 (9)
咳嗽[12]	40 (22)	1 (< 1)
胸水	23 (13)	5 (3)
臨床検査		
心電図QT延長	46 (26)	18 (10)
皮膚および皮下組織障害		
発疹[13]	46 (26)	4 (2)
代謝および栄養障害		
食欲減退	33 (18)	3 (2)
腫瘍崩壊症候群	14 (8)	11 (6)
神経系障害		
頭痛	28 (16)	0
ニューロパチー[14]	21 (12)	2 (1)
血管障害		
低血圧[15]	22 (12)	7 (4)

1 グループ化した用語：無力症及び疲労
2 グループ化した用語：末梢性浮腫、浮腫、水分過負荷、体液貯留及び顔面腫脹
3 グループ化した用語：狭心症、胸痛、胸部不快感及び非心臓性胸痛
4 グループ化した用語：白血球増加症、著明な白血球増多及び白血球数増加
5 分化症候群は、末梢性浮腫、白血球増加症、発熱、呼吸困難、胸水、低血圧、低酸素症、肺水腫、肺炎、心嚢液貯留、発疹、水分過負荷、腫瘍崩壊症候群及びクレアチニン増加など、よく報告される他の事象と関連することがある。
6 グループ化した用語：関節痛、背部痛、筋骨格硬直、頚部痛及び四肢痛
7 グループ化した用語：筋肉痛、筋力低下、筋骨格痛、筋骨格系胸痛、筋骨格不快感及び肋間筋肉痛
8 グループ化した用語：アフタ性潰瘍、食道痛、食道炎、歯肉痛、歯肉炎、口腔内潰瘍形成、粘膜の炎症、口腔内痛、口腔咽頭痛、肛門周囲痛及び口内炎
9 グループ化した用語：嘔吐及びレッチング
10 グループ化した用語：腹痛、上腹部痛、腹部不快感及び腹部圧痛
11 グループ化した用語：呼吸困難、呼吸不全、低酸素症及び労作性呼吸困難
12 グループ化した用語：咳嗽、湿性咳嗽及び上気道咳症候群
13 グループ化した用語：ざ瘡様皮膚炎、皮膚炎、発疹、斑状丘疹状皮疹、蕁麻疹、紅斑性皮疹、斑状皮疹、そう痒性皮疹、全身性皮疹、丘疹性皮疹、皮膚剥脱及び皮膚潰瘍
14 グループ化した用語：運動失調、灼熱感、歩行障害、ギラン・バレー症候群、末梢性ニューロパチー、錯感覚、末梢性感覚ニューロパチー、末梢性運動ニューロパチー及び感覚障害
15 グループ化した用語：低血圧及び起立性低血圧

再発又は難治性のAML患者に認められたベースライン後の臨床検査値の変化（一部）を表7に示す。

表7：再発又は難治性のAML[1]患者に最もよく（10%以上）又は5%以上（Grade 3以上）に報告された新規の又は悪化した臨床検査値異常

	本剤（500 mg1日1回） N=179	
臨床検査値異常	**全Grade n（%）**	**Grade 3以上 n（%）**
ヘモグロビン減少	108 (60)	83 (46)
ナトリウム減少	69 (39)	8 (4)
マグネシウム減少	68 (38)	0
尿酸増加	57 (32)	11 (6)
カリウム減少	55 (31)	11 (6)
アルカリホスファターゼ増加	49 (27)	1 (1)
アスパラギン酸アミノトランスフェラーゼ増加	49 (27)	1 (1)
リン酸塩減少	45 (25)	15 (8)
クレアチニン増加	42 (23)	2 (1)
アラニンアミノトランスフェラーゼ増加	26 (15)	2 (1)
ビリルビン増加	28 (16)	1 (1)

1 臨床検査値異常は、新規若しくはベースライン時より1グレード以上悪化した場合、又はベースライン時の値が不明な場合と定義した。

<u>再発又は難治性の骨髄異形成症候群</u>

AG120-C-001試験において本剤を1日1回500 mg投与した再発又は難治性の成人MDS患者19例を対象に本剤の安全性を検討した。*[臨床成績（14.3）を参照]*本剤の曝露期間の中央値は9.3カ月（範囲3.3～78.8カ月）であった。曝露期間は、14例（74%）は少なくとも6カ月以上、8例（42%）は少なくとも1年以上であった。

重篤な副作用（5%以上）は、分化症候群（11%）、疲労（5%）及び発疹（5%）であった。

患者の5%が副作用により本剤を中止した。本剤の中止に至った副作用は疲労であった。

患者の16%が副作用により本剤を休薬した。本剤の休薬に至った副作用（5%以上）は、分化症候群、白血球増加症及び発疹であった。

患者の16%が副作用により本剤を減量した。本剤の減量に至った副作用（5%以上）は、分化症候群、疲労及び発疹であった。

最もよくみられた臨床検査値異常を含む副作用（25%以上）は、クレアチニン増加、ヘモグロビン減少、関節痛、アルブミン減少、アスパラギン酸アミノトランスフェラーゼ増加、疲労、下痢、咳嗽、ナトリウム減少、粘膜炎、食欲減退、筋肉痛、リン酸塩減少、そう痒症及び発疹であった。

AG120-C-001試験でみられた副作用を表8に要約する。

表8：AG120-C-001試験の再発又は難治性のMDS患者における副作用（10%以上）

	本剤（500 mg1日1回） N=19	
器官分類 副作用	**全Grade** **%**	**Grade 3又は4** **%**
筋骨格系および結合組織障害		
関節痛[1]	42	16
筋肉痛[2]	26	0
一般・全身障害および投与部位の状態		
疲労[3]	37	11
呼吸器、胸郭および縦隔障害		
咳嗽	32	0
呼吸困難[4]	21	0
胃腸障害		
下痢	32	0
粘膜炎[5]	26	5
便秘	16	0
悪心	16	0
皮膚および皮下組織障害		
そう痒症	26	0
発疹[6]	26	0
代謝および栄養障害		
食欲減退	26	0
血液およびリンパ系障害		
白血球増加症[7]	16	5
分化症候群	11	0
神経系障害		
頭痛	16	0
血管障害		
高血圧	16	16
臨床検査		
心電図QT延長	11	0

1 グループ化した用語：関節痛、背部痛、四肢痛、側腹部痛、関節腫脹及び頚部痛
2 グループ化した用語：筋肉痛、筋痙縮、筋不快感及び筋骨格系胸痛
3 グループ化した用語：疲労及び無力症
4 グループ化した用語：呼吸困難及び労作性呼吸困難
5 グループ化した用語：口腔咽頭痛、歯肉炎、口腔内潰瘍形成及び口内炎
6 グループ化した用語：発疹、カテーテル留置部位紅斑及び蕁麻疹
7 グループ化した用語：白血球増加症、著明な白血球増多及び白血球数増加

AG120-C-001試験でみられた臨床検査値異常を表9に要約する。

表9：AG120-C-001試験の再発又は難治性のMDS患者においてベースラインから悪化した臨床検査値異常の一部（15%以上）

	本剤[1] N=19	
臨床検査値異常	**全Grade %**	**Grade 3又は4 %**
クレアチニン増加	95	5
ヘモグロビン減少	42	32
アルブミン減少	37	0
アスパラギン酸アミノトランスフェラーゼ増加	37	5
ナトリウム減少	32	5
リン酸塩減少	26	5
アラニンアミノトランスフェラーゼ増加	21	5
ビリルビン増加	21	0
マグネシウム減少	21	0
アルカリホスファターゼ増加	16	0
カリウム増加	16	0

1 臨床検査値異常は、新規若しくはベースライン時より1グレード以上悪化した場合、又はベースライン時の値が不明な場合と定義した。

<u>局所進行性又は転移性の胆管癌</u>

AG120-C-005試験において治療歴のある局所進行性又は転移性の胆管癌患者を対象に本剤の安全性を検討した。*［臨床成績（14.4）を参照］*本剤1日1回500 mg（N=123）又はプラセボ（N=59）を少なくとも1回以上投与した。本剤の曝露期間の中央値は2.8カ月（範囲0.1～34.4カ月）であった。

本剤を投与した患者の34%に重篤な副作用が認められた。本剤群の2%以上にみられた重篤な副作用は、肺炎、腹水、高ビリルビン血症及び胆汁うっ滞性黄疸であった。

本剤を投与した患者の4.9%に致死的な副作用が認められた。内訳は敗血症（1.6%）及び肺炎、腸閉塞、肺塞栓症、肝性脳症（各0.8%）であった。

患者の7%が本剤を中止した。本剤の中止に至った最もよくみられた副作用は急性腎障害（1.6%）であった。

本剤を投与した患者の29%が副作用により本剤を休薬した。本剤の休薬に至った最もよくみられた副作用（2%超）は、高ビリルビン血症、アラニンアミノトランスフェラーゼ増加、アスパラギン酸アミノトランスフェラーゼ増加、腹水及び疲労であった。

患者の4.1%が副作用により本剤を減量した。本剤の減量に至った副作用は、心電図QT延長（3.3%）及び末梢性ニューロパチー（0.8%）であった。

最もよくみられた副作用（15%以上）は、疲労、悪心、腹痛、下痢、咳嗽、食欲減退、腹水、嘔

吐、貧血及び発疹であった。

AG120-C-005試験でみられた副作用及び臨床検査値異常を表10及び表11に示す。

表10：AG120-C-005試験で本剤を投与した患者の10%以上に認められた副作用

	本剤（500 mg1日1回） N=123		プラセボ N=59	
器官分類 副作用	**全Grade** **n（%）**	**Grade 3以上** **n（%）**	**全Grade** **n（%）**	**Grade 3以上** **n（%）**
一般・全身障害および投与部位の状態				
疲労[1]	53 (43)	4 (3)	18 (31)	3 (5)
胃腸障害				
悪心	51 (41)	3 (2)	17 (29)	1 (2)
下痢	43 (35)	0	10 (17)	0
腹痛[2]	43 (35)	3 (2)	13 (22)	2 (3)
腹水	28 (23)	11 (9)	9 (15)	4 (7)
嘔吐[3]	28 (23)	3 (2)	12 (20)	0
呼吸器、胸郭および縦隔障害				
咳嗽[4]	33 (27)	0	5 (9)	0
代謝および栄養障害				
食欲減退	30 (24)	2 (2)	11 (19)	0
血液およびリンパ系障害				
貧血	22 (18)	8 (7)	3 (5)	0
皮膚および皮下組織障害				
発疹[5]	19 (15)	1 (1)	4 (7)	0
神経系障害				
頭痛	16 (13)	0	4 (7)	0
末梢性ニューロパチー[6]	13 (11)	0	0	0
臨床検査				
心電図QT延長	12 (10)	2 (2)	2 (3)	0

1 グループ化した用語：無力症及び疲労
2 グループ化した用語：腹痛、上腹部痛、腹部不快感、下腹部痛、心窩部不快感、腹部圧痛及び消化器痛
3 グループ化した用語：嘔吐及びレッチング
4 グループ化した用語：咳嗽及び湿性咳嗽
5 グループ化した用語：発疹、斑状丘疹状皮疹、紅斑、斑状皮疹、全身性剥脱性皮膚炎、薬疹及び薬物過敏症
6 グループ化した用語：末梢性ニューロパチー、末梢性感覚ニューロパチー及び錯感覚

表11：AG120-C-005試験[1]で本剤を投与した患者に認められた臨床検査値異常の一部（10%以上）

	本剤（500 mg1日1回） N=123		プラセボ N=59	
臨床検査値異常	**全Grade** **n（%）**	**Grade 3以上** **n（%）**	**全Grade** **n（%）**	**Grade 3以上** **n（%）**
AST増加	41 (34)	5 (4)	14 (24)	1 (2)
ビリルビン増加	36 (30)	15 (13)	11 (19)	2 (3)
ヘモグロビン減少	48 (40)	8 (7)	14 (25)	0

1 臨床検査値異常は、新規若しくはベースライン時より1グレード以上悪化した場合、又はベースライン時の値が不明な場合と定義した。

7. 薬物相互作用

7.1 本剤に対する他剤の影響

強い又は中程度のCYP3A4阻害剤	
臨床的影響	• 本剤と強い又は中程度のCYP3A4阻害剤を併用投与すると、本剤の血漿中濃度が上昇した。*［臨床薬理試験（12.3）を参照］* • 本剤の血漿中濃度が上昇すると、QTc間隔延長のリスクが増加する可能性がある。*［警告及び使用上の注意（5.2）を参照］*
予防及び管理	• 本剤の治療期間中は強い又は中程度のCYP3A4阻害剤以外の代替治療法を考慮する。 • 強いCYP3A4阻害剤の併用投与が避けられない場合、本剤を1日1回250 mgに減量する。*［用法及び用量（2.3）を参照］* • QTc間隔延長のリスクの増加についてモニタリングする。*［警告及び使用上の注意（5.2）を参照］*
強いCYP3A4誘導剤	
臨床的影響	• 本剤と強いCYP3A4誘導剤を併用投与すると、本剤の血漿中濃度が低下した。*［臨床薬理試験（12.3）を参照］*
予防及び管理	• 本剤と強いCYP3A4誘導剤の併用投与を避ける。
QTc間隔延長を起こすことが知られている薬剤	
臨床的影響	• 本剤とQTc間隔延長を起こすことが知られている薬剤を併用投与すると、QTc間隔延長のリスクが増加する可能性がある。*［警告及び使用上の注意（5.2）を参照］*
予防及び管理	• 本剤とQTc間隔延長を起こすことが知られている薬剤の併用投与を避けるか、代替治療法に置き換える。 • 本剤とQTc間隔延長を起こすことが知られている薬剤の併用投与が避けられない場合、QTc間隔延長のリスクの増加についてモニタリングする。*［警告及び使用上の注意（5.2）を参照］*

7.2 他剤に対する本剤の影響

本剤はCYP3A4の誘導作用があり、CYP2C9を誘導する可能性も示唆されている。併用投与によりCYP3A4感受性の基質である薬剤の濃度が減少し、CYP2C9感受性の基質である薬剤の濃度が減少する可能性も示唆されている。*［臨床薬理試験（12.3）を参照］*本剤の治療期間中はCYP3A4及びCYP2C9感受性の基質ではない代替治療法を用いる。本剤とCYP3A4感受性の基質又はCYP2C9感受性の基質との併用が避けられない場合は、これらの薬剤の治療効果が失われていないかモニタリングする。

CYP3A4の基質である抗真菌薬と本剤を併用投与すると、抗真菌薬の効果が失われることが予想されるため、併用投与しない。

本剤との併用によりホルモン避妊薬濃度が減少する可能性があるため、本剤を投与している患

者には代替避妊法を考慮する。

8.　特定の集団への投与

8.1　妊婦

リスクの要約

動物での胚･胎児毒性試験成績から、妊婦に本剤を投与すると胎児に害を及ぼす可能性がある。妊婦において本剤の投与による重大な先天性欠損及び流産のリスクに関するデータはない。動物での胚・胎児毒性試験で、器官形成期の妊娠ラット及び妊娠ウサギに本剤を経口投与したとき、ヒト推奨用量でのAUCに基づく定常状態の臨床曝露量の2倍に相当する用量から、胚･胎児の死亡率及び成長の変化との関連が認められた。*(データ参照)* 妊娠期間中での本剤の投与又は本剤の投与中に患者が妊娠した場合、患者に胎児への潜在的リスクを説明する。

本剤の適応となる患者集団における重大な先天性欠損及び流産のリスクは不明である。妊婦の健康状態や薬剤の使用にかかわらず、妊娠の転帰は不良となることがある。米国の一般集団では、臨床的に確認された妊娠のうち重大な先天性欠損のリスクが2%～4%、流産のリスクが15%～20%と推定されている。

データ

動物データ

器官形成期（妊娠6～17日）の妊娠ラットに本剤500 mg/kg/dayを投与したところ、胎児の体重減少や骨格変異など胚・胎児への影響が認められた。これらの影響は、ヒト推奨用量である1日1回500 mgの曝露量の約2倍に相当する用量で観察された。

器官形成期（妊娠7～20日）の妊娠ウサギにおいて本剤180 mg/kg/dayの用量（ヒト推奨用量である1日1回500 mgの曝露量の約3.9倍に相当する曝露量）で母動物に毒性がみられ、自然流産のほか、胎児の体重減少、骨格変異及び内臓変異が認められた。

8.2　授乳婦

リスクの要約

イボシデニブ又はその代謝物のヒト乳汁中への移行、母乳哺育児への影響又は乳汁産生への影響に関するデータはない。ヒト乳汁中には多くの薬物が分泌され、母乳哺育児に副作用が発現する可能性があるため、本剤の治療期間中及び最終投与後1カ月間は授乳を避けるよう授乳中の女性に指導する。

8.4　小児

小児患者における本剤の安全性及び有効性は確立されていない。

8.5　高齢者

AML及びMDSを対象とした臨床試験で本剤を投与した304例のうち、75%が65歳以上、35%が75歳以上であった。

AG120-C-005試験で本剤を投与した胆管癌患者124例のうち37%が65歳以上、11%が75歳以上であった。

65歳以上の患者と若年患者との間には、有効性及び安全性において全体的な差異は認められなかった。

8.6　腎機能障害

軽度又は中等度の腎機能障害（eGFR ≥30 mL/min/1.73m^2、MDRD）患者での開始用量の調節は推奨されない。重度の腎機能障害（eGFR <30 mL/min/1.73m^2、MDRD）患者又は透析を要する腎機能障害の患者における本剤の薬物動態及び安全性は不明である。*［臨床薬理試験（12.3）を参照］*重度の腎機能障害を有する患者又は透析を要する患者には本剤による治療開始前にリスクと予想されるベネフィットを考慮する。

8.7　肝機能障害

軽度又は中等度の肝機能障害（Child-Pugh分類A又はB）患者での開始用量の調節は推奨されない。*［臨床薬理試験（12.3）を参照］*重度の肝機能障害（Child-Pugh分類C）患者における本剤の薬物動態及び安全性は不明である。重度の肝機能障害を有する患者には本剤による治療開始前にリスクと予想されるベネフィットを考慮する。

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Tibsovo 250 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg of ivosidenib.

Excipient with known effect

Each film-coated tablet contains lactose monohydrate equivalent to 9.5 mg lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Blue, oval shaped, film-coated tablets approximately 18 mm in length, debossed with 'IVO' on one side and '250' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tibsovo in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy (see section 5.1).

Tibsovo monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated under the supervision of physicians experienced in the use of anti-cancer medicinal products.

Before taking Tibsovo, patients must have confirmation of an IDH1 R132 mutation using an appropriate diagnostic test.

Posology

Acute myeloid leukaemia
The recommended dose is 500 mg ivosidenib (2 x 250 mg tablets) taken orally once daily.
Ivosidenib should be started on Cycle 1 Day 1 in combination with azacitidine at 75 mg/m^2 of body surface area, intravenously or subcutaneously, once daily on Days 1-7 of each 28-day cycle. The first treatment cycle of azacitidine should be given at 100% of the dose. It is recommended that patients be treated for a minimum of 6 cycles.

For the posology and method of administration of azacitidine, please refer to the full product information for azacitidine.

Treatment should be continued until disease progression or until treatment is no longer tolerated by the patient.

Cholangiocarcinoma
The recommended dose is 500 mg ivosidenib (2 x 250 mg tablets) taken orally once daily.

Treatment should be continued until disease progression or until treatment is no longer tolerated by the patient.

Missed or delayed doses

If a dose is missed or not taken at the usual time, the tablets should be taken as soon as possible within 12 hours after the missed dose. Two doses should not be taken within 12 hours. The tablets should be taken as usual the following day.

If a dose is vomited, replacement tablets should not be taken. The tablets should be taken as usual the following day.

Precautions to be taken prior to administration and monitoring

An electrocardiogram (ECG) must be performed prior to treatment initiation. Heart rate corrected QT (QTc) should be less than 450 msec prior to treatment initiation and, in the presence of an abnormal QT, practitioners should thoroughly reassess the benefit/risk of initiating ivosidenib. In case QTc interval prolongation is between 480 msec and 500 msec, initiation of treatment with ivosidenib should remain exceptional and be accompanied by close monitoring.

An ECG must be performed prior to treatment initiation, at least weekly during the first 3 weeks of therapy and then monthly thereafter if the QTc interval remains ≤ 480 msec. QTc interval abnormalities should be managed promptly (see Table 1 and section 4.4). In case of suggestive symptomatology, an ECG should be performed as clinically indicated.

Concomitant administration of medicinal products known to prolong the QTc interval, or moderate or strong CYP3A4 inhibitors may increase the risk of QTc interval prolongation and should be avoided whenever possible during treatment with Tibsovo. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible. An ECG should be performed prior to co-administration, weekly monitoring for at least 3 weeks and then as clinically indicated (see below and sections 4.4, 4.5 and 4.8).

Complete blood count and blood chemistries should be assessed prior to the initiation of Tibsovo, at least once weekly for the first month of treatment, once every other week for the second month, and at each medical visit for the duration of therapy as clinically indicated.

Dose modification for concomitant administration of moderate or strong CYP3A4 inhibitors

If use of moderate or strong CYP3A4 inhibitors cannot be avoided, the recommended dose of ivosidenib should be reduced to 250 mg (1 x 250 mg tablet) once daily. If the moderate or strong CYP3A4 inhibitor is discontinued, the dose of ivosidenib should be increased to 500 mg after at least 5 half-lives of the CYP3A4 inhibitor (see above and sections 4.4 and 4.5).

Dose modifications and management recommendations for adverse reactions

Table 1 - Recommended dose modifications for adverse reactions

Adverse reaction	**Recommended action**
Differentiation syndrome (see sections 4.4 and 4.8)	• If differentiation syndrome is suspected, administer systemic corticosteroids for a minimum of 3 days and taper only after symptom resolution. Premature discontinuation may result in symptom recurrence. • Initiate haemodynamic monitoring until symptom resolution and for a minimum of 3 days. • Interrupt Tibsovo if severe signs/symptoms persist for more than 48 hours after initiation of systemic corticosteroids. • Resume treatment at 500 mg ivosidenib once daily when signs/symptoms are moderate or lower and upon improvement in clinical condition.
Leukocytosis (white blood cell count > 25 x 10^9/L or an absolute increase in total white blood cell count > 15 x 10^9/L from baseline, see sections 4.4 and 4.8)	• Initiate treatment with hydroxycarbamide according to institutional standards of care and leukapheresis as clinically indicated. • Taper hydroxycarbamide only after leukocytosis improves or resolves. Premature discontinuation may result in recurrence. • Interrupt Tibsovo if leukocytosis has not improved after initiation of hydroxycarbamide. • Resume treatment at 500 mg ivosidenib once daily when leukocytosis has resolved.
QTc interval prolongation > 480 to 500 msec (Grade 2, see sections 4.4, 4.5 and 4.8)	• Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medicinal products with known QTc interval-prolonging effects (see section 4.5). • Interrupt Tibsovo until QTc interval returns to ≤ 480 msec. • Resume treatment at 500 mg ivosidenib once daily after the QTc interval returns to ≤ 480 msec. • Monitor ECGs at least weekly for 3 weeks and as clinically indicated following return of QTc interval to ≤ 480 msec.

QTc interval prolongation > 500 msec (Grade 3, see sections 4.4, 4.5 and 4.8)	• Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medicinal products with known QTc interval prolonging effects (see section 4.5). • Interrupt Tibsovo and monitor ECG every 24 h until QTc interval returns to within 30 msec of baseline or ≤ 480 msec. • In case of QTc interval prolongation > 550 msec, in addition to the interruption of ivosidenib already scheduled, consider placing the patient under continuous electrocardiographic monitoring until QTc returns to values < 500 msec. • Resume treatment at 250 mg ivosidenib once daily after QTc interval returns to within 30 msec of baseline or ≤ to 480 msec. • Monitor ECGs at least weekly for 3 weeks and as clinically indicated following return of QTc interval to within 30 msec of baseline or ≤ 480 msec. • If alternative aetiology for QTc interval prolongation is identified, dose may be increased to 500 mg ivosidenib once daily.
QTc interval prolongation with signs/symptoms of life-threatening ventricular arrhythmia (Grade 4, see sections 4.4, 4.5 and 4.8)	• Permanently discontinue treatment.
Other Grade 3 or higher adverse reactions	• Interrupt Tibsovo until toxicity resolves to Grade 1 or lower, or baseline, then resume at 500 mg daily (Grade 3 toxicity) or 250 mg daily (Grade 4 toxicity). • If Grade 3 toxicity recurs (a second time), reduce Tibsovo dose to 250 mg daily until the toxicity resolves, then resume 500 mg daily. • If Grade 3 toxicity recurs (a third time), or Grade 4 toxicity recurs, discontinue Tibsovo.

Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

Special populations

Elderly

No dose adjustment is required in elderly patients (≥ 65 years old, see sections 4.8 and 5.2). No data are available for patients aged 85 years or older.

Renal impairment

No dose adjustment is required in patients with mild (eGFR ≥ 60 to < 90 mL/min/1.73 m^2) or moderate (eGFR ≥ 30 to < 60 mL/min/1.73 m^2) renal impairment. A recommended dose has not been determined for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2). Tibsovo should be used with caution in patients with severe renal impairment and this patient population should be closely monitored (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A). A recommended dose has not been determined for patients with moderate and severe hepatic impairment (Child-Pugh classes B and C). Tibsovo should be used with caution in patients with moderate and severe hepatic impairment and this patient population should be closely monitored (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Tibsovo in children and adolescents < 18 years old have not been established. No data are available.

Method of administration

Tibsovo is for oral use.

The tablets are taken once daily at about the same time each day. Patients should not eat anything for 2 hours before and through 1 hour after taking the tablets (see section 5.2). The tablets should be swallowed whole with water.

Patients should be advised to avoid grapefruit and grapefruit juice during treatment (see section 4.5). Patients should also be advised not to swallow the silica gel desiccant found in the tablet bottle (see section 6.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant administration of strong CYP3A4 inducers or dabigatran (see section 4.5).

Congenital long QT syndrome.

Familial history of sudden death or polymorphic ventricular arrhythmia.

QT/QTc interval > 500 msec, regardless of the correction method (see section 4.2 and 4.4).

4.4 Special warnings and precautions for use

Differentiation syndrome in patients with acute myeloid leukaemia

Differentiation syndrome has been reported following treatment with ivosidenib (see section 4.8). Differentiation syndrome may be life-threatening or fatal if not treated (see below and section 4.2). Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells. Symptoms include: non-infectious leukocytosis, peripheral oedema, pyrexia, dyspnoea, pleural effusion, hypotension, hypoxia, pulmonary oedema, pneumonitis, pericardial effusion, rash, fluid overload, tumour lysis syndrome and creatinine increased.
Patients must be informed of signs and symptoms of differentiation syndrome, be advised to contact their physician immediately if these occur and the need to carry the Patient Alert Card with them at all times.

If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution and for a minimum of 3 days.

If leukocytosis is observed, initiate treatment with hydroxycarbamide according to institutional standards of care and leukapheresis as clinically indicated (see section 4.5).

Taper corticosteroids and hydroxycarbamide only after resolution of symptoms. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxycarbamide treatment. Interrupt treatment with Tibsovo if severe signs/symptoms persist for more than 48 hours after the initiation of systemic corticosteroids and resume treatment at 500 mg ivosidenib once daily when the signs/symptoms are moderate or lower and upon improvement in the patient's clinical condition.

QTc interval prolongation

QTc interval prolongation has been reported following treatment with ivosidenib (see section 4.8). An ECG must be performed prior to treatment initiation, at least weekly during the first 3 weeks of therapy and then monthly thereafter if the QTc interval remains ≤ 480 msec (see section 4.2). Any abnormalities should be managed promptly (see section 4.2). In case of suggestive symptomatology, an ECG should be performed as clinically indicated. In case of severe vomiting and/or diarrhoea, an assessment of serum electrolytes abnormalities, especially hypokalaemia and magnesium, must be performed.

Patients should be informed of the risk of QT prolongation, its signs and symptoms (palpitation, dizziness, syncope or even cardiac arrest) and be advised to contact their physician immediately if these occur.

Concomitant administration of medicinal products known to prolong the QTc interval, or moderate or strong CYP3A4 inhibitors may increase the risk of QTc interval prolongation and should be avoided whenever possible during treatment with Tibsovo. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible. ECG should be performed prior to co-administration, weekly monitoring for at least 3 weeks and then as clinically indicated. The recommended dose of ivosidenib should be reduced to 250 mg once daily if use of moderate or strong CYP3A4 inhibitors cannot be avoided (see sections 4.2 and 4.5).

If administration of furosemide (an OAT3 substrate) is clinically indicated to manage signs/symptoms of differentiation syndrome, patients should be closely monitored for electrolyte imbalances and QTc interval prolongation.

Patients with congestive heart failure or electrolyte abnormalities should be monitored closely, with periodic monitoring of ECGs and electrolytes, during treatment with ivosidenib.
Treatment with Tibsovo should be permanently discontinued if patients develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia (see section 4.2).

Ivosidenib should be used with caution in patients who have either albumin levels below the normal range or are underweight.

Severe renal impairment

The safety and efficacy of ivosidenib have not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2). Tibsovo should be used with caution in patients with severe renal impairment and this patient population should be closely monitored
(see sections 4.2 and 5.2).

Hepatic impairment

The safety and efficacy of ivosidenib have not been established in patients with moderate and severe hepatic impairment (Child-Pugh classes B and C). Tibsovo should be used with caution in patients with moderate and severe hepatic impairment and this patient population should be closely monitored (see sections 4.2 and 5.2).
Tibsovo should be used with caution in patients with mild hepatic impairment (Child-Pugh class A) (see section 4.8).

CYP3A4 substrates

Ivosidenib induces CYP3A4 and it may, therefore, decrease systemic exposure to CYP3A4 substrates. Patients should be monitored for loss of antifungal efficacy if use of itraconazole or ketoconazole cannot be avoided (see section 4.5).

Women of childbearing potential / contraception

Women of childbearing potential should have a pregnancy test prior to starting treatment with Tibsovo and should avoid becoming pregnant during therapy (see section 4.6).

Women of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment with Tibsovo and for at least 1 month after the last dose.

Ivosidenib may decrease the systemic concentrations of hormonal contraceptives and, therefore, concomitant use of a barrier method of contraception is recommended (see sections 4.5 and 4.6).

Lactose intolerance

Tibsovo contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should avoid this medicinal product.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on ivosidenib

Strong CYP3A4 inducers

Ivosidenib is a CYP3A4 substrate. Concomitant administration of strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, St. John's wort (*Hypericum perforatum*)) is expected to decrease plasma concentrations of ivosidenib and is contraindicated during treatment with Tibsovo (see section 4.3). Clinical studies evaluating the pharmacokinetics of ivosidenib in the presence of a CYP3A4 inducer have not been conducted.

Moderate or strong CYP3A4 inhibitors

In healthy subjects, administration of a single dose of 250 mg ivosidenib and 200 mg itraconazole once daily for 18 days increased the ivosidenib AUC by 169% (90% CI: 145, 195) with no change in C_{max}. Concomitant administration of moderate or strong CYP3A4 inhibitors increases plasma concentrations of ivosidenib. This may increase the risk of QTc interval prolongation and suitable alternatives that are not moderate or strong CYP3A4 inhibitors should be considered whenever possible during treatment with Tibsovo. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible. If use of moderate or strong CYP3A4 inhibitors cannot be avoided, the recommended dose of ivosidenib should be reduced to 250 mg once daily (see sections 4.2 and 4.4).

- Moderate CYP3A4 inhibitors include: aprepitant, ciclosporin, diltiazem, erythromycin, fluconazole, grapefruit and grapefruit juice, isavuconazole, verapamil.
- Strong CYP3A4 inhibitors include: clarithromycin, itraconazole, ketoconazole, posaconazole, ritonavir, voriconazole.

Medicinal products known to prolong the QTc interval

Concomitant administration of medicinal products known to prolong the QTc interval (e.g. anti-arrhythmics, fluoroquinolones, 5-HT3 receptor antagonists, triazole antifungals) may increase the risk of QTc interval prolongation and should be avoided whenever possible during treatment with Tibsovo. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible (see sections 4.2 and 4.4).

Effect of ivosidenib on other medicinal products

Interactions with transporters

Ivosidenib inhibits P-gp and has the potential to induce P-gp. Therefore, it may alter systemic exposure to active substances that are predominantly transported by P-gp (e.g. dabigatran). Concomitant administration of dabigatran is contraindicated (see section 4.3).

Ivosidenib inhibits OAT3, organic anion-transporting polypeptide 1B1 (OATP1B1) and organic anion-transporting polypeptide 1B3 (OATP1B3). Therefore, it may increase systemic exposure to OAT3 or OATP1B1/1B3 substrates. Concomitant administration of OAT3 substrates (e.g. benzylpenicillin, furosemide) or sensitive OATP1B1/1B3 substrates (e.g. atorvastatin, pravastatin, rosuvastatin) should be avoided whenever possible during treatment with Tibsovo (see section 5.2). Patients should be treated with caution if use of a suitable alternative is not possible. If administration of furosemide is clinically indicated to manage signs/symptoms of differentiation syndrome, patients should be closely monitored for electrolyte imbalances and QTc interval prolongation.

Enzyme induction

Cytochrome P450 (CYP) enzymes
Ivosidenib induces CYP3A4, CYP2B6, CYP2C8, CYP2C9 and may induce CYP2C19. Therefore, it may decrease systemic exposure to substrates of these enzymes. Suitable alternatives that are not CYP3A4, CYP2B6, CYP2C8 or CYP2C9 substrates with a narrow therapeutic index, or CYP2C19 substrates should be considered during treatment with Tibsovo. Patients should be monitored for loss of substrate efficacy if use of such medicinal products cannot be avoided (see section 5.2).

- CYP3A4 substrates with a narrow therapeutic index include: alfentanil, ciclosporin, everolimus, fentanyl, pimozide, quinidine, sirolimus, tacrolimus.
- CYP2B6 substrates with a narrow therapeutic index include: cyclophosphamide, ifosfamide, methadone.
- CYP2C8 substrates with a narrow therapeutic index include: paclitaxel, pioglitazone, repaglinide.
- CYP2C9 substrates with a narrow therapeutic index include: phenytoin, warfarin.
- CYP2C19 substrates include: omeprazole.

Itraconazole or ketoconazole should not be used concomitantly with Tibsovo due to the expected loss of antifungal efficacy.

Ivosidenib may decrease the systemic concentrations of hormonal contraceptives and, therefore, concomitant use of a barrier method of contraception is recommended for at least 1 month after the last dose (see sections 4.4 and 4.6).

Uridine diphosphate glucuronosyltransferases (UGTs)
Ivosidenib has the potential to induce UGTs and it may, therefore, decrease systemic exposure to substrates of these enzymes (e.g. lamotrigine, raltegravir). Suitable alternatives that are not UGT substrates should be considered during treatment with Tibsovo. Patients should be monitored for loss of UGT substrate efficacy if use of such medicinal products cannot be avoided (see section 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential should have a pregnancy test prior to starting treatment with Tibsovo and should avoid becoming pregnant during therapy (see section 4.4).

Women of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment with Tibsovo and for at least 1 month after the last dose.

Ivosidenib may decrease the systemic concentrations of hormonal contraceptives and, therefore, concomitant use of an alternative contraceptive method such as barrier contraceptives is recommended (see sections 4.4 and 4.5).

Pregnancy

There are no adequate data on the use of ivosidenib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Tibsovo is not recommended for use during pregnancy and in women of childbearing potential not using effective contraception. Patients should be informed of the potential risk to the foetus if it is used during pregnancy or if a patient (or female partner of a treated male patient) becomes pregnant during treatment or during the one-month period after the last dose.

Breast-feeding

It is unknown whether ivosidenib and its metabolites are excreted in human milk. No studies in animals have been conducted to evaluate the excretion of ivosidenib and its metabolites in milk. A risk to the newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with Tibsovo and for at least 1 month after the last dose.

Fertility

There are no human data on the effect of ivosidenib on fertility. No fertility studies in animals have been conducted to evaluate the effect of ivosidenib. Undesirable effects on reproductive organs were observed in a 28-day repeat-dose toxicity study (see section 5.3). The clinical relevance of these effects is unknown.

4.7 Effects on ability to drive and use machines

Ivosidenib has minor influence on the ability to drive and use machines. Fatigue and dizziness have been reported in some patients taking ivosidenib (see section 4.8) and should be considered when assessing a patient’s ability to drive or operate machines.

4.8 Undesirable effects

Newly diagnosed acute myeloid leukaemia in combination with azacitidine

Summary of the safety profile

The most common adverse reactions were vomiting (40%), neutropenia (31%), thrombocytopenia (28%), electrocardiogram QT prolonged (21%), insomnia (19%).

The most common serious adverse reactions were differentiation syndrome (8%) and thrombocytopenia (3%).

In patients treated with ivosidenib in combination with azacitidine, the frequency of discontinuation of ivosidenib due to adverse reactions was 6%. Adverse reactions leading to discontinuation were electrocardiogram QT prolonged (1%), insomnia (1%), neutropenia (1%) and thrombocytopenia (1%).

The frequency of dose interruption of ivosidenib due to adverse reactions was 35%. The most common adverse reactions leading to dose interruption were neutropenia (24%), electrocardiogram QT prolonged (7%), thrombocytopenia (7%), leukopenia (4%) and differentiation syndrome (3%).

The frequency of dose reduction of ivosidenib due to adverse reactions was 19%. Adverse reactions leading to dose reduction were electrocardiogram QT prolonged (10%), neutropenia (8%) and thrombocytopenia (1%).

Tabulated list of adverse reactions

The frequencies of adverse reactions are based on Study AG120-C-009 which included 72 patients with newly diagnosed AML randomised to and treated with ivosidenib (500 mg daily) in combination with azacitidine. The median duration of treatment with Tibsovo was 8 months (range 0.1 to 40.0 months). The adverse reaction frequencies are based on all-cause adverse event frequencies, where a proportion of the events for an adverse reaction may have other causes than ivosidenib, such as the disease, other medicinal products or unrelated causes.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2 - Adverse drug reactions reported in patients with newly diagnosed AML treated with ivosidenib in combination with azacitidine in clinical study AG120-C-009 (N=72)

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very common	Differentiation syndrome, Leukocytosis, Thrombocytopenia, Neutropenia
	Common	Leukopenia
Psychiatric disorders	Very common	Insomnia
Nervous system disorders	Very common	Headache, Dizziness
	Common	Neuropathy peripheral
Gastrointestinal disorders	Very common	Vomiting[1]
	Common	Oropharyngeal pain
Musculoskeletal and connective tissue disorders	Very common	Pain in extremity, Arthralgia, Back pain
Investigations	Very common	Electrocardiogram QT prolonged

[1] Grouped term includes vomiting and retching.

Previously treated, locally advanced or metastatic cholangiocarcinoma

Summary of the safety profile

The most common adverse reactions were fatigue (43%), nausea (42%), abdominal pain (35%), diarrhoea (35%), decreased appetite (24%), ascites (23%), vomiting (23%), anaemia (19%) and rash (15%).

The most common serious adverse reactions were ascites (2%), hyperbilirubinemia (2%), and jaundice cholestatic (2%).

In patients treated with ivosidenib, the frequency of treatment discontinuation due to adverse reactions was 2%. Adverse reactions leading to discontinuation were ascites (1%) and hyperbilirubinemia (1%).

The frequency of dose interruption of ivosidenib due to adverse reactions was 16%. The most common adverse reactions leading to dose interruption were hyperbilirubinemia (3%), alanine aminotransferase increased (3%), aspartate aminotransferase increased (3%), ascites (2%) and fatigue (2%).

The frequency of dose reduction of ivosidenib due to adverse reactions was 4%. Adverse reactions leading to dose reduction were electrocardiogram QT prolonged (3%) and neuropathy peripheral (1%).

Tabulated list of adverse reactions

The frequencies of adverse reactions are based on Study AG120-C-005 which included 123 patients with previously treated, locally advanced or metastatic cholangiocarcinoma, randomised to and treated with 500 mg ivosidenib once daily. The median duration of treatment with Tibsovo was 2.8 months (range 0.1 to 45.1 months; mean (standard deviation [SD]) 6.7 (8.2) months).

The adverse reaction frequencies are based on all-cause adverse event frequencies, where a proportion of the events for an adverse reaction may have other causes than ivosidenib, such as the disease, other medicinal products or unrelated causes.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3 - Adverse drug reactions reported in patients with locally advanced or metastatic cholangiocarcinoma treated with ivosidenib in clinical study AG120-C-005 (N=123)

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very common	Anaemia
Metabolism and nutrition disorders	Very common	Decreased appetite
Nervous system disorders	Very common	Neuropathy peripheral, Headache
Gastrointestinal disorders	Very common	Ascites, Diarrhoea, Vomiting, Nausea, Abdominal pain
Hepatobiliary disorders	Common	Jaundice cholestatic, Hyperbilirubinemia
Skin and subcutaneous tissue disorders	Very common	Rash[1]
General disorders and administration site conditions	Very common	Fatigue
	Common	Fall
Investigations	Very common	Aspartate aminotransferase increased, Blood bilirubin increased
	Common	Electrocardiogram QT prolonged, Alanine aminotransferase increased, White blood cell count decreased, Platelet count decreased

[1] Grouped term includes rash, rash maculo-papular, erythema, rash macular, dermatitis exfoliative generalized, drug eruption, and drug hypersensitivity.

Description of selected adverse reactions

Differentiation syndrome in patients with acute myeloid leukaemia (see sections 4.2 and 4.4)

In study AG120-C-009, in the 72 patients with newly diagnosed AML treated with Tibsovo in combination with azacitidine, 14% experienced differentiation syndrome. No patient discontinued ivosidenib treatment due to differentiation syndrome and dose interruptions (3%) to manage signs/symptoms were required in a minority of patients. Of the 10 patients who experienced

differentiation syndrome, all recovered after treatment or after dose interruption of Tibsovo. The median time to onset of differentiation syndrome was 20 days. Differentiation syndrome occurred as early as 3 days and up to 46 days after treatment initiation during combination therapy.

QTc interval prolongation (see sections 4.2, 4.4 and 4.5)

In Study AG120-C-009, in the 72 patients with newly diagnosed AML treated with ivosidenib in combination with azacitidine, electrocardiogram QT prolonged was reported in 21%; 11% experienced Grade 3 or higher reactions. Based on the analysis of the ECGs, 15% of patients treated with ivosidenib in combination with azacitidine, who had at least one post-baseline ECG assessment, were found to have a QTc interval > 500 msec, 24% had an increase from baseline QTc > 60 msec. One percent (1%) of patients discontinued ivosidenib treatment due to electrocardiogram QT prolonged, dose interruption and reduction were required in 7% and 10% of patients, respectively. The median time to onset of QT prolongation in patients treated with ivosidenib was 29 days. Electrocardiogram QT prolonged occurred as early as 1 day and up to 18 months after treatment initiation.
In Study AG120-C-005, in the 123 patients with locally advanced or metastatic cholangiocarcinoma treated with ivosidenib monotherapy, electrocardiogram QT prolonged was reported in 10%; 2% experienced Grade 3 or higher reactions. Based on the analysis of the ECGs, 2% of patients had a QTc interval > 500 msec and 5% QTc interval prolongation > 60 msec from baseline. Dose reduction to manage signs/symptoms was required in 3% of patients. The median time to onset of QT prolongation in patients treated with ivosidenib monotherapy was 28 days. Electrocardiogram QT prolonged occurred as early as 1 day and up to 23 months after treatment initiation.

Special populations

Hepatic impairment

The safety and efficacy of ivosidenib have not been established in patients with moderate and severe hepatic impairment (Child-Pugh classes B and C). A trend to a higher incidence of adverse reactions was observed in patients with mild hepatic impairment (Child-Pugh class A) (See sections 4.2 and 5.2.).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of overdose, toxicity is likely to manifest as exacerbation of the adverse reactions associated with ivosidenib (see section 4.8). Patients should be closely monitored and provided with appropriate supportive care (see sections 4.2 and 4.4). There is no specific antidote for ivosidenib overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents; other antineoplastic agents
ATC code: L01XX62

Mechanism of action

Ivosidenib is an inhibitor of the mutant IDH1 enzyme. Mutant IDH1 converts alpha- ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG) which blocks cellular differentiation and promotes tumorigenesis in both hematologic and non-hematologic malignancies. The mechanism of action of ivosidenib beyond its ability to reduce 2-HG and restore cellular differentiation is not fully understood across indications.

Pharmacodynamic effects

Multiple doses of ivosidenib 500 mg daily decreased plasma concentrations of 2-HG in patients with hematological malignancies and cholangiocarcinoma with mutated IDH1 to levels approximating those observed in healthy subjects. In bone marrow of patients with hematological malignancies and in tumour biopsy of patients with cholangiocarcinoma, the mean (% coefficient of variation [%CV]) reduction in 2-HG concentrations were 93.1% (11.1%) and 82.2% (32.4%), respectively.

Using an ivosidenib concentration-QTc model, a concentration-dependent QTc interval prolongation of approximately 17.2 msec (90% CI: 14.7, 19.7) was predicted at the steady-state C_{max} based on an analysis of 173 patients with AML who received 500 mg ivosidenib once daily. A concentration-dependent QTc interval prolongation of approximately 17.2 msec (90% CI: 14.3, 20.2) was observed at the steady-state C_{max} following a 500 mg daily dose based on an analysis of 101 patients with cholangiocarcinoma who received ivosidenib 500 mg daily (see sections 4.2 and 4.4).

Clinical efficacy

Newly diagnosed acute myeloid leukaemia in combination with azacitidine

The efficacy and safety of Tibsovo was evaluated in a randomised, multicenter, double-blind, placebo-controlled clinical study (AG120-C-009) of 146 adult patients with previously untreated AML with an IDH1 mutation who were ineligible for intensive induction chemotherapy, based on at least one of the following criteria: 75 years or older, Eastern Cooperative Oncology Group (ECOG) performance status of 2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin > 1.5 times the upper limit of normal, creatinine clearance < 45 mL/min, or other comorbidity. Gene mutation analysis for central confirmation of IDH1 mutation from bone marrow and/or peripheral blood were conducted for all subjects using the Abbott RealTime™ IDH1 Assay. Patients were randomised to receive either Tibsovo 500 mg or matched placebo orally once daily with azacitidine 75 mg/m^2/day subcutaneously or intravenously for 1 week every 4 weeks until the end of the study, disease progression or unacceptable toxicity.

The median age of patients treated with Tibsovo was 76 years (range: 58 to 84); 58% were male; 21% Asian, 17% were White, 61% not reported; and had an ECOG performance status of 0 (19%), 1 (44%), or 2 (36%). Seventy-five percent of patients had de novo AML. Overall, patients had documented favourable (4%), intermediate (67%) or poor/other (26%) cytogenetic risk as assessed by investigators based on the National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology (2017).

Efficacy was based on the primary efficacy endpoint event-free survival (EFS), measured from the date of randomisation until treatment failure, relapse from remission, or death by any cause. Treatment failure was defined as failure to achieve complete remission (CR) by week 24. Overall survival (OS), CR rate, CR + CR with partial hematologic recovery (CR + CRh) rate and objective response rate (ORR) were key secondary efficacy endpoints (Table 4 and Figure 1).

Table 4 - Efficacy results in patients with newly diagnosed AML in combination with azacitidine

Endpoint	Ivosidenib (500 mg daily) + azacitidine N=72	Placebo + azacitidine N=74
Event-free survival, events (%)	46 (63.9)	62 (83.8)
Treatment failure	42 (58.3)	59 (79.7)
Relapse	3 (4.2)	2 (2.7)
Death	1 (1.4)	1 (1.4)
Hazard ratio[1] (95% CI)	0.33 (0.16, 0.69)	
OS events (%)	28 (38.9)	46 (62.2)
Median OS (95% CI) months	24.0 (11.3, 34.1)	7.9 (4.1, 11.3)
Hazard ratio[1] (95% CI)	0.44 (0.27, 0.73)	
CR, n (%)	34 (47.2)	11 (14.9)
95% CI[2]	(35.3, 59.3)	(7.7, 25.0)
Odds ratio[3] (95% CI)	4.76 (2.15, 10.50)	
CR + CRh rate, n (%)	38 (52.8)	13 (17.6)
95% CI[2]	(40.7, 64.7)	(9.7, 28.2)
Odds ratio[3](95% CI)	5.01 (2.32, 10.81)	
CR + CRi rate, n (%)	39 (54.2)	12 (16.2)
95% CI[2]	(42.0, 66.0)	(8.7, 26.6)
Odds ratio[3] (95% CI)	5.90 (2.69, 12.97)	

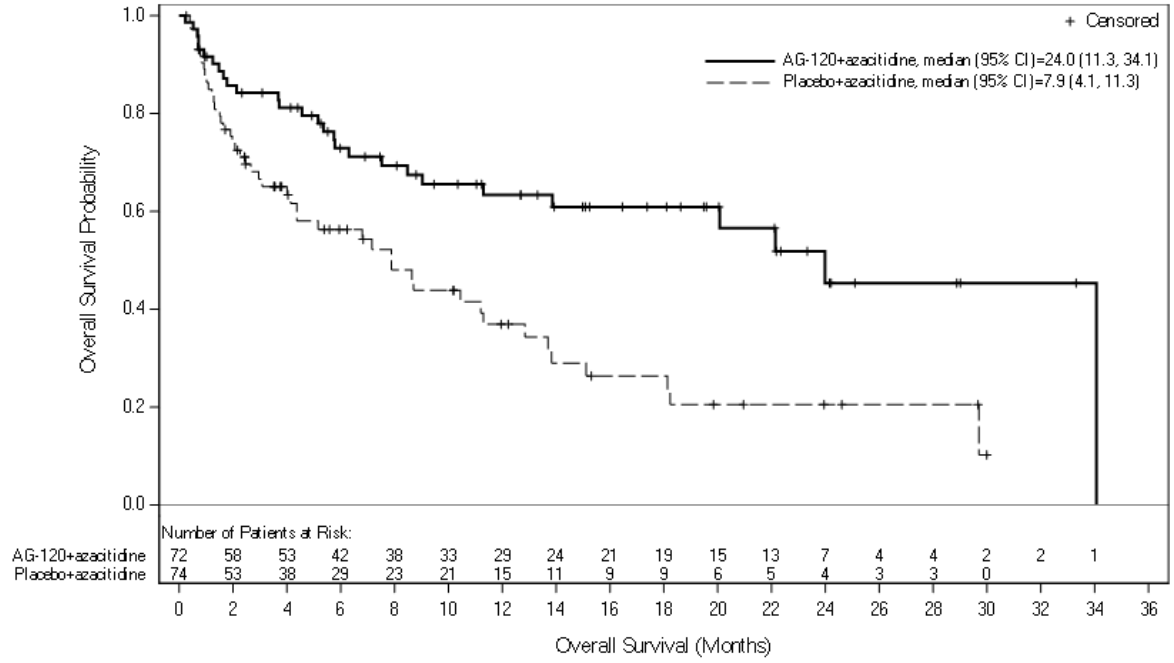
CI: confidence interval; CR = Complete remission; CRh = Complete remission with partial hematologic recovery; CRi = Complete remission with incomplete hematologic recovery; OS = Overall survival; PR = Partial response.

[1] Hazard ratio is estimated using a Cox's proportional hazards model stratified by the randomisation stratification factors (AML status and geographic region) with PBO+AZA as the denominator.

[2] CI of percentage is calculated with the Clopper and Pearson (exact Binomial) method.

[3] Cochran-Mantel-Haenszel (CMH) estimate for odds ratio is calculated with PBO+AZA as the denominator.

Figure 1: Kaplan Meier plot of overall survival (OS)



AG120=ivosidenib

An updated OS analysis, carried out at 64.2% (N = 95) of events, confirmed the overall survival benefit of Tibsovo in combination with azacitidine compared to placebo in combination with azacitidine with a median OS of 29.3 months vs 7.9 months, respectively (HR = 0.42; 95% CI: 0.27 to 0.65).

Previously treated, locally advanced or metastatic cholangiocarcinoma

The efficacy of Tibsovo was evaluated in a randomised (2:1), multicenter, double-blind, placebo-controlled, phase 3 clinical trial (Study AG120-C-005) of 185 adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation whose disease had progressed following at least 1 but not more than 2 prior treatment regimens including at least one gemcitabine- or 5-FU-containing regimen and an expected survival of ≥ 3 months.

Patients were randomised to receive either Tibsovo 500 mg orally once daily or matched placebo until disease progression or development of unacceptable toxicity. Randomisation was stratified by number of prior therapies (1 or 2). Eligible patients who were randomised to placebo were allowed to cross over to receive Tibsovo after documented radiographic disease progression as assessed by the Investigator. Gene mutation analysis for central confirmation of IDH1 mutation from tumour tissue biopsy were conducted on all subjects using the Oncomine™ Dx Target Test.

The median age was 62 years (range: 33 to 83). Majority of patients were female (63%), 57% were White and 37% had an ECOG performance status of 0 (37%) or 1 (62%). All patients received at least 1 prior line of systemic therapy and 47% received two prior lines. Most patients had intrahepatic cholangiocarcinoma (91%) at diagnosis and 92% had metastatic disease. Across both arms, 70% patients had an R132C mutation, 15% had an R132L mutation, 12% had an R132G mutation, 1.6% had an R132S mutation, and 1.1% had an R132H mutation.

The primary efficacy outcome measure was progression free survival (PFS) as determined by Independent Radiology Center (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, which was defined as time from randomisation to disease progression or death due to any cause.

Overall survival (OS) was a secondary efficacy endpoint. As allowed per protocol, a large proportion (70.5%) of patients in the placebo arm crossed over to receive Tibsovo following radiographic disease progression as assessed by the Investigator.

Efficacy results are summarised in Table 5.

Table 5 - Efficacy results in patients with locally advanced or metastatic cholangiocarcinoma

Endpoint	**Ivosidenib (500 mg daily)**	**Placebo**
Progression-free survival (PFS) by IRC assessment	**N=124**	**N=61**
Events, n (%)	76 (61)	50 (82)
Progressive Disease	64 (52)	44 (72)
Death	12 (10)	6 (10)
Median PFS, months (95% CI)	2.7 (1.6, 4.2)	1.4 (1.4, 1.6)
Hazard ratio (95% CI)[1]	0.37 (0.25, 0.54)	
P-value[2]	<0.0001	
PFS rate (%)[3]		
6 months	32.0	NE
12 months	21.9	NE
	Ivosidenib (500 mg daily)	**Placebo**
Overall survival[4]	**N=126**	**N=61**

Deaths, n (%)	100 (79)	50 (82)
Median OS (months, 95% CI)	10.3 (7.8, 12.4)	7.5 (4.8, 11.1)
Hazard ratio (95% CI)[1]	0.79 (0.56, 1.12)	
P-value[2]	0.093	

IRC: Independent Radiology Center; CI: Confidence Interval; NE = not estimable.

[1] Hazard ratio is calculated from stratified Cox regression model. Stratification factor is the number of prior line of therapies at randomisation.

[2] P-value is calculated from the one-sided stratified log-rank test without adjusting for crossover. Stratification factor is the number of prior line of therapies at randomisation.

[3] Based on Kaplan-Meier estimation. No patients randomised to placebo achieved PFS of 6 months or longer.

[4] OS results are based on the final analysis of OS (based on 150 deaths; data cut off: 30 May 2020) which occurred 16 months after the final analysis of PFS (data cut off: 31 January 2019).

Figure 2: Kaplan Meier plot of progression-free survival (PFS) per IRC

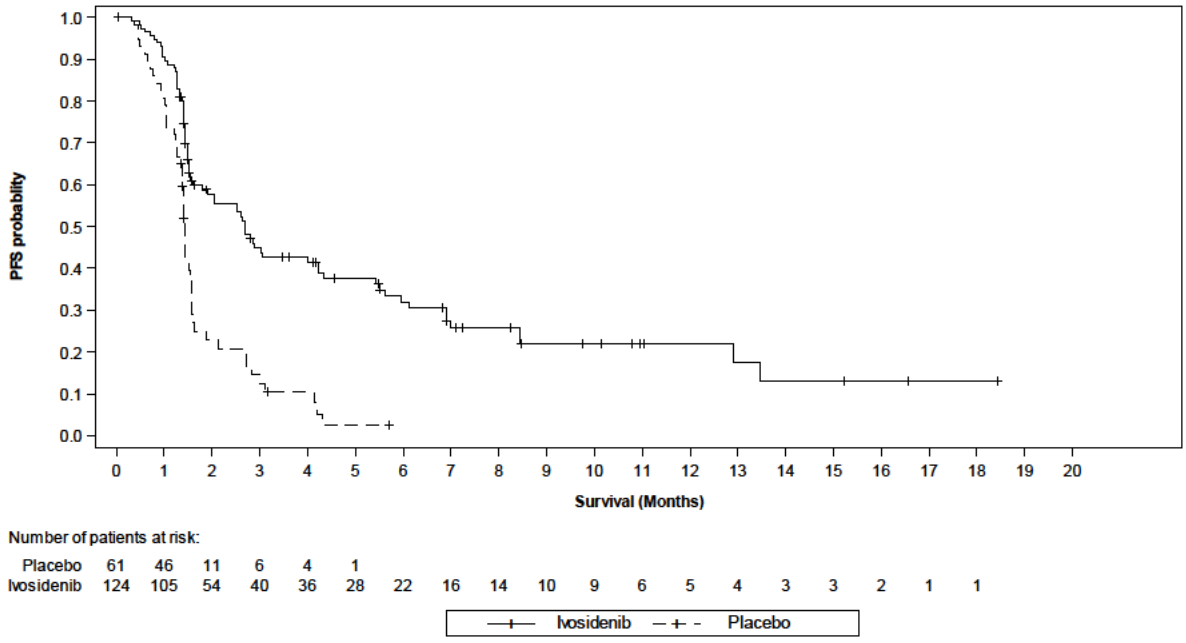
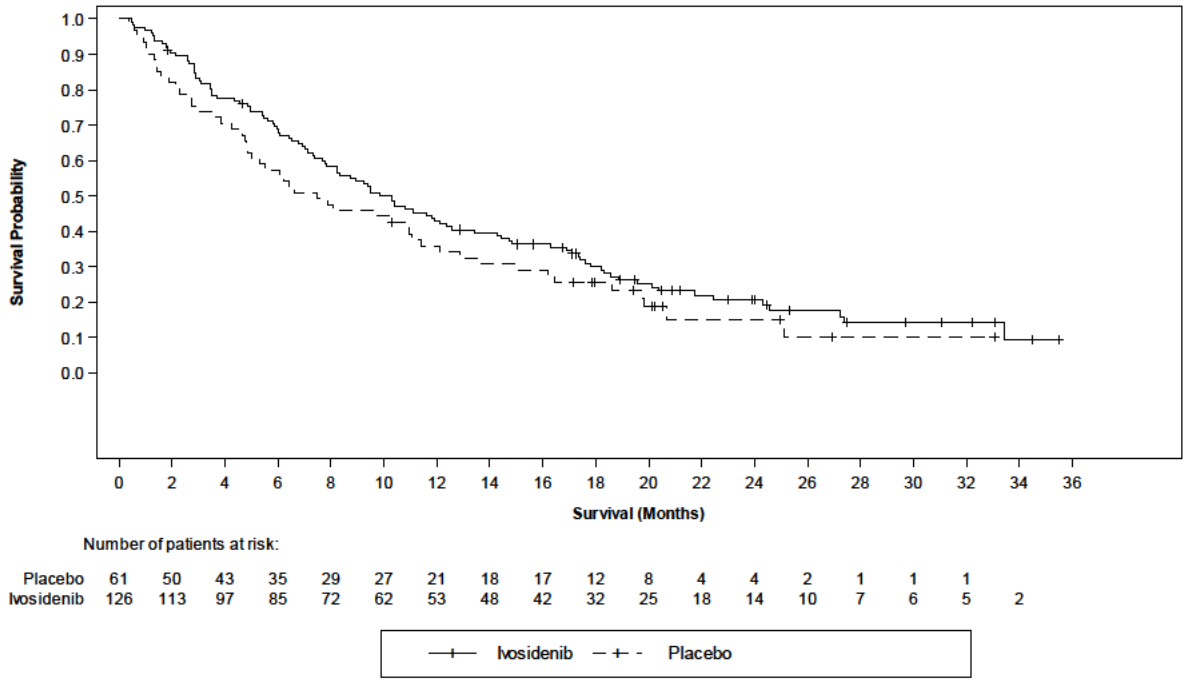


Figure 3: Kaplan-Meier plot of overall survival



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Tibsovo in all subsets of the paediatric population in the treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) and in the treatment of malignant neoplasms of the central nervous system.
The European Medicines Agency has deferred the obligation to submit the results of studies with Tibsovo in one or more subsets of the paediatric population in the treatment of acute myeloid leukaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

A total of 10 clinical studies have contributed to the characterisation of the clinical pharmacology of ivosidenib. Five studies have been conducted in healthy subjects and 3 studies have been conducted in patients with advanced malignancies including 2 studies in patients with cholangiocarcinoma. Two studies have been conducted in patients with newly diagnosed AML receiving ivosidenib in combination with azacitidine. Pharmacokinetic endpoints have been assessed in plasma and urine. Pharmacodynamic endpoints have been assessed in plasma, urine, tumour biopsy, and bone marrow (for studies in patients with advanced malignancies only).
The steady-state pharmacokinetics of ivosidenib 500 mg were comparable between patients with newly diagnosed AML and cholangiocarcinoma.

Absorption

After a single 500 mg oral dose, the median time to C_{max} (T_{max}) was approximately 2 hours in newly diagnosed AML patients treated with a combination of ivosidenib and azacitidine and in cholangiocarcinoma patients.

In patients with newly diagnosed AML treated with a combination of ivosidenib (500 mg daily dose) and azacitidine, the mean steady-state C_{max} was 6,145 ng/mL (CV%: 34) and the mean steady-state AUC was 106,326 ng hr/mL (CV%: 41).

In patients with cholangiocarcinoma, the mean C_{max} was 4,060 ng/mL (%CV: 45) after a single dose of 500 mg and 4,799 ng/mL (CV%: 33) at steady state for 500 mg daily. The AUC was 86,382 ng·hr/mL (CV%: 34).

Accumulation ratios were approximately 1.6 for AUC and 1.2 for C_{max} in patients with newly diagnosed AML treated with a combination of ivosidenib and azacitidine and approximately 1.5 for AUC and 1.2 for C_{max} in patients with cholangiocarcinoma, over one month, when ivosidenib was administered at 500 mg daily. Steady-state plasma levels were reached within 14 days of once daily dosing.

Significant increases in ivosidenib C_{max} (by approximately 98%; 90% CI: 79, 119) and AUC_{inf} (by approximately 25%) were observed following administration of a single dose with a high-fat meal (approximately 900 to 1,000 calories, 56% to 60% fat) in healthy subjects (see section 4.2).

Distribution

Based on a population pharmacokinetic analysis the mean apparent volume of distribution of ivosidenib at steady-state (Vc/F) is 3.20 L/kg (CV%: 47.8) in patients with newly diagnosed AML treated with a combination of ivosidenib and azacitidine and 2.97 L/kg (CV%: 25.9) in patients with cholangiocarcinoma treated with ivosidenib monotherapy.

Biotransformation

Ivosidenib was the predominant component (> 92%) of total radioactivity in plasma from healthy subjects. It is primarily metabolised by oxidative pathways mediated largely by CYP3A4 with minor contributions by N-dealkylation and hydrolytic pathways.

Ivosidenib induces CYP3A4 (including its own metabolism), CYP2B6, CYP2C8, CYP2C9, and may induce CYP2C19 and UGTs. Therefore, it may decrease systemic exposure to substrates of these enzymes (see sections 4.4, 4.5 and 4.6).

Ivosidenib inhibits P-gp *in vitro* and has the potential to induce P-gp. Therefore, it may alter systemic exposure to active substances that are predominantly transported by P-gp (see sections 4.3 and 4.5).

In vitro data suggest that ivosidenib has the potential to inhibit OAT3, OATP1B1 and OATP1B3 at clinically relevant concentrations and it may, therefore, increase systemic exposure to OAT3, OATP1B1 or OATP1B3 substrates (see sections 4.5).

Elimination

In patients with newly diagnosed AML treated with a combination of ivosidenib and azacitidine, the mean apparent clearance of ivosidenib at steady state was 4.6 L/hour (35%) with a mean terminal half-life of 98 hours (42%).

In patients with cholangiocarcinoma, the mean apparent clearance of ivosidenib at steady state was 6.1 L/hour (31%) with a mean terminal half-life of 129 hours (102%).

In healthy subjects, 77% of a single ivosidenib oral dose was found in the faeces of which 67% was recovered unchanged. Approximately 17% of a single oral dose was found in the urine of which 10% was recovered unchanged.

Linearity/non-linearity

The AUC and C_{max} of ivosidenib increased in a less than dose proportional manner from 200 mg to 1,200 mg once daily (0.4 to 2.4 times the recommended dose).

Special populations

Elderly

No clinically meaningful effects on the pharmacokinetics of ivosidenib were observed in older patients up to 84 years. The pharmacokinetics of ivosidenib in patients 85 years of age or older is unknown (see section 4.2).

Renal impairment

No clinically meaningful effects on the pharmacokinetics of ivosidenib were observed in patients with mild or moderate renal impairment (eGFR $\geq$ 30 mL/min/1.73 m^2). The pharmacokinetics of ivosidenib in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) or renal impairment requiring dialysis are unknown (see section 4.2).

Hepatic impairment

Using the NCI classification, no clinically meaningful effects on the pharmacokinetics of ivosidenib were observed in patients with mild hepatic impairment. The pharmacokinetics of ivosidenib in patients with moderate and severe hepatic impairment are unknown in patients with newly diagnosed AML and with cholangiocarcinoma (see section 4.2). No PK data in patients with hepatic impairment stratified by the Child-Pugh classification are available.

Other

No clinically meaningful effects on the pharmacokinetics of ivosidenib were observed based on gender, race, body weight or ECOG performance status.

5.3 Preclinical safety data

Safety pharmacology

The potential of ivosidenib for QT prolongation was evidenced in *in vitro* and *in vivo* preclinical studies at clinically relevant plasma levels.

Repeat-dose toxicity

In animal studies at clinically relevant exposures, ivosidenib induced haematologic abnormalities (bone marrow hypocellularity, lymphoid depletion, decreased red cell mass together with extramedullary haematopoiesis in the spleen), gastrointestinal toxicity, thyroid findings (follicular cell hypertrophy/hyperplasia in rats), liver toxicity (elevated transaminases, increased weights, hepatocellular hypertrophy and necrosis in rats and hepatocellular hypertrophy associated with increased liver weights in monkeys) and kidney findings (tubular vacuolation and necrosis in rats). Toxic effects observed on haematologic system, GI system and kidney were reversible whereas the toxic effects observed on liver, spleen and thyroid were still observed at the end of the recovery period.

Genotoxicity and carcinogenicity

Ivosidenib was not mutagenic or clastogenic in conventional *in vitro* and *in vivo* genotoxicity assays. Carcinogenicity studies have not been conducted with ivosidenib.

Reproductive and developmental toxicity

Fertility studies have not been conducted with ivosidenib. In the 28-day repeat dose toxicity study in rats, uterine atrophy was observed in females at non-tolerated dose levels approximately 1.7-fold the clinical exposure (based on AUC) and was reversible after a 14-day recovery period. Testicular degeneration was observed in males at non-tolerated dose levels approximately 1.2-fold the clinical exposure (based on AUC) in animals prematurely euthanized.

In embryofoetal development studies in rats, lower foetal body weights and delayed skeletal ossification occurred in the absence of maternal toxicity. In rabbits, maternal toxicity, spontaneous abortions, decreased foetal body weights, increased post implantation loss, delayed skeletal ossification and visceral development variation (small spleen) were observed. Animal studies indicate that ivosidenib crosses the placenta and is found in foetal plasma. In rats and rabbits, the no adverse effect levels for embryofoetal development were 0.4-fold and 1.4-fold the clinical exposure (based on AUC), respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Croscarmellose sodium
Hypromellose acetate succinate
Colloidal silica, anhydrous
Magnesium stearate
Sodium lauryl sulfate (E487)

Film-coating

Hypromellose
Titanium dioxide (E171)
Lactose monohydrate
Triacetin
Indigo carmine aluminum lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with polypropylene (PP) child resistant closure and polyethylene (PE) faced induction heat seal liner. Each bottle contains 60 film-coated tablets and a silica gel desiccant in a HDPE canister.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1728/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 May 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Les Laboratoires Servier Industrie
905, route de Saran
45520 Gidy
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The Marketing Authorisation Holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Tibsovo in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at patients with AML prescribed Tibsovo, to further provide information regarding the important identified risk of differentiation syndrome.

The MAH shall ensure that in each Member State where Tibsovo is marketed, all patients who are expected to use Tibsovo are provided with the following educational package:

The patient information pack:

- Patient information leaflet
- Patient alert card:
    - Information for patients with AML that Tibsovo treatment may cause differentiation syndrome.
    - Description of signs or symptoms of the safety concern and when to seek medical care if differentiation syndrome is suspected.
    - A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Tibsovo.
    - Contact details of the treating physician who has prescribed Tibsovo.
    - Need to be carried all the time and presented to any healthcare professional.

The patient alert card will be integrated in the packaging and the content will be agreed as part of the labelling (Annex III).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tibsovo 250 mg film-coated tablets
ivosidenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 250 mg ivosidenib.

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1728/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tibsovo 250 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Tibsovo 250 mg film-coated tablets
ivosidenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 250 mg ivosidenib.

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1728/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

CONTENT OF THE PATIENT ALERT CARD

PATIENT ALERT CARD – ACUTE MYELOID LEUKAEMIA

Tibsovo 250 mg film-coated tablets
ivosidenib

Information for the patient treated for acute myeloid leukaemia

This Patient Alert Card contains important information for you and healthcare professionals about Tibsovo.

- Keep this card with you at all times.
- Tell any doctor, pharmacist or nurse that you are taking Tibsovo.
- Contact immediately a healthcare professional and show him the Patient Alert Card if you get any of the symptoms listed below.
- Make sure you use the latest version of this card. This will be the one found in your latest box of tablets.

About your treatment

- Tibsovo is used to treat adults with acute myeloid leukaemia (AML) and is given in combination with another anti-cancer medicine called 'azacitidine'. Tibsovo is only used in patients whose AML is related to a change (mutation) in the IDH1 protein.
- Tibsovo can cause **serious side effects** including a serious condition known as **differentiation syndrome**.
- Differentiation syndrome may be life-threatening if not treated.
- Differentiation syndrome in patients with AML happened up to 46 days after starting treatment.

Seek urgent medical attention if you get any of the following **symptoms** of differentiation syndrome:

- fever
- cough
- trouble breathing
- rash
- decreased urination
- dizziness or light-headedness
- rapid weight gain
- swelling of your arms or legs

See the Tibsovo Package Leaflet for more information.

Information for healthcare professionals

- Patients treated with Tibsovo have experienced differentiation syndrome which may be life-threatening or fatal if not treated.
- Differentiation syndrome in patients with AML happened up to 46 days after starting treatment.
- Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells.
  Symptoms include:

  Non-infectious leukocytosis, peripheral oedema, pyrexia, dyspnoea, pleural effusion, hypotension, hypoxia, pulmonary oedema, pneumonitis, pericardial effusion, rash, fluid overload, tumour lysis syndrome and creatinine increased.

- If differentiation syndrome is suspected, administer systemic corticosteroid and initiate haemodynamic monitoring until symptom resolution and for a minimum of 3 days.

See the Tibsovo Summary of Product Characteristics for more information.

Please complete this section

Name of patient:_____

Date of birth: _____

Tibsovo start date and dose: _____

Prescriber/Hospital emergency contact: _____

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tibsovo 250 mg film-coated tablets
ivosidenib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tibsovo is and what it is used for
2. What you need to know before you take Tibsovo
3. How to take Tibsovo
4. Possible side effects
5. How to store Tibsovo
6. Contents of the pack and other information

1. What Tibsovo is and what it is used for

What Tibsovo is
Tibsovo contains the active substance ivosidenib. It is a medicine used to treat specific cancers that contain a mutated (changed) gene that makes a protein known as IDH1, which plays an important role in making energy for cells. When the IDH1 gene is mutated, the IDH1 protein is changed and does not function properly, and this results in changes in the cell which can lead to the development of cancer. Tibsovo blocks the mutated form of the IDH1 protein and helps to slow or stop the cancer from growing.

What Tibsovo is used for
Tibsovo is used to treat adults with:
- acute myeloid leukaemia (AML). When used for patients with AML, Tibsovo will be given in combination with another anti-cancer medicine called ‘azacitidine’.
- bile duct cancer (also known as ‘cholangiocarcinoma’). Tibsovo is used on its own to treat patients whose bile duct cancer has spread to other parts of the body and who have been treated with at least one prior therapy.

Tibsovo is only used in patients whose AML or bile duct cancer is related to a change (mutation) in the IDH1 protein.

2. What you need to know before you take Tibsovo

Your doctor will perform a test to check if you have a mutation in the IDH1 protein before deciding if this medicine is the right treatment for you.

Do not take Tibsovo

- if you are **allergic** to **ivosidenib** or any of the **other ingredients** of this medicine (listed in section 6);
- if you are already taking medicines such as dabigatran (a medicine used for preventing the formation of blood clots), St. John's wort (an herbal remedy used for depression and anxiety), rifampicin (a medicine used for treating bacterial infections) or certain medicines used to treat epilepsy (e.g. carbamazepine, phenobarbital, phenytoin).
- if you have a heart problem that you were born with called 'congenital long QTc syndrome'.
- if you have a familial history of sudden death or an abnormal or irregular heartbeat in the lower chambers of the heart.
- if you have a severe abnormality of electrical activity of the heart that affects its rhythm called 'QTc prolongation'.

Do not take Tibsovo if any of the above applies to you. If you are not sure, talk to your doctor or nurse.

Warnings and precautions

Differentiation syndrome in patients with AML:

Tibsovo can cause a serious condition known as **differentiation syndrome** in patients with AML. This is a condition that affects your blood cells and may be life-threatening if not treated.

Seek urgent medical attention if you have any of the following symptoms after taking Tibsovo:

- fever,
- cough,
- trouble breathing,
- rash,
- decreased urination,
- dizziness or light-headedness,
- rapid weight gain
- swelling of your arms or legs.

These may be signs of differentiation syndrome.

The pack contains a patient alert card to carry with you at all times. It contains important information for you and your healthcare professionals about what to do if you get any of the symptoms of differentiation syndrome (see section 4).

QTc interval prolongation:

Tibsovo can cause a serious condition known as **QTc interval prolongation** which can cause irregular heartbeats and life-threatening arrythmias (abnormal electrical activity of the heart that affects its rhythm). Your doctor must check the electrical activity of your heart before and during treatment with Tibsovo (see 'Regular tests').

Seek urgent medical attention if you feel dizzy, light-headed, palpitations or faint (see also section 4) after taking Tibsovo.

During treatment, tell your doctors you are taking Tibsovo before starting any new medicine as these may increase the risk of an abnormal heart rhythm.

If you get any of the above serious side effects, your doctor may give you other medicines to treat them and they may tell you to stop taking Tibsovo for a while or stop taking it altogether.

Talk to your doctor **before taking** Tibsovo if:
- you have **heart problems** or have **problems with abnormal electrolytes levels** (such as sodium, potassium, calcium or magnesium);
- you are **taking certain medicines that can affect the heart** (e.g. those used to prevent arrhythmia called anti-arrhythmics, some antibiotics, some antifungals and those used to prevent nausea and vomiting - see 'Other medicines and Tibsovo');
- you have kidney problems;
- you have liver problems.

Regular tests
You will be monitored closely by your doctor before and during treatment with Tibsovo. You will need to have regular electrocardiograms (ECGs; a recording of the electrical activity in your heart) to monitor your heartbeat. You will be given an ECG before you start treatment with Tibsovo, once a week for the first three weeks of treatment, and then monthly thereafter. Additional ECG may be given as instructed by your doctor. If you start taking certain medicines that can affect your heart, you will be given an ECG before starting and during treatment with the new medicine as needed.
You will also have a blood test before starting treatment with Tibsovo and then regularly thereafter. If necessary, your doctor may reduce your dose of Tibsovo, interrupt it temporarily or stop it altogether.

Children and adolescents
Do not give this medicine to children and adolescents under 18 years old because there is no information about its use in this age group.

Other medicines and Tibsovo
Tell your doctor if you are taking, have recently taken or might take any other medicines. This is because they may reduce how well Tibsovo works or increase the risk of side effects, or Tibsovo may affect the way these other medicines work.

In particular, you should **tell your doctor** if you are taking any of the following medicines so that they can decide if your treatment needs to change:
- **antibiotics** used for bacterial infections (e.g. erythromycin, clarithromycin, benzylpenicillin, ciprofloxacin, levofloxacin);
- **warfarin** (used to prevent blood clots);
- **medicines used for fungal infections** (e.g. itraconazole, ketoconazole, fluconazole, isavuconazole, posaconazole, voriconazole);
- **medicines that affect your heartbeat** known as anti-arrhythmics (e.g. diltiazem, verapamil, quinidine);
- **medicines used to stop nausea and vomiting** known as anti-emetics (e.g. aprepitant, ondansetron, tropisetron, granisetron);
- **medicines used after organ transplants** known as immunosuppressants (e.g. ciclosporin, everolimus, sirolimus, tacrolimus);
- **medicines used for HIV** (e.g. raltegravir, ritonavir);
- **alfentanil** (used for anaesthesia in surgery);
- **fentanyl** (used for severe pain);
- **pimozide** (used for schizophrenia);
- **medicines used for cancer** (e.g. cyclophosphamide, ifosfamide, paclitaxel);
- **methadone** (used for morphine or heroin addiction, or severe pain);
- **medicines used for type 2 diabetes** (e.g. pioglitazone, repaglinide);
- **omeprazole** (used for stomach ulcers and acid reflux);
- **furosemide** (used for fluid build-up known as oedema);
- **medicines used for high cholesterol** known as statins (e.g. atorvastatin, pravastatin, rosuvastatin).
- **lamotrigine** (used for epilepsy).

Tibsovo with food and drink
Do not have grapefruit or grapefruit juice during treatment with Tibsovo as it can affect how this medicine works.

Pregnancy, breast-feeding and fertility
Tibsovo is not recommended for use during pregnancy as it may harm the unborn baby. Women of child-bearing age should have a pregnancy test prior to starting treatment with Tibsovo and should avoid becoming pregnant during therapy.

If you are pregnant, think you might be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Contact your doctor or nurse immediately if you become pregnant whilst taking Tibsovo.

Contraception
Tibsovo should not be used in pregnancy as it can harm the unborn baby. Women who might become pregnant or men with partners who might become pregnant must use effective contraception to avoid pregnancy during treatment with Tibsovo and for at least 1 month after the last dose.

Tibsovo may stop hormonal contraceptives from working properly. If you or your partner use a hormonal contraceptive (e.g. birth control pills, or contraceptive patches or implants), you must **also use a barrier method** (e.g. condoms or a diaphragm) to avoid pregnancy. Talk to your doctor or nurse about the right contraceptive method for you.

Breast-feeding
It is not known if Tibsovo passes into breast milk. **Do not** breast-feed your baby during treatment with Tibsovo and for at least 1 month after the last dose.

Fertility
It is not known if Tibsovo affects fertility. If you are concerned about your fertility whilst taking Tibsovo talk to your doctor.

Driving and using machines
This medicine has minor influence on your ability to drive or use any tools or machines. If you feel unwell after taking Tibsovo, do not drive or use any tools or machines until you feel well again.

Tibsovo contains lactose and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to take Tibsovo

Always take this medicine exactly as your doctor has told you. Check with your doctor or nurse if you are not sure.

The recommended dose is **2 tablets** (500 mg ivosidenib) to be taken once daily at approximately the **same time each day**.

Your doctor may tell you to take **1 tablet** (250 mg ivosidenib) if you are **taking some other medicines** or to help you **better tolerate some possible side effects.**

- Take the tablets **without food**. Do not eat anything for **2 hours before** through **1 hour after** taking the tablets.
- Swallow the tablets whole with water.

- **Do not** swallow the **desiccant** found in the bottle. The desiccant helps protect the tablets from moisture. (see section 5 and section 6.).
- If you vomit after taking your usual dose, **do not** take additional tablets. Take your next dose as usual the following day.

If you take more Tibsovo than you should
If you accidentally take more tablets than your doctor prescribed, **seek urgent medical attention** and take the medicine bottle with you.

If you forget to take Tibsovo
If you miss a dose or do not take it at the usual time, take the tablets as soon as possible unless the next dose is due within 12 hours. **Do not** take two doses within 12 hours. Take the next dose as usual the following day.

How long to take Tibsovo
You should keep taking this medicine until your doctor tells you to stop. **Do not** stop taking the tablets before discussing it with your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Seek urgent medical attention if you get any of the following side effects. The symptoms listed below could be due to serious conditions known as **differentiation syndrome** or **QTc interval prolongation**, which can both be life-threatening:

- **Differentiation syndrome**
  Contact your doctor straight away if you have any of the following symptoms:
  - fever,
  - cough,
  - trouble breathing,
  - rash,
  - decreased urination,
  - dizziness or light headedness,
  - rapid weight gain,
  - swelling of your arms or legs.

  Some or all of these symptoms may be signs of a condition called differentiation syndrome (may affect more than 1 in 10 people).
  Differentiation syndrome in patients with AML happened up to 46 days after starting Tibsovo.

- **Heart rhythm problems (QTc interval prolongation)**
  Contact your doctor straight away if you have a change in your heartbeat, or if you feel: dizzy, lightheaded, or faint. These may be signs of a heart problem called QT prolongation (may affect more than 1 in 10 people).

Other side effects
Tell your doctor if you notice any of the following side effects:

For patients with AML
Very common (may affect more than 1 in 10 people):
- vomiting;
- neutropenia (low levels of neutrophils, a type of white blood cell that fights infections);
- thrombocytopenia (low levels of blood platelets which can lead to bleeding and bruising);
- leukocytosis (high levels of white blood cells);
- insomnia (difficulty sleeping);
- pain in extremity, joint pain;
- headache;
- dizziness;
- back pain.

Common (may affect more than 1 in 100 people):
- pain in your mouth or throat;
- peripheral neuropathy (nerve damage in arms and legs causing pain or numbness, burning and tingling);
- leukopenia (low levels of white blood cells).

For patients with bile duct cancer
Very common (may affect more than 1 in 10 people):
- fatigue;
- nausea;
- abdominal pain;
- diarrhoea;
- decreased appetite;
- ascites (a build-up of fluid in the abdomen);
- vomiting;
- anaemia (low levels of red blood cells);
- headache;
- changes in liver function tests (Aspartate aminotransferase increased);
- peripheral neuropathy (nerve damage in arms and legs causing pain or numbness, burning and tingling);
- rash;
- blood bilirubin (a breakdown product of red blood cells) increased which can cause yellowing of the skin and eyes.

Common (may affect more than 1 in 100 people):
- white blood cell count decreased;
- platelet count decreased;
- changes in liver function tests (Alanine aminotransferase increased);
- falls;
- hyperbilirubinemia (high levels of blood bilirubin);
- jaundice cholestatic (build-up of bile causing yellowing of the skin or eyes).

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tibsovo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and box after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions. Keep the bottle tightly closed in order to protect from moisture. Keep the desiccant inside the bottle (see section 6).

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tibsovo contains

- The active substance is ivosidenib. Each tablet contains 250 milligrams of ivosidenib.
- The other ingredients are microcrystalline cellulose, croscarmellose sodium, hypromellose acetate succinate, colloidal silica anhydrous, magnesium stearate, sodium lauryl sulfate (E487), hypromellose, titanium dioxide (E171), lactose monohydrate, triacetin and indigo carmine aluminum lake (E132) (see section 2 ‘Tibsovo contains lactose and sodium’).

What Tibsovo looks like and contents of the pack

- The film-coated tablets are blue, oval shaped, with “IVO” on one side and “250” on the other side.
- Tibsovo is available in plastic bottles containing 60 film-coated tablets and a desiccant. The bottles are packaged in a cardboard box; each box contains 1 bottle.

Marketing Authorisation Holder
Les Laboratoires Servier
50 rue Carnot
92284 Suresnes Cedex
France

Manufacturer
Les Laboratoires Servier Industrie
905, route de Saran
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

2.4　欧州製品概要日本語訳

欧州製品概要の和訳を以下に示す。

1.　販売名

Tibsovo 250 mg フィルムコーティング錠

2.　成分及び含量

フィルムコーティング錠 1 錠あたりイボシデニブ 250 mg を含有する。

作用が既知の添加物

フィルムコーティング錠 1 錠あたりラクトース 9.5 mg に相当するラクトース一水和物を含有する（4.4 項を参照）。

添加剤の一覧は 6.1 項を参照。

3.　剤形

フィルムコーティング錠（錠剤）

長径約 18 mm の楕円形の青色フィルムコーティング錠で、錠剤の片面に「IVO」、反対面に「250」と刻印されている。

4.　臨床に関する詳細

4.1　効能又は効果

本剤とアザシチジンの併用投与は、標準的な寛解導入療法の適応とならないイソクエン酸脱水素酵素 1（IDH1）R132 変異陽性の未治療の成人の急性骨髄性白血病（AML）患者の治療を適応とする（5.1 項を参照）。

本剤の単剤投与は、少なくとも 1 ライン以上の全身療法の治療歴があり、IDH1 R132 変異陽性の局所進行性又は転移性の成人の胆管癌患者の治療を適応とする（5.1 項を参照）。

4.2　用法及び用量

抗悪性腫瘍剤の使用経験がある医師の監督のもとで治療を開始する。

本剤を投与する前に適切な診断検査により IDH1 R132 の変異の有無を確認する必要がある。

用法及び用量

急性骨髄性白血病

本剤の推奨用量はイボシデニブ 500 mg（250 mg 錠×2）の 1 日 1 回経口投与である。本剤はサイクル 1 の 1 日目に投与開始し、併用薬であるアザシチジンは 28 日サイクルの 1～7 日目に 1 日 1 回 75 mg/m^2（体表面積）で点滴静注又は皮下投与する。アザシチジンはサイクル 1 では投与量

のうち全量投与する。最低 6 サイクルの治療が推奨される。

アザシチジンの用法及び用量については、アザシチジンの製品情報全文を参照。

疾患進行が認められるか患者に許容できない毒性が確認されるまで治療を継続する。

胆管癌

本剤の推奨用量はイボシデニブ 500 mg（250 mg 錠×2）の 1 日 1 回経口投与である。

疾患進行が認められるか患者に許容できない毒性が確認されるまで治療を継続する。

飲み忘れ又は服用のタイミングが遅れた場合

本剤の飲み忘れや、所定の時刻に服用されなかった場合、本来服用すべき時点から 12 時間以内であれば気づいた時点で直ちに服用し忘れた分を服用する。12 時間以内に 2 回服用しない。翌日から所定の時刻に服用する。

本剤を嘔吐した場合、再度服用せず、翌日から所定の時刻に服用する。

投与前の注意及びモニタリング

治療開始前に心電図（ECG）を測定する。治療開始前に心拍数で補正した QT 間隔（QTc）は 450 msec 未満である。QT の異常が認められた場合、本剤を開始することのベネフィット／リスクを医師が十分に再評価する。QTc 間隔延長が 480 msec から 500 msec の場合、本剤による治療を開始することは例外的なケースとし、治療を開始した場合は密にモニタリングする。

治療開始前、治療開始後 3 週間は週 1 回以上、その後は月 1 回 ECG を測定し、QTc 間隔が 480 msec 以下であるか確認する。QTc 間隔の異常が認められた場合は速やかに処置を行う（表 1 及び 4.4 項を参照）。徴候が示唆された場合、臨床上必要に応じて ECG を測定する。

QTc 間隔延長を起こすことが知られている薬剤又は中程度若しくは強い CYP3A4 阻害剤と本剤とを併用投与すると、QTc 間隔延長のリスクが上昇する可能性があるため、本剤の治療期間中は可能な限り併用投与を避ける。適切な代替薬を使用できない場合、慎重に投与し、QTc 間隔延長について密にモニタリングする。併用投与開始前、投与開始後少なくとも 3 週間は週 1 回、その後は臨床上必要に応じて ECG を測定する（4.4、4.5 及び 4.8 項を参照）。

全血球数及び血液生化学の評価は、本剤による治療開始前、治療開始の 1 カ月目は週 1 回以上、2 カ月目は隔週 1 回、治療期間中は来院時に臨床上必要に応じて実施する。

中程度又は強い CYP3A4 阻害剤を併用投与した場合の用量調節

中程度又は強い CYP3A4 阻害剤の投与が避けられない場合、本剤の推奨用量を 1 日 1 回 250 mg（250 mg 錠×1）に減量する。中程度又は強い CYP3A4 阻害剤の投与を中止する場合、CYP3A4 阻害剤の 5 半減期以上経過後に本剤の用量を 500 mg に増量する（上記、4.4 及び 4.5 項を参照）。

副作用に対する用量調節及び推奨される管理

表 1 - 副作用に対する推奨される用量調節

副作用	推奨される対応
分化症候群（4.4 及び 4.8 項を参照）	• 分化症候群が疑われる場合、全身性コルチコステロイドを 3 日以上投与し、症状が消失した後に限り漸減する。早期投与中止により、症状再発の可能性がある。 • 3 日以上かつ症状が消失するまで血行動態モニタリングを実施する。 • 全身性コルチコステロイド投与開始後 48 時間以降も重度の徴候／症状が続いた場合、本剤を休薬する。 • 徴候／症状が中等度又は軽度に回復し、臨床状態に改善がみられた場合、本剤を 1 日 1 回 500 mg で再開する。
白血球増加症（白血球数が 25×10^9/L 超又は総白血球数の絶対数がベースラインより 15×10^9/L 超増加、4.4 及び 4.8 項を参照）	• 医療機関ごとの治療基準に従いヒドロキシカルバミドによる治療を開始し、臨床上必要に応じて白血球アフェレーシスを実施する。 • 白血球増加症が改善又は消失した後に限りヒドロキシカルバミドを漸減する。早期投与中止により再発の可能性がある。 • ヒドロキシカルバミドによる治療を開始後白血球増加症が改善しなかった場合、本剤を休薬する。 • 白血球増加症が消失した場合、本剤を 1 日 1 回 500 mg で再開する。
QTc 間隔延長 480 msec 超 500 msec 以下 （Grade 2；4.4、4.5 及び 4.8 項を参照）	• 電解質濃度をモニタリングし、臨床上必要に応じて電解質を補給する。 • QTc 間隔延長を起こすことが知られている併用薬を確認し調節する（4.5 項を参照）。 • QTc 間隔が 480 msec 以下に回復するまで本剤を休薬する。 • QTc 間隔が 480 msec 以下に回復した後、本剤を 1 日 1 回 500 mg で再開する。 • QTc 間隔が 480 msec 以下に回復した後は、投与再開後 3 週間は週 1 回以上及び臨床上必要に応じて ECG をモニタリングする。
QTc 間隔延長 500 msec 超 （Grade 3；4.4、4.5 及び 4.8 項を参照）	• 電解質濃度をモニタリングし、臨床上必要に応じて電解質を補給する。 • QTc 間隔延長を起こすことが知られている併用薬を確認し調節する（4.5 項を参照）。 • 本剤を休薬し、QTc 間隔がベースライン時の

副作用	推奨される対応
	30 msec 以内又は 480 msec 以下に回復するまで 24 時間ごとに ECG をモニタリングする。 • QTc 間隔延長が 550 msec 超の場合、予定されていた本剤の休薬に加えて QTc 間隔が 500 msec 未満に回復するまで連続的な心電図モニタリングの実施を検討する。 • QTc 間隔がベースライン時の 30 msec 以内又は 480 msec 以下に回復した後、本剤を 1 日 1 回 250 mg で再開する。 • QTc 間隔がベースライン時の 30 msec 以内又は 480 msec 以下に回復した後は、投与再開後 3 週間は週 1 回以上及び臨床上必要に応じて ECG をモニタリングする。 • QTc 間隔延長に他の原因が特定された場合、本剤の用量を 1 日 1 回 500 mg に増量してもよい。
生命を脅かす心室性不整脈の徴候／症状を伴う QTc 間隔延長（Grade 4；4.4、4.5 及び 4.8 項を参照）	• 本剤を中止する。
その他の Grade 3 以上の副作用	• 副作用が Grade 1 以下又はベースラインに回復するまで本剤を休薬し、その後本剤を 1 日 1 回 500 mg（Grade 3 の副作用）又は 1 日 1 回 250 mg（Grade 4 の副作用）で再開する。 • Grade 3 の副作用が再発した場合（2 回目）、本剤の用量を 1 日 1 回 250 mg に減量し、副作用が消失してから 1 日 1 回 500 mg で再開する。 • Grade 3 の副作用が再発した場合（3 回目）、又は Grade 4 の副作用が再発した場合、本剤を中止する。

Grade 1 は軽症、Grade 2 は中等症、Grade 3 は重症、Grade 4 は生命を脅かす副作用。

特定の集団

高齢者

高齢患者での本剤の用量調節は不要である（65 歳以上、4.8 及び 5.2 項を参照）。85 歳以上の患者を対象としたデータはない。

腎機能障害

軽度（eGFR ≥60～<90 mL/min/1.73 m^2）又は中等度（eGFR ≥30～<60 mL/min/1.73 m^2）の腎機能障害患者での用量調節は不要である。重度（eGFR <30 mL/min/1.73 m^2）の腎機能障害患者に対する推奨用量は決定されていない。重度の腎機能障害患者には慎重に本剤を投与し密にモニタリングする（4.4 及び 5.2 項を参照）。

肝機能障害

軽度の肝機能障害（Child-Pugh 分類 A）患者での本剤の用量調節は不要である。中等度及び重度の肝機能障害（Child-Pugh 分類 B 及び C）患者に対する推奨用量は決定されていない。中等度及び重度の肝機能障害患者には慎重に本剤を投与し密にモニタリングする（4.4 及び 5.2 項を参照）。

小児等

18 歳未満の小児及び青少年の患者における本剤の安全性及び有効性は確立されていない。入手可能なデータはない。

投与方法

本剤は経口投与用である。

錠剤は毎日所定の時刻に 1 日 1 回投与する。錠剤服用前 2 時間から服用後 1 時間は食事を摂らない（5.2 項を参照）。錠剤は水とともにそのまま服用する。

治療中はグレープフルーツ及びグレープフルーツジュースの摂取を避けるよう指導する（4.5 項を参照）。錠剤の容器に入っているシリカゲル乾燥剤の誤飲を避けるよう指導する（6.5 項を参照）。

4.3　禁忌

6.1 項に示す有効成分又は添加剤に対する過敏症の既往歴。

強い CYP3A4 誘導剤又はダビガトランの併用投与（4.5 項を参照）。

先天性 QT 延長症候群。

突然死又は多形性心室性不整脈の家族歴。

補正法を問わず QT/QTc 間隔が 500 msec 超（4.2 及び 4.4 項を参照）。

4.4　警告及び使用上の注意

急性骨髄性白血病患者における分化症候群

本剤による治療後に分化症候群が報告されている（4.8 項を参照）。分化症候群は治療をしなかった場合、生命を脅かす又は死亡に至る可能性がある（以下の記載及び 4.2 項を参照）。分化症候群は骨髄系細胞の急激な増殖及び分化に関連する。分化症候群の症状には、非感染性の白血球増加症、末梢性浮腫、発熱、呼吸困難、胸水、低血圧、低酸素症、肺水腫、肺臓炎、心嚢液貯留、

発疹、水分過負荷、腫瘍崩壊症候群及びクレアチニン増加が挙げられる。

患者には分化症候群の徴候及び症状を伝え、発症した場合は速やかに医師に連絡するよう指導し、常に Patient Alert Card を所持する必要性を伝える。

分化症候群が疑われる場合、全身性コルチコステロイドを投与し、血行動態モニタリングを 3 日以上かつ症状が消失するまで継続する。

白血球増加症が認められた場合、医療機関ごとの治療基準に従いヒドロキシカルバミドによる治療を開始し、臨床上必要に応じて白血球アフェレーシスを実施する（4.5 項を参照）。

症状が消失した後に限りコルチコステロイド及びヒドロキシカルバミドを漸減する。コルチコステロイド及び／又はヒドロキシカルバミドの投与を早期に中止すると、分化症候群の症状が再発する可能性がある。全身性コルチコステロイド投与開始後 48 時間以降も重度の徴候／症状が続いた場合、本剤を休薬し、徴候／症状が中等度以下に回復し患者の臨床状態に改善がみられたとき、本剤を 1 日 1 回 500 mg で再開する。

<u>QTc 間隔延長</u>

本剤による治療後に QTc 間隔延長が報告されている（4.8 項を参照）。治療開始前、治療開始後 3 週間は週 1 回以上、その後は月 1 回 ECG を測定し、QTc 間隔が 480 msec 以下であるか確認する（4.2 項を参照）。異常が認められた場合、速やかに処置を行う（4.2 項を参照）。徴候が示唆された場合、臨床上必要に応じて ECG を測定する。重度の嘔吐及び／又は下痢の場合、特に低カリウム血症及びマグネシウムなどの血清中電解質異常を評価する必要がある。

患者に QT 延長のリスク、徴候及び症状（動悸、浮動性めまい、失神又は心停止）を伝え、発症した場合は速やかに医師に連絡するよう指導する。

QTc 間隔延長を起こすことが知られている薬剤又は中程度若しくは強い CYP3A4 阻害剤と本剤とを併用投与すると、QTc 間隔延長のリスクが上昇する可能性があるため、本剤の治療期間中は可能な限り併用投与を避ける。適切な代替薬を使用できない場合、慎重に投与し、QTc 間隔延長について密にモニタリングする。併用投与開始前、投与開始後少なくとも 3 週間は週 1 回、その後は臨床上必要に応じて ECG を測定する。中程度又は強い CYP3A4 阻害剤の投与が避けられない場合、本剤の推奨用量を 1 日 1 回 250 mg に減量する（4.2 及び 4.5 項を参照）。

分化症候群の徴候／症状を管理するためにフロセミド（OAT3 の基質）の投与が臨床上必要な場合、電解質失調及び QTc 間隔延長について密にモニタリングする。

うっ血性心不全の患者又は電解質異常の患者には、本剤の治療期間中は定期的に ECG 及び電解質検査を行い、密にモニタリングする。

生命を脅かす不整脈の徴候又は症状を伴う QTc 間隔延長があった場合、本剤を中止する（4.2

項を参照）。

アルブミンが基準値以下の患者又は低体重の患者には慎重に本剤を投与する。

重度の腎機能障害

重度の腎機能障害（eGFR <30 mL/min/1.73 m^2）患者において本剤の安全性及び有効性は確立されていない。重度の腎機能障害患者には慎重に本剤を投与し密にモニタリングする（4.2 及び 5.2 項を参照）。

肝機能障害

中等度及び重度の肝機能障害（Child-Pugh 分類 B 及び C）患者において本剤の安全性及び有効性は確立されていない。中等度及び重度の肝機能障害患者には慎重に本剤を投与し密にモニタリングする（4.2 及び 5.2 項を参照）。

軽度の肝機能障害（Child-Pugh 分類 A）患者には慎重に本剤を投与する（4.8 項を参照）。

CYP3A4 の基質

本剤は CYP3A4 を誘導するため、CYP3A4 の基質の全身曝露量が減少する可能性がある。イトラコナゾール又はケトコナゾールとの併用が避けられない場合、抗真菌薬の効果が失われていないかモニタリングする（4.5 項を参照）。

妊娠する可能性のある女性／避妊

妊娠する可能性のある女性は本剤による治療開始前に妊娠検査を実施し、治療中の妊娠を避ける（4.6 項を参照）。

妊娠する可能性のある女性及び女性パートナーが妊娠する可能性のある男性は、本剤の治療期間中及び最終投与後 1 カ月以上は効果的な避妊法を用いる。

本剤はホルモン避妊薬の全身濃度を低下させる可能性があるため、バリア法との併用が推奨される（4.5 及び 4.6 項を参照）。

ラクトース不耐性

本剤にはラクトースが含まれる。ガラクトース不耐症、ラクターゼ欠乏症又はグルコース・ガラクトース吸収不良症の希少遺伝性疾患の患者には本剤の投与を避ける。

ナトリウム含有量

本剤 1 錠中に含まれるナトリウムは 1 mmol（23 mg）未満であるため、実質的に「sodium-free」

である。

4.5　他剤との相互作用及びその他の相互作用

本剤に対する他剤の影響

強い CYP3A4 誘導剤

本剤は CYP3A4 の基質である。強い CYP3A4 誘導剤（カルバマゼピン、フェノバルビタール、フェニトイン、リファンピシン、セントジョーンズワート［セイヨウオトギリソウ］など）を併用投与すると、本剤の血漿中濃度の低下が予想されるため、本剤の治療期間中は禁忌である（4.3 項を参照）。CYP3A4 誘導剤の併用下における本剤の薬物動態を評価するための臨床試験は実施していない。

中程度又は強い CYP3A4 阻害剤

健康被験者に本剤 250 mg 単回投与及びイトラコナゾール 200 mg を 1 日 1 回 18 日間投与したところ本剤の AUC が 169%（90% CI：145～195）増加したが、C_{max} には変化がみられなかった。中程度又は強い CYP3A4 阻害剤を併用投与すると、本剤の血漿中濃度が上昇する。QTc 間隔延長のリスクが上昇する可能性があるため、本剤の治療期間中は可能な限り中程度又は強い CYP3A4 阻害剤以外の適切な代替薬を考慮する。適切な代替薬を使用できない場合、慎重に投与し、QTc 間隔延長について密にモニタリングする。中程度又は強い CYP3A4 阻害剤の投与が避けられない場合、本剤の推奨用量を 1 日 1 回 250 mg に減量する（4.2 及び 4.4 項を参照）。

- 中程度の CYP3A4 阻害剤：アプレピタント、シクロスポリン、ジルチアゼム、エリスロマイシン、フルコナゾール、グレープフルーツ及びグレープフルーツジュース、イサブコナゾール、ベラパミル
- 強い CYP3A4 阻害剤：クラリスロマイシン、イトラコナゾール、ケトコナゾール、ポサコナゾール、リトナビル、ボリコナゾール

QTc 間隔延長を起こすことが知られている薬剤

QTc 間隔延長を起こすことが知られている薬剤（抗不整脈薬、フルオロキノロン、5-HT3 受容体拮抗薬、トリアゾール系抗真菌薬など）を併用投与すると、QTc 間隔延長のリスクが上昇する可能性があるため、本剤の治療期間中は可能な限り併用投与を避ける。適切な代替薬が使用できない場合、慎重に投与し、QTc 間隔延長について密にモニタリングする（4.2 及び 4.4 項を参照）。

他剤に対する本剤の影響

トランスポーターを介した相互作用

本剤は P-糖タンパク質（P-gp）の阻害作用があり、P-gp を誘導する可能性がある。そのため、主に P-gp を介して輸送される有効成分（ダビガトランなど）の全身曝露量を変化させる可能性がある。ダビガトランとの併用投与は禁忌である（4.3 項を参照）。

本剤は有機アニオントランスポーター3（OAT3）、有機アニオン輸送ポリペプチド 1B1（OATP1B1）及び有機アニオン輸送ポリペプチド 1B3（OATP1B3）を阻害する。そのため、OAT3 又は OATP1B1／1B3 の基質の全身曝露量が増加する可能性がある。本剤の治療期間中は OAT3 の基質（ベンジルペニシリン、フロセミドなど）又は OATP1B1／1B3 感受性の基質（アトルバスタチン、プラバスタチン、ロスバスタチンなど）との併用は可能な限り避ける（5.2 項を参照）。適切な代替薬が使用できない場合、慎重に投与する。分化症候群の徴候／症状の管理にあたりフロセミドの投与が臨床上必要な場合、電解質失調及び QTc 間隔延長について密にモニタリングする。

酵素誘導

チトクロム P450（CYP）酵素

本剤は CYP3A4、CYP2B6、CYP2C8 及び CYP2C9 の誘導作用があり、CYP2C19 を誘導する可能性がある。そのため、これらの酵素の基質の全身曝露量が減少する可能性がある。本剤の治療期間中は、治療域の狭い CYP3A4、CYP2B6、CYP2C8 若しくは CYP2C9 の基質又は CYP2C19 の基質以外の適切な代替薬を考慮する。これらの薬剤との併用が避けられない場合は基質の有効性が失われていないかモニタリングする（5.2 項を参照）。

- 治療域の狭い CYP3A4 の基質：アルフェンタニル、シクロスポリン、エベロリムス、フェンタニル、ピモジド、キニジン、シロリムス、タクロリムス
- 治療域の狭い CYP2B6 の基質：シクロホスファミド、イホスファミド、メサドン
- 治療域の狭い CYP2C8 の基質：パクリタキセル、ピオグリタゾン、レパグリニド
- 治療域の狭い CYP2C9 の基質：フェニトイン、ワルファリン
- CYP2C19 の基質：オメプラゾール

抗真菌薬の効果が失われることがあるため、イトラコナゾール又はケトコナゾールと本剤を併用投与しない。

本剤はホルモン避妊薬の全身濃度を低下させる可能性があるため、最終投与後少なくとも 1 カ月間はバリア法との併用が推奨される（4.4 及び 4.6 項を参照）

ウリジン二リン酸グルクロン酸転移酵素（UGTs）

本剤は UGT を誘導する可能性があることから、UGT の基質（ラモトリギン及びラルテグラビルなど）の全身曝露量を減少させる可能性がある。本剤の治療期間中は UGT の基質以外の適切な代替薬を考慮する。これらの薬剤との併用が避けられない場合は UGT の基質の有効性が失われていないかモニタリングする（5.2 項を参照）。

4.6　　妊孕性、妊娠及び授乳

妊娠する可能性のある女性／避妊

妊娠する可能性のある女性は本剤による治療開始前に妊娠検査を実施し、治療中の妊娠を避ける（4.4 項を参照）

妊娠する可能性のある女性及び女性パートナーが妊娠する可能性のある男性は、本剤の治療期間中及び最終投与後 1 カ月以上は効果的な避妊法を用いる。

本剤はホルモン避妊薬の全身濃度を低下させる可能性があるため、バリア法などの代替避妊法との併用が推奨される（4.4 及び 4.5 項を参照）

妊婦

妊婦における本剤の使用に関する十分なデータは得られていない。非臨床試験において生殖毒性が認められている（5.3 項を参照）。

妊娠中の女性及び効果的な避妊法を用いていない妊娠する可能性のある女性に、本剤の投与は推奨されない。妊娠中に本剤を投与した場合や、治療期間中又は最終投与後 1 カ月間に患者（又は治療した男性患者の女性パートナー）が妊娠した場合に胎児に与える可能性のあるリスクを患者に伝える。

授乳

イボシデニブ及びその代謝物のヒト乳汁中への移行は明らかではない。イボシデニブ及びその代謝物の乳汁移行を評価した非臨床試験は実施されていないため新生児／乳幼児へのリスクは除外できない。

本剤の治療期間中及び最終投与後 1 カ月以上は授乳を中止する。

妊孕性

ヒトの妊孕性に対するイボシデニブの影響に関するデータは得られていない。イボシデニブの影響の評価を目的とした動物を用いた受胎能試験は実施されていない。28 日間反復投与毒性試験

では、生殖器官に望ましくない影響が観察された（5.3 項を参照）。これらの影響がもたらす臨床的意義は不明である。

4.7　運転及び機械操作能力への影響

本剤は運転及び機械操作に軽微な影響を及ぼす。本剤の投与を受けている一部の患者に疲労及び浮動性めまいが報告されているため（4.8 項を参照）、患者の運転能力及び機械の操作能力を評価する場合は考慮する。

4.8　望ましくない作用

未治療の急性骨髄性白血病に対するアザシチジンとの併用療法

安全性プロファイルの要約

最もよくみられた副作用は、嘔吐（40%）、好中球減少症（31%）、血小板減少症（28%）、心電図 QT 延長（21%）及び不眠症（19%）であった。

最もよくみられた重篤な副作用は、分化症候群（8%）及び血小板減少症（3%）であった。

本剤とアザシチジンを併用投与した患者では、副作用による本剤の投与中止の割合は 6%であった。本剤の投与中止に至った副作用は、心電図 QT 延長（1%）、不眠症（1%）、好中球減少症（1%）及び血小板減少症（1%）であった。

副作用による本剤の休薬の割合は 35%であった。本剤の休薬に至った最もよくみられた副作用は、好中球減少症（24%）、心電図 QT 延長（7%）、血小板減少症（7%）、白血球減少症（4%）及び分化症候群（3%）であった。

副作用による本剤の減量の割合は 19%であった。本剤の減量に至った副作用は、心電図 QT 延長（10%）、好中球減少症（8%）及び血小板減少症（1%）であった。

副作用の一覧

副作用の発現頻度は、未治療の AML 患者 72 例を本剤（1 日 1 回 500 mg）及びアザシチジン群に無作為に割り付け、併用投与した AG120-C-009 試験の結果に基づく。本剤の投与期間の中央値は 8 カ月であった（範囲 0.1～40.0 カ月）。副作用の発現頻度は、あらゆる原因による有害事象の発現頻度に基づいているため、副作用の発現事象の割合には疾患、他剤又は関連のない原因など、本剤以外の原因が含まれている可能性がある。

発現頻度は次のように、極めて高頻度（≥1/10）、高頻度（≥1/100～<1/10）、低頻度（≥1/1000～<1/100）、まれ（≥1/10000～<1/1000）、極めてまれ（<1/10000）と定義した。同一の発現頻度グループ内では、重篤なものから副作用を記載した。

表 2 - AG120-C-009 試験において本剤とアザシチジンを併用投与した未治療 AML 患者に報告された副作用（N=72）

MedDRA 器官別大分類	発現頻度	副作用
血液およびリンパ系障害	極めて高頻度	分化症候群、白血球増加症、血小板減少症、好中球減少症
	高頻度	白血球減少症
精神障害	極めて高頻度	不眠症
神経系障害	極めて高頻度	頭痛、浮動性めまい
	高頻度	末梢性ニューロパチー
胃腸障害	極めて高頻度	嘔吐 [1]
	高頻度	口腔咽頭痛
筋骨格系および結合組織障害	極めて高頻度	四肢痛、関節痛、背部痛
臨床検査	極めて高頻度	心電図 QT 延長

[1] グループ化した用語：嘔吐及びレッチング

治療歴のある局所進行性又は転移性の胆管癌

安全性プロファイルの要約

最もよくみられた副作用は、疲労（43%）、悪心（42%）、腹痛（35%）、下痢（35%）、食欲減退（24%）、腹水（23%）、嘔吐（23%）、貧血（19%）及び発疹（15%）であった。

最もよくみられた重篤な副作用は、腹水（2%）、高ビリルビン血症（2%）及び胆汁うっ滞性黄疸（2%）であった。

本剤を投与した患者では、副作用による本剤の投与中止の割合は 2%であった。本剤の投与中止に至った副作用は、腹水（1%）及び高ビリルビン血症（1%）であった。

副作用による本剤の休薬の割合は 16%であった。本剤の休薬に至った最もよくみられた副作用は、高ビリルビン血症（3%）、アラニンアミノトランスフェラーゼ増加（3%）、アスパラギン酸アミノトランスフェラーゼ増加（3%）、腹水（2%）及び疲労（2%）であった。

副作用による本剤の減量の割合は 4%であった。本剤の減量に至った副作用は、心電図 QT 延長（3%）及び末梢性ニューロパチー（1%）であった。

副作用の一覧

副作用の発現頻度は、治療歴のある局所進行性又は転移性の胆管癌患者 123 例を本剤群に無作為に割り付け、1 日 1 回 500 mg を投与した AG120-C-005 試験の結果に基づく。本剤の投与期間の中央値は 2.8 カ月（範囲 0.1～45.1 カ月）、平均値（標準偏差［SD］）は 6.7（8.2）カ月であった。

副作用の発現頻度は、あらゆる原因による有害事象の発現頻度に基づいているため、副作用の発現事象の割合には疾患、他剤又は関連のない原因など、本剤以外の原因が含まれている可能性

がある。

発現頻度は次のように、極めて高頻度（≥1/10）、高頻度（≥1/100～<1/10）、低頻度（≥1/1000～<1/100）、まれ（≥1/10000～<1/1000）、極めてまれ（<1/10000）と定義した。同一の発現頻度グループ内では、重篤なものから副作用を記載した。

表 3 - AG120-C-005 試験において本剤を投与した局所進行性又は転移性の胆管癌患者に報告された副作用（N=123）

MedDRA 器官別大分類	発現頻度	副作用
血液およびリンパ系障害	極めて高頻度	貧血
代謝および栄養障害	極めて高頻度	食欲減退
神経系障害	極めて高頻度	末梢性ニューロパチー、頭痛
胃腸障害	極めて高頻度	腹水、下痢、嘔吐、悪心、腹痛
肝胆道系障害	高頻度	胆汁うっ滞性黄疸、高ビリルビン血症
皮膚および皮下組織障害	極めて高頻度	発疹 [1]
一般・全身障害および投与部位の状態	極めて高頻度	疲労
	高頻度	転倒
臨床検査	極めて高頻度	アスパラギン酸アミノトランスフェラーゼ増加、血中ビリルビン増加
	高頻度	心電図 QT 延長、アラニンアミノトランスフェラーゼ増加、白血球数減少、血小板数減少

[1] グループ化した用語：発疹、斑状丘疹状皮疹、紅斑、斑状皮疹、全身性剥脱性皮膚炎、薬疹及び薬物過敏症

副作用の詳細（一部）

急性骨髄性白血病患者における分化症候群（4.2 及び 4.4 項を参照）

AG120-C-009 試験において本剤とアザシチジンを併用投与した未治療 AML 患者の 72 例のうち 14%に分化症候群が認められた。分化症候群が原因で本剤を中止した患者はいなかったが、少数の患者において徴候／症状の管理のため本剤の休薬が必要とされた（3%）。分化症候群が認められた 10 例のうち、治療後又は本剤の休薬後に全例が回復した。分化症候群の発症までの中央値は 20 日であった。分化症候群は、併用療法期間中において治療開始から早い患者で 3 日後から最長 46 日後までに発症した。

QTc 間隔延長（4.2、4.4、及び 4.5 項を参照）

AG120-C-009 試験において本剤とアザシチジンを併用投与した未治療 AML 患者 72 例のうち、21%に心電図 QT 延長が報告され、そのうち 11%が Grade 3 以上であった。ECG 解析に基づくと、本剤とアザシチジンを併用投与し、ベースライン後に ECG を 1 回以上評価した患者のうち 15%は QTc 間隔が 500 msec 超であり、24%は QTc がベースラインより 60 msec 超上昇した。心電図 QT 延長が原因で本剤を中止した患者は 1%、本剤を休薬した患者は 7%、本剤を減量した患者は 10%であった。本剤を投与した患者が QT 延長を発症するまでの中央値は 29 日であった。心電図

QT 延長は、治療開始から早い患者で 1 日後から最長 18 カ月後までに発症した。

AG120-C-005 試験において本剤を単剤投与した局所進行性又は転移性の胆管癌患者 123 例のうち、10%に心電図 QT 延長が報告され、そのうち 2%が Grade 3 以上であった。ECG 解析に基づくと、2%は QTc 間隔が 500 msec 超であり、5%は QTc がベースラインより 60 msec 超上昇した。徴候／症状を管理するために本剤の減量が必要であった患者は 3%であった。本剤を単剤投与した患者が QT 延長を発症するまでの中央値は 28 日であった。心電図 QT 延長は、治療開始から早い患者で 1 日後から最長 23 カ月後までに発症した。

特定の集団

肝機能障害

中等度及び重度の肝機能障害（Child-Pugh 分類 B 及び C）患者において本剤の安全性及び有効性は確立されていない。軽度の肝機能障害（Child-Pugh 分類 A）患者において副作用の発現率が高い傾向が認められた（4.2 及び 5.2 項を参照）。

疑わしい副作用の報告

承認後の疑わしい副作用の報告は重要である。本剤のベネフィットリスクバランスを継続的に監視することが可能となる。医療従事者はいかなる疑わしい副作用も各国の報告システム（別添 V 参照）から報告する。

4.9　過量投与

本剤を過量投与した場合、本剤に関連する副作用の増悪として毒性があらわれる可能性が高い（4.8 項を参照）。患者を密にモニタリングし、適切な支持療法を行う（4.2 及び 4.4 項を参照）。本剤の過量投与に対する特定の解毒剤はない。

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Company Core Data Sheet

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