Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Tibsovo

Active ingredient: Ivosidenib

Sponsor: Servier Laboratories (Aust) Pty Ltd

October 2023

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
AML	Acute myeloid leukemia(s)
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
AUC	Area under the plasma concentration time curve
AUC_{0-24}	Area under the plasma concentration time curve from 0 to 24 hours post dose
AUC_{0-inf}	Area under the plasma concentration time curve from time zero to infinity
AUC_{SS}	Area under the plasma concentration versus time curve at steady state
BCS	Biopharmaceutics Classification System
CCA	Cholangiocarcinoma
CI	Confidence interval
C_{max}	Maximum plasma concentration
CMI	Consumer Medicines Information
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DDI	Drug-drug interactions
dMMR	Mismatch repair deficiency
ECG	Electrocardiograph
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FDA	Food and Drug Administration (United States of America)
FOLFOX	Chemotherapy regimen, made up of folinic acid, 5-fluorouracil and oxaliplatin
IC_{50}	Half maximal inhibition
IDH	isocitrate dehydrogenase
IRC	Independent Review Committee
MedDRA	Medical Dictionary for Regulatory Activities
MSI-H	Microsatellite instability-high
NADPH	Nicotinamide adenine dinucleotide phosphate
OAT	Organic anion transporter
ORR	Objective response rate

Abbreviation	Meaning
OS	Overall survival
PBPK	Physiologically-based pharmacokinetic(s)
PD	Pharmacodynamic(s)
PFS	Progression-free survival
PI	Product Information
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)
PSUR	Periodic safety update report
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RMP	Risk management plan
TEAE	Treatment-emergent adverse event(s)
TGA	Therapeutic Goods Administration
ULN	Upper limit of normal
USA	United States of America

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Tibsovo
Active ingredient:	Ivosidenib
Decision:	Approved
Date of decision:	4 April 2023
Date of entry onto ARTG:[1]	5 April 2023
ARTG number:	391874
, *Black Triangle Scheme*	Yes
for the current submission:	This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	Servier Laboratories (Aust) Pty Ltd Level 4 Building 9, 588A Swan Street Burnley VIC 3121
Dose form:	Film-coated tablet
Strength:	250 mg
Container:	Bottle
Pack size:	60
Approved therapeutic use for the current submission:	*Tibsovo is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) R132 mutation after at least one prior line of systemic therapy.*
Route of administration:	Oral
Dosage:	Treatment should be initiated by a physician experienced in the use of anti-cancer therapies. Before taking Tibsovo, patients must have confirmation of an *IDH1* mutation using an appropriate diagnostic test, and an electrocardiogram (ECG) to assess heart rate-corrected QT (QTc) interval. The recommended dose of ivosidenib is 500 mg orally once daily until disease progression or unacceptable toxicity. For further information regarding dosage, including method of administration, monitoring, dose modifications for concomitant administration of strong CYP3A4 inhibitors, and dose

[1] Therapeutic goods must be entered in the Australian Register of Therapeutic Goods (ARTG) before they can be lawfully supplied in or exported from Australia, unless exempt from being entered in the ARTG, or otherwise authorised by the TGA. For further information visit: https://www.tga.gov.au/australian-register-therapeutic-goods.

	modifications for adverse reactions, refer to the Product Information.
Pregnancy category:	D
	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
	The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Servier Laboratories (Aust) Pty Ltd (the sponsor) to register Tibsovo (ivosidenib) 250 mg film-coated tablets supplied in a bottle for the following proposed indication:[2]

> *Tibsovo monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) mutation, who were previously treated by at least one prior line of systemic therapy.*

Condition

Cholangiocarcinoma (CCA) is a heterogeneous group of malignant cancers which may arise from the bile duct epithelium at any part of the biliary tree. It is broadly classified based on anatomical location as intrahepatic CCA or extrahepatic CCA, the latter incorporating perihilar CCA, or Klatskin tumours and distal CCA.[3,4]

Cholangiocarcinoma accounts for an estimated 3% of all gastrointestinal cancers globally,[3] and approximately 10% to 25% of all hepatobiliary malignancies (the second most common primary hepatic malignancy after hepatocellular carcinoma).[4] The incidence of CCA is higher in men than women, higher in people of Asian ethnicity, and increases with age, commonly presenting in the seventh decade and rarely occurring in those aged under 40 years.[4,5]

The substantial geographic and demographic variability of CCA incidence is generally ascribed to variation of risk factors, notably the endemicity of hepatobiliary flukes *Clonorchis sinensis* and

[2] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered on the Australian Register of Therapeutic Goods.

[3] Khan SA, et al. Cholangiocarcinoma: Epidemiology and risk factors. *Liver Int.* 2019. 39 Suppl 1:19-31. doi: 10.1111/liv.14095.

[4] Tyson GL, El-Serag HB. Risk factors for cholangiocarcinoma. *Hepatology.* 2011; 54: 173-84. doi: 10.1002/hep.24351.

[5] Mosadeghi S, et al. Sex-specific and race/ethnicity-specific disparities in cholangiocarcinoma incidence and prevalence in the USA: an updated analysis of the 2000-2011 Surveillance, Epidemiology and End Results registry. *Hepatol Res.* 2016; 46: 669–677. doi: 10.1111/hepr.12605.

Optisthorchis viverrini.[6] Other risk factors include choledochal cysts and other congenital fibrocystic liver disease, cholelithiasis and choledocholithiasis, liver cirrhosis, primary sclerosing cholangitis, hepatitis B and hepatitis C infection, inflammatory bowel disease, type 2 diabetes mellitus, alcohol, smoking and occupational exposure to organic solvents.[4,7,8] Many of the risk factors share an association with biliary stasis and chronic inflammation of the biliary epithelium. Whilst some of these may explain the global trend of increasing incidence,[9] cases outside of Asia remain predominantly sporadic, without any identifiable risk factor present.[10]

The incidence of CCA appears to have generally increased in Western countries over the last few decades,[4] though it remains rare in most parts of the world.[11] A notable outlier is Thailand, where infection with *O. viverrini* is a major public health issue, and rates of CCA are as high as 113 per 100,000 in men and 50 per 100,000 in women.[4] Increases in incidence of CCA in Australia have been attributed to migration from Southeast Asia and potentially to increased prevalence of primary sclerosing cholangitis.[12] CCA is still a rare condition in Australia, however, diagnosed in 771 people in Australia in 2013.[13]

The prognosis for CCA is poor due to the aggressive nature of the disease, typically advanced stage at diagnosis and lack of effective treatment options. Five-year disease-specific survival in Australia was 16% between 1998 and 2007.[12] Survival rates differ depending on stage (per the American Joint Committee on Cancer staging system)[14] at diagnosis, estimated to be 50%, 30%, 10% and 0% for stages I, II, III and IV, respectively.[15]

At least 4 genetic conditions (Lynch syndrome, *BRCA*-associated protein-1 (BAP1) tumour predisposition syndrome, cystic fibrosis, and biliary papillomatosis) are associated with an increased risk of developing CCA.[16] Of these, a medicine with a condition-specific approved

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[6] Kirstein MM, Vogel A. Epidemiology and Risk Factors of Cholangiocarcinoma. *Visc Med.* 2016;32:395-400. doi: 10.1159/000453013. Erratum in: *Visc Med.* 2017; 33(3): 226.

[7] Kubo S, et al. Screening and surveillance for occupational cholangiocarcinoma in workers exposed to organic solvents. *Surg Today.* 2016; 46: 705–712. doi: 10.1007/s00595-015-1229-9.

[8] Clements O, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: a systematic review and meta-analysis. *J. Hepatol.* 2020; 72: 95–103. doi: 10.1016/j.jhep.2019.09.007.

[9] Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. *Semin Liver Dis.* 2004; 24: 115-25. doi: 10.1055/s-2004-828889.

[10] Banales JM, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol.* 2020; 17: 557-588. doi: 10.1038/s41575-020-0310-z.

[11] Banales JM, et al. Expert consensus document: Cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). *Nat Rev Gastroenterol Hepatol.* 2016; 13: 261-80. doi: 10.1038/nrgastro.2016.51.

[12] Luke C, et al. Epidemiology of cancer of the liver and intrahepatic bile ducts in an Australian population. *Asian Pac J Cancer Prev.* 2010; 11: 1479-85.

[13] Australian Institute of Health and Welfare (AIHW) 2017. Australian Cancer Incidence and Mortality (ACIM) books: Gallbladder and extrahepatic bile duct cancer. Canberra: AIHW. <http://www.aihw.gov.au/acim-books>.

[14] The American Joint Committee on Cancer (AJCC) staging system, better known as the TNM Staging System is a widely used cancer staging system, developed and maintained by the AJCC and the Union for International Cancer Control (UICC). The TNM Staging System is based on the extent of the tumour (T), extent of spread to lymph nodes (N) and presence of metastasis. The T category describes the original (primary) tumour: TX = Primary tumour cannot be evaluated; T0 = No evidence of primary tumour; Tis = Carcinoma in situ (early cancer that has not spread to neighbouring tissue); T1 to T4: Size and/or extent of the primary tumour. The N category describes whether or not the cancer has reached nearby lymph nodes: NX = Regional lymph nodes cannot be evaluated; N0 = No regional lymph node involvement (no cancer found in the lymph nodes); N1 to N3 = Involvement of regional lymph nodes (number and/or extent of spread). The M category tells whether there are distant metastases (spread of cancer to other parts of the body): M0 = No distant metastasis (cancer has not spread to other parts of the body); M1 = Distant metastasis (cancer has spread to distant parts of the body).

[15] Valle JW, et al. New Horizons for Precision Medicine in Biliary Tract Cancers. Cancer Discov. 2017; 7: 943-962. doi: 10.1158/2159-8290.CD-17-0245.

[16] Garikipati SC, Roy P. Biliary Tract Cholangiocarcinoma. (Updated 2022 May 2)]. In: StatPearls (Internet). Treasure Island (FL): StatPearls Publishing; 2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK560708/.

indication is only available for Lynch syndrome-related CCA (mismatch repair deficiency (dMMR), with its phenotypic corollary (microsatellite instability-high (MSI-H)) being the underlying abnormality in Lynch syndrome).[17]

As molecular profiling techniques have emerged, including next-generation sequencing, 'actionable' mutations (against which targeted drugs have been developed) in the isocitrate dehydrogenase (*IDH1* and *IDH2*), *FGFR2*, *BRAF*, and *HER2*/neu genes have been identified in CCA and gallbladder cancer.[18]

Mutations of *IDH* occur in around 10% of CCA overall, and the prevalence is much higher in intrahepatic CCA (13%) than extrahepatic CCA (less than 1%).[19] Of interest, the prognostic value of *IDH1* mutation does not appear to be consistent across cancer types: in glioma, *IDH1* mutations are associated with vastly improved survival times, in the order of double to triple the survival duration.[20] In contrast, most studies have found no significant association between *IDH1* mutation and prognostic outcomes in CCA.[19] The natural history of CCA similarly does not appear to differ significantly between CCA with or without an *IDH* mutation.[21]

Current treatment options

Surgical resection can be undertaken for the fraction (as low as 10%) of patients with CCA who do not present with advanced stage disease, and is curative in only half of cases.[6, 22]The majority of CCA tumours are diagnosed at an advanced stage, for which no curative therapies are currently available, and which is associated with a median overall survival (OS) of 12 to 15 months and a 5-year survival rate of less than 5% with standard therapy.[23,24,25]

Standard-of-care first line systemic treatment of advanced (unresectable or metastatic) CCA (for tumours without specific genetic aberrations) consists of combination chemotherapy with gemcitabine and cisplatin.[26] This regimen has been associated with objective response rates (ORR) of around 20 to 26%,[24,25] in populations that had a median progression-free survival (PFS) of 8.4 months (95% confidence interval (CI): 5.9, 8.9) and median OS duration of 15.4 months (95% CI: 11.1, 17.9).[27]

[17] Australian Product Information (PI) for pembrolizumab (Keytruda). Last updated 17 November 2022. Available from the TGA website.

[18] Zori AG, et al. Advances in the management of cholangiocarcinoma. *World J Hepatol.* 2021; 13: 1003-1018. Doi: 10.4254/wjh.v13.i9.1003.

[19] Boscoe AN, et al. Frequency and prognostic significance of isocitrate dehydrogenase 1 mutations in cholangiocarcinoma: a systematic literature review. *J Gastrointest Oncol.* 2019; 10: 751-765. Doi: 10.21037/jgo.2019.03.10.

[20] Yan H, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med.* 2009;360:765-73. Doi: 10.1056/NEJMoa0808710.

[21] Goyal L, et al. Prognosis and Clinicopathologic Features of Patients With Advanced Stage Isocitrate Dehydrogenase (IDH) Mutant and IDH Wild-Type Intrahepatic Cholangiocarcinoma. *Oncologist.* 2015; 20: 1019-27. doi: 10.1634/theoncologist.2015-0210.

[22] Nathan H, et al. Trends in survival after surgery for cholangiocarcinoma: a 30-year population-based SEER database analysis. *J Gastrointest Surg.* 2007; 11: 1488-96; discussion 1496-7. doi: 10.1007/s11605-007-0282-0.

[23] Bridgewater J, et al. Quality of life, long-term survivors and long-term outcome from the ABC-02 study. *Br J Cancer.* 2016; 114: 965-71. doi: 10.1038/bjc.2016.64.

[24] Okusaka T, et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. *Br J Cancer*. 2010; 103: 469–474. doi: 10.1038/sj.bjc.6605779.

[25] Valle J, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010; 362: 1273–1281. DOI: 10.1056/NEJMoa0908721.

[26] Cancer Institute NSW (New South Wales Government). eviQ guidelines: Pancreas and biliary list of regimens. Accessed 12 April 2022. Available at: https://www.eviq.org.au/medical-oncology/upper-gastrointestinal/pancreas-and-biliary.

[27] Lamarca A, et al. Advanced Intrahepatic Cholangiocarcinoma: Post Hoc Analysis of the ABC-01, -02, and -03 Clinical Trials. *J Natl Cancer Inst.* 2020; 112: 200-210. doi: 10.1093/jnci/djz071.

After progression of disease on first-line chemotherapy (in agreement with the National Comprehensive Cancer Network (USA) guidelines),[28] eviQ recommends a modified FOLFOX regimen (folinic acid, 5-fluorouracil and oxaliplatin) [29] for patients with ECOG Performance Status 0 or 1,[30,31] based on the ABC-06 trial, in which treatment with FOLFOX increased survival time compared to active symptom control (median OS of 6.2 versus 5.3 months, respectively).[32] Only a fraction (15 to 25%)[33] of patients are expected to be fit enough to qualify. The ORR with second-line chemotherapy in a molecularly unselected population of 761 patients with advanced biliary tract cancers was 7.7% (95% CI: 4.6, 10.9), in association with a median PFS of 3.2 months (95% CI: 2.7, 3.7) and median OS of 7.2 months (95% CI: 6.2, 8.2).[34]

Beyond second line, there is no high-level evidence to support the use of systemic treatment in clinical practice.[35]

Until recently, there were no products on the Australian Register of Therapeutic Goods (ARTG) with a registered indication specifically for the treatment of CCA; the use of the chemotherapeutics that are considered standard-of-care remains off-label in Australia.

For patients with dMMR or MSI-H CCA, pembrolizumab may be used, as it was granted provisional approval by TGA in July 2019 for advanced MSI-H/dMMR solid tumours for which no suitable alternative treatment options are available.[36] Similarly, entrectinib (in May 2020) and larotrectinib (in September 2020) have each been granted provisional approval by TGA for advanced *NTRK*-positive solid tumours for which no suitable alternative treatment options are available.[37,38] In the last 18 months, infigratinib (in November 2021) and pemigatinib (in

[28] National Comprehensive Cancer Network (NCCN) guidelines for biliary tract cancers. Version 3.2022, dated 14 October 2022. Accessed 7 December 2022 at https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pd.

[29] eviQ is a free online resource of cancer treatment protocols developed by multidisciplinary teams of cancer specialists for the Australian clinical context.

[30] ECOG Performance Status: The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following definitions are used: Status 0 = Fully active, able to carry on all pre-disease performance without restriction; Status 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work; Status 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; Status 3 = Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; Status 4 = Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair; Status 5 = Death.

[31] Cancer Institute NSW (New South Wales Government). eviQ guidelines: Biliary and gallbladder advanced FOLFOX6 (modified) (fluorouracil leucovorin oxaliplatin). Accessed 12 April 2022. Available at: https://www.eviq.org.au/medical-oncology/upper-gastrointestinal/pancreas-and-biliary/3875-biliary-and-gallbladder-advanced-folfox6-mod#indications-and-patient-population.

[32] Lamarca A, et al. Advanced Biliary Cancer Working Group. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *Lancet Oncol.* 2021; 22: 690-701. doi: 10.1016/S1470-2045(21)00027-9.

[33] Brieau B, et al. Second-line chemotherapy for advanced biliary tract cancer after failure of the gemcitabine-platinum combination: A large multicenter study by the Association des Gastro-Entérologues Oncologues. *Cancer.* 2015; 121: 3290-7. doi: 10.1002/cncr.29471.

[34] Lamarca A, et al. Second-line chemotherapy in advanced biliary cancer: a systematic review. *Ann Oncol.* 2014; 25: 2328-2338. doi: 10.1093/annonc/mdu162.

[35] Salati M, et al. IDH Signalling Pathway in Cholangiocarcinoma: From Biological Rationale to Therapeutic Targeting. *Cancers (Basel)*. 2020; 12: 3310. doi: 10.3390/cancers12113310.

[36] TGA registration short summary webpage: https://www.tga.gov.au/resources/prescription-medicines-registrations/keytruda-merck-sharp-dohme-australia-pty-ltd-5.

[37] Australian Product Information for entrectinib (Rozlytrek). Last updated 25 March 2022. Available from TGA website.

[38] Australian Product Information for larotrectinib (Vitrakvi). Last updated 20 September 2022. Available from TGA website.

September 2022) have each been granted provisional approval by TGA for the treatment of CCA harbouring a fibroblast growth factor receptor 2 (*FGFR2*) fusion or other rearrangement.[39,40]

The National Comprehensive Cancer Network (USA) guideline includes ivosidenib as 'useful' in the second line for CCA with *IDH1* mutations based on Study AG120-C-005,[28] and ivosidenib is registered in the United States of America (USA) for this indication, as well as for patients with acute myeloid leukaemia harbouring a susceptible *IDH1* variant.

Isocitrate dehydrogenase 1 in cancer

Ivosidenib is an inhibitor of certain mutant alleles of the *IDH1* gene. The gene product of *IDH1* is a cytosolic and peroxisomal enzyme with a central role in cellular metabolism (including glucose sensing), epigenetic regulation, cellular redox homeostasis, and DNA repair.[41] IDH1 catalyses the oxidative decarboxylation of isocitrate to α-ketoglutarate as part of the Krebs cycle in glucose metabolism, generating carbon dioxide and reduced nicotinamide adenine dinucleotide phosphate (NADPH) in the process.[42] IDH1 is a key source of cellular NADPH generation in most tissues, and NADPH and α-ketoglutarate both function in cellular responses to oxidative stress.[43] It is rational, therefore, that loss of function of IDH1 could impair cellular detoxification and be associated with DNA damage and genome instability.

Mutations of the *IDH1* gene were first described in 2006 amongst 189 genes that were mutated with significant frequency across a set of 22 human breast and colorectal carcinomas.[44] Subsequent studies have revealed the presence of mutations in either *IDH1* or its mitochondrial counterpart *IDH2*, in over 70% of Grade II to III gliomas and secondary glioblastomas,[45] approximately 75% of diffuse astrocytomas and oligodendroglial tumours, 20% of acute myeloid leukemias (AML), 50% of chondrosarcomas, 20% of intrahepatic CCA and 20% of angioimmunoblastic T-cell lymphoma.[46] Cancer-associated mutation of *IDH1* is almost always a missense mutation in the arginine 132 codon leading to a single amino acid substitution in the active site.[47] In CCA, the most common substitution (approximately 60%) is for cysteine, that is, R132C.[19] In contrast, in gliomas R132H is predominant.[48]

[39] Australian Product Information for infigratinib (Truseltiq). Last updated 5 November 2021. Available from TGA website.
[40] Australian Product Information for pemigatinib (Pemazyre). Last updated 14 September 2022. Available from TGA website.
[41] Crispo F, et al. IDH1 Targeting as a New Potential Option for Intrahepatic Cholangiocarcinoma Treatment-Current State and Future Perspectives. *Molecules.* 2020; 25: 3754. doi: 10.3390/molecules25163754.
[42] Dang L, et al. IDH mutations in cancer and progress toward development of targeted therapeutics. *Ann Oncol.* 2016; 27: 599-608. doi: 10.1093/annonc/mdw013.
[43] Reitman ZJ, Yan H. Isocitrate dehydrogenase 1 and 2 mutations in cancer: alterations at a crossroads of cellular metabolism. *J Natl Cancer Inst.* 2010; 102: 932-41. doi: 10.1093/jnci/djq187.
[44] Sjoblom T, et al. The consensus coding sequences of human breast and colorectal cancers. *Science.* 2006; 314: 268-74. doi: 10.1126/science.1133427.
[45] Yan H, et al. Mutant metabolic enzymes are at the origin of gliomas. *Cancer Res.* 2009; 69(24): 9157-9. doi: 10.1158/0008-5472.CAN-09-2650.
[46] Pusch S, et al. D-2-Hydroxyglutarate producing neo-enzymatic activity inversely correlates with frequency of the type of isocitrate dehydrogenase 1 mutations found in glioma. *Acta Neuropathol Commun.* 2014; 2: 19. doi: 10.1186/2051-5960-2-19.
[47] Waitkus MS, et al Biological Role and Therapeutic Potential of IDH Mutations in Cancer. *Cancer Cell.* 2018; 34: 186-195. doi: 10.1016/j.ccell.2018.04.011.
[48] Duncan CG, et al. A heterozygous IDH1R132H/WT mutation induces genome-wide alterations in DNA methylation. *Genome Res.* 2012; 22: 2339-55. doi: 10.1101/gr.132738.111.

Across cancers, mutations of *IDH1* and *IDH2* share the following biochemical features:[49]

- They are predominantly somatic or rarely germline.
- They rarely co-occur.
- They are almost always missense mutations of one of three residues in the catalytic site (R132 in *IDH1*, the corresponding R172 in *IDH2*, or R140X in *IDH2*), consistent with a direct impact on enzyme function.
- They are always heterozygous, consistent with gain of function and with dominance over the remaining wild-type allele.

The presence of *IDH* mutations in a very specific set of cancers (for example, seen frequently in Grade 2 and-3 gliomas and secondary glioblastomas, but not in primary glioblastoma, and frequently in cytogenetically normal AML, but not in other sub-types of AML), and the fact that they occur at an early stage of tumorigenesis led to the hypothesis that *IDH* mutations may impair cell fate determination and differentiation.[49]

In vitro, tumour-derived mutant IDH was found to exhibit a loss of normal catalytic function.[50] Subsequently, it was demonstrated that *IDH* mutations also lead to simultaneous gain of a new, pathological function.[51] The neomorphic activity of the mutant IDH enzymes reduces α-ketoglutarate to a structurally similar compound, the D-enantiomer of 2-hydroxyglutarate, consuming NADPH in the process.[42]

2-hydroxyglutarate is widely referred to as an 'oncometabolite', and has been found to be elevated in patients with several tumour types, including solid and haematological malignancies.[42,52] It has no known physiological function in mammals, but occurs at low levels (less than 300 μM) as a product of metabolic error, and is rapidly converted by 2-hydroxyglutarate-dehydrogenase back to α-ketoglutarate.[42] In the presence of IDH mutation, this clearance mechanism is overwhelmed by the supraphysiological levels of 2-hydroxyglutarate generated by neomorphic IDH activity.[47] 2-hydroxyglutarate thereby accumulates to millimolar concentrations, becoming one of the most abundant metabolites in affected cells.[42]

As 2-hydroxyglutarate competitively inhibits α-ketoglutarate-dependent enzymes, including histone and DNA demethylases, its accumulation produces widespread epigenetic dysregulation, including of genes involved in cell differentiation and survival.[41,42,53,54] Impedance of cellular differentiation is believed to be the major tumorigenic mechanism of *IDH* mutation, and is thought to occur early in the process of malignant transformation.[42] However, elevation of 2-hydroxyglutarate and the attendant genetic instability has also been implicated in dysregulation of epithelial-mesenchymal transition and thus propensity to development of metastasis in colorectal cancer specimens.[52]

[49] Yang H, et al. IDH1 and IDH2 mutations in tumorigenesis: mechanistic insights and clinical perspectives. *Clin Cancer Res.* 2012; 18: 5562-71. doi: 10.1158/1078-0432.CCR-12-1773.

[50] Zhao S, et al. Glioma-Derived Mutations in IDH1 Dominantly Inhibit IDH1 Catalytic Activity and Induce HIF-1alpha. *Science.* 2009; 324: 261-5. doi: 10.1126/science.1170944.

[51] Dang L, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature.* 2009; 462: 739–744. https://doi.org/10.1038/nature09132.

[52] Colvin H, et al. Oncometabolite D-2-Hydroxyglurate Directly Induces Epithelial-Mesenchymal Transition and is Associated with Distant Metastasis in Colorectal Cancer. *Sci Rep.* 2016; 6: 36289. doi: 10.1038/srep36289.

[53] Xu W, et al. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of α-ketoglutarate-dependent dioxygenases. *Cancer Cell.* 2011; 19: 17-30. doi: 10.1016/j.ccr.2010.12.014.

[54] Turcan S, et al. IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. *Nature.* 2012; 483: 479-83. doi: 10.1038/nature10866.

Though it is clear that accumulated intracellular 2-hydroxyglutarate has the potential to lead to neoplastic development, a specific mechanism by which reduction of 2-hydroxyglutarate levels are expected to cause tumour regression once cancer has developed has not been proposed.

Of note, 2-hydroxyglutarate elevation has been reported to occur in other cancers such as breast and colon cancer in the absence of *IDH* mutation, through glutamine anaplerosis.[52,55] Elevated 2-hydroxyglutarate levels leading to widespread genetic dysregulation and neoplastic transformation may therefore not be unique to cancers harbouring an *IDH1* mutation, confounding the usefulness of 2-hydroxyglutarate as a biomarker.

The clinical development of ivosidenib commenced in AML, rather than CCA, so whilst this priority application focusses on the CCA indication, aspects are reliant on data generated from studies in AML patients (for example, aspects of clinical pharmacology).

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.[56]

This product received orphan drug designation on 29 April 2022 for the following indication:

> *Tibsovo monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) mutation, who were previously treated by at least one prior line of systemic therapy*

At the time the TGA considered this submission, a similar submission had been approved in the United States of America on 25 August 2021 for the following indication:

> *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 (14.3))*

A similar submission was under consideration in the European Union (submitted on 3 March 2022).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the priority registration process.

[55] Terunuma A, et al. MYC-driven accumulation of 2-hydroxyglutarate is associated with breast cancer prognosis. *J Clin Invest.* 2014; 124: 398-412. doi: 10.1172/JCI71180.

[56] In August 2022 the sponsor submitted a separate submission for Tibsovo (ivosidenib) for the treatment of leukaemia. Evaluation of this submission proceeded by the standard pathway. The indication for the treatment of acute myeloid leukaemia was registered on the ARTG on 20 September 2023.

Table 1: Timeline for Submission PM-2022-02134-1-4

Description	Date
Designation (Orphan)	29 April 2022
Submission dossier accepted and first round evaluation commenced	1 August 2022
Second round evaluation completed	21 December 2022
Delegate's Overall benefit-risk assessment	31 March 2023
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	4 April 2023
Administrative activities and registration on the ARTG completed	5 April 2023
Number of working days from submission dossier acceptance to registration decision*	136

*Target timeframe for priority submissions is 150 working days from acceptance for evaluation to the decision.

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Relevant guidelines or guidance documents referred to by the Delegate are listed below:

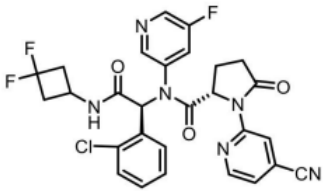
- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), ICH Guideline S9 on Nonclinical Evaluation for Anticancer Pharmaceuticals, EMA/CHMP/ICH/646107/2008, May 2010.
- Food and Drug Administration (FDA), Guidance for Industry, Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling, May 2003.

Quality

Ivosidenib is a white to light yellow solid, practically insoluble in aqueous solutions and variably soluble in organic solvents. Ivosidenib is a BCS Class II compound (low solubility, high permeability).[57] Ivosidenib has the structure and chemical name as described in Figure 1 below.

[57] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

Figure 1: Structure and chemical name of ivosidenib



Chemical name: (2S)-N-{(1S)-1-(2-chlorophenyl)-2-[(3,3-difluorocyclobutyl)amino]-2-oxoethyl}-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide

Molecular formula: C28H22ClF3N6O3 (MW 583.0)

Ivosidenib is produced by chemical synthesis. The specifications are sufficient to ensure the quality and consistency. The drug substance will be stored in double low-density polyethylene bags placed inside an aluminium foil bag. The aluminium foil bag is placed into a high-density polyethylene drum and closed. The stability of ivosidenib has been demonstrated when stored at 30°C and 65% relative humidity in the proposed container closure system.

The drug product contains 250 mg of the active substance as well as excipients that are conventional for a tablet dosage form. The tablet is film-coated, oval, blue, debossed with 'IVO' on one side and '250' on the other side. The approximate tablet dimensions are length of 18.0 mm and width of 8.4 mm.

The tablets will be supplied in a high-density polyethylene bottle with a polypropylene child resistant closure and induction seal. Each bottle will contain 60 film-coated tablets and a silica gel desiccant canister. The bottle will be contained in a cardboard box.

The proposed labelling is considered acceptable.

The finished product specifications are sufficient to ensure the quality of the product at release and throughout the shelf life. A shelf life of 60 months, stored below 30°C, is supported by the stability data.

Chemistry and quality control aspects were found to be acceptable. Approval is recommended from a pharmaceutical chemistry perspective.

Nonclinical

The submitted nonclinical dossier was compliant with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline[58,59] and of high overall quality. All pivotal safety-related studies were Good Laboratory Practice-compliant.[60]

In biochemical and cell-based assays, ivosidenib inhibited a variety of IDH1 R132 mutants (R132C, R132G, R132H, R132S and R132L; with concentrations of drug that achieved half maximal inhibition (IC_{50}) of 2 to 17 nM) at much lower concentrations than wild-type IDH1 and

[58] The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together regulatory authorities and the pharmaceutical industry. It makes recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration.

[59] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), ICH Guideline S9 on Nonclinical Evaluation for Anticancer Pharmaceuticals, EMA/CHMP/ICH/646107/2008, May 2010.

[60] Good Laboratory Practice is a code of standards following the International Council on Harmonisation (ICH) relevant to testing of medicines in laboratories during drug development.

reduced 2-hydroxyglutarate concentrations at IC_{50} values of 2 to 20 nM, which is below the unbound clinical minimum plasma concentration of 554 nM.[61]

Ivosidenib induced cellular differentiation in a human erythroleukaemia cell line and in primary patient-derived AML blast cells expressing IDH1 R132C or R132H in *ex vivo* culture. *In vivo* studies included mouse patient-derived xenograft models of IDH1-mutant AML (expressing IDH1 R132H or R132C) and cholangiocarcinoma (expressing IDH1 R132C). Inhibition of 2-hydroxyglutarate with ivosidenib in primary human AML cells in this model promoted the induction of differentiation *in vivo*, however, this was not associated with a reduction in disease burden or increased survival. Overall, the nonclinical studies are consistent with the proposed mechanism of action but did not provide nonclinical evidence of tumour regression or survival benefit.

No significant off-target activity is anticipated based on secondary pharmacodynamic screening studies against a panel of 80 receptors, ion channels and enzymes. Ivosidenib had no significant activity against wild-type or mutant IDH2 R140Q but inhibited wild-type IDH1 at subclinical exposures (exposure ratio based on AUC of 0.6) in mice bearing HCT116 xenograft tumours. Inhibition of wild type IDH1 is of possible clinical relevance. In the repeat-dose toxicity studies, target organs in animals were identified as the liver, haematopoietic system, gastrointestinal system and kidney, and are of high or likely clinical relevance.

Ivosidenib crosses the blood-brain barrier in animals and is primarily (98%) metabolised by CYP3A4[62]. No unique human metabolites of ivosidenib were observed.

Based on *in vitro* data, ivosidenib weakly inhibits CYP2C8, CYP2C19, CYP2D6, and CYP3A4/5 (IC_{50} values over 50 µM), but not CYP1A2, CYP2B6, or CYP2C9. Ivosidenib also inhibits OAT3, OATP1B1, OATP1B3 and P-glycoprotein *in vitro*, but not BCRP, OAT1 or organic cation transporter 2. Ivosidenib induces CYP2B6, CYP2C8, CYP2C9, and CYP3A4, but not CYP1A2. Ivosidenib is a substrate for P-glycoprotein but not a substrate for BCRP or hepatic transporters OATP1B1 and OATP1B3.

Based on *in vitro* data, ivosidenib has a moderate potential to inhibit hERG channels (IC_{50} of 12.6 µM; exposure ratio based on the maximum plasma concentration (C_{max}) is 15). Consistent with clinical findings-ivosidenib treatment in monkeys was associated with prolonged QT interval[63] and QT interval corrected for heart rate (QTc)[64] using Bazett's formula, most likely due to hERG channel inhibition. Ivosidenib-related ventricular bigeminy was also observed in monkeys, with no underlying mechanism identified.

[61] Based on MW of 583, geometric mean Cmax and Cmin (Study AG120-C-001) was 5,990 ng/mL (10,300 nM) and 4,250 ng/mL (7,290 nM), respectively. Assuming 92% protein binding, the unbound Cmax and Cmin are 479.2 ng/mL (822 nM) and 340 ng/mL (583 nM), respectively.

[62] Cytochrome P450 (CYP) enzymes: CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds. Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

[63] The QT interval is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.

[64] The corrected QT interval (QTc) estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.

Embryofetal toxicity included increased post-implantation loss (rabbits) and decreased fetal weight associated with developmental variations in both species. In rabbits, but not in rats, adverse fetal findings were most likely secondary to maternal toxicity. Pregnancy Category D is considered appropriate based on the finding of embryofetal lethality in rabbits at a low exposure.[65]

Ivosidenib showed no genotoxic potential: it was not mutagenic in the bacterial mutation assay or clastogenic *in vitro* (in human lymphocytes) or *in vivo* (in the rat micronucleus test). No carcinogenicity studies were conducted, which is considered acceptable given the proposed indication for use. The proposed clinical formulation of ivosidenib, including the excipient hypromellose acetate succinate, does not pose a potential for phototoxicity.

The proposed specifications for impurities or degradants in the drug substance are below the ICH qualification thresholds.

The nonclinical evaluation concluded that based on the review of the nonclinical data, there was no objections to the registration of ivosidenib.

Clinical

Summary of clinical studies

The clinical dossier consisted of:

- six Phase I studies
  - Study AG120-C-002, an open label dose escalation and expansion, safety, pharmacokinetics (PK), pharmacodynamics (PD) and clinical activity study of oral ivosidenib in *IDH1* mutation advanced solid tumours
  - Study AG120-C-003, an open label study to investigate the absorption, metabolism, and excretion of [^{14}C] ivosidenib following single oral dose administration in healthy male participants
  - Study AG-120-004, an open label, randomised, two-period crossover study to evaluate the effect of food on ivosidenib PK following single oral dose administration to healthy patients
  - Study AG-120-006, a single dose, open label study to evaluate the PK and safety of ivosidenib in healthy male Japanese patients relative to healthy male Caucasian patients
  - Study AG120-C-007, an open label, 2-period, fixed sequence study to determine the effect of multiple oral doses of itraconazole on the single dose PK of ivosidenib in healthy adult patients
  - Study AG120-C-012, an open label, single dose study to evaluate the PK, safety, and tolerability of ivosidenib in patients with mild or moderate hepatic impairment or normal hepatic function

[65] Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

- one Phase III study: Study AG120-C-005 (also known as the ClarIDHy trial), a randomised, double blind, placebo controlled study of ivosidenib in previously treated advanced *IDH1* mutation cholangiocarcinoma.

Pharmacology

Formulation

The commercial product intended for marketing only differs from the clinical product used in the pivotal study (Study AG120-C-005) by the addition of a debossed product identifier ('IVO' on one side of the tablet and '250' on the opposite side). Comparative dissolution studies between non-debossed clinical lots and debossed proposed commercial lots demonstrated the debossing does not impact product performance.

Dose selection

Studies AG120-C-001 and AG120-C-002

The dose used in the pivotal study (500 mg daily) was previously studied in early phase studies Study AG120-C-001 (dose escalation and expansion in patients with advanced *IDH1*-positive haematological malignancies), and Study AG120-C-002 (dose escalation and expansion in patients with advanced *IDH1*-positive solid tumours).

Study AG120-C-001 was a Phase I, multicentre, open label, dose escalation and expansion study of ivosidenib in patients with advanced haematologic malignancies harbouring an *IDH1* mutation. The study included a dose escalation phase utilising a standard 3+3 design[66] to determine the maximum tolerated dose and/or recommended Phase II dose followed by expansion arms to further evaluate the chosen dose. Dose-limiting toxicities in this study were defined as all non-haematological toxicities of Grade 3 or above according to Common Terminology Criteria (CTCAE)[67,68] and either prolonged myelosuppression with the persistence of Grade 4 neutropenia or thrombocytopenia in the absence of leukemia (blast count less than 5%) at least 42 days after the initiation of Cycle 1 therapy. A dose was to be considered above the maximum tolerated dose if 2 or more subjects in a cohort receiving that dose experienced dose-limiting toxicities during the first cycle. Specific guidelines were included in Study AG120-C-001 for the management of QT prolongation and suspected differentiation syndrome.

Study AG120-C-002 was a similar study of ivosidenib in patients with advanced solid tumours, including glioma, harbouring an *IDH1* mutation. The study incorporated a 3+3 dose escalation phase to determine the maximum tolerated dose in solid tumours and/or the recommended Phase II dose followed by expansion in a range of *IDH1*-mutated solid tumours. Dose escalation in glioma was undertaken in a separate cohort to non-glioma solid tumours.

Both studies explored doses from 100 mg twice daily to 1,200 mg daily. The initial cohort in each study received twice daily dosing, however based on the emerging PK data, subsequent cohorts received daily dosing. Across the evaluated dose range, plasma levels of ivosidenib generally

[66] The 3+3 design has dose escalation and stopping rules suited to Phase I cancer clinical trials. The study begins with the first 3 patients given a dose considered to be safe based on animal toxicological data. If none of the three patients experiences a dose-limiting toxicity, another 3 patients will be treated at the next higher dose level.
[67] The Common Terminology Criteria (CTC) is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is Grade 1 – Mild, Grade 2 – Moderate, Grade 3 – Severe, Grade 4 - Life threatening, Grade 5 – Death.
[68] National Cancer Institute (U.S.). Common Terminology Criteria for Adverse Events: (CTCAE). V4.03 ed. Bethesda Md: U.S. Department of Health and Human Services; 2010. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

increased less than dose proportionally, with overlapping exposures with daily doses from 500 to 800 mg suggesting a plateauing of exposure above 500 mg daily.

A daily ivosidenib dose of 500 mg was associated with decreased 2-hydroxyglutarate levels in plasma (and in haematology patients, in bone marrow). Although sample size precluded statistical comparison, there did not appear to be additional reduction in plasma 2-hydroxyglutarate levels at doses above500 mg once daily, while there was some suggestion that doses below 500 mg once daily could be associated with lower levels of 2-hydroxyglutarate inhibition.

In Study AG120-C-001, dose-limiting toxicities of Grade 3 rash and Grade 3 QT prolongation were observed in the 1,200 mg daily and 800 mg daily cohorts, respectively, however, expansion of these dose cohorts did not result in identification of a maximum tolerated dose. No dose-limiting toxicities were reported in Study AG120-C-002. Amongst all cancer patients receiving 500 mg daily, dose interruptions were common in both studies (39% of 228 patients in Study AG120-C-001 (data cut-off 2 November 2018) and 19% of 130 patients in Study AG120-C-002), while dose reductions were uncommon (4.4% and 3.8%, respectively). Permanent discontinuation due to adverse events (AE) was common in Study AG120-C-001 at the 500 mg daily dose (13% of 179) but was rare in Study AG120-C-002 at any dose (1.2% of 168).

In total, there were 73 patients with CCA treated across both portions of Study AG120-C-002, 62 of whom received ivosidenib at a dose of 500 mg daily. Most had an *IDH1* R132C variant. Four partial responses were seen: one in a patient who received ivosidenib 300 mg daily and three in patients who received 500 mg daily.

A 500 mg daily dose was chosen as the recommended Phase II dose for further study, based on:

- the PK profile supporting daily dosing and indicating plateauing of exposure above 500 mg
- the PD data suggesting no additional reduction in plasma 2-hydroxyglutarate levels at doses above 500 mg daily
- no dose-limiting toxicities at the 500 mg daily dose
- tumour responses amongst CCA patients at the 500 mg daily dose.

Pharmacokinetics

Summary of pharmacokinetics

The PK of ivosidenib across indications, including in CCA, are summarised in the approved FDA label.[69] Selected PK parameters for ivosidenib in CCA patients are reflected below.

Absorption:

- Biopharmaceutics Classification System (BCS): Class II (low solubility, high intestinal permeability).
- Absolute bioavailability: not determined.
- Median time to reach C_{max}: 2.6 hours following a single dose, 2.1 hours with multiple doses.

Distribution

- Plasma protein-bound fraction: 92-96%

[69] FDA label for ivosidenib (Tibsovo), revised May 2022. Available from FDA website.

- Mean steady-state volume of distribution (based on PopPK analysis): 222 L (coefficient of variation (CV) 26%)
- Steady-state exposure reached within 14 days
- With the proposed dosing regimen (500 mg daily), mean C_{max} was 4,547 ng/mL (29% CV) and mean area under the curve from 0 to 24 hours post dose (AUC_{0-24}) was 74,956 ng.hr/mL (33% CV)

Metabolism:

Ivosidenib is the predominant component (over 92%) of total radioactivity in plasma. Of the fraction that is metabolised, CYP3A enzymes are the primary catalysts. Ivosidenib induces CYP3A, so is an autoinducer.

Elimination

The mean (CV) apparent terminal half-life of ivosidenib at steady-state in CCA was 129 hours (102% CV), and the mean steady-state apparent clearance in CCA was 6.1 L/h (31% CV).[69] The apparent clearance at steady state increased with increasing dose: 3.45 L/h to 12.8 L/h across the 100 mg twice daily to 1,200 mg once daily dose range. Ivosidenib exposure increased less than proportionally to dose with single doses from 100 mg to 1,200 mg or with multiple doses from 100 mg twice daily to 1,200 mg once daily. Based on the mass balance study, 77% of the dose was recovered in the faeces (67% unchanged) and 17% of the dose was recovered in the urine (9% as unchanged).

Population pharmacokinetics

The clinical development of ivosidenib was conducted in AML prior to CCA, however, due to differences in the use of CYP3A-modifying concomitant medications (known to impact ivosidenib clearance) across cancer types, a dedicated CCA-specific population PK (PopPK) analysis was undertaken.

The main CCA PopPK analysis (Report AG120-C-002-005-PPK) included data from 229 patients with CCA (73 from Phase I Study AG120-C-002 and 159 from pivotal Phase III Study AG120-C-005) who had a median (range) age of 61 (32 to 83) years. Age, sex, race, ECOG Performance Status, concomitant acid-reducing medications (proton pump inhibitors and histamine H2 antagonists), mild hepatic impairment (n = 98) and mild (n = 76) or moderate (n = 27) renal impairment did not meaningfully affect ivosidenib PK. There was not a clear effect of moderate hepatic impairment. Further clinical data are expected to elucidate the effect of moderate or severe hepatic impairment, and severe renal impairment on PK. Body weight had a modest effect on derived steady-state peak concentration.

The CCA PopPK model was compared to one previously developed based on data from patients with advanced haematological malignancies who received ivosidenib in Study AG120-C-001. PK parameter estimates were similar across the 2 PopPK models. There was good agreement between structural PK parameters, except for apparent peripheral volume of distribution, which was three-fold higher in CCA (420 L versus 151 L). This explains the differing median terminal half-life at steady state (53.3 h in CCA versus 95.5 h in AML). The apparent clearance at steady state is about 60% higher, and AUC_{0-24} and C_{max} are about 30% lower in CCA than in AML. Relevantly, there was a higher incidence of concurrent CYP3A4 inhibitor use in AML: 10% in CCA versus 65% in AML. Additionally, concurrent inhibitors taken by patients with AML tended to be moderate or strong inhibitors, whilst those taken by patients with CCA were most likely to be mild. Covariate effects in the 2 models were also similar, with body weight and CYP3A4 inhibitors identified previously for Study AG120-C-001.

Pharmacokinetic interactions

Gastric pH

The aqueous solubility of ivosidenib is pH-independent as ivosidenib does not contain ionisable groups under physiological conditions.[70] The PopPK analysis did not identify acid-reducing medications as significant covariates affecting ivosidenib exposure. The most commonly used gastric pH modulators among the CCA PopPK population were omeprazole (20%) and ranitidine (8%).

Food effect

A high-fat meal increased ivosidenib C_{max} by 98% and area under the curve to infinity ($AUC_{0\text{-}inf}$) by 25% (Study AG120-C-004). The impact on exposure of administration with food other than a high-fat meal has not been established. The current proposed wording in the PI advises dosing can be with or without food, but not with a high-fat meal. As this was the dosing strategy studied in the pivotal trial, this is acceptable.

Drug-drug interactions

A physiologically-based PK (PBPK) model of ivosidenib was developed to assess the expected perpetrator (CYP induction and transporter inhibition) and victim (CYP inhibition or induction) drug-drug interaction potential for ivosidenib in patients with AML (Report AG120-C-001-PBPK-ADD1). The model was initially developed in healthy volunteers using *in vitro* and clinical data, then qualified using the clinical data from a clinical drug-drug interaction study (Study AG120-C-007). Auto-induction of CYP3A was then incorporated and the model was qualified using observed data from Study AG120-C-001, conducted in AML patients.

The model adequately predicted exposure at the 500 mg dose level but at later time points underpredicted exposure with low doses (300 mg daily) and overpredicted exposure at high doses (800 mg and 1,200 mg daily). The observed and model-predicted effects of itraconazole on ivosidenib were also noted to be quite divergent. Whilst ketoconazole provided a better model, it has its own limitations, including non-linear PK.

Based on the similarities between the PopPK models in CCA and AML, the AML PBPK model is considered adequate to predict that regular dosing of ivosidenib at 500 mg daily is likely to impact CYP3A4 substrates and be impacted by CYP3A4 inhibitors or inducers in CCA, but may not accurately quantify the magnitude.

Drug-drug interactions (ivosidenib as victim)

Ivosidenib is mostly (98%) metabolised by CYP3A4, so this is the only CYP enzyme likely to be implicated in clinically meaningful drug-drug interactions affecting ivosidenib PK.

Cytochrome P450 3A4 enzyme inhibitors

Itraconazole (a strong CYP3A inhibitor) increased the exposure (based on AUC) of a single 250 mg dose of ivosidenib by 2.7-fold in healthy volunteers (Study AG120-C-007). There was no change in C_{max}.

In patients with AML, the PBPK model-based simulations predicted ivosidenib AUC (after multiple doses) to be unchanged in the presence of a weak CYP3A4 inhibitor (fluvoxamine) but increased in the presence of moderate (fluconazole: 1.9-fold) and strong (ketoconazole: 3.2-fold) CYP3A4 inhibitors. Increases were smaller after a single dose (1.7- and 2.5-fold, respectively). Paradoxically, co-administered itraconazole resulted in a smaller increase in AUC after multiple dosing (1.4-fold) than after single dosing (2.1-fold) of ivosidenib. This may be explained by itraconazole being both a strong inhibitor and a substrate of CYP3A4: ivosidenib-related induction of CYP3A4 after multiple ivosidenib doses would lead to lower itraconazole exposures

[70] Multidisciplinary Review, from FDA Drug Approval Package for ivosidenib (Tibsovo), NDA 211192. Approval Date: 20 July 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211192Orig1s000TOC.cfm.

which, in turn, would lead to less itraconazole inhibition of CYP3A4 and less impact on ivosidenib AUC.

Steady-state drug-drug interaction effects of concurrent moderate and strong CYP 3A4 inhibitors in the PopPK analysis of AML patients (Study AG120-C-001-PPK) corroborated the findings of the PBPK analysis. An additional PBPK model analysis conducted by the FDA (also in AML patients) predicted a similar (2.8-fold) increase in ivosidenib AUC at steady state after administration of multiple doses of ivosidenib with a strong CYP3A4 inhibitor. [70]

In the CCA PopPK analysis, concurrent use of weak CYP3A4 inhibitors resulted in a 20% to 30% increase in ivosidenib steady-state AUC, which was less than the magnitude of interindividual variability in apparent clearance.

Overall, the magnitude of impact from concurrently administered CYP3A4 inhibitors is not able to be clearly predicted from the modelling, but is likely to be meaningful, even with moderate CYP3A4 inhibitors. The PI text proposed by the sponsor to avoid co-administration of both moderate and strong CYP3A4 inhibitors is considered appropriate, based on the uncertainty over the magnitude of the prolongation effect, the safety risks associated with higher exposure (QT prolongation in particular), and the possibility of a superimposed food effect. The sponsor has also proposed a dose reduction with strong CYP3A inhibitors to 250 mg daily, which is also appropriate and is supported by the PBPK modelling.[71]

Cytochrome P450 3A4 enzyme inducers

In patients with AML, PBPK model-based simulations predicted ivosidenib AUC to be decreased in the presence of strong (rifampin) and moderate (efavirenz) CYP3A4 inducers, with a greater effect on exposure after the first ivosidenib dose (0.35- and 0.5-fold, respectively) than after multiple ivosidenib doses (0.67- to 0.89-fold, respectively). Co-administration of strong CYP3A4 inducers should be avoided. Avoiding co-administration of moderate CYP3A4 inducers is not considered necessary, based on the predicted approximate magnitude of change, the fact that one of four partial responses in patients with CCA in Study AG120-C-002 occurred in someone receiving a daily dose of 300 mg, and the lack of a clear dose-response relationship based on PD or efficacy.

P-glycoprotein inhibitors or inducers

Efflux transporters can affect the extent of oral bioavailability and the rate of absorption of BCS Class II drugs.[72] Ivosidenib is a substrate of P-glycoprotein, so ivosidenib exposure may be affected by P-glycoprotein inhibitors.

Drug-drug interactions (ivosidenib as perpetrator)

Cytochrome P450 enzymes inhibition

In patients with AML, the PBPK model-based simulations suggested that ivosidenib-mediated CYP inhibition (hepatic and intestinal) when taken at a dose of 500 mg daily was unlikely to be clinically significant.

Cytochrome P450 enzymes induction

Ivosidenib induces CYP3A4 resulting in autoinduction and a clinically relevant increase in the clearance of CYP3A4 substrates in subjects with AML. The model-predicted AUC of sensitive CYP3A4 substrate midazolam was 83% lower when co-administered with ivosidenib 500 mg daily. Itraconazole is another substrate of CYP3A4, as well as an inhibitor of CYP3A4, and FDA's PBPK model simulation (in AML patients) predicted an approximate 90% decrease in steady

[71] A summary of the FDA PBPK evaluation is available in the OCP Appendices, on page 166 of the Multidisciplinary Review, from FDA Drug Approval Package for TIBSOVO (ivosidenib), NDA 211192. Approval Date 20 July 2018. Accessed 14 December 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211192Orig1s000TOC.cfm.

[72] Custodio JM, et al. Predicting drug disposition, absorption/elimination/transporter interplay and the role of food on drug absorption. *Adv Drug Deliv Rev.* 2008; 60: 717-33. Doi: 10.1016/j.addr.2007.08.043.

state AUC of itraconazole when co-administered with ivosidenib.[70] Sensitive CYP3A4 substrates should be avoided whilst on ivosidenib, or the possibility of reduced exposure managed per their product information.

In addition to CYP3A4, ivosidenib induces CYP2B6, CYP2C8, and CYP2C9 *in vitro*. The proposed PI (in line with the approved FDA label)[69] states '*Ivosidenib may induce CYP2B6, CYP2C8, and CYP2C9*'. The clinical relevance of this is unclear. In patients with AML, the PBPK model-based simulations suggested that ivosidenib-mediated induction of CYP2B6, CYP2C8 and CYP2C9 following a 500 mg daily ivosidenib was unlikely to be clinically significant.

Despite the model-based information, the FDA label advises avoidance of co-administration of sensitive CYP2C9 substrates, noting that these include warfarin which is a common medication and has a narrow therapeutic window. [69]

Transporter inhibition

Ivosidenib inhibits OAT3, OATP1B1, OATP1B3 and P-glycoprotein *in vitro* at clinically relevant concentrations. Based on the PBPK modelling (based on data from AML patients), ivosidenib is expected to increase the AUC of concurrently administered OAT3 substrates (such as methotrexate) by approximately 27% at the 500 mg daily ivosidenib dose. However, the PBPK model-based simulations indicate that ivosidenib-mediated inhibition of OATP1B1 and OATP1B3 following a 500 mg daily ivosidenib is unlikely to be clinically significant. This is reflected in the approved US labelling. The PBPK model was inadequate to predict the inhibitory potential of ivosidenib on P-glycoprotein transport.[70]

Pharmacokinetics in special populations

Elderly and paediatric patients

Age and ECOG Performance Status did not meaningfully affect ivosidenib PK. There are no data in paediatric patients.

Hepatic impairment

A clinical study investigating the effect of hepatic impairment on ivosidenib PK was conducted in patients with chronic stable hepatic insufficiency with Child-Pugh classification score in the mild range (score 5 or 6, Class A) or moderate range (score 7 to 9, Class B)[73] who had current or history of at least one physical sign consistent with liver cirrhosis, and acceptable platelet count and renal function (Study AG120-C-012). Data from this study were included in the PopPK model. There are no data regarding the effect of severe (Child-Pugh C) hepatic impairment on ivosidenib PK.

The clinical study report for Study AG120-C-012 concluded that moderate hepatic impairment but not mild hepatic impairment '*appears to reduce total AG-120 exposure by approximately 28-44%'* although it notes that '*the 90% CIs for $AUC_{0\text{-}inf}$ also included 1.00'.*[74] The clinical study report speculates that the unexpected lower exposure in moderate hepatic impairment could be related to factors such as:

> *reduced GI absorption; decreased protein binding due to reduced AAG [alpha-1-acid glycoprotein] levels in patients with moderate HI [Hepatic impairment]; altered tissue distribution; competing protein binding components such as bilirubin (bilirubin was higher in patients with mild and moderate HI compared to patients with normal hepatic function); ascites due to cirrhosis.*

[73] The Child-Pugh score is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1 to 3, with 3 indicating most severe derangement. Class A: 5 to 6 points, least severe liver disease, one to five year survival rate of 95%. Class B: 7 to 9 points, moderately severe liver disease, one to five year survival of 75%. Class C: 10 to 15 points, most severe liver disease, 1 to 5 year survival rate 50%.

[74] AG-120 is sponsor's product development code for ivosidenib.

It is also possible that these are not real differences and a reflection of the small study size and the high interindividual variability of ivosidenib PK.

The dosing advice in the approved FDA label reflects that they considered these data adequate to support a recommendation for no dose adjustment in mild or moderate hepatic impairment, but a post-market requirement (PMR 3596-1) is in place that requires the sponsor to provide a clinical study to support dosing recommendations in moderate and severe hepatic impairment as follows:[75]

> *Since Tibsovo (ivosidenib) was approved on July 20, 2018, we have become aware of changes in ivosidenib exposure with severity of hepatic impairment based on the results of the hepatic impairment study (AG120-C-012) and the need for appropriate dose recommendations for this patient population who have co-morbidities (i.e., organ impairment) that preclude the use of intensive induction chemotherapy.*
>
> *… [the sponsor] are required to conduct the following:*
>
> *PMR 3596-1 Conduct a clinical pharmacokinetic trial to determine an appropriate safe dose of ivosidenib in patients with hematologic malignancies who have a susceptible IDH1 mutation with moderate (total bilirubin > 1.5 to 3 x [upper limit of normal] ULN and any AST) and severe (total bilirubin > 3 x ULN and any AST) hepatic impairment dosed with ivosidenib to steady-state versus patients with normal hepatic function dosed with ivosidenib to steady-state. This may be performed as a substudy in the ongoing Phase 1 Study AG120-C-001, A Phase 1, multicenter, open-label, dose-escalation and expansion, safety, pharmacokinetic, pharmacodynamic, and clinical activity study of orally administered AG-120 in subjects with advanced hematologic malignancies with an IDH1 mutation. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.*
>
> *The timetable [the sponsor] submitted on April 2, 2019, states that [the sponsor] will conduct this study according to the following schedule:*
>
> *Final Protocol Submission: 02/20*
> *Trial Completion: 02/25*
> *Final Report Submission: 09/25*

These data remain pending at the time the TGA considered this submission. The proposed Product Information (in line with the approved FDA label) states no dose adjustment is required for mild or moderate hepatic impairment, but that ivosidenib has not been studied in severe impairment, and that a recommended dose, safety and efficacy are not known in the severe hepatic impairment population.

Renal impairment

No dedicated study was conducted of the effect of renal impairment on ivosidenib PK, and renal clearance is minimal. There were 73 patients with CCA in a Phase I dose escalation and expansion study (Study AG120-C-002) and 159 patients with CCA in the pivotal Phase III study (Study AG120-C-005) who had mild or moderate renal impairment and who contributed data to the PopPK analysis. There are no data to support a dose recommendation for patients with severe renal impairment.

A relevant post-market requirement (PMR 3596-2) is noted to be in place related to FDA's approval of ivosidenib, as follows:[75]

[75] FDA approval letter for NDA 211192/S-001, dated 2 May 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/211192Orig1s001ltr.pdf.

PMR 3596-2 Conduct a clinical pharmacokinetic trial to determine an appropriate safe dose of ivosidenib in patients with hematologic malignancies who have a susceptible IDH1 mutation with severe renal impairment (creatinine clearance 15-29 mL/min) dosed with ivosidenib to steady-state versus patients with normal renal function dosed with ivosidenib to steady-state. This may be performed as a substudy in the ongoing Phase 1 Study AG120-C-001, A Phase 1, multicenter, open-label, dose-escalation and expansion, safety, pharmacokinetic, pharmacodynamic, and clinical activity study of orally administered AG-120 in subjects with advanced hematologic malignancies with an IDH1 mutation. this trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

The timetable [the sponsor] submitted on April 2, 2019 states that [the sponsor] will conduct this study according to the following schedule:

Final Protocol Submission: 02/20
Trial Completion: 02/25
Final Report Submission: 09/25.

Pharmacodynamics

2-hydroxyglutarate

Complete characterisation of the exposure-response relationship between plasma ivosidenib level and plasma 2-hydroxyglutarate was not possible due to insufficient data. A clinically important level of serum 2-hydroxyglutarate reduction required to demonstrate a treatment effect on tumours was therefore not defined.

Serum 2-hydroxyglutarate data from the early phase dose escalation or expansion Study AG120-C-002 and from pivotal Phase III Study AG120-C-005 demonstrate that, in most patients who received the recommended dose (500 mg daily) of ivosidenib, a decline in plasma 2-hydroxyglutarate occurred within 4 hours of dosing. After a cycle (28 days) of continued daily dosing, mean plasma 2-hydroxyglutarate level was similar to that of a group of external controls (30 healthy volunteers, who had not been exposed to ivosidenib). Decreased mean serum 2-hydroxyglutarate persisted on longitudinal assessment through to Cycle 19.

In support of nonclinical findings, inhibition of 2-hydroxyglutarate serum levels appeared to occur for all IDH1 variants represented in Study AG120-C-002 (R132C, R132G, R132L, R132S and R132H). Overall, there was no apparent difference in the degree of inhibition of patients with CCA by IDH variant.

In keeping with frequencies reported in the literature, R132H was not seen in any CCA patients, but was only found (and was the predominant mutant allele) in gliomas in this study. The percentage of 2-hydroxyglutarate inhibition from baseline in this study may have been less among patients with R132H mutated *IDH1*-positive glioma (median 20% among 22 non-enhancing R132H-positive gliomas, and median 30% among 11 non-enhancing gliomas) than among patients with CCA (median around 90% among 44 CCA with R132C alleles), however, sample sizes and high interindividual variability prevent meaningful interpretation. Importantly, tumour-specific factors may also confound this observation: whilst ivosidenib can cross the blood-brain barrier, it showed low exposure in brain in nonclinical models.[76]

[76] Konteatis Z, et al. Vorasidenib (AG-881): A First-in-Class, Brain-Penetrant Dual Inhibitor of Mutant IDH1 and 2 for Treatment of Glioma. *ACS Med Chem Lett.* 2020; 11: 101-107. doi: 10.1021/acsmedchemlett.9b00509.

In Study AG120-C-002, tumour biopsies to assess tumour levels of 2-hydroxyglutarate were planned at screening and at first response assessment, however there was a high level of missing data, likely due to the invasive nature of biopsy for this tumour type. Of 73 patients with CCA treated in Study AG120-C-002, 63 had at least a single biopsy, but 21 had only a follow-up and 15 had only a baseline. As a result, paired samples (prior to and after ivosidenib treatment) were reported for only 17 patients, precluding meaningful analysis. No correlating clinical data were presented (such as context of biopsy or tumour response at time of biopsy).

For a small proportion of patients, there was little or no reduction of serum or tumour 2-hydroxyglutarate from their baseline. The reasons for this are unclear but could include poor drug penetrance of the solid tumour, primary resistance, a less responsive variant or reduced exposure due to drug-drug, or food interactions.

QT prolongation

Two modelling analyses were submitted of the relationship between time-matched serum ivosidenib concentration and Fridericia-corrected QT interval (QTcF)[77], derived from PK and electrocardiograph (ECG) data from clinical studies.

Report AG120-C-META-CQT

This report contains an analysis conducted using PK and triplicate 12-lead ECG data from 3 Phase I studies (Study AG120-C-001 in haematological malignancies, Study AG120-C-002 in solid tumours and Study AG120-C-004, a single dose food-effect study in healthy volunteers).

Subjects included in the analysis were primarily male (52%), White race (71%), with AML tumour type (44%), mean age of 58.5 years and mean body weight 77 kg. In Study AG120-C-001 and Study AG120-C-002, 77.5% and 22.6% of subjects, respectively, were on medication with a known QT prolongation risk.

A total of 79 of 236 subjects in Study AG120-C-001 and 48 of 164 subjects in Study AG120-C-002 had a change from baseline QTcF greater than 30 msec. Two subjects in Study AG120-C-001 had a change from baseline QTcF greater than100 msec.

There was a significant linear relationship between increase from baseline in QTcF and increasing ivosidenib concentration. A linear model with additive random effects on the intercept and slope parameters and a study effect on the slope was the selected base model. An increase in QTcF of 2.58, 3.79 and 1.20 msec was predicted for every 1,000 ng/mL increase in ivosidenib concentration in Studies AG120-C-001, AG120-C-002 and AG120-C-004, respectively.

Based on the final model, at the geometric mean ivosidenib C_{max} (that is, 6,551 ng/mL in Study AG120-C-001 or 4,186 ng/mL in Study AG120-C-002), the model-predicted mean and 90% CI for change from baseline in QTcF on Cycle 2 Day 1 for 500 mg daily ivosidenib was 17.2 msec (14.7, 19.7) in Study AG120-C-001 (AML) and 16.1 msec (14.0, 18.3) in Study AG120-C-002 (solid tumours). The predicted change from baseline in QTcF on Cycle 2 Day 1 at the 95th percentile of C_{max} (12,640 ng/mL) was 32.9 msec. At supratherapeutic doses of 800 mg and 1,200 mg, the change from baseline QTcF is predicted to exceed 20 msec.

Report AG120-C-002-005-CQT

This analysis was conducted using data from patients with solid tumours only. The majority (63%) of records from the study were excluded from analysis due to a lack of time-matching

[77] The QT interval is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation. The corrected QT interval (QTc) estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias. The QTcF is the QT interval corrected for heart rate according to Fridericia's formula.

between ECG and PK, or other data or sample issues, leading to substantial missingness in the data. Usable QT-concentration data were available from 322 patients (154 from Study AG120-C-002 and 168 from Study AG120-C-005) and triplicate ECG data were only available for 101 of those (all from Study AG120-C-002).

Based on the primary (triplicate) final model, at the geometric mean ivosidenib C_{max} (that is, 4,185 ng/mL in Study AG120-C-002 overall, or 4,708 ng/mL in CCA patients only), the model-predicted mean and 90% CI for change from baseline in QTcF for 500 mg daily ivosidenib was 15.4 msec (12.8, 18.0) in Study AG120-C-002 (solid tumours) and 17.2 msec (14.3, 20.2) in Study AG120-C-002 (CCA patients only). At the C_{max} for subjects with cholangiocarcinoma (4,708 ng/mL), 90% CI upper bounds reached 20.6 msec in the AG120-C-002 population and 15.8 msec in the Study AG120-C005 population.

Efficacy

Study AG120-C-005

Design

The pivotal study for this CCA submission is Study AG120-C-005 (also known as the ClarIDHy trial), a Phase III, randomised, double-blind, placebo-controlled trial conducted in 49 study centres across the USA, France, Italy, South Korea, Spain and the United Kingdom.[78] The last tumour assessments were completed in 2019 and final OS analysis was conducted in May 2020.

Eligible patients had advanced (unresectable or metastatic) CCA harbouring an *IDH1* mutation (R132C/L/G/H/S according to a central diagnostic next generation sequencing assay) that was not eligible for curative resection, transplantation, or ablative therapies. Patients must have received treatment with one or two prior lines of systemic therapy including at least one gemcitabine or 5-fluorouracil based chemotherapy regimen. Systemic adjuvant chemotherapy could be considered a line of treatment if there was documented disease progression during or within 6 months of completing it.

The 187 patients were randomised in a 2:1 ratio to receive ivosidenib orally at a dose of 500 mg daily (with or without food) or a matching placebo, in continuous 28-day cycles. Randomisation was stratified by number of prior therapies (one versus two). Due to the lack of standard treatment options for patients who had progressed on a gemcitabine- or 5-fluorouracil-based chemotherapy regimen, a placebo control was considered acceptable.

On-study treatment was continued until disease progression or unacceptable toxicity. Treatment beyond radiographic progression was allowed at the discretion of the treating physician in the absence of clinical deterioration, worsening ECOG Performance Status, or disease progression that may have compromised organ function. On disease progression, patients who had been receiving placebo and continued to meet the eligibility criteria could 'crossover' to receive ivosidenib. Palliative radiotherapy to treat symptomatic nontarget lesions that could not otherwise be medically managed was also permitted after disease progression had been verified.

[78] Zhu AX, et al. Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With IDH1 Mutation: The Phase 3 Randomized Clinical ClarIDHy Trial. *JAMA Oncol.* 2021; 7: 1669–1677. doi:10.1001/jamaoncol.2021.3836.

The primary efficacy endpoint was PFS by Independent (Radiological) Review Committee (IRC) using RECIST version 1.1 criteria.[79] Radiography assessments (computerised tomography or magnetic resonance imaging, consistently used for any given patient) were conducted every 6 weeks for 8 assessments, then every 8 weeks, or as clinically indicated. Survival follow-up was conducted every 12 weeks after progression. Secondary endpoints included OS, ORR per IRC, time to response, duration of response, safety, with adverse events graded for severity according to the CTCAE version 4.03.[68] Health-related Quality of Life assessments were incorporated using survey-based instruments developed by the European Organisation for Research and Treatment of Cancer: the Quality of Life Questionnaire Core 30[80] and the Quality of Life Questionnaire Cholangiocarcinoma and Gallbladder Cancer.[81] However, these exploratory endpoints are not presented in this AusPAR, as there were substantial missing data, preventing meaningful inference.

Sequential testing of PFS followed by OS, then ORR was used to control type 1 error. For the primary analysis of PFS, IRC imaging assessments after locally determined disease progression were excluded, to account for the allowing of treatment beyond locally determined progression and subsequent re-imaging. A sensitivity analysis was conducted re-including all such excluded scans. All imaging assessments after crossover from placebo to ivosidenib were excluded from all PFS analyses.

Recognising the likelihood of notable rates of crossover from placebo, the trial prespecified a sensitivity analysis of OS using the rank-preserving structural failure time approach.[82]

Population

Overall, 187 patients were randomised. The primary efficacy analysis (data cut-off date 31 January 2019) was conducted prior to randomisation of 2 patients, so the efficacy population for PFS included 185 people, and for final OS analysis (data cut-off date 31 May 2020) included 187 people. Demographics and baseline disease characteristics below refer to the final randomised population of 187 as at data cut-off date 31 May 2020.

A majority of patients were female (64%), Caucasian (57%, though ethnicity data were missing for 28% of all patients) and enrolled at study sites in North America (67%). The median age overall was 62 years (range, 33-83 years). Around half of patients (53%) had one prior line of therapy, and most CCAs were intrahepatic (91%). Most patients (93%) had metastatic disease, 25% had ascites, 11% had a biliary stent and 5% had cirrhosis at screening. A slightly higher proportion of patients in the ivosidenib arm than placebo arm had an ECOG Performance Status

[79] The Response Evaluation Criteria In Solid Tumours (RECIST) is a voluntary international standard with unified and easily applicable criteria to define when a patient's tumour has improved ('respond'), stayed the same ('stabilise'), or worsened ('progress') during treatment. The criteria were published in February 2000 by an international collaboration including the European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group. Today, the majority of clinical trials evaluating cancer treatments for objective response in solid tumours use RECIST. These criteria were developed and published in February 2000, and subsequently updated in 2009.

[80] Groenvold M, et al. Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. *J Clin Epidemiol*. 1997; 50: 441-50. doi: 10.1016/s0895-4356(96)00428-3.

[81] Kaupp-Roberts SD, et al. Validation of the EORTC QLQ-BIL21 questionnaire for measuring quality of life in patients with cholangiocarcinoma and cancer of the gallbladder. *Br J Cancer.* 2016; 115: 1032-1038. doi: 10.1038/bjc.2016.284.

[82] Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. *Communications in Statistics - Theory and Methods*, 1991. 20: 2609-2631. doi: 10.1080/03610929108830654.

[83] of zero (40% versus 31%) and moderate renal impairment (approximately 30% versus approximately 10%) at baseline.

The median time between initial diagnosis and randomisation was similar (12.4 months in the placebo arm and 13.4 months in the ivosidenib arm). However, there were outliers in both arms, up to 88 months in the placebo arm and 102.4 months in the ivosidenib arm. Similarly, the longest response time to prior therapy was 22 months among patients randomised to placebo, and 41 months among patients randomised to ivosidenib, However, interquartile ranges for this metric indicated that the patients with very long durations of disease and time on prior therapy were outliers in both arms.

The most common mutant *IDH1* allele by central laboratory testing was R132C (70%), followed by R132L (15%) and R132G (12%). Three patients with R132S (1.6%) and two patients with R132H (1.1%) were randomised. Neither patient with R132H was randomised to ivosidenib, and both switched to ivosidenib on progression. There was no significant difference in target lesion size after crossover for either patient.

Exposure to study drug was longer (median 2.8 months, mean 6.0 months) in the ivosidenib arm than in the placebo arm (median 1.6 months, mean 2.2 months); 48% and 17% patients in the ivosidenib and placebo arms, respectively, were still on treatment after 3 months of commencing. Mean relative dose intensity was 96% in the ivosidenib arm, and in placebo-treated patients after crossover to ivosidenib, and was 98% in the placebo arm.

Results

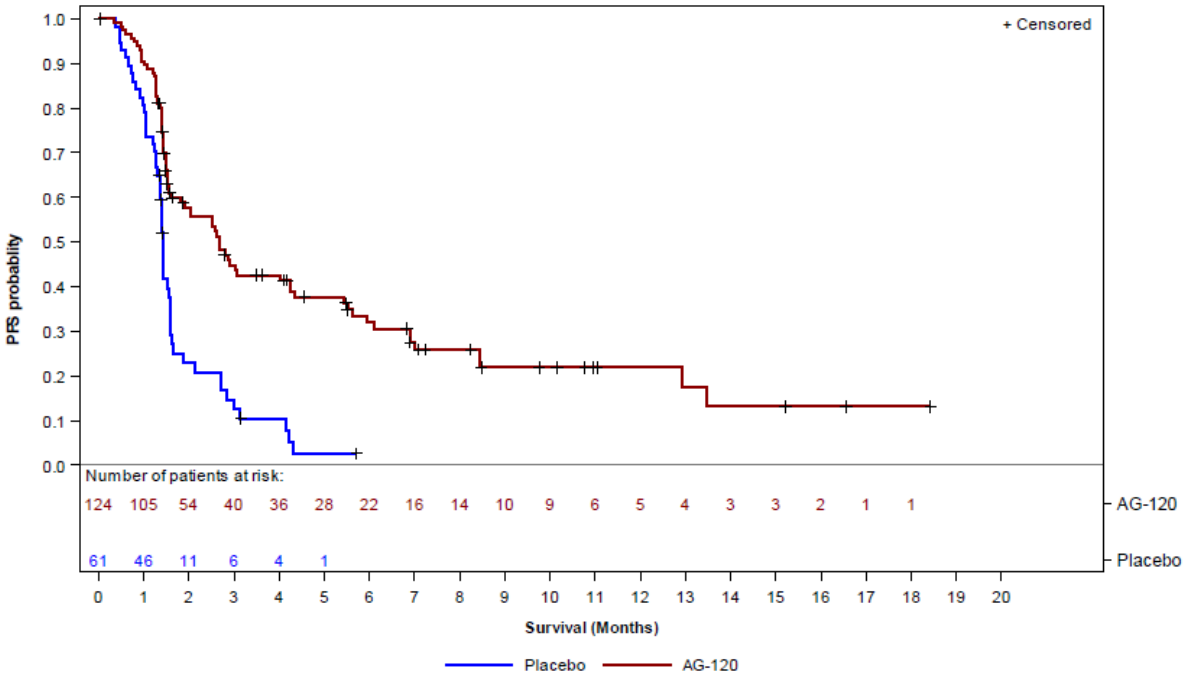
The median PFS was 2.7 months (95% CI: 1.6, 4.2) among 124 subjects randomised to ivosidenib and 1.4 months (95% CI:1.4, 1.6) among 61 subjects randomised to placebo in the intention-to-treat analysis[84] set at data cut-off date 31 January 2019, corresponding to a hazard ratio of 0.37 (0.25, 0.54) (one-sided p-value < 0.0001). The PFS rate by IRC assessment was 32% at 6 months and 22% at 12 months for ivosidenib, and 0% and 0% respectively with placebo. Although the difference in median PFS is modest, the Kaplan-Meier curves show a clear separation between arms, reflected in the hazard ratio of PFS (see Figure 2 below).

The PFS benefit was consistent across prespecified subgroup analyses including by number of prior lines of therapy (one or two), extent of disease at screening (locally advanced versus metastatic), intrahepatic versus extrahepatic CCA, ECOG Performance Status (zero versus one), and enrolment site region (North America versus Europe versus Asia).

[83] Oken MM, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982; 5: 649-655.

[84] The randomised clinical trials analysed by the intention-to-treat (ITT) approach provide unbiased comparisons among the treatment groups. In the ITT population, none of the subjects are excluded, regardless of treatment compliance or attrition due to dropout or crossover, and the subjects are analysed according to the randomisation scheme.

Figure 2: Study AG120-C-005 Kaplan-Meier plot of progression-free survival per Independent Radiological Review Committee (intention-to-treat population)



Abbreviations: AG-120 = sponsor's product development code for ivosidenib; PFS = progression-free survival

Progression-free survival = (earliest date of progressive disease or death – randomisation date + 1) / 30.4375.

Subjects with no baseline and no death are censored at randomisation date; new anticancer therapy started before progression or death are censored at the last adequate assessment prior to the new anticancer therapy; no post-baseline assessment and no death are censored at randomisation date; no progression or death by data cut-off date are censored at the last adequate assessment date; progression or death following a long gap (2 or more consecutive scheduled assessments missing) are censored at date of last adequate assessment prior to the gap.

A statistically significant difference in OS was not demonstrated between the ivosidenib and placebo arms.[78] At final analysis, median OS was 10.3 months (95% CI: 7.8, 12.4) with ivosidenib versus 7.5 months (95% CI: 4.8, 11.1) with placebo, corresponding to a hazard ratio of 0.79 (0.56, 1.12), with a nominal one-sided p-value of 0.093.

A substantial proportion of patients (43 patients; 70%) crossed over from placebo to ivosidenib on progression, confounding the analysis of OS. The median time to crossover was 2.4 months from randomisation.

The prespecified sensitivity analysis using the rank-preserving structural failure time model to adjust for crossover from placebo to ivosidenib showed a hazard ratio of 0.49 (95% CI: 0.34, 0.70) in favour of ivosidenib, supporting that the crossover may have affected survival time between arms, and could explain the lack of a significant demonstrated difference. After being adjusted for crossover, the median OS of 5.1 months[85]in the placebo arm was similar to the median OS of 5.3 months[27] reported in published literature for patients with CCA not treated with active therapy.

The ORR in the ivosidenib arm was 2%, suggesting that the PFS benefit was primarily driven by disease control or stable disease, which is consistent with the proposed mechanism of action.

[85] Demols A, et al. Regorafenib after failure of gemcitabine and platinum-based chemotherapy for locally advanced/metastatic biliary tumors: REACHIN, a randomized, double-blind, phase II trial. *Ann Oncol.* 2020; 31(9): 1169-1177. doi: 10.1016/j.annonc.2020.05.018.

Two patients with CCA harbouring an R132H *IDH1* variant were randomised in Study AG120-C-005, but neither of these patients were in the investigational arm, so there is no direct pharmacodynamic or efficacy data to support usage to treat this mutation variant. Both patients with this variant in Study AG120-C-005 switched to ivosidenib upon progression. For one, a decrease in the sum of diameters was observed after crossover per investigator, but neither of these patients had an objective response per RECIST. There were no tumour assessments performed by the blinded review panel for patients who crossed over to ivosidenib.

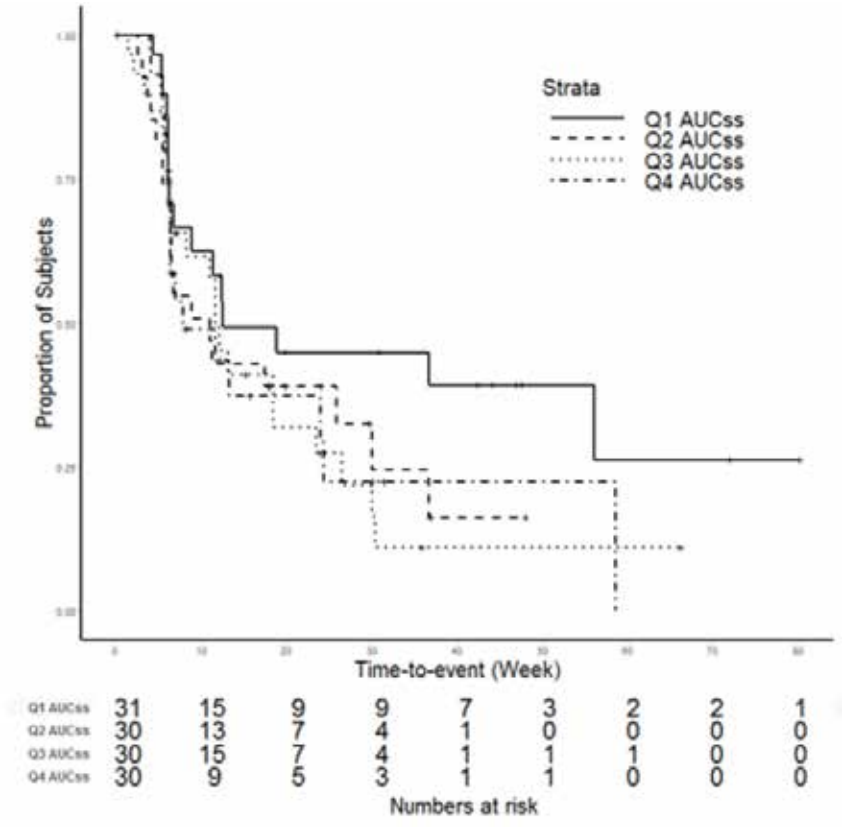
Exploratory exposure-efficacy analysis (Report AG120-C-002-005-ER)

An exploratory exposure-response Cox proportional hazards regression analysis of IRC-assessed PFS (data cut-off date 31 January 2019) in Study AG120-C-002-005 (n = 121; see Figure 3 below) did not identify a clear difference in response between exposure quartiles based on area under the curve at steady state (AUC_{ss}).

A similar analysis of OS (data cut-off date 31 May 2020) indicated a negative relationship between AUC_{ss} quartile and OS (n = 123). However, baseline ECOG Performance Status was a predictor of OS and the observed relationship was confounded by a higher prevalence of ECOG Performance Status 1 in quartile 3 and quartile 4. After correction for baseline ECOG Performance Status, OS was similar across quartiles.

The small number of subjects with an objective response precludes meaningful assessment of the exposure-ORR relationship.

Figure 3: Study AG120-C-002 Assessed progression-free survival by exposure quartile per Independent Radiological Review Committee (based on area under the plasma concentration versus time curve at steady state)



Abbreviations: AUC_{ss} = area under the plasma concentration versus time curve at steady state; IRC = Independent Review Committee; PFS = progression-free survival; Q = quartile; + = censored subjects on the Kaplan-Meier curve.

Log-rank two-sided test p-value = 0.266.

Safety

Safety profile in cholangiocarcinoma in Study AG120-C-005

Compared to placebo, patients receiving ivosidenib 500 mg once daily for the treatment of locally advanced or metastatic CCA in the Study AG120-C-005 study had a higher incidence of the following treatment-emergent adverse events (TEAEs): gastrointestinal TEAEs (including ascites, nausea, diarrhoea, and abdominal pain), hyperbilirubinemia, anaemia/decreased haemoglobin, fatigue/asthenia, cough, hypertension, decreased appetite, headache, QT prolongation, peripheral neuropathy, rash, hyperglycaemia, infections and laboratory abnormalities (haemoglobin decreased, aspartate aminotransferase increased, alanine aminotransferase increased, white blood cell count decreased, lymphocyte count decreased).

Of these, the Grade 3 or higher TEAEs in ivosidenib-treated patients with an incidence at least 2% greater than placebo) were anaemia, ascites, vomiting, hyperbilirubinaemia, falls, cholestatic jaundice, cholangitis, and laboratory abnormalities (aspartate aminotransferase increased, platelet count decreased, and blood bilirubin increased). The 2 patients who discontinued treatment due to a TEAE experienced generalised oedema (one patient) and hyperbilirubinaemia (one patient).

The incidence of on-treatment death (death within 28 days of last dose of treatment) was 15% in the ivosidenib arm and 32% in the placebo arm. There were six patients in the ivosidenib arm (4.9%) and zero in the placebo arm with a TEAE leading to on-treatment death. The six TEAEs with fatal outcomes in the ivosidenib arm did not suggest a common drug-related causality and appeared to be related to underlying disease or comorbidities; there was one fatal case each of pneumonia, intestinal obstruction, pulmonary embolism. and hepatic encephalopathy, as well as 2 fatal cases of sepsis.

The approved FDA label for ivosidenib includes a summary of safety data from Study AG120-C-005 using clinically rational adverse event term groupings.[69] This presentation of the data is clearer and more informative than the proposed draft PI text.

Exploratory exposure-safety analysis for cholangiocarcinoma in Studies AG120-C-005 and AG120-C-002

An exploratory logistic regression-based analysis was conducted of the relationship between ivosidenib exposure and 14 selected safety outcomes across Study AG120-C-002 (at data cut-off date 16 January 2019) and Study AG120-C-005 (at data cut-off date 31 May 2020). The outcomes were chosen based on potential association with ivosidenib treatment:

- rash (all grades, and Grade 3 or higher)
- gastrointestinal symptoms (Grade 2 and higher)
- liver dysfunction with alanine aminotransferase or aspartate aminotransferase three-fold or more above ULN, and associated with an increase in bilirubin two-fold or more above ULN (± 10 days))
- hepatic enzyme elevation (newly occurring or worsening laboratory abnormalities compared to baseline, all grades and Grade 2 and higher, for alanine aminotransferase, aspartate aminotransferase, bilirubin)
- renal dysfunction (all grades)
- polyneuropathy (all grades, and Grade 3 and higher)
- myalgia (all grades).

In total, data were included for 239 patients with CCA for whom exposure estimates were available: 73 (62 who received 500 mg once daily) from AG120-C-002 and 166 from Study AG120-C-005. Among the 166 patients from Study AG120-C-005, 43 were randomised to placebo treatment and subsequently crossed over to ivosidenib. Data from the latter group were included from the day of switching.

A total of 486 events were observed across the 14 safety endpoints. For each endpoint, the distributions of exposure were similar between the group of patients in whom that endpoint was seen versus those in whom it was not. With increasing exposure based on AUC_{ss}, there was a trend of higher incidence of all-grade new or worsening bilirubin, ≥ Grade 2 new or worsening bilirubin, Grade 2 and higher gastrointestinal symptoms, and liver dysfunction. However, logistic regression did not identify a statistically significant relationship between ivosidenib AUC_{ss} and incidence of any of the selected safety endpoints.

Safety profile in CCA across studies

Across Study AG120-C-005 and Study AG120-C-002, 185 patients had received ivosidenib at the recommended dose at the safety data cut-offs (21 June 2021 and 16 January 2019, respectively, with additional SAE follow-up available from Study AG120-C-002 to 21 June 2021). A further 43 patients received ivosidenib on progression after being randomised to placebo in Study AG120-C-005.

In the overall CCA population (n = 228), patients received 500 mg ivosidenib once daily for a median duration of 3.6 months (range 0.1 to 45.1) and exposure was at least 12 months in 17.1% of patients. Amongst patients randomised to ivosidenib in Study AG120-C-005, the median duration of exposure was 2.8 months.

Half of the ivosidenib-treated patients (n = 228), and 37% of patients who received placebo (n = 59), experienced TEAEs of CTCAE Grade 3 or higher (see Table 2). Serious TEAEs occurred in 31% of patients treated with ivosidenib, and treatment interruption was required in 29% of patients for TEAEs. TEAEs leading to study treatment discontinuation were reported in 5% of patients taking ivosidenib (most commonly due to QT prolongation, with one due to peripheral neuropathy) and 8% of patients taking placebo.

Table 2: Overall summary of treatment-emergent adverse events in cholangiocarcinoma population (safety analysis set)

	Ivosidenib 500 mg QD, n (%)				Placebo, n (%)
	AG120-C-005 Without Crossover N=123	AG120-C-005 Post-Crossover N=43	AG120-C-002 N=62	Overall[1] N=228	AG120-C-005 Pre-Crossover N=59
Subjects with Any TEAE	120 (97.6)	41 (95.3)	62 (100.0)	223 (97.8)	57 (96.6)
Subjects with Grade ≥3 TEAE	63 (51.2)	26 (60.5)	25 (40.3)	114 (50.0)	22 (37.3)
Subjects with Related TEAE	81 (65.9)	23 (53.5)	40 (64.5)	144 (63.2)	23 (39.0)
Subjects with Grade ≥3 Related TEAE	8 (6.5)	3 (7.0)	3 (4.8)	14 (6.1)	0
Subjects with SAE	43 (35.0)	12 (27.9)	16 (25.8)	71 (31.1)	14 (23.7)
Subjects with Related SAE	3 (2.4)	0	0	3 (1.3)	0
Subjects with TEAE Leading to Study Treatment Reduction	5 (4.1)	0	2 (3.2)	7 (3.1)	0
Subjects with Related TEAE Leading to Study Treatment Reduction	5 (4.1)	0	2 (3.2)	7 (3.1)	0
Subjects with TEAE Leading to Study Treatment Interrupted	37 (30.1)	14 (32.6)	14 (22.6)	65 (28.5)	11 (18.6)
Subjects with Related TEAE Leading to Study Treatment Interrupted	5 (4.1)	5 (11.6)	4 (6.5)	14 (6.1)	0
Subjects with TEAE Leading to Study Treatment Discontinuation	9 (7.3)	2 (4.7)	0	11 (4.8)	5 (8.5)
Subjects with Related TEAE Leading to Study Treatment Discontinuation	2 (1.6)	0	0	2 (0.9)	0
Subjects with TEAE Leading to Death	6 (4.9)	2 (4.7)	2 (3.2)	10 (4.4)	0
Subjects with Related TEAE Leading to Death	0	0	0	0	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in group; n=number of participants contributing to the analysis; PT = Preferred Term; QD = once daily; SAE = serious adverse event; TEAE = treatment-related adverse event.

Notes: Data cut-off date: 16 January 2019 (Study AG120-C-002); Database lock date: 21 June 2021 (Study AG120-C-005).

Death was defined as any death that occurred between first dose and 28 days after last dose of study treatment.

Percentages were calculated based on N in each column.

A subject with multiple occurrences of a TEAE (PT using MedDRA version 23.1) was counted only once in the TEAE category.

Related refers to study treatment-related. A TEAE with relationship missing (unknown) was counted as related.

One subject [patient ID redacted] took only placebo after crossover, thus TEAEs after crossover were not summarised in the 'AG120-C-005 Post Crossover' column and were not included in this table.

1 Includes all cholangiocarcinoma subjects in Studies AG120-C-005 and AG120-C-002 who had been exposed to ivosidenib 500 mg once daily.

Amongst ivosidenib-treated patients, 32 (14%) died within 28 days of last dose of treatment, 10 of whom experienced on-treatment TEAEs leading to death. In addition to the 6 deaths noted above there were 2 deaths in patients who crossed over to receive ivosidenib after randomisation to placebo (one fatal case each of intestinal pseudo-obstruction and hepatic cirrhosis) and 2 deaths in patients in Study AG120-C-002 (one fatal case each of procedural haemorrhage (during unsuccessful banding of pre-existing oesophageal varices) and *Clostridium difficile* infection). The additional events do not show a commonality that might suggest drug-related causality and are also in keeping with the underlying disease and complications.

The most common TEAEs in patients who were received ivosidenib were nausea, fatigue, abdominal pain, decreased appetite, vomiting, cough and ascites. Noting the small population sizes, nausea, fatigue and diarrhoea, cough and anaemia were more frequent in groups of patients who received ivosidenib (n = 123 or n = 228) than placebo (n = 59), by margins of at least 10% incidence (see Table 3). The only Grade 3 or higher TEAE that was at least 5% more common in ivosidenib-treated patients was anaemia.

Table 3: Summary of treatment-emergent adverse events that occurred in at least 10% of subjects by Preferred Term in cholangiocarcinoma population (safety analysis set)

Preferred Term	Ivosidenib 500 mg QD, n (%)				Placebo, n (%)
	AG120-C-005 Without Crossover N=123	AG120-C-005 Post-Crossover N=43	AG120-C-002 N=62	Overall[a] N=228	AG120-C-005 Pre-Crossover N=59
Subjects with Any TEAE	120 (97.6)	41 (95.3)	62 (100.0)	223 (97.8)	57 (96.6)
Nausea	52 (42.3)	12 (27.9)	22 (35.5)	86 (37.7)	17 (28.8)
Fatigue	38 (30.9)	10 (23.3)	29 (46.8)	77 (33.8)	10 (16.9)
Diarrhoea	43 (35.0)	12 (27.9)	20 (32.3)	75 (32.9)	10 (16.9)
Abdominal pain	30 (24.4)	7 (16.3)	19 (30.6)	56 (24.6)	9 (15.3)
Decreased appetite	30 (24.4)	6 (14.0)	20 (32.3)	56 (24.6)	11 (18.6)
Vomiting	28 (22.8)	6 (14.0)	15 (24.2)	49 (21.5)	11 (18.6)
Cough	31 (25.2)	5 (11.6)	10 (16.1)	46 (20.2)	5 (8.5)
Ascites	28 (22.8)	5 (11.6)	10 (16.1)	43 (18.9)	9 (15.3)
Anaemia	23 (18.7)	8 (18.6)	9 (14.5)	40 (17.5)	3 (5.1)
Oedema peripheral	17 (13.8)	9 (20.9)	13 (21.0)	39 (17.1)	6 (10.2)
Constipation	20 (16.3)	5 (11.6)	8 (12.9)	33 (14.5)	11 (18.6)
Back pain	16 (13.0)	3 (7.0)	13 (21.0)	32 (14.0)	7 (11.9)
Arthralgia	14 (11.4)	5 (11.6)	12 (19.4)	31 (13.6)	6 (10.2)
Pyrexia	18 (14.6)	2 (4.7)	11 (17.7)	31 (13.6)	6 (10.2)
Aspartate aminotransferase increased	14 (11.4)	3 (7.0)	8 (12.9)	25 (11.0)	3 (5.1)
Asthenia	17 (13.8)	5 (11.6)	3 (4.8)	25 (11.0)	8 (13.6)
Abdominal distension	14 (11.4)	2 (4.7)	8 (12.9)	24 (10.5)	5 (8.5)
Dyspnoea	13 (10.6)	4 (9.3)	6 (9.7)	23 (10.1)	10 (16.9)
Insomnia	12 (9.8)	3 (7.0)	8 (12.9)	23 (10.1)	3 (5.1)
Electrocardiogram QT prolonged	12 (9.8)	1 (2.3)	8 (12.9)	21 (9.2)	2 (3.4)
Headache	16 (13.0)	2 (4.7)	3 (4.8)	21 (9.2)	4 (6.8)
Hypokalaemia	10 (8.1)	2 (4.7)	9 (14.5)	21 (9.2)	4 (6.8)
Blood alkaline phosphatase increased	11 (8.9)	4 (9.3)	5 (8.1)	20 (8.8)	6 (10.2)
Weight decreased	10 (8.1)	6 (14.0)	4 (6.5)	20 (8.8)	3 (5.1)
Blood bilirubin increased	13 (10.6)	3 (7.0)	3 (4.8)	19 (8.3)	4 (6.8)
Hyponatraemia	14 (11.4)	1 (2.3)	4 (6.5)	19 (8.3)	7 (11.9)
Hypomagnesaemia	9 (7.3)	1 (2.3)	7 (11.3)	17 (7.5)	3 (5.1)
Myalgia	6 (4.9)	0	7 (11.3)	13 (5.7)	0
Hypercalcaemia	3 (2.4)	2 (4.7)	5 (8.1)	10 (4.4)	7 (11.9)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in group; n=number of participants contributing to the analysis; PT = Preferred Term; QD = once daily; TEAE = treatment-emergent adverse event.

Notes: Data cut-off date: 16 January 2019 (Study AG120-C-002); Database lock date: 21 June 2021 (Study AG120-C-005).

The summary includes TEAEs that occurred in at least 10% of subjects in any column at the PT level; 'Subjects with Any TEAE' are summarised for all TEAEs. PTs are sorted in descending frequency of the Overall column. A subject with multiple occurrences of a TEAE under one treatment was counted only once in the PT for that treatment. PTs were coded from MedDRA version 23.1. Percentages were calculated based on N in each column.

1 Includes all cholangiocarcinoma subjects in Studies AG120-C-005 and AG120-C-002 who had been exposed to ivosidenib 500 mg once daily.

Safety profile in acute myeloid leukemias

Ivosidenib is approved in the USA for both haematology (AML) and solid tumour (CCA) indications. Separate assessments of safety are reflected in the approved FDA label for each approved indication.[69] The different safety profiles reflect different regimens (monotherapy versus combination with other drugs) and different patient populations (including baseline demographics, biological and disease characteristics, and concurrent medications).

A detailed integrated assessment of safety is described in the published FDA multidisciplinary review document for the first indication approved in the USA (in relapsed and refractory (R/R) AML).[70] Some notable adverse events of special interest observed in those with haematological malignancies were differentiation syndrome, tumour lysis syndrome, Guillain-Barré syndrome, progressive multifocal leukoencephalopathy, and posterior reversible encephalopathy syndrome. No such events were reported in Study AG120-C-005 in patients with cholangiocarcinoma.

Cardiac safety / QT prolongation

Prolongation of the QT interval on ECG is a known risk associated with ivosidenib treatment Nonclinical data showed ivosidenib to inhibit the hERG channel and prolong the QTc interval on animal ECG. Exposure-response modelling of triplicate ECG data from early phase studies in patients with haematological malignancies, patients with solid tumours, and healthy volunteers showed ivosidenib to cause concentration-dependent QTc prolongation, with a mean change from baseline of 16 msec at the geometric mean C_{max} (in patients with solid tumours) and 33 msec at the 95th percentile of C_{max}.

The pivotal study (Study AG120-C-005) excluded enrolment of patients with baseline QTc ≥ 450 msec, or taking medications known to prolong the QT interval, or who had other risk factors (such as heart failure, hypokalaemia, family history of long QT interval syndrome).

Prolongation of the QT interval was an adverse event of special interest in the safety analysis of Study AG120-C-005. Adverse events of QT prolongation (2 of which were Grade 3) were reported in 10% of the ivosidenib arm (n = 123), and there were 2 cases (3%) in the placebo arm.

Among 43 patients who crossed over from placebo to ivosidenib, QT prolongation as an AE was reported in one patient (2%), whose concurrent medications included esomeprazole. It occurred 28 days after starting ivosidenib, with a QT of 467 msec (QTcF 454 msec), on a pre-dose ECG which also showed sinus bradycardia (rate 55 bpm). No treatment was administered, and cardiologist was not consulted. The patient's ECG was '*abnormal but not clinically significant*' at initial randomisation (QT 466 msec and QTcF 441 msec). This subject also had Grade 3 syncope 11 days after the first dose. A subsequent ECG displayed normal sinus rhythm with no acute ischemic changes and no ST-elevation myocardial infarction (STEMI); QT 444 msec, QTcF 435 msec.

There were no events of Torsades de pointes and no Grade 4 or 5 events in Study AG120-C-005. The median time to onset of QT prolongation among patients randomised to ivosidenib was 28 days (range 1 day to 698 days) after treatment initiation.

In the ivosidenib arm, 2% of patients had an ECG with a QTc interval greater than 500 msec (zero in the placebo arm) and 5% of patients experienced an increase from baseline QTc of above 60 msec (zero in the placebo arm).

No patient discontinued treatment due to QT prolongation, but it was the most common reason for dose reduction (3% of patients). In all 4 such cases, the QT prolongation was Grade 1 or 2, and resolved with dose reduction. The dose was re-increased back to 500 mg daily for one patient, and the event recurred.

An exploratory analysis was submitted of the relationship between incidence of events in the Torsades de pointes/QT prolongation Standardised MedDRA Query[86,87] that occurred in Study AG120-C-005 (28 among 12 patients), or events in patients with CCA who received ivosidenib (45 events among 21 patients) across Study AG120-C-005 or AG120-C-002, according to whether a weak or moderate CYP3A4 inhibitor was being concurrently used by the patient. An association was not demonstrated; however, this analysis is very limited by the small event numbers, and lack of direct PK measurement, in light of the high interindividual variability.

There was generally a higher incidence of QT prolongation (20% to 26%, with 10% to 11% Grade 3 or higher) in the AML studies than CCA (10%, with 2% Grade 3 or higher). A description of QT prolongation seen in the haematology study population is contained in the public multidisciplinary review document published by the FDA.[70] Events in the AML population included multiple cases of ventricular arrhythmia and possible Torsades de pointes, though confounding factors were present. The rates of QTc greater than 500 msec or increase from baseline QTc of greater than 60 msec, respectively, were 10% and 13% amongst patients with relapsed and refractory AML (n = 178) treated in Study AG120-C-001, compared to 2% and 5% among patients with CCA treated in Study AG120-C-005.

Among the post-market data, it is noted that 2 cases of fatal cardiac arrests occurred in AML patients receiving ivosidenib, however, no further case details were provided.

The observation of more frequent QT prolongation in patients with AML is in keeping with the modelling indicating a relationship between exposure and QT prolongation) along with the observed higher exposure at the recommended dose, and higher usage rates and inhibitory strengths of co-administered CYP3A4 inhibitors in patients with haematological malignancies. It is unclear whether increased exposure is the only contributing factor, but this is very likely to at least explain part of the relationship.

Overall, QT prolongation is a significant safety concern, requiring warning or precautionary text in the PI. Text in the PI should include descriptions of the exposure-QT prolongation relationship, the relevance of dosing in proximity to a high fat meal, the importance of ECG analysis at baseline and throughout treatment, the exclusion of at-risk populations from the

[86] The Medical Dictionary for Regulatory Activities (MedDRA) is a single standardised international medical terminology, developed as a project of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) which can be used for regulatory communication and evaluation of data pertaining to medicinal products for human use. As a result, MedDRA is designed for use in the registration, documentation and safety monitoring of medicinal products through all phases of the development cycle (that is, from clinical trials to post-marketing surveillance). Furthermore, MedDRA supports ICH electronic communication within the ICH's Electronic Common Technical Document (eCTD) and the E2B Individual Case Safety Report.

[87] Standardised MedDRA Queries (SMQs) are groupings of terms from one or more MedDRA System Organ Classes (SOCs) that relate to a defined medical condition or area of interest. They are intended to aid in case identification.

pivotal study, and a note that QT prolongation can cause fatal arrhythmias such as Torsades de pointes.

Polyneuropathy

Sensorimotor neuropathy, including the rare autoimmune severe acute paralytic neuropathy Guillain-Barré syndrome, was investigated as a potential risk in the ivosidenib clinical development program for haematological malignancies, as 2 cases of Guillain-Barré syndrome and one serious adverse event of lumbosacral plexopathy were reported within the haematology study population. All 3 events were assessed as treatment-related, but no clear mechanism of action has emerged.

The FDA label includes a precaution regarding Guillain-Barré syndrome as follows: [69]

> *Guillain-Barré syndrome can develop in patients treated with Tibsovo. Guillain-Barré syndrome occurred in <1% (2/258) of patients treated with Tibsovo in Study AG120-C-001.*
>
> *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.*

The TGA clinical evaluation raised with the sponsor whether a warning regarding Guillain-Barré syndrome should be added to the PI. The sponsor responded that Guillain-Barré syndrome was not considered a potential risk in CCA, based on:

- a lack of non-clinical data suggesting the CNS as a target organ for ivosidenib toxicity
- a lack of mechanism of action to explain a relationship between ivosidenib and polyneuropathy
- a lack of any cases of Guillain-Barré syndrome in patients with solid tumours.

The Summary of Clinical Safety submitted by the sponsor includes tables of data reflecting a search among patients in the safety analysis set[88] for any TEAE with MedDRA High Level Term of acute polyneuropathies, chronic polyneuropathies, mononeuropathies, or peripheral neuropathies not elsewhere classified. Among 228 patients who had ivosidenib at the recommended dose, whilst peripheral neuropathy was common (19 (8%) experienced such an event, compared to zero of 59 patients in the placebo group), there was no case of Guillain-Barré syndrome. All the events of peripheral neuropathy were Grade 1 or 2, and one led to dose reduction.

The Delegate agreed with the sponsor that Guillain-Barré syndrome has not been reported in patients with CCA taking ivosidenib; however, as there is no rationale for a mechanism of action, there is no reason to think this event should be specific to the haematological malignancy setting. Given the relatively small size of the safety dataset (and the rarity of CCA), it is plausible that ivosidenib rarely causes Guillain-Barré syndrome but by chance, no cases have yet been seen in the CCA setting.

A warning will be proposed for inclusion in the PI, with text reflecting the limitations of the data. Guillain-Barré syndrome must be added to the list of important potential risks in the risk management plan (RMP) for post-market monitoring.

[88] All patients from AG120-C-005 who received at least 1 dose of ivosidenib or placebo, patients from AG120-C-002 who received at least 1 dose of 500 mg daily ivosidenib, and patients from AG120-881-C-001 who received at least 1 dose of 500 mg daily ivosidenib.

Companion diagnostic considerations

Any device seeking companion diagnostic registration from TGA needs to demonstrate clinical validity and utility, as well as analytical validity and utility.

In Study AG120-C-005, central determination of *IDH1* mutation status (presence or absence of any of the following variants: R132C, R132CL, R132G, R132H or R132S) was performed using the Oncomine Focus Assay, a diagnostic next generation sequencing assay. The findings of Study AG120-C-005 can be considered evidence of the clinical validity and utility of this device for this usage. For a device other than the Oncomine Focus Assay to be considered for TGA registration as a companion diagnostic for this proposed medicine indication, it would need to show adequate comparability to the Oncomine Focus Assay for detection of these variants in order to bridge to the clinical validity and utility data.

Risk management plan

The sponsor submitted European Union (EU)-RMP version 0.1 (1 March 2022; data lock point 31 October 2021) and Australia-specific annex (ASA) version 1.0 (2 May 2022) in support of this application. Australia-specific annex version 0.2 (19 August 2022) and then an updated ASA version 0.2 (19 August 2022) were provided by the sponsor in response to questions raised by the TGA. It was noted that the ASA had been amended but the version number and date had not been changed. At the third round of evaluation, ASA version 0.3 (27 January 2023) was provided by the sponsor in response to the Delegate's proposed actions.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 4. The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.

Table 4: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Electrocardiogram QT prolonged	ü	–	ü	–
Important potential risks	Embryo-foetal toxicity	ü	–	ü	–
	Guillain-Barré syndrome[1]	ü	–	ü	–
Missing information	Use in patients with severe hepatic impairment	ü	ü[2]	ü	–
	Use in patients with severe renal impairment	ü	ü[2]	ü	–

1 Australia-specific safety concern

2 Clinical trial (Organ impairment substudy of Study AG120-C-001)

- Summary of safety concerns is considered acceptable from an RMP perspective.
- Routine pharmacovigilance activities have been proposed for all risks. Additional pharmacovigilance activities, in the form of clinical trials, has been proposed for the missing information. This is acceptable.
- Routine risk minimisation activities, through the draft PI and CMI, has been proposed for all risks. There are no additional risk minimisation activities for this submission. Routine risk minimisation measures are considered acceptable to address the risks from an RMP perspective.

Risk-benefit analysis

Delegate's considerations

Beyond the first-line setting, standard of care treatment for patients with locally advanced or metastatic CCA (including those with *IDH1* mutation-positive disease) is FOLFOX chemotherapy, based on a recent randomised study which had not reported at the time of the pivotal trial design and conduct. FOLFOX was associated with an almost one month longer median OS time, and a 12 month survival rate of 26% compared to 11% in the active supportive care (control) arm.[27] Rates of Grade 3 to 5 adverse events were 52% with active supportive care and 69% with the addition of FOLFOX, including 3 chemotherapy-related deaths (one each due to infection, acute kidney injury, and febrile neutropenia).[27] Locally advanced or metastatic CCA is not a specifically registered usage in Australia for any of the components of FOLFOX.

The pivotal study for this submission, Study AG120-C-005, provides evidence that for patients with advanced CCA harbouring an *IDH1* mutation, treatment with ivosidenib at 500 mg daily results in an improvement in PFS compared to placebo. Whilst the absolute difference between medians was small (1.3 months), this represents a hazard ratio of 0.37, indicative of the rapidly progressive and aggressive nature of the disease. Exploratory analyses of PFS rates also illustrate the clinical meaningfulness of the difference, with 22% of ivosidenib-treated patients remaining alive and progression-free at 12 months compared with zero in the placebo arm.

The use of placebo as the comparator in the study is acceptable, as the data for FOLFOX were not published before the design and conduct of Study AG120-C-005. A direct comparison between ivosidenib and FOLFOX for patients with *IDH1*-mutated CCA is not available.

A statistically significant survival benefit was not demonstrated, but a pre-specified exploratory RPFST analysis adjusting for the substantial (70%) rate of post-progression crossover from placebo to ivosidenib supports the meaningfulness of the PFS findings.

Ivosidenib use in this heavily pre-treated population with CCA who had received at least one prior line of systemic therapy was associated with an acceptable toxicity profile, manageable with dose modification and standard supportive care. Rates of Grade 3 or higher adverse events were 51% among patients randomised to ivosidenib, compared to 37% among placebo-treated patients. Its safety profile is distinctly different from the chemotherapy options used 'off-label' for patients with CCA and (based on cross-trial comparison) may involve less high-grade toxicities.[27]

The most significant safety concern in the CCA setting is QT prolongation. The rates and severity do not appear to be as high in the CCA setting as has been observed among patients with haematological malignancies, possibly due to lower rates of concurrent administration of CYP3A4 inhibitors and thus reduced average exposure in the CCA setting. ECG monitoring is essential for safe use.

No event of Guillain-Barré syndrome has been reported in patients with solid tumours to date but have been reported in patients with AML. This may be a rare adverse effect and will be included in the PI, noting the limitations of the data, and in the RMP as an important potential risk for monitoring.

Question for the sponsor

1. ***The initial proposed Australian indication was not specific regarding what type of IDH mutations were included.***

   The European indication is limited to R132 mutations, whilst the US indication stipulates 'susceptible' mutations are eligible for treatment with a definition contained later in the label regarding what susceptibility entails.

The sponsor provided the following response to the question:

The Sponsor suggested an update to the indication to specify 'R132' as was done in Europe, with the rationale:

> *While these rare IDH1 mutations have been detected in clinical samples, no Applicant derived data demonstrating the effect of ivosidenib against non-R132 mutations have been produced.*
>
> *No data demonstrating the oncogenic potential of non-R132 mutations are known to have been reported. Rare non-R132 mutations have been examined in the literature for neomorphic activity, with only a few capable of producing the oncometabolite D-2-hydroxyglutarate (i.e. G97, R100) (Ward et al, 2012).*[89]
>
> *Given the lack of biochemical activity data available for ivosidenib in non-R132 IDH1 variants, if a non-R132 variant was identified in the absence of a co-occurring R132 IDH1 mutation, the use of ivosidenib would not be recommended.*

The sponsor's proposal to include 'R132' in the indication is accepted by the Delegate.

Proposed action

On the whole, the risk-benefit balance of approval for this medicine for the treatment of CCA that harbours certain *IDH1* mutations is positive.

The Delegate proposed to approve the registration of the product, and to impose standard conditions of registration as well as RMP-specific conditions.

Advisory Committee considerations

The Delegate did not refer this submission to the Advisory Committee on Medicines for advice.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Tibsovo (ivosidenib) 250 mg film-coated tablets bottle, indicated for:

> *Tibsovo is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) R132 mutation after at least one prior line of systemic therapy.*

Specific conditions of registration applying to these goods

- Tibsovo (ivosidenib) is to be included in the Black Triangle Scheme. The PI and CMI for Tibsovo must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Tibsovo EU-risk management plan (RMP) (version 0.1, dated 1 March 2022, data lock point 31 October 2021), with Australia-specific annex (version 0.3, dated 27 January 2023), included with Submission PM-2022-02134-1-4, to be updated to the satisfaction of the TGA, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

[89] Ward PS, Cross JR, Lu C, et al. Identification of additional IDH mutations associated with oncometabolite *R*(-)-2-hydroxyglutarate production. *Oncogene* 2012; 31: 2491–2498. doi: 10.1038/onc.2011.416

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII- periodic safety update report ([Revision] 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Attachment 1. Product Information

The PI for Tibsovo approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

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Reference/Publication #