CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	COSTA RICA		PRIVACY		Unk	Unk	Unk		Unk	

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [LOWER LEVEL TERM] (Related symptoms if any separated by commas)

Serious toxicities (grade 3-5) including upper gastrointestinal bleeding [Upper gastrointestinal bleeding]
Serious toxicities (grade 3-5) including upper gastrointestinal bleeding [Drug toxicity]
CTCAE Grade1-2 Hypertension [Hypertension]
CTCAE Grade1-2 Proteinuria [Proteinuria]
Bevacizumab used in treatment of Hepatocellular carcinoma [Off label use in unapproved indication]

Case Description: Publication in Journal of Clinical Oncology:

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☒ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING
- ☐ CONGENITAL ANOMALY
- ☐ OTHER

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) bevacizumab (bevacizumab) Unknown formulation
#2) Atezolizumab (Atezolizumab)
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) UNK	#1) Unknown
#2) UNK	#2) Unknown

17. INDICATION(S) FOR USE
#1) unresectable or metastatic Hepatocellul
#2) unresectable or metastatic Hepatocellul
(Continued on Additional Information Page)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) Unknown	#1) Unknown
#2) Unknown	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Current Condition	

(Continued on Additional Information Page)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Amgen Biotecnológica S.A.S.
Ana Carolina Uribe
Cra 7 No. 123-35 Torre 123 Piso 6
Bogotá, COLOMBIA
Phone: 57 3157008539

26. REMARKS

24b. MFR CONTROL NO.
CRISP2025161980

24c. DATE RECEIVED BY MANUFACTURER
11-AUG-2025

24d. REPORT SOURCE
☐ STUDY ☒ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
18-AUG-2025

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Real-world data on the effectiveness and toxicity of atezolizumab and bevacizumab as first-line therapy in patients with unresectable or metastatic hepatocellular carcinoma in Costa Rica: 2025; 43 (16): e16189.

This serious Literature report (CRISP2025161980) (Incomplete Case/ Cluster Case) was reported to Amgen on 11/AUG/2025 by an other health professional and involves the patients who had serious toxicities (grade 3-5) including upper gastrointestinal bleeding [PT: upper gastrointestinal haemorrhage, PT: toxicity to various agents], CTCAE grade1-2 hypertension [PT: hypertension], CTCAE grade1-2 proteinuria [PT: proteinuria] while receiving bevacizumab (manufacturer unknown). Off label use was reported.

No historical medical condition was reported. The patient's current medical condition included unresectable or metastatic hepatocellular carcinoma. No concomitant medications were provided. The patient's co-suspect medication included Atezolizumab.

The patients began bevacizumab on an unknown date. The literature article did not provide sufficient information to determine which individual patients experienced specific event. The patients, who had been diagnosed with unresectable or metastatic hepatocellular carcinoma (HCC), started receiving first-line combination therapy with bevacizumab (off-label use) and atezolizumab. Most of the patients were classified as Barcelona Clinic Liver Cancer (BCLC) stage C. Chronic hepatitis B and hepatitis C were the most common aetiologies followed by non-alcoholic steatohepatitis (NASH). Progression-free survivals (PFS), overall survivals (OS) were estimated using Kaplan-Meier analysis. Treatment related toxicities were graded according to Common Terminology Criteria for Adverse Events (CTCAE). The following treatment-related toxicities were reported: Adverse events occurred in 90% of patients, with hypertension and proteinuria being the most common (22%), primarily of grade 1-2. Serious toxicities (grade 3-5), including upper gastrointestinal bleeding, were reported in 3.77% of patients. Dose modifications were necessary in 16% of cases but did not negatively affect survival outcomes. On an unknown date, the patient died. The cause of death was reported as serious toxicities (grade 3-5) including upper gastrointestinal bleeding. No treatment information was received. The outcome of the events hypertension, proteinuria were reported as unknown. Action taken with bevacizumab was reported as unknown for the events hypertension, and proteinuria.

The authors reported that the events hypertension, proteinuria, upper gastrointestinal haemorrhage, toxicity to various agents were possibly related to bevacizumab. Follow-up has been requested to obtain additional patient specific information.

Company Comment: This safety report does not necessarily reflect a conclusion by Amgen that bevacizumab caused or contributed to the adverse events reported; however, consistent with regulatory reporting requirements, this case is being reported because it contains one or more suspected adverse reactions.

This individual case report does not change the safety profile of the product.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Unevaluable investigation Done Progression -free survival (PFS), overall survival (OS) were estimated using Kaplan-Meier analysis	absent	

13. Relevant Tests

On an unknown date, Progression -free survival (PFS), overall survival (OS) were estimated using Kaplan-Meier analysis.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) bevacizumab (bevacizumab) Unknown formulation; Regimen #1	UNK; Unknown	unresectable or metastatic Hepatocellular carcinoma (Hepatocellular carcinoma)	Unknown; Unknown
#2) Atezolizumab (Atezolizumab) ; Regimen #1	UNK; Unknown	unresectable or metastatic Hepatocellular carcinoma (Hepatocellular carcinoma)	Unknown; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing 18-Aug-2025 10:08	Current Condition	Hepatocellular carcinoma metastatic (Hepatocellular carcinoma);

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description

24d. Report Source Literature
Journal: Journal of Clinical Oncology
Author: Fernandez P.; Landaverde D.U.
Title: Real-world data on the effectiveness and toxicity of atezolizumab and bevacizumab as first-line therapy in patients with unresectable or metastatic hepatocellular carcinoma in Costa Rica
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Author: Fernandez P.; Landaverde D.U.
Title: Real-world data on the effectiveness and toxicity of atezolizumab and bevacizumab as first-line therapy in patients with unresectable or metastatic hepatocellular carcinoma in Costa Rica
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