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Article

Evaluation of a Post-Marketing Safety Signal Associated with a Novel Innovative Medicinal Product and Coordination with Regulatory Authorities

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Abstract

Background/Objectives: Following the market authorization of innovative medicinal products, continuous monitoring of safety signals is essential to ensure a favorable benefit–risk balance. This is particularly relevant for biological therapies used in oncology, where complex mechanisms of action and patient-related risk factors may contribute to rare but serious adverse events. The objective of this paper is to describe and critically evaluate the internal pharmacovigilance processes applied by a pharmaceutical company in response to a potential post-marketing safety signal of stroke associated with a newly authorized biological medicinal product for colorectal cancer. **Methods:** A structured signal management approach was applied in line with international regulatory guidance. The evaluation included detailed clinical assessment of reported post-marketing cases, review of safety data from completed and ongoing clinical trials, epidemiological comparison with background stroke incidence, assessment of potential risk factors, and review of the pharmacological and biological plausibility. Additional data sources, including scientific literature, safety databases, and periodic safety reports, were systematically reviewed. Multidisciplinary collaboration among pharmacovigilance, medical, and regulatory teams supported the assessment and regulatory interactions. **Results:** The cumulative evidence did not allow confirmation of a definitive causal relationship between the medicinal product and stroke but identified the event as a potential safety signal requiring close monitoring. The assessment supported the preparation of an evidence-based company position and informed discussions with regulatory authorities, including the European Medicines Agency. **Conclusions:** This case illustrates the practical implementation of structured signal management in the post-marketing setting. Timely evaluation, interdisciplinary coordination, and regulatory engagement are essential to ensure patient safety, maintain regulatory compliance, and support informed benefit–risk decision-making for innovative biological medicinal products.

Keywords: pharmacovigilance; safety signal; biological medicinal product; stroke; benefit–risk assessment; post-marketing surveillance

1. Introduction

Innovative medicinal products have transformed the therapeutic landscape of oncology by enabling targeted and personalized treatment approaches. Biological and first-in-class therapies, in

particular, have demonstrated substantial clinical benefit in the management of malignant diseases; however, their complex mechanisms of action and interactions with patient-specific factors also introduce uncertainty regarding long-term safety outcomes [1,2]. As a result, the comprehensive evaluation of safety profiles extends beyond clinical development and remains a critical obligation throughout the post-marketing phase of the medicinal product life cycle.

Pharmacovigilance plays a central role in ensuring the ongoing assessment of the benefit–risk balance once a medicinal product is exposed to broader and more heterogeneous patient populations than those enrolled in pre-authorization clinical trials [3,4]. While randomized clinical studies are designed to evaluate efficacy and common adverse reactions, they are inherently limited in their ability to detect rare, delayed, or population-specific adverse events, particularly in elderly patients or those with multiple comorbidities [5]. Consequently, post-marketing safety surveillance, including spontaneous reporting systems and structured signal management processes, represents a cornerstone of public health protection.

Stroke is a serious and potentially life-threatening adverse event with a multifactorial etiology. Epidemiological evidence indicates an increased risk of cerebrovascular events in patients with cancer, driven by cancer-related hypercoagulability, systemic inflammation, and treatment-related factors [2,6–8]. Colorectal cancer, in particular, has been associated with elevated stroke risk, especially in advanced disease stages and in older patient populations [4,5,9]. These findings underscore the complexity of attributing causality when cerebrovascular events are reported in oncology settings and highlight ongoing debate regarding the relative contribution of underlying malignancy versus anticancer therapies [6,10].

Against this background, the identification of post-marketing reports of stroke in patients treated with a newly authorized, first-in-class biological medicinal product for colorectal cancer raises important scientific and regulatory questions. The emergence of such reports, especially when the adverse event is not previously characterized in core safety documents, necessitates a structured and transparent evaluation in accordance with Good Pharmacovigilance Practice and international regulatory guidance [11–13]. Diverging hypotheses regarding biological plausibility, background risk, and treatment-related effects must be critically examined to avoid both underestimation of potential risks and premature regulatory conclusions.

The primary aim of this work is to describe and critically analyze the internal pharmacovigilance processes applied by a pharmaceutical company in response to a potential post-marketing safety signal of stroke. By integrating clinical case evaluation, epidemiological context, pharmacological considerations, and regulatory requirements, this paper illustrates a practical and systematic approach to signal management. The findings highlight the importance of interdisciplinary collaboration, evidence-based decision-making, and proactive regulatory engagement in maintaining patient safety and confidence in innovative biological medicinal products.

2. Results

During the post-marketing phase of the medicinal product life cycle, particularly for newly authorized innovative therapies, continuous monitoring of the safety profile represents a fundamental responsibility of pharmaceutical companies and regulatory authorities. The timely identification, evaluation, and management of safety signals are essential not only for the protection of public health but also for ethical conduct and the maintenance of trust in innovative therapeutic approaches.

A novel innovative medicinal product has been developed by a pharmaceutical company as a first-in-class therapy for the treatment of colorectal cancer. The product was approved for use in combination with established therapies with proven clinical efficacy. Its regulatory status includes the granting of a Marketing Authorization (MA) in the European Union and approval via a New Drug Application (NDA) in the United States. The clinical development program comprised multiple phases of clinical trials and included more than 3000 patients across various oncological indications. Approximately 1500 of these patients were diagnosed with colorectal cancer. In addition, the

development program incorporated investigator-initiated studies (IIS), providing supplementary clinical experience outside company-sponsored trials. During the clinical development phase, nine cases of stroke were reported, all occurring in elderly patients. Based on the available data, investigators did not establish a direct causal relationship between the medicinal product and the reported cerebrovascular events [14,15].

In the post-marketing period, an oncologist from a European Union Member State reported three cases of stroke in patients treated with the new innovative biological medicinal product at a single clinical center. Following these events, the physician suspended the use of the product within the institution and submitted a spontaneous report to the European Medicines Agency (EMA). In parallel, the oncologist prepared a letter to a scientific journal describing the clinical cases and proposing a potential biological mechanism by which the active substance could be associated with cerebrovascular events. Subsequent to product launch, the company received two additional spontaneous reports of stroke. Notably, stroke was not listed as an adverse event in either the Investigator's Brochure (IB) or the Company Core Data Sheet (CCDS) at the time of reporting [16].

Clinical Case: Patient A—Assessment of a Possible Association between Biological Therapy and Stroke

Patient A was a 68-year-old male diagnosed with metastatic colorectal cancer and treated with the novel medicinal product in combination with capecitabine, a standard chemotherapeutic component for this indication. Twelve days after initiation of combination therapy, the patient experienced a stroke, leading to immediate treatment interruption and raising suspicion of a possible therapy-related adverse reaction. This case was considered particularly relevant because traditional stroke risk factors were not reported [26]. There was no prior cardiovascular disease, no comorbidities such as hypertension, diabetes, or atrial fibrillation, and no concomitant medications known to be strongly associated with cerebrovascular events. Laboratory parameters were reportedly stable. After discontinuation (dechallenge), no recurrence of neurological symptoms was observed; rechallenge was not performed. The absence of rechallenge limits confirmation but does not exclude causality. Based on WHO-UMC criteria, the case was classified as "probable/likely" [17,18], supported by a plausible temporal relationship, absence of clear alternative causes, and clinical stability after withdrawal. Using the Naranjo algorithm, the case achieved a total score of 7, corresponding to a "probable" association. Taken together, this case represents a clinically meaningful individual signal that, when evaluated in combination with other reports, may influence the evolving risk profile and support consideration of additional risk minimization measures, particularly for specific subgroups.

Clinical Case: Patient B—Assessment of a Potential Association in a High Baseline-Risk Patient

Patient B was a 75-year-old male with a complex medical history including type 2 diabetes mellitus, arterial hypertension, and a prior stroke two years earlier. He received the novel medicinal product for six weeks before experiencing another stroke. Blood pressure elevation was noted in the days preceding the event, and the patient was receiving antihypertensive therapy. Dechallenge and rechallenge were not performed, precluding evaluation of reversibility. This patient represented a high baseline-risk population independent of exposure to the novel therapy, and several alternative explanations were present. While temporal association existed, it was insufficient to establish a probable causal relationship. Using the Naranjo algorithm, the total score was 2, corresponding to a "possible" association [19]. Under WHO-UMC principles, the presence of strong alternative causes substantially reduced the likelihood of attributing the event to the medicinal product. Methodologically, this case highlights the need for stratifying cases by baseline risk and underscores the complexity of signal evaluation in patients with multiple comorbidities. Inclusion of such cases is important for cumulative assessment of frequency, pattern, and consistency within a broader pharmacoepidemiological framework.

In response to these reports and the potential public and scientific interest generated by the planned publication, the European Medicines Agency requested an urgent meeting with representatives of the pharmaceutical company, scheduled within three days. At this meeting, the company was required to present a comprehensive overview of all available clinical and post-

marketing safety data, an assessment of the potential safety signal, proposed risk management measures, and a strategy for appropriate communication with health authorities and the scientific community.

3. Discussion

Following receipt of a total of 14 additional reports of stroke after the introduction of the novel innovative medicinal product some originating from clinical studies and others from the post-marketing setting the company activated its established safety signal management process and immediately initiated actions aligned with Good Pharmacovigilance Practice. The response was guided primarily by GVP Module IX (Signal Management), relevant recommendations from the Heads of Medicines Agencies (HMA), and the Council for International Organizations of Medical Sciences (CIOMS) framework for evaluating safety signals [17,13]. According to these guidance documents, any new or unconfirmed observation that may indicate a previously unknown adverse reaction or a change in the frequency or severity of a known adverse reaction constitutes a potential signal that must undergo a formalized assessment and management process. The number of cases, their temporal relationship to product exposure, and the clinical seriousness of the event were considered sufficient indicators of a potential safety signal requiring structured evaluation in accordance with internationally accepted principles.

The signal management process followed sequential steps of validation, prioritization, assessment, and regulatory communication. Signal identification was supported by multiple sources, including clinical trials, spontaneous post-marketing reports, and information emerging from the scientific literature. The convergence of these independent sources increased the credibility of the observation and supported classification of stroke as a potential safety signal warranting further evaluation.

During the validation phase, the company sought to confirm that the reported events were medically plausible, sufficiently documented, and appropriate for signal assessment. Full medical documentation was requested for all 14 cases, including patient history, timing of onset relative to product administration, concomitant therapies, comorbidities, diagnostic confirmation, and outcomes. Independent medical experts were engaged to strengthen objectivity and minimize interpretive bias.

In line with GVP Module IX, the signal was prioritized as serious due to the nature of the event and the high baseline vascular risk in oncology patients. Following prioritization, the company performed a structured signal assessment incorporating epidemiological comparison of reported rates with expected background incidence in oncology populations, systematic literature review of potential pathophysiological mechanisms, and evaluation of whether similar events have been reported for products with comparable mechanisms of action (class effect). The analysis specifically explored biological plausibility, temporal association, evidence of dose–response, re-exposure patterns where available, and potential alternative explanations.

While the evaluation was ongoing, the company informed the European Medicines Agency (EMA) and relevant national competent authorities as part of the signal communication phase. A preliminary safety communication to healthcare professionals was prepared in the form of a Direct Healthcare Professional Communication (DHPC), and discussions were initiated within the Pharmacovigilance Risk Assessment Committee (PRAC) at the EMA. In line with regulatory expectations, the company committed to submitting a Signal Assessment Report (SAR) presenting the complete dataset and the conclusions of the internal review [17]. In parallel, internal procedures were triggered to ensure potential updates to core safety documents (including the CCDS, Investigator’s Brochure, and SmPC), to prepare additional informational materials for healthcare professionals, and to plan enhanced follow-up activities such as real-world evidence generation or a potential non-interventional study [18].

The ultimate objective of the process, consistent with GVP Module IX.C, is to support a regulatory decision grounded in an updated benefit–risk assessment. If evidence were to support a

causal association, possible regulatory actions could include updates to product information (SmPC, PIL, CCDS), restrictions for higher-risk subgroups, modifications to monitoring recommendations, or, in extreme circumstances, suspension or withdrawal if risk were to outweigh benefit. At the time of writing, the available evidence is not sufficiently robust to confirm a direct causal relationship. However, given the seriousness of the event, continuous monitoring remains active and new data will be reviewed in subsequent periodic benefit–risk evaluation reports (PBRER/PSUR).

Communication with regulatory authorities particularly the EMA constitutes an integral component of the process, ensuring transparency, timely data exchange, and alignment regarding appropriate actions. In this way, the company demonstrated a proactive and structured approach to signal management, recognizing the importance of early detection, transparent evaluation, and timely regulatory engagement in safeguarding public health and maintaining confidence in innovative biological therapies. [20].

3.1. Review of Safety Data from Clinical Trials

After approval in the European Union and the United States, the novel first-in-class biological medicinal product entered clinical use in patients with colorectal cancer. Within the clinical development program involving approximately 3000 patients across various oncologic diagnoses, around 1500 patients had confirmed colorectal cancer. Up to that point, the overall safety profile was considered acceptable, with expected and well-characterized adverse reactions. Nevertheless, nine cases of stroke were reported during the clinical program. Although no direct causal relationship was established for any of these cases, their occurrence prompted additional safety scrutiny.

These events were evaluated in the context of the established epidemiological background risk of stroke in oncology populations. Evidence from observational studies and meta-analytic data suggests that approximately 1.4% of patients with cancer experience stroke within the first year after diagnosis, with ischemic events accounting for the majority and hemorrhagic events representing a smaller proportion. When considering that all nine cases occurred within a colorectal cancer population of approximately 1500 patients, the observed incidence within the clinical program would be approximately 0.6%, which is below the reported annual background rate for oncology populations [19,21]. However, incidence estimates alone are insufficient to exclude a potential risk. The critical question is whether the events exhibit a consistent clinical pattern such as clustering in early post-diagnosis periods, association with concomitant therapies known to increase vascular risk, or enrichment among patients with predisposing factors (e.g., hypertension, arrhythmias, prior thromboembolic disease).

The literature also indicates that patients with colorectal cancer may have an increased risk of stroke during the early months after diagnosis, which supports the possibility that the underlying malignancy, rather than the medicinal product, could contribute substantially to risk. This consideration became more pressing after commercialization, when two additional post-marketing reports were received, and an oncologist from an EU Member State submitted a spontaneous report describing three stroke cases occurring within one month at a single clinical center. Local use of the product was suspended, the EMA was notified, and a letter to a scientific journal proposed a plausible mechanism by which the biological therapy might affect vascular function and contribute to stroke risk. Although the total number of cases (14 overall: 9 from clinical development and 5 post-marketing) does not appear alarmingly high within the context of oncology, the complexity of clinical scenarios, the nature of the product, and a proposed mechanistic hypothesis justified a systematic analysis.

Accordingly, detailed medical documentation was collected for all cases, focusing on temporal relationship to exposure, clinical context, comorbidities, and concomitant medications. In parallel, a provisional timeline for possible updates to regulatory documentation (e.g., CCDS and SmPC) was prepared in case the cumulative evidence suggested a plausible association. At this stage, a definitive conclusion that the product causes stroke could not be supported; equally, a causal contribution could not be fully excluded given potential mechanistic pathways through which innovative biological

therapies might influence endothelial function, hemostasis, or inflammatory processes. Therefore, enhanced monitoring of future cases and stratification by indication, baseline risk profile, duration of treatment, and stroke subtype were prioritized. Where feasible, comparative analyses using suitable control groups were considered to determine whether a statistically and clinically meaningful signal exists or whether the observed cases reflect variability within a population with an inherently high baseline risk [22].

3.2. Review of Post-Marketing Safety Data

After market introduction, five post-marketing reports of stroke were received. Two reports were spontaneous cases submitted through routine pharmacovigilance channels; however, the information was limited, preventing robust assessment of causality. Key clinical elements were missing, including temporal relationship to exposure, concomitant therapies, medical history, and diagnostic confirmation. Three additional cases were reported by an oncologist in the European Union who observed stroke events in patients treated at the same clinical center over a one-month period. These cases were more comprehensively documented and contained sufficient clinical information to support a preliminary causality assessment (Table 1). The oncologist suspended use locally and informed the EMA, while also notifying a scientific journal and proposing a pathophysiological hypothesis [23].

Table 1. Summary of post-marketing stroke cases reported after product commercialization.

Case No.	Data Source	Seriousness	Outcome	Causality Assessment*
1	Spontaneous report	Serious	Unknown	Unassessable (insufficient data)
2	Spontaneous report	Serious	Unknown	Unassessable (insufficient data)
3	Oncology center (EU)	Serious	Recovered	Possible
4	Oncology center (EU)	Serious	Ongoing	Possible
5	Oncology center (EU)	Serious	Fatal	Possible

*Causality was assessed according to WHO-UMC criteria based on available clinical information.

Overall, although the number of post-marketing cases was limited, the occurrence of serious events in close temporal proximity particularly the clustering of cases within a single clinical center supported the classification of this observation as a potential safety signal requiring further benefit-risk contextualization and assessment [24].

A key component of post-marketing signal evaluation is estimating the likelihood that the reported adverse event (stroke) is causally related to the medicinal product. Two established approaches were applied: the WHO-UMC causality assessment system and the Naranjo algorithm. The WHO-UMC system categorizes causality as certain, probable/likely, possible, unlikely, conditional/unclassified, or unassessable, based on factors such as time-to-onset, biological plausibility, response to withdrawal (dechallenge), recurrence on re-exposure (rechallenge), and alternative explanations [23,24]. The Naranjo algorithm provides a structured, quantitative scoring approach based on ten standardized questions; total scores classify causality as definite (≥ 9), probable (5–8), possible (1–4), or doubtful (≤ 0). Applying these tools supports a more standardized internal evaluation, strengthens readiness for regulatory communication, and aligns with GVP Module IX and CIOMS IV recommendations for signal management [13–17]. In the present case, where cases originated from clinical trials, an oncologist-reported cluster, and routine post-marketing reports, use of these methodologies enabled (i) objective classification of individual cases, (ii) assessment of whether a probable or certain association is supported, (iii) informed decision-making on whether the signal may be confirmed, and (iv) evidence-based justification for potential updates to product information if warranted.

3.3. Internal Organization and Communication Mechanisms After Signal Identification

Following identification of a potential signal of stroke in patients treated with the novel medicinal product, the company proactively mobilized internal resources to ensure a timely, coordinated, and professionally managed response. This approach aligns with good signal management practices and the principles of high-quality medical communication with stakeholders. A key initial step was the engagement of all functions that interact directly with healthcare professionals and patients, including Medical Information, customer support units, and call center services for inquiries and reports [25,26].

Medical information teams were instructed to manage neurological adverse event inquiries with heightened vigilance and signal awareness. Medical Information teams, supported by validated scientific information resources, were integrated into an internal communication network enabling consultation with relevant experts (pharmacovigilance, clinical development, medical advisors). When inquiries required medical judgement or when case credibility needed assessment, calls were escalated to pharmacovigilance or complaint-handling pathways for formal documentation and further evaluation as potential signal-generating inputs.

In parallel, the company implemented continuous updating of an internal “position report” for the signal [22]. This living document functioned as a centralized single source of truth, compiling initial and subsequent clinical/post-marketing reports, causality assessments (WHO-UMC, Naranjo), epidemiological and analytical evaluations, literature review outputs, and proposed or implemented regulatory actions. The document formed the basis for consistent external communication, DHPC preparation, regulatory engagement, and potential updates to SmPC and CCDS. This integrated approach ensures that responses provided to healthcare professionals are consistent, accurate, and aligned with the most current evidence particularly important in contexts where transparency and trust are critical. The system further strengthens regulatory and legal compliance and enables rapid escalation and assessment of emerging risks, reflecting not only technical capability but also a culture of quality and responsibility toward patients and the healthcare community [27].

3.4. Preparation for Potential Risk Communication

Beyond internal coordination, the company prepared for the possibility of formal communication to the healthcare community. In pharmacovigilance practice, the DHPC is a recognized tool for timely dissemination of new or changed safety information that may influence prescribing decisions. Although it had not yet been determined whether a DHPC would be issued in this case, the company proactively alerted Medical Information to prepare for this possibility [16]. DHPCs, typically coordinated through EMA/PRAC or national competent authorities, are part of risk minimization measures and aim to mitigate risk by modifying clinical behavior or increasing awareness. Their content depends on the signal, but commonly includes newly identified serious adverse reactions, changes to indications, new contraindications, dosing or administration changes, recommendations for enhanced monitoring, and interaction warnings [17].

When a potential signal is under evaluation but not confirmed, preparatory steps remain essential. In this case, scientific, legal, and regulatory teams initiated structured activities including synthesis of available evidence, definition of target populations most affected, development of draft key messages, legal/regulatory review of language and format, and preparation of distribution and effectiveness monitoring plans [18,20]. Evidence indicates that DHPC effectiveness may vary and depends on severity, clarity, targeting, and distribution strategy [20,24,28]. Accordingly, both proximal outcomes (e.g., changes in dosing or monitoring) and distal outcomes (e.g., reduction in adverse events) should be considered when evaluating effectiveness [25,28]. Proactive preparation enables rapid and appropriately formulated communication should the signal become confirmed, while supporting patient protection and preserving trust even if the DHPC ultimately proves unnecessary [23,26].

3.5. Review of the Global Literature on Stroke in Patients with Cancer

As part of signal management, a detailed review of the published literature was conducted to identify relevant evidence on stroke occurrence among patients with colorectal cancer and cancer populations more broadly [4,6,7,13,19]. This review supported contextualization of reported cases and interpretation against baseline incidence and risk factors [10,11,14,16]. The pharmacovigilance unit systematically searched databases including PubMed, Embase, and Scopus using combinations of keywords (e.g., “stroke”, “cerebrovascular event”, “colorectal cancer”, “oncology”, “biological therapy”) [12,15,20]. The review included clinical studies, meta-analyses, retrospective registries, and case reports focusing on incidence, risk factors (age, comorbidity burden, concomitant chemo/targeted therapy), and reports relevant to therapies with similar mechanisms [4,6,7,10,11,13,25].

Published evidence indicates an increased stroke risk in cancer patients, particularly in advanced disease and early post-diagnosis periods [4,6,7,13,19]. For colorectal cancer, retrospective data suggest increased thromboembolic and cerebrovascular risk driven by inflammation and hemostatic alterations related to the tumor and treatment [2,17]. Direct evidence linking therapies with similar mechanisms to stroke was not conclusive, although thrombotic risks have been reported with certain immunotherapies and anti-angiogenic therapies [6,13,25,29]. Individual case reports describe stroke events under immunotherapy or biological combinations but do not provide sufficient evidence for causality [10,11,14,16]. More recent studies reinforce the association between malignancy and cerebrovascular events: increased early post-diagnosis risk [29], thromboembolic associations with immunotherapy [30], metastatic disease as an independent predictor [31], anti-VEGF-associated case descriptions [32], and meta-analytic evidence indicating approximately two- to three-fold increased risk in cancer populations.

3.6. Requests for Epidemiological Data from Registries and Automated Databases

Within an integrated and evidence-based approach to signal assessment, the company initiated pharmacoepidemiological analyses as an additional tool to evaluate risk [14–17,20,25,28]. The objective was to obtain independent, comparative, real-world estimates of stroke incidence among exposed patients versus suitable unexposed comparators [20,25,28]. The company planned access to established healthcare databases capturing diagnoses, treatments, outcomes, and demographics from routine clinical practice [19,20,28].

Key sources considered included VigiBase (WHO/UMC) as a global repository of adverse reaction reports supporting detection of rare serious events [13,25]; the UK General Practice Research Database/Clinical Practice Research Datalink (GPRD/CPRD) enabling linkage across prescriptions, diagnoses, laboratory parameters, and outcomes [19,20]; and large US systems such as Medicaid and Kaiser Permanente, widely used for population-level real-world evidence and recognized by regulators for post-marketing evaluation [20,26]. Planned analytical approaches included cohort analyses for incidence comparisons, case–control studies for association testing, propensity score methods to reduce confounding, and stratified analyses by key risk factors such as age, comorbidities, cancer subtype, and treatment duration [19,20,26]. These analyses aimed to clarify whether stroke incidence is increased under exposure, whether risk differs across subgroups, whether there is temporal clustering early in treatment, and whether patterns are consistent across settings (Figure 1) [7,19,25,32].

The approach aligns with pharmacoepidemiology guidance and supports potential regulatory decision-making, including updates to product information or population restrictions if a clinically meaningful association is identified [14–17,20,28].

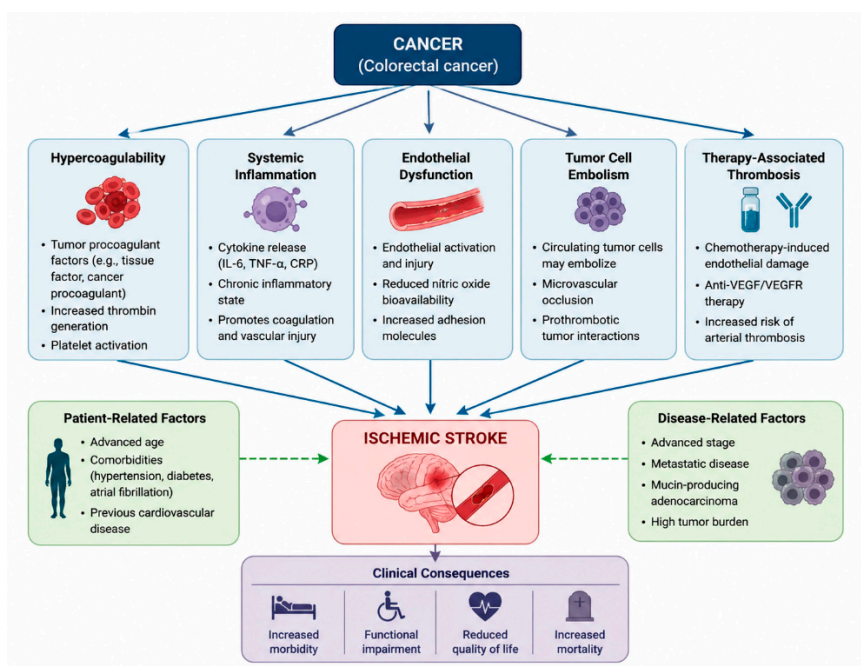


Figure 1. Proposed mechanisms linking cancer and stroke in oncology patients.

3.7. Pharmacovigilance Activities—Routine and Additional Measures

Throughout the signal management process, the company continued routine and additional pharmacovigilance activities in accordance with international regulatory requirements [14–16]. Routine activities included systematic collection, processing, and assessment of suspected adverse reactions through established procedures, continuous monitoring for new signals, scientific evaluation of emerging safety information, and timely updates to core safety documents (CCDS, SmPC, PIL), alongside appropriate regulatory engagement.

Given the seriousness of stroke as an event—irrespective of whether causality is ultimately confirmed the company also initiated additional activities coordinated with clinical functions [15,16,18,25,26]. A pharmacoepidemiological study was planned to generate real-world evidence from larger populations and provide quantitative risk estimates, identify risk factors and susceptible subgroups, and strengthen inference regarding potential association [20,21,25,28]. Ongoing clinical studies, including investigator-initiated studies, were maintained to support long-term safety characterization, with particular attention to cerebrovascular outcomes [20,28]. The company position report continued to be updated in parallel as new evidence emerged, supporting a proactive and regulatorily compliant approach to signal management and patient safety protection [15,25,28].

3.8. Risk Minimization Measures

If the potential association between the novel medicinal product and stroke were to be confirmed, the company would implement appropriate risk minimization measures in line with European regulatory guidance [17]. Routine measures would include updates to official product information. Specifically, the SmPC would be revised to include the potential risk in Section 4.4 (“Special warnings and precautions for use”), particularly for higher-risk populations such as older patients, patients with comorbidities (e.g., hypertension), advanced disease, or concomitant oncologic therapies [18]. If supported by causality assessment, stroke would be included in Section 4.8 (“Undesirable effects”), with corresponding updates to the Patient Information Leaflet (PIL). Given the product’s novelty and the likelihood of enhanced monitoring status, intensified post-marketing surveillance would be maintained to enable rapid detection of evolving risk patterns.

Additional measures would include development and distribution of educational materials for healthcare professionals to raise awareness and support identification and monitoring of patients at

higher risk [15–17,26]. Materials would focus on risk factors, monitoring, and early symptom recognition. Such proactive communication is expected to improve patient safety and strengthen trust among clinicians and the public, reflecting the company's ethical and transparent pharmacovigilance commitment [6,7,13,32].

In parallel, timely notification of the public relations function and legal department was considered essential while the company position was still being defined. Public relations would be prepared to deliver consistent, verified communications for different audiences, including the general public and the medical community, preserving corporate integrity and public trust. Legal counsel would assess potential legal implications and readiness for possible regulatory or litigation processes arising from safety concerns or public dissemination of information. These measures enhance internal alignment, reduce communication and legal risks, and support an organized response to external challenges.

Based on the available clinical and post-marketing evidence, there is currently insufficient evidence to confirm that stroke is causally related to the medicinal product. In clinical trials, nine stroke cases were identified and assessed as unrelated. Two routine post-marketing spontaneous cases lacked sufficient information for causality assessment, whereas the three cases reported by an EU oncologist suggested possible association but are not sufficient alone to confirm a signal. Additional clinical review is therefore required, including potential on-site follow-up at the reporting hospital to obtain validated and complete clinical datasets. The company position report will be updated accordingly. The literature indicates that cancer patients have increased stroke risk, particularly in the early months after diagnosis, regardless of cancer type or therapy, but does not provide consistent evidence linking stroke specifically to the product under evaluation [15–17,20,25,28].

The company therefore requested additional epidemiological data from relevant registries and automated databases; findings will further inform updates to the internal assessment. If the signal is not confirmed, routine pharmacovigilance monitoring will continue. Nevertheless, because stroke is a serious outcome, a pharmacoepidemiological study will be conducted to provide a robust quantitative risk assessment [20,28]. Ongoing clinical studies will continue to provide long-term safety data, including cerebrovascular outcomes, supporting consolidation of the scientific position and ongoing benefit–risk evaluation (Figure 2) [19,20,28].

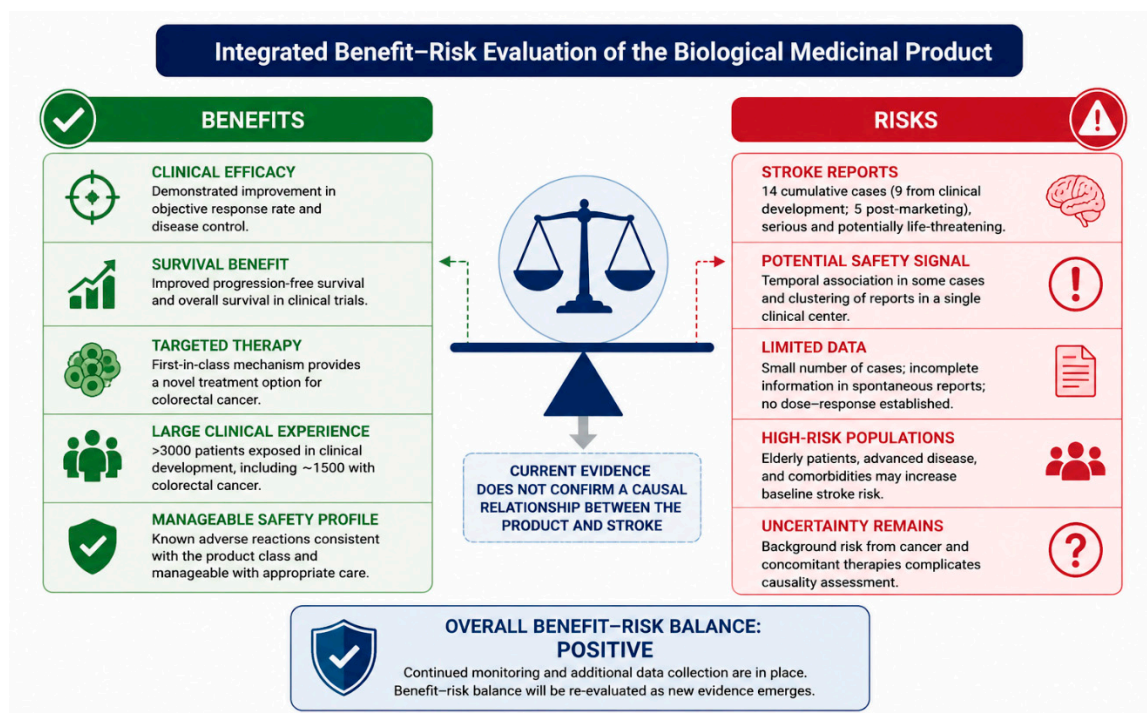


Figure 2. Integrated benefit–risk profile of the innovative biological medicinal product for colorectal cancer treatment.

Overall, the benefit–risk balance remains positive at the current stage, but requires continuous evaluation and proactive risk management as core elements of responsible pharmacovigilance and public health protection [15–17,23–26,32].

4. Materials and Methods

The assessment of the potential safety signal related to stroke was conducted in accordance with the principles and requirements of Good Pharmacovigilance Practice (GVP), specifically GVP Module IX (Signal Management) and GVP Module VI (Management and Reporting of Adverse Reactions). The methodological approach followed a structured, stepwise process comprising five integrated activities with clearly defined responsibilities, documentation standards, and timelines [16].

Signal identification and initial verification involved the receipt and formal documentation of the spontaneous report submitted by an oncologist within the European Union. The clinical information provided through written correspondence was reviewed in parallel with verification of the case(s) in the EudraVigilance database. A comprehensive search was subsequently performed in the company’s global safety database to identify any additional cases of stroke. An internal preliminary evaluation was then conducted to determine whether the reported events represented a new, serious, and previously uncharacterized safety signal.

Quantitative and qualitative analyses were performed by extracting all relevant cases of stroke from clinical trials (interventional and non-interventional), post-marketing spontaneous reports, and investigator-initiated studies. Each case underwent detailed medical review using established causality assessment criteria, including temporal relationship, dose exposure, presence of confounding factors, and alternative etiologies. Standardized causality assessment tools, such as the WHO–UMC system and/or the Naranjo algorithm, were applied to evaluate the likelihood of a causal association. Where appropriate, disproportionality analyses (e.g., Proportional Reporting Ratio or Reporting Odds Ratio) were conducted in comparison with reference medicinal products.

A systematic review of the scientific literature was undertaken using databases such as PubMed and Embase, focusing on class effects, previously reported cerebrovascular events associated with similar therapies, and proposed mechanisms of action. Medical experts and internal scientific specialists were engaged to assess the biological plausibility and potential pathophysiological basis for a relationship between the medicinal product and stroke.

Effective coordination and internal communication were ensured through the establishment of a dedicated signal assessment working group. This group included the Qualified Person Responsible for Pharmacovigilance (QPPV), representatives from regulatory affairs, medical affairs, quality, and legal functions. Regular internal meetings were conducted, and all discussions, evaluations, and decisions were formally documented within a signal assessment protocol to ensure traceability and regulatory compliance.

Preparation for regulatory communication involved the development of a comprehensive Company Position Paper summarizing all available evidence. This document included an integrated analysis of reported cases, an evaluation of the benefit–risk balance [17], and recommendations for potential risk management actions, such as updates to the Company Core Data Sheet (CCDS), Summary of Product Characteristics (SmPC), or Risk Management Plan (RMP) [16,18]. A structured presentation was prepared for the meeting with the European Medicines Agency (EMA), outlining key findings, proposed next steps, and the company’s position. The potential need for submission of a Type II variation was also considered in the event that updates to product information were deemed necessary.

This methodological framework ensured a transparent, scientifically robust, and regulatorily compliant approach to the evaluation of a new safety signal. The assessment of the stroke signal associated with the novel innovative medicinal product represents a clear example of the importance

of active pharmacovigilance following market authorization. Although clinical trials did not indicate a clear safety risk and the number of reported stroke cases during development was low and without confirmed causality, the increased frequency of spontaneous reports in the post-marketing phase particularly the clustering of multiple events within a single clinical center necessitated an urgent and thorough evaluation.

The pharmacovigilance response incorporated a comprehensive analysis ranging from epidemiological context to biological plausibility, enabling a balanced and rational assessment without precipitating disproportionate or unjustified regulatory action. Nevertheless, despite the absence of a definitive causal relationship, the temporal association and clinical seriousness of the reported events warranted heightened caution. Consequently, interim risk minimization measures and clear communication with healthcare professionals were proposed while additional evidence continues to be collected.

From a regulatory perspective, the company's timely response and initiation of an internal assessment within defined timelines demonstrate a robust pharmacovigilance system and compliance with GVP standards. The willingness to update core safety documents and to consider enhanced monitoring through real-world evidence further reflects a proactive and responsible approach. While the identified signal is serious and requires ongoing monitoring, it does not currently alter the overall positive benefit–risk assessment of the medicinal product. Continued surveillance, potential updates to relevant documentation, and consideration of additional non-interventional studies are therefore warranted. Transparent, data-driven communication with regulatory authorities and proactive management of potential media impact are essential to maintaining trust among healthcare professionals and patients. This case highlights the inherent challenges associated with monitoring innovative therapies and underscores the necessity of a well-organized, integrated, and evidence-based pharmacovigilance system capable of responding rapidly and responsibly to emerging safety information.

5. Conclusions

The pharmaceutical company's preparedness for engagement with the European Medicines Agency (EMA) reflects a structured and responsible approach to the management of potential safety signals. Following the identification of a possible association between stroke and a newly authorized innovative biological medicinal product for colorectal cancer, a coordinated multidisciplinary evaluation was conducted to establish a scientifically and regulatorily sound position.

Available evidence from clinical trials, post-marketing reports, epidemiological data, and published literature does not currently support a definitive causal relationship between the medicinal product and stroke. Although several post-marketing cases suggest a possible association, the overall findings indicate that stroke represents a potential safety concern rather than a regulatory crisis. The occurrence of cerebrovascular events in oncology patients is multifactorial and may be influenced by underlying disease, comorbidities, and concomitant therapies.

The company remains prepared to act in accordance with regulatory expectations. If the signal is confirmed, appropriate risk minimization measures including updates to product information, educational materials for healthcare professionals, and additional pharmacoepidemiological studies will be implemented. If not confirmed, routine pharmacovigilance activities and continued monitoring will be maintained.

At this stage, the benefit–risk balance of the medicinal product remains positive. Ongoing surveillance, transparent regulatory communication, and evidence-based decision-making are essential to ensure patient safety and sustain confidence in innovative biological therapies.

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Abbreviations

The following abbreviations are used in this manuscript:

CCDS Company Core Data Sheet

CIOMS Council for International Organizations of Medical Sciences

CPRD Clinical Practice Research Datalink

DHPC Direct Healthcare Professional Communication

EMA European Medicines Agency

FDA U.S. Food and Drug Administration

GPRD General Practice Research Database

GVP Good Pharmacovigilance Practices

HCP Healthcare Professional

HMA Heads of Medicines Agencies

MedInfo Medical Information

PIL Patient Information Leaflet

PRAC Pharmacovigilance Risk Assessment Committee

PSUR Periodic Safety Update Report

PBRER Periodic Benefit–Risk Evaluation Report

QPPV Qualified Person Responsible for Pharmacovigilance

SmPC Summary of Product Characteristics

UMC Uppsala Monitoring Centre

WHO World Health Organization

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