Roche’s commitment to safety

Pharmacovigilance with emicizumab▼

▼ Emicizumab (HEMLIBRA®) is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

M-XX-00008945
Date of preparation April 2022

Patient safety is a top priority for Roche

Roche follows all regulatory reporting requirements and is committed to:

- **Monitoring** the safety of all of our medicines through established reporting mechanisms[1]
- **Reporting** all serious and unexpected adverse drug experiences to regulatory authorities[2]
- **Investigating** the details of serious and unexpected adverse drug experiences[1,2]
- **Communicating** all important safety information to healthcare providers in a timely fashion[1]

The quality of processes and systems are regularly audited internally and inspected by regulatory authorities

It is important to note, however, that Roche is not authorized to compel the provision of information on safety events in the post-marketing setting

1. F. Hoffmann-La Roche Ltd. Protecting Patient Safety. https://www.roche.com/about/sustainability/patient-safety/. Accessed Apr 2022; 2. US Food & Drug Administration. CFR – Code of Federal Regulations Title 21. https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=05854c5c8fcd51dc6ddefc54716eaa02&ty=HTML&h=L&mc=true&r=SECTION&n=se21.5.314_180. Accessed Apr 2022.

We monitor safety throughout the product lifecycle

- This process includes[1]:
  - **Risk management plans**
  - **Ongoing database review**
  - **Regular review of published literature**
  - **Product quality monitoring**

- Everyone who works at Roche (or on behalf of Roche), regardless of role, is mandated to report adverse events that they become aware of to the Roche pharmacovigilance team

- For emicizumab, we have enhanced monitoring and expedited reporting of **all thrombotic microangiography (TMA) and thrombotic events** to the regulatory authorities for 5 years following approval[2]

*The **most important sources** for product **safety information** are the **product label and patient information** that are included in the packaging of all medications. The product label and patient information must all be approved by regulatory authorities[1]*

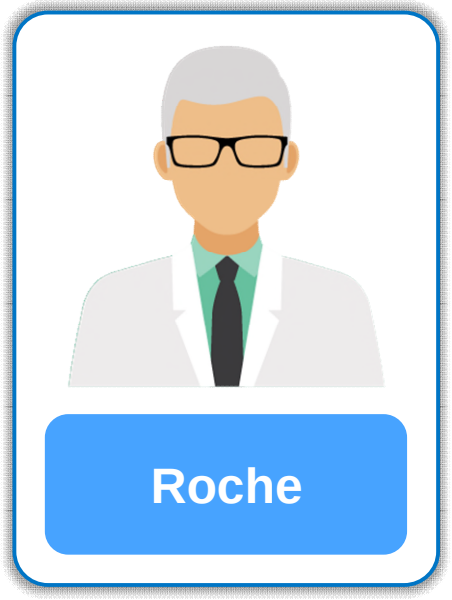
1. F. Hoffmann-La Roche Ltd. Protecting Patient Safety. https://www.roche.com/about/sustainability/patient-safety/. Accessed Apr 2022; 2. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Hemlibra BLA 761083 approval letter Nov 16, 2017. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/761083Orig1s000ltr.pdf. Accessed Apr 2022.

Roles and responsibilities

Roche

Monitoring, Reviewing and Training

- Weekly literature report review[1]
- Reviewing investigator causality assessments[2]
- Regular digital media and press screening[1]
- Training all employees and contractors on safety reporting processes[1]
- Individual Case Safety Report (ICSR) submission to local databases (e.g. FAERS for the US and EudraVigilance for the EU)[2–4]
- Expectedness assessments[2]



Reporting and Communications

- Suspected unexpected serious adverse reaction (SUSAR) reporting to all required authorities
- Reporting emerging safety issues to the regulatory authorities
- Periodic benefit–risk evaluation reports (PBRERs), which are also submitted to the regulatory authorities

1. EMA/873138/2011. Guideline on Good Pharmacovigilance Practices (GVP)-Module VI (2017); 2. European Commission. CT3 Official Journal of the European Union 2011;172:1–13; 3. Kaeding et al. Pharmacovigilance in the European Union. Springer 2017, DOI: https://doi.org/10.1007/978-3-658-17276-3; 4. FDA Adverse Events Reporting System (FAERS) - FDA Adverse Events Reporting System (FAERS) Public Dashboard Center for Drug Evaluation and Research - https://www.fda.gov/drugs/surveillance/fda-adverse-event-reporting-system-faers. Accessed Apr 2022.

Roles and responsibilities

Roche

Roche

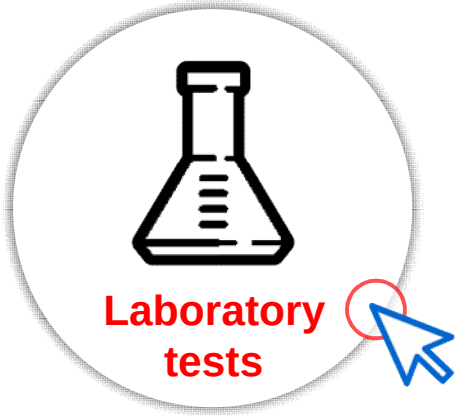
Additional commitments from Roche

- External clinical trial safety committees
- Internal data safety committees
- Regular internal safety audits
- Consultations on the safety profiles of drugs with regulators
- Regular communication of safety information for events of special interest
- Prioritising safety as a topic for seeking advice at advisory boards/consultancies

Roles and responsibilities

Healthcare professionals

- AE causality assessments[1]
- AE seriousness assessments[1]
- Notifying the sponsor/marketing authorisation holder of serious adverse events or reactions[1]
- Disseminating safety information to patients and/or their carers[2]
- Spontaneous adverse event reporting via local practices[3]
- Timely reporting of safety events relating to specific requirements (e.g. black triangle products in the EU▼)[3]



Unexplained abnormal laboratory test results should also be reported as AEs[1]

In trial: typically reported to the sponsor via the principal investigator

Out of trial: typically reported via the Yellow Card scheme or other local reporting systems by the responsible HCP

AE, adverse event; HCP, healthcare professional

1. European Commission. CT3 Official Journal of the European Union 2011;172:1–13;
2. EMA/118465/2012. Guideline on Good Pharmacovigilance Practices (GVP)-Module XV (2017);
3. Kaeding et al. Pharmacovigilance in the European Union. Springer 2017, DOI: https://doi.org/10.1007/978-3-658-17276-3.

Roles and responsibilities

Regulatory authorities

- Implementing and operating PV legislation[1]
- Coordinating activities relating to the authorisation and maintenance of medicines licences[1]
- Guiding pharmaceutical companies and HCPs in their obligation to appropriately report adverse safety events[1]
- Approving risk minimisation materials[2]
- Review of clinical trials

Regulatory Authorities

- Designing and evaluating post-licensing safety studies and PV inspections[3]
- Organising the additional monitoring of products that have a black triangle▼ or black box warning, including approving the list of such products that are subject to additional monitoring[1,4]
- Maintaining and reviewing key databases for ICSRs[1]

1. Kaeding et al. Pharmacovigilance in the European Union. Springer 2017, DOI: https://doi.org/10.1007/978-3-658-17276-3;
2. Calvo & Zuniga. Drug Safety 2014;37:9–18;
3. ABPI Pharmacovigilance Expert Network. Patient Safety and Pharmacovigilance 2014;
4. Food and Drug Administration. A guide to drug safety terms https://www.fda.gov/media/74382/download, Accessed Apr 2022.

HCP: healthcare professional; ICSR: Individual Case Safety Report; PV: pharmacovigilance

Roles and responsibilities

Patients and caregivers

Roles and Responsibilities

- Clear labelling of biological or newly licensed medications with a black triangle (▼) or similar label encourages patients or carers to report any adverse events[1]
- Patients or caregivers can report adverse events via their local regulatory authority
- Patients or caregivers can also report directly to Roche via their local Roche representative

Impact

- Additional monitoring of products ensures their safer use[1]
- Treatment of a patient's adverse reaction by HCPs may be advised by previous reports[2]
- Collection of safety information can initiate changes to risk management plans, product information and product licensing, facilitating safer use of medicines[2,3]

1. Kaeding et al. 2017, DOI: https://doi.org/10.1007/978-3-658-17276-3;
2. ABPI Pharmacovigilance Expert Network. Patient Safety and Pharmacovigilance 2014;
3. Global Clinical Trials Playbook: Ch.13. Elsevier 2012, https://www.sciencedirect.com/book/9780124157873/global-clinical-trials-playbook. Accessed Apr 2022.

HCP, healthcare professional

Clinical trials sponsored by industry

Confidential reporting

Adverse event

Investigator

Notifies Roche of serious adverse event **within 24 hours** of learning of the event

Roche

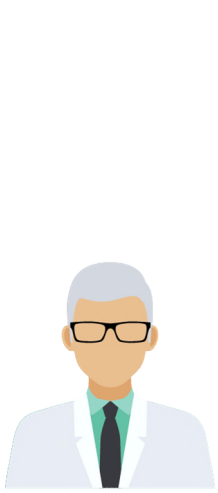
Within 7 days of the event, Roche must report unexpected **fatal or life-threatening** suspected adverse reactions to the regulatory authorities

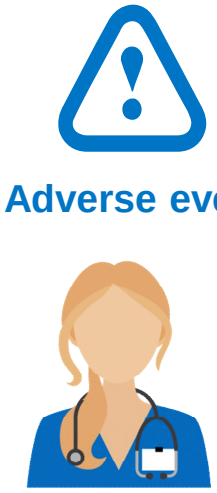
Other adverse reactions are reported **within 15 days** of the event

Regulatory Authorities

Post-marketing setting

Industry must promptly review all adverse drug experience information





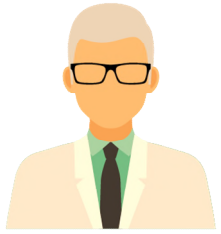
Investigators

Healthcare Professionals

Patients and caregivers

Anyone can report an adverse drug event directly to the manufacturer and/or the regulatory authorities

Adverse event



Roche

Post-marketing surveillance

Published literature

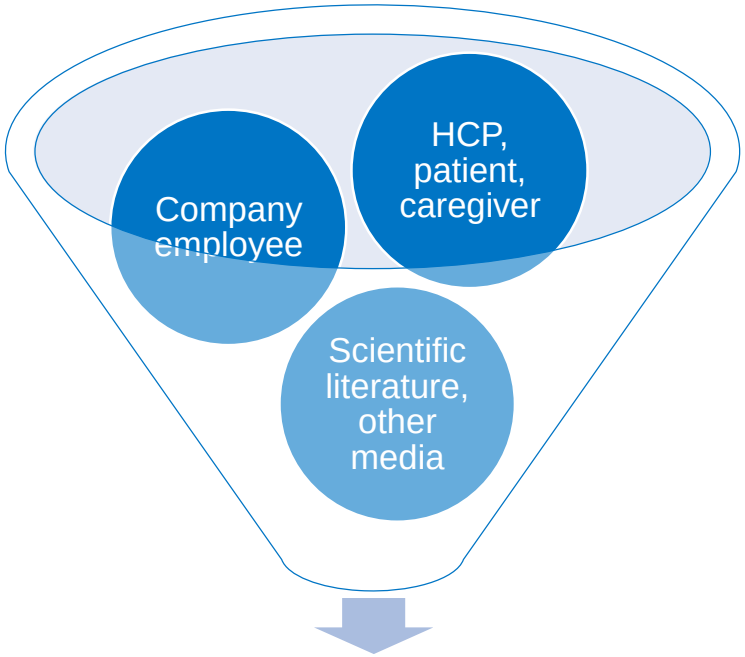
Spontaneous reports from
- Healthcare providers
- Patients
- Caregivers

Solicited information (e.g. market research, patient support programmes)

Regulatory Authorities

How is an adverse event report handled by Roche?

Reports of adverse events can come from many different sources



Roche

Reviews all adverse event reports

Enters information into a safety database for aggregate assessment

Follow up via fax, email, or mail

- With healthcare provider
- With patient or reporter if healthcare provider contact information is not available

Follow up via phone call

- For cases involving events that are currently of high interest for oversight of safety profile
- If no fax, email or address has been provided

Additional follow-up may be needed

- Our understanding of the safety profile may change over time, and sometimes there is a need to perform additional follow-up of an adverse event after the initial review and follow-up

Roche depends on bidirectional communication to gain better understanding of the adverse event reported and inform the overall safety profile of a medication

U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, 2005. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-pharmacovigilance-practices-and-pharmacoepidemiologic-assessment, Accessed Apr 2022.

HCP, healthcare professional

What does Roche do with adverse event information?

Ongoing, aggregate review of data in the safety database (signal detection, cross-comparison of case)

- Based on findings from aggregate reviews, additional follow-up for some cases may be required
- HCPs may be contacted again for additional information

Report to Global Health Authorities and, in some cases, directly communicate to the HCP community as per regulations

Update the prescribing information, if indicated

HCP, healthcare professional

Regulatory reporting requirements in the post-marketing setting

- ***As soon as possible and within the time limit imposed by local regulations,*** Roche is required to report to the regulatory authorities each adverse drug experience that is both serious and unexpected.
  - for emicizumab, some regions also have enhanced monitoring and expedited reporting of **all thrombotic microangiopathy (TMA) and thromboembolic events** for a period of time (e.g. 5 years in the US) after approval
- ***Once every 6 months,*** a Periodic Benefit–Risk Evaluation Report (PBRER) is prepared that includes relevant new safety information that could have an impact on the benefit–risk profile
- The PBRER is a report by the manufacturer that provides **an analysis of new/emerging information** on the risks of a product and on its benefit in approved indications, to enable an appraisal of the product's overall benefit–risk profile
  - **includes new safety information** relevant to the product that has become available during the reporting interval as well as an evaluation of the product's benefit–risk profile
  - **includes new information on effectiveness** under conditions of actual use for approved indications
  - **used to determine whether changes should be made** to the product information included in the packaging

How do we communicate emicizumab safety information?[1]

The local product label is the primary source of information on the indication and known risks of emicizumab

In addition to the information in the product label, we will ensure that healthcare providers, patient advocacy groups, and patients/caregivers receive appropriate and timely safety information

WHERE

Channels:

- **Publication of clinical trial results**, positive as well as negative, in scientific journals
- **Presentation at scientific conferences**
- **Registered and posted summary reports** for trials involving patients on clinicaltrials.gov and on roche-trials.com
- **Medical information** on websites and through responses to enquiries from healthcare professionals as well as patients

1. F. Hoffmann-La Roche Ltd. Protecting Patient Safety. https://www.roche.com/about/sustainability/patient-safety/. Accessed Apr 2022.

How do we communicate emicizumab safety information?[1]

The local product label is the primary source of information on the indication and known risks of emicizumab

In addition to the information in the product label, we will ensure that healthcare providers, patient advocacy groups, and patients/caregivers receive appropriate and timely safety information

WHEN

- We **proactively communicate when there is a change in the safety profile** of emicizumab after appropriate notification to regulatory authorities
- We **respond to enquiries** from healthcare professionals, patients and caregivers as part of our standard scientific communication

HOW

- We **respect and maintain patient confidentiality** in all of our communications
- **Post-marketing reports** are included in continued monitoring of the safety profile of emicizumab, although these reports may contain missing or incomplete information, with limited ability to ascertain or verify the information

1. F. Hoffmann-La Roche Ltd. Protecting Patient Safety. https://www.roche.com/about/sustainability/patient-safety/. Accessed Apr 2022.

Patients and healthcare professionals can help us support safe medication use

Healthcare Professionals

Assess causality and seriousness of adverse reactions

Notify the manufacturer and the local regulatory authorities of adverse reactions

Disseminate safety information to patients and/or their caregivers

Patients and Caregivers

Report side effects to your healthcare provider

- Patients, caregivers and/or healthcare professionals can then report side effects to the manufacturer and/or the local regulatory authority

Patient safety is a top priority for Roche

- We are **committed to monitoring** the safety of all our medicines through established reporting mechanisms
- We are **committed to timely and responsible communication** of safety information following necessary interactions with the authorities
- The most important sources for product safety information are the product label and patient information that are included in the packaging of all medications

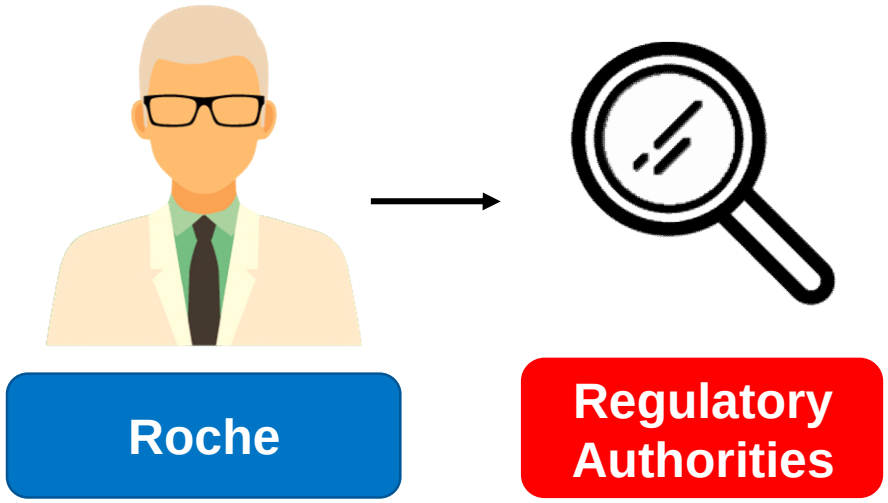
Implications of safety reports in clinical trials and post-marketing

Signal detection

- **A safety signal refers to a concern about an excess of adverse events compared with what would normally be expected to be associated with use of a product[1]**
- In most cases, more than one case report is needed to create a safety signal

When a signal is detected, further investigation by the Roche Safety Science Department determines whether a causal relationship exists

If a validated signal or safety issue meets the definition of an **emerging safety issue**, then we report it to the regulatory authorities as soon as possible[1,2]



Regulatory authorities then decide whether the issue requires action

1. U.S. Food & Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, 2005. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-pharmacovigilance-practices-and-pharmacoepidemiologic-assessment Accessed Apr 2022; 2. US Food & Drug Administration. CFR – Code of Federal Regulations Title 21. https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=05854c5c8fcd51dc6ddefc54716eaa02&ty=HTML&h=L&mc=true&r=SECTION&n=se21.5.314_180. Accessed Apr 2022.

Causality assessment in clinical trials

- Causality assessments consider criteria such as temporal associations, plausibility and alternative explanations[1]
- The process is initiated by the investigator in a clinical trial (healthcare provider) completing a causality assessment[2]
  - a safety physician employed by Roche also assesses causality independent of the investigator's assessment
  - Roche cannot downgrade the investigator's assessment
    - should Roche's opinion differ from that of the investigator's, both must be clearly stated in the narrative of the individual case safety report
  - causality is reviewed on a regular basis because it may change due to new evidence

There are a number of scales and algorithms that can be used to assess causality. While these can be helpful, clinical judgement is the most important factor in assessing causality

1. The Uppsala Monitoring Center 2013. https://www.who.int/publications/m/item/WHO-causality-assessment;
2. Council for International Organizations of Medical Sciences (CIOMS) 2005. https://cioms.ch/wp-content/uploads/2017/01/Mgment_Safety_Info.pdf_Accessed Apr 2022.

Additional resources

Please remember to report any adverse events to Roche via your local online process or by contacting your local Roche representative

The EUHASS website, which provides information on safety events experienced by those with haemophilia or other inherited bleeding disorders that have been reported across Europe: https://www.euhass.org/[1]

Roche patient safety webpage, outlining the Roche safety processes: https://www.roche.com/sustainability/patient_safety.htm[2]

Slides giving further information on the challenges surrounding causality assessments: https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/risk/Conferences/Documents/First-Causality-Israel-2013.pdf[3]

1. EUHASS. Available at https://www.euhass.org. Accessed Apr 2022; 2. Protecting Patient Safety. Available at https://www.roche.com/sustainability/patient_safety. Accessed Apr 2022; 3. Cobert B. Causality Assessment 2013. Available at: https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/risk/Conferences/Documents/First-Causality-Israel-2013.pdf. Accessed Apr 2022.

Doing now what patients need next