Signal

Alectinib – Rhabdomyolysis

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Summary

Alectinib is a highly selective and potent ALK (anaplastic lymphoma kinase) and RET ("rearranged during transfection") tyrosine kinase inhibitor. Alectinib (Alecensa® in the EU, US; Alecensaro® in Canada) is indicated as first-line monotherapy for adults with ALK-positive advanced non-small-cell lung cancer (NSCLC). As monotherapy it is also indicated for the treatment of adults with ALK-positive advanced NSCLC who have been previously treated with crizotinib. The EU Summary of Product Characteristics (SmPC) lists myalgia or musculoskeletal pain and raised creatine phosphokinase (CPK) as reported in patients in pivotal trials with alectinib, including grade 3 events. The median time to increased grade 3 CPK was 14 days across clinical trials. Myalgia and increased blood CPK are labelled for alectinib in the EU and the US product labels. However, it is not labelled for rhabdomyolysis.

As of 19 May 2019, there were eight reports in VigiBase, the WHO global database of individual case safety reports, for alectinib and the adverse drug reaction (ADR), rhabdomyolysis. The reports support a relationship between alectinib and rhabdomyolysis, with six cases giving alectinib as the only suspected drug, and six cases reporting a positive dechallenge, of which two also had a positive rechallenge. In addition, the time-to-onset is consistent in the cases where this information is available (12-14 days).

Current product information for alectinib does not contain sufficient precautions and warnings to inform healthcare professionals and patients about the potential of rhabdomyolysis as an adverse effect.

Restricted

Introduction

Tyrosine kinases such as anaplastic lymphoma kinase (ALK) are becoming major areas of interest for the development of new chemotherapy agents. ALK plays an important role in the development of the brain; it also drives the progression of several cancers, including anaplastic large-cell lymphoma, neuroblastoma, and non-small-cell lung cancer (NSCLC). Alectinib is a highly selective and potent ALK and RET ("rearranged during transfection") tyrosine kinase inhibitor. In preclinical studies, inhibition of ALK tyrosine kinase activity led to blockage of downstream signalling pathways including STAT 3 ("signal transducer and activator of transcription 3") and PI3K/AKT ("phosphoinositide 3-kinase"/"protein kinase B", also called AKT) and induction of tumour cell death (apoptosis).[1,2] Alectinib demonstrated *in vitro* and *in vivo* activity against mutant forms of the ALK enzyme, including mutations responsible for resistance to crizotinib. The major metabolite of alectinib (M4), metabolised by CYP3A4, has shown similar *in vitro* potency and activity.[1,2]

Activating mutations or translocations in the gene encoding ALK have been identified in different tumours, including NSCLC, where it is present in about 2 to 5% of cases and in 3 to 7% of adenocarcinomas.[3-5] ALK is a receptor tyrosine kinase that shows striking homology with members of the insulin receptor family, whose physiological function is still unclear.[6] The translocation of ALK determines the expression of the resulting fusion protein and the consequent aberrant signalling of ALK in the NSCLC. The identification of ALK as a potential therapeutic target in the treatment of NSCLC has led to the development of drugs aimed at inhibiting its activity. The first two with this mechanism of action to be authorized were crizotinib (Xalkori®), and subsequently ceritinib (Zykadia®), both for patients not previously treated and for those who have already received treatment for the disease.[7-10] Other tyrosine kinase inhibitors (with stem *–tinib*) that are used in NSCLC include alectinib, brigatinib and lorlatinib.

Alectinib was granted an accelerated approval by the US Food and Drug Administration (FDA) in December 2015 to treat patients with ALK-positive advanced NSCLC whose disease worsened after, or who could not tolerate, treatment with crizotinib; this was converted into full approval in November 2017. It had conditional approval from the European Medicines Agency (EMA) in February 2017 for the same indication, which was extended in October 2017 with the indication to first-line treatment of adult patients with ALK-positive advanced NSCLC.[11]

Currently alectinib as monotherapy is indicated for the first-line treatment of adult patients with ALK-positive advanced NSCLC; and as monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.[1] Alectinib is available as capsules (150 mg). The recommended dose is four capsules taken twice a day with food (a total of 1,200 mg daily). For patients with severe hepatic impairment the recommended dose is three capsules twice a day with food (900 mg). The doctor may reduce the dose or stop treatment temporarily if side effects occur. In certain cases, treatment should be permanently stopped.[1] Most adverse effects due to ALK inhibitors can be managed efficiently via dose modifications or interruptions.[12-14]

Medicines-related myotoxicities such as rhabdomyolysis or myoglobinuria are the most serious medical emergencies. Rhabdomyolysis is an acute and fulminant necrotizing myopathy that can cause severe myalgia, muscle swelling and weakness, and increased serum CPK as high as 2,000 times upper limit of normal (ULN). It is associated with myoglobinuria (urine that appears dark brown or pink due to the presence of pigmented myoglobin), which can cause acute renal failure and death. If the offending agent is removed and patients are aggressively treated, the muscle typically heals well.[15]

Reports in VigiBase

The combination alectinib–rhabdomyolysis was first identified in 2016 in a screening of VigiBase, the WHO global database of individual case safety reports (ICSRs), focussing on new drugs and serious adverse drug reactions (ADRs). Alectinib is labelled for myalgia and increased blood CPK in both the EU and the US product labels. However, it is not labelled for rhabdomyolysis.[1,2]

As of May 2019, out of over 20 million ICSRs in VigiBase, there were 1,993 ICSRs with alectinib as a suspected medicine. A total of eight ICSRs (0.4% of the alectinib reports), with the combination alectinib and rhabdomyolysis were retrieved from VigiBase on

19 May 2019 and reviewed case by case. The number expected was three; the $IC_{0.25}$ was -0.1; the most recent report was 19 May 2019; the number of reports where it was the single suspected drug was six; the number of positive dechallenges was six; the number of positive rechallenges two. There were eight ICSRs classified as 'serious'.

The reports were submitted from six countries: Germany (two reports), Portugal (two), Austria, Canada, USA, and Australia (one each). Details of case reports are set out in Table 1.

Illustrative case reports

Three of the eight ICSRs can illustrate important details: one index case, the first documented ICSR in the onset of this signal (alectinib and rhabdomyolysis) with positive dechallenge; one case with clear temporal sequence and rechallenge; and a third with pharmacological interactions for rhabdomyolysis syndrome:

Case 1: is the index case, from an oncologist, concerning a 57-year-old male patient. On 29 October laboratory tests showed blood CPK to be 420 U/L (normal range 39-190); one day later, the patient started oral alectinib, 600 mg twice daily for NSCLC, ALK positive; on 13 November, CPK was 1,615 U/L and the patient was diagnosed with rhabdomyolysis (severity not reported). The patient had muscle pain, but no increase in creatinine level was noted for the time of the event. No further investigations were performed to confirm the diagnosis, as the combination of clinical condition and the laboratory tests appeared to be sufficient. Therapy with alectinib was interrupted on the same day. No treatment was reported for the event. On 17 November CPK was 705 U/L, and according to the reporter, the rhabdomyolysis had resolved, as he described in the suspected ADR report. On 19 November, it was decided to restart therapy with oral alectinib at a reduced dose of 450 mg twice daily, with close monitoring. On 24 November CPK was 380 U/L.

Case 4: a 49-year-old adult male, who had increased CPK and rhabdomyolysis, associated with the use of alectinib, for ALK-positive lung cancer, started oral alectinib on 28 June, 600 mg twice daily for NSCLC. He was also taking dexamethasone for an unknown indication. The ADR occurred 13 days after the start of the administration of the suspected drug. The reporter noted that the medication was halted on 12 July due to symptoms of rhabdomyolysis, and that it was restarted with the same dose when CPK had decreased sufficiently. The reporter noted in his ADR report, "treatment resumed on 20 July maintaining an effective treatment". He did not mention if there was a dose reduction. With reintroduction, rhabdomyolysis reoccurred and the patient again experienced myalgia, asthenia and oedema of the lower limbs; but only a moderate to light increase of the CPK.

Case 7: an elderly male patient with type 2 diabetes, started therapy on 11 May with oral alectinib, 600 mg twice daily for NSCLC. Concomitant medication included tamsulosin, finasteride, bisoprolol, pantoprazole, linagliptin, rosuvastatin calcium, folic acid, vitamin D, crizotinib, apixaban, magnesium and simvastatin. On an unknown date, he had rhabdomyolysis and was admitted to hospital. Therapy with alectinib was interrupted; the outcome of the rhabdomyolysis was reported as unknown. Simultaneous treatment with two statins (rosuvastatin calcium and simvastatin), known potential causes of myopathy and rhabdomyolysis, was present in this ICSR, but the reporter did not consider statins as suspected for the ADR. By contrast, in Case 6 in Table 1 the reporter also included rosuvastatin calcium as a suspected drug, as well as alectinib. In conclusion, in this case, there could also have been a pharmacological interaction due to a synergistic effect.

A screening of VigiBase on 25 June 2019 using the MedDRA SMQ "*Rhabdomyolysis/Myopathy - Narrow*" with alectinib found 13 ICSRs, of which eight were those with rhabdomyolysis previously described (Table 1), and five other cases with MedDRA preferred terms (PTs) such as "myopathy" (four cases) and "myoglobin blood increased" (one), plus several co-reported preferred terms, such as "myalgia", "blood CPK increased", "asthenia", "oedema peripheral", "blood creatinine increased", and so on. A search with the SMQ "*Rhabdomyolysis/Myopathy - Broad*" with alectinib resulted in 258 ICSRs, with more PT related: myalgia, myositis, CPK increased, muscular weakness, etc.

Literature and labelling

As of 25 June 2019, no published cases of rhabdomyolysis associated with alectinib (or other ALK inhibitors such as ceritinib, crizotinib, brigatinib, lorlatinib) could be found in the literature. A recent alectinib review[12] found the same results. Also, two systematic reviews[13,14], the first with 15 trials (2,005 patients), the second with 14 studies (2,793 patients) found no rhabdomyolysis cases were associated with alectinib (or other ALK inhibitors).

Among the ALK inhibitors, alectinib is considered well tolerated. Compared to crizotinib, alectinib is associated with lower rates of vision disorder (10%) and gastrointestinal ADRs, but higher rates of serious hepatic or musculoskeletal ADRs.[12]

The EMA Committee for Medicinal Products for Human Use (CHMP) European Public Assessment Report[11] already indicates that the only signal of increased toxicity related to alectinib was myalgia/ CPK increase. The most common side effects of alectinib in the EU SmPC[1] and US FDA product label[2] include: tiredness; constipation; swelling in hands, feet, ankles, face and eyelids; anaemia; muscle pain, tenderness and weakness (myalgia). Myalgia or musculoskeletal pain occurred in 26% of patients in pivotal clinical studies NP28761, NP28673 and BO28984=ALEX. Raised CPK occurred in 41% of 347 patients, with CPK laboratory data available in pivotal clinical studies NP28761, NP28673 and ALEX.

The EU SmPC1 published by EMA in 2017 mentions safety data collected during drug development:

> *Severe myalgia and creatine phosphokinase (CPK) elevation:* cases of myalgia (28%) including myalgia events (22%) and musculoskeletal pain (7.4%) have been reported in patients treated with alectinib across pivotal clinical trials (NP28761, NP28673, BO28984=ALEX).

There is similar information on the US FDA and Canada product labels:[2,16]

> Elevations of CPK occurred in 41% of 347 patients with CPK laboratory data available across pivotal clinical trials (NP28761, NP28673, BO28984=ALEX) with alectinib. The incidence of grade 3 elevations of CPK was 4%. Median time to grade 3 CPK elevation was 14 days (interquartile range 13-28 days). Dose modifications for elevation of CPK occurred in 3.2% of patients.

There is a warning about severe myalgia and increases in CPK: patients should be advised to report any unexplained muscle pain, or muscle pain that does not go away, muscle tenderness or weakness, as mentioned in the EU SmPC, US FDA and Canada product labels.[1, 2, 16] CPK levels should be assessed every two weeks (14 days) for the first month of treatment, and as clinically indicated in patients reporting symptoms. Based on the degree of the CPK increase, alectinib should be withheld, then resumed or have the dose reduced. In the EU, US, Canada product labelling, details are given on how to modify and reduce the dose according to CPK elevations, and other serious ADRs (ALT/AST or bilirubin elevations, bradycardia, renal impairment among other ADRs).[1,2,16]

In the EU, US and Canada product labelling, there is no information on pharmacological interactions with medicines that could increase blood CPK or induce rhabdomyolysis, such as statins.[1,2,16]

Discussion and conclusion

Besides hepatotoxicity, myalgia and CPK increase are the next category of ADRs to be watchful for. Among available ALK inhibitors, this is unique to alectinib, and brigatinib to a lesser extent (43% versus 30% respectively for CPK elevation of any grade).[12] As myalgia and CPK increase is not well recognized for patients, prior to treatment initiation, they need to be informed of potential symptoms such as muscle pain or weakness. As with hepatic ADRs, CPK increase also has an early onset, with mean time to grade 3 increase (>5 × ULN) occurring at approximately day 14, so CPK levels need to be monitored every two weeks for the first month and then as often as clinically indicated. If severe myalgia or an increase in CPK occurs, it is reasonable to withhold alectinib until it resolves to at least grade 1 in severity.

Currently rhabdomyolysis is not described in the labels for alectinib; only myalgia and increased CPK are.[1,2,16] However, the cases in VigiBase support an association between alectinib and rhabdomyolysis, with six cases reporting alectinib as the only suspected drug, and with six cases reporting a

positive dechallenge, of which two also report a positive rechallenge. In addition, the time-to-onset is consistent in the cases where this was provided (12-14 days). Current product information for alectinib does not inform patients and health care providers about the potential interactions with statins and their synergistic effect on rhabdomyolysis.

References

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Table 1: Characteristics of case reports in VigiBase of rhabdomyolysis in association with alectinib

Case	Age/ Sex	Suspected (S) or concomitant (C) drugs	Daily dose	Reactions	Time-to-onset (TTO)	Dechallenge/ Rechallenge	Outcome
1*	57/m	Alectinib (S), pantoprazole (C), levetiracetam (C)	1,200 mg	Rhabdomyolysis	14 days	Positive/Not applicable, negative due to reduced dosage (450 mg twice daily)	First doses were withdrawn after TTO, recovered in 5 days, two days later new dose reduced to 900mg/day
2	53/m	Alectinib (S), tinzaparin sodium(C)	unknown	Rhabdomyolysis, CPK increased	14 days	Positive/Positive at lower dose	
3	64/f	Alectinib (S), enoxaparin (C), dexamethasone (C), nadroparin (C), mirtazapine (C), pantoprazole (C), zopiclone (C), naloxone (C), oxycodone (C), torasemide (C), calcium carbonate + colecalfiferol (C)	1,200 mg	Decreased appetite, blood CPK increased, pyrexia; gastritis; nausea; arthralgia; pelvic pain; large intestine perforation: peritonitis; pyelonephritis; rhabdomyolysis; sepsis; transaminases increased; pelvic hematoma; general physical health deterioration; retroperitoneal hematoma; retroperitoneal hemorrhage; diverticulitis	12 days	Unknown / Unknown with reduced dosage (450 mg twice daily, and 300 mg twice daily)	Recovered with some sequelae
4	49/m	Alectinib (S), dexamethasone (C)	1,200 mg	Rhabdomyolysis, edema lower limb, myalgia, blood CPK increased, asthenia, grip strength decreased	13 days	Positive/Positive	Recovering
5	?/m	Alectinib (S), dexamethasone (C), furosemide (C)	1,200 mg	Rhabdomyolysis, hepatic function abnormal, edema lower limb	No data	Positive/Negative	Recovered; but hepatic function abnormal - Not recovered
6	64/f	Alectinib (S), rosuvastatin calcium (S)	---	Rhabdomyolysis (CPK >10,000)	No data	Positive/No data	Recovering/resolving
7	-/m	Alectinib (S), tamsulosin (C), finasteride (C), bisoprolol (C), pantoprazole (C), linagliptin (C), rosuvastatin calcium (C), folic acid (C), crizotinib (C), apixaban (C), simvastatin (C),	1,200 mg	Rhabdomyolysis	No data	Unknown/No data	Unknown
8	58/m	Alectinib (S), pirfenidone (S)	1,200 mg	Rhabdomyolysis, blood CPK increased, myalgia, swelling, peripheral swelling, wrong patient received product	No data	Positive/No data	Recovered

**Index case*

Response from Roche

First, we would like to thank you for the opportunity to review the signal report prepared by the Uppsala Monitoring Center (UMC) in which an association between alectinib and rhabdomyolysis is postulated.

Roche has been and is continuously monitoring events reported as rhabdomyolysis as part of its standard signal detection process. To date, this monitoring has not rendered evidence that the cases reported with the Preferred Term of 'rhabdomyolysis' are confirmed cases of drug-induced rhabdomyolysis which could be attributed to alectinib.

As noted in the signal report prepared by the UMC, rhabdomyolysis is a serious medical emergency which can be life-threatening. Upon the review of the cases reported during clinical trials and from the post-marketing experience with alectinib, Roche has observed cases of myalgia and of creatine phosphokinase (CPK) increase but none with a degree of severity and elements required to confirm the diagnosis of rhabdomyolysis. For the assessment of the cases reporting the verbatim "rhabdomyolysis" in this comment document, a case definition described by Holbrook et al (2011) was used. This considers the following 3 main criteria to establish a case of rhabdomyolysis:

- Muscle symptoms (such as unexplained myalgia or muscle weakness)
- Increase of CPK above 10000 U/L or above 10 times the upper limit of normal (ULN) [for the Health Canada definition; above 50 times ULN for the US MedWatch definition]
- and renal involvement such as:
    - serum creatinine elevation temporally linked to CPK elevation
    - and/or myoglobinemia
    - and/or myoglobinuria
    - and/or brown urine
    - or renal compromise.

The eight cases retrieved and described by the UMC have been reviewed by Roche and assessments for these cases are proposed in the paragraph below.

Case 1: In this case the patient reported muscle pain and a CPK increase up to 1615 U/L, corresponding 8.5 time the ULN (ULN=190). There were no renal signs or symptoms and there was no creatinine elevation at the time of the event. Concomitant medications include levetiracetam for which rhabdomyolysis, muscular weakness and CPK elevations are labeled events. Hence, there were elements lacking to confirm the diagnosis of rhabdomyolysis and an alternative explanation available.

Case 2: In this case the patient reported muscle pain, a CPK increase up to 16.42 µmol/L, that is 5.2 the ULN (ULN<3.17 µmol/L), and creatinine increased at 132 µmol/L (ULN=106 µmol/L) at the time when the highest CPK level was reported, and up to 152 µmol/L one month later, when CPK levels were back to normal. Serum myoglobin was also increased at 127 µg/L. The reported events do not match the definition of rhabdomyolysis as the maximum CPK increase reported remained below 10 time the ULN. In addition, there was an alternative explanation provided by the reporter since the patient did strenuous physical exercise followed by pain (he had cut a 50 meter long and 3 m high hedgerow by hand).

Case 3: In this case the patient reported many events among which CPK increase above 1500 UI/L, that is over 10 times the ULN (ULN=140), and elevated creatinine to a maximum of 1.9 mg/dL (ULN=0.9). Myalgia or muscular weakness are not described explicitly, but she reportedly had pain in the pelvis. These results could confirm the diagnosis of rhabdomyolysis. However the rhabdomyolysis occurred in a context of life threatening retroperitoneal bleeding and impaired medical condition including brain metastasis and cachexia. Concomitant medications included mirtazapine for which rhabdomyolysis is a labeled event. Therefore, a causal role of alectinib is not confirmed in the presence of strong alternative explanations from the patient concurrent conditions and concomitant medication.

Case 4: In this case the patient reported myalgia, muscle weakness ('grip strength decreased') and CPK increase without reported values. There was no renal signs or symptoms and no creatinine elevation. The reported elements are insufficient to confirm a diagnosis of rhabdomyolysis.

Case 5: In this case the patient reported none of the elements pertaining to the rhabdomyolysis definition, therefore it is not possible to confirm the diagnosis due to insufficient information.

Case 6: As this case was not identified in Roche safety database, an evaluation is not possible due to insufficient information; however it is noted that a statin is reported as a co-suspect medication and rhabdomyolysis is a known adverse reaction with statins.

Case 7: In this case the patient reported extreme muscle weakness and pleural effusion leading to hospitalization. Rhabdomyolysis is reported but without CPK values, and no renal involvement is reported. In addition, and as noted by the UMC, a statin is reported as a concomitant medication.

Case 8: In this case the patient reported muscle pain and CPK increase at 3000 UI/L (no ULN reported). There was no renal involvement reported, so a diagnosis of rhabdomyolysis is not confirmed.

Roche found that one (Case 3) of the eight cases identified by the UMC matches the criteria for the diagnosis of rhabdomyolysis proposed by Holbrook et al. with CPK increase above 10 times the ULN and renal involvement. However, alternative explanations for the event were present in this case, therefore a causal relationship between the rhabdomyolysis and alectinib is deemed to be not confirmed. While the criteria for the diagnosis of rhabdomyolysis are not met in the remaining evaluable cases, the reported events of myalgia and CPK elevation are adequately reflected as adverse drug reaction in the alectinib product labels, including corresponding warning and precautionary information, monitoring of CPK levels as well as dose interruption/reduction guidelines in case of CPK elevations > 5 times the ULN.

References

Holbrook A, Wright M, Sung M, Ribic C, Baker S. Statin-associated rhabdomyolysis: is there a dose-response relationship? Canadian Journal of Cardiology. 2011 Mar 1;27(2):146-51.

SIGNAL

WHO defines a signal as:

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". An additional note states: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with supporting data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

Signals communicated by UMC are derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in the signals represent varying levels of suspicion. Signals contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of signals is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Signals are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the WHO Pharmaceuticals Newsletter.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all readers of signals to comment on individual topics.

* Edwards I.R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994;10:93-102.

Responses from industry

Signals on products under patent are submitted to patent holders for comments. Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

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Caveat Document

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs). Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

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