Aciclovir or valaciclovir - Acute generalised exanthematous pustulosis

Camilla Westerberg, Uppsala Monitoring Centre

Summary

The combination of aciclovir and acute generalised exanthematous pustulosis (AGEP) was found in a routine signal detection screening of VigiBase, the WHO global database of individual case safety reports, performed in December 2018, and valaciclovir was later added to the assessment. Based on the overall reporting of adverse reactions for aciclovir or valaciclovir and the adverse reaction AGEP in VigiBase, the expected value for the number of reports for the combinations was five and three respectively, while the observed numbers were 10 and 14. The combinations were highlighted as disproportionately reported by IC analysis. Age range, time-to-onset (TTO) and drug withdrawal were similarly described in the case series and corresponded with the clinical picture of AGEP in most reports. However, the valaciclovir case series had few narratives, and a number of co-suspected drugs known to cause skin eruptions, making the assessment difficult. In many of the reports in both case series, co-reported drugs included labelled causes of AGEP or other severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Though inconsistently, SJS and TEN are labelled for some aciclovir products. It is possible that initial presentations of these SCARs could be confused with AGEP.

In these two case series, despite the limitations, there are several reports indicating that aciclovir/valaciclovir can be strongly suspected to have been the cause of the drug induced skin reaction, and in two published case reports, this was confirmed by patch tests. In addition, since AGEP can be confused with a herpes eruption, it seems important to warn that aciclovir and valaciclovir can potentially cause AGEP.

WHO Collaborating Centre for International Drug Monitoring
Box 1051, S-751 40, Uppsala, Sweden
Tel: +46 18 65 60 60 www.who-umc.org

Introduction

Aciclovir is an antiviral drug used to treat herpes simplex and zoster infections. The antiviral effect is due to inhibition of the herpes virus DNA polymerase enzyme, thereby inhibiting viral DNA synthesis and replication. When taken orally, aciclovir is slowly and poorly absorbed. Aciclovir is widely distributed in tissues and body fluids, including brain, kidney, lung, liver, muscle, spleen, uterus, vaginal mucosa, vaginal secretions, cerebrospinal fluid, and herpetic vesicular fluid. Valaciclovir is the L-valine ester of aciclovir and is almost completely converted to aciclovir and valine in the body.[1,2]

Acute generalised exanthematous pustulosis (AGEP) is a severe skin reaction, characterized by an acute onset (less than 10 days and typically within 48 hours)[3,4] of mainly small non-follicular pustules on an erythematous base. Systemic involvement sometimes occurs, but only in about one fifth of cases. The reaction is usually drug-related, with more than 90% of AGEP cases provoked by medications. Most often these are beta-lactam antibiotics (penicillins, cephalosporins, quinolones). Other medicines that have been implicated include pristinamycin, tetracyclines, sulphonamides, oral antifungals, diltiazem, hydroxychloroquine, carbamazepine, and paracetamol.[4,5] However, AGEP is not listed in the product labelling for all of these medicines. Treatment consists of the removal of the drug causing the reaction and use of potent topical or systemic steroids, plus symptom management and infection prevention. Spontaneous resolution usually occurs within two weeks after discontinuation of the causative drug.[4,5,6]

AGEP is classified among the severe cutaneous adverse reactions (SCARs), which are very rare but potentially life-threatening reactions of delayed hypersensitivity. SCARs include AGEP, drug reactions with eosinophilia and systemic symptoms (DRESS), and the most severe form of SCARs: the Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) spectrum.

The mechanism and classification of SCARs are described by Bellón as "delayed T-cell-mediated type IV hypersensitivity reactions in the Gell and Coombs classification in which drug-specific T cells can be identified in the peripheral blood or skin infiltrates. The variation in clinical conditions has resulted in type IV reactions being further sub-classified according to different cytokine production patterns by T cell subsets and to the contribution of certain subpopulations of leukocytes to the inflammation and tissue damage. Traditionally, DRESS is considered a type IVb Th2-driven reaction, SJS/TEN a type IVc cytotoxic reaction, and AGEP a type IVd reaction".[7]

Reports in VigiBase

The combination of aciclovir and AGEP was found in a routine signal detection screening of VigiBase, the WHO global database of individual case safety reports, performed in December 2018. As of 6 October 2019, there were 16 cases reporting the combination. The expected value for the number of reports on the combination was five, and the association was highlighted as disproportionally reported, by IC analysis (IC_{025} = 0.8). After excluding suspected duplicates, 10 cases remained in the series. Age ranged between 20 and 96 years, with a median of 65 years, and there was an equal distribution of men and women. Valaciclovir was added to the assessment at a later stage. As of 1 December 2019, there were 14 cases of valaciclovir and AGEP found in VigiBase (de-duplicated data). Age ranged between 33 years and 86 years (two unknown), with a median of 66 years and, as with aciclovir, half of the reports concerned women, and half men. The expected number of cases was three and the IC_{025} value for valaciclovir and AGEP was 1.2.

All but two aciclovir reports, where the reporter was unknown, were submitted by a healthcare professional. For eight patients, the drug was stopped, and the reaction was reported to have abated in six cases. An outcome 'recovering' or 'recovered' was reported for eight of the aciclovir cases. Six of these eight patients had stopped the drug; it was not stated what action was taken in the other two reports.

In 10 of the 14 valaciclovir reports, the patient had recovered or was recovering after stopping the drug, and for one patient the outcome after stopping valaciclovir was stated as unknown. In three reports however, the patients had not improved or recovered despite a documented withdrawal of valaciclovir in one of these. For aciclovir, the time-to-onset (TTO) ranged between one and 21 days, and for valaciclovir, between one day and six months.

Countries represented in the combined case series were Australia, China, Czech Republic, France, India, Italy, Japan, Malaysia, Portugal, Switzerland, Thailand and the United States of America (US). The characteristics of the case series are set out in Table 1 for the aciclovir cases, and in Table 2 for valaciclovir.

Case 2 in Table 1 has venlafaxine as a co-reported drug, however, the narrative describes the start of aciclovir treatment for submammary erythema and the eruption of AGEP after two days. Case 4 was from a dermatologist who described how the patient took aciclovir and shortly after developed eruptions all over the body. The patient was admitted to the intensive care unit (ICU). The reporter assesses the causality as probable. The narrative of case 7 indicates that an antibiotic taken concomitantly was discontinued but oral aciclovir was continued, after which the reaction was aggravated.

Narratives of valaciclovir cases 12 and 13 describe clinical scenarios where the patient took valaciclovir and developed pustular eruptions shortly after. The patient in case 12 was treated for herpes zoster with "bétadine" and valaciclovir. After three days, about five days after stopping codeine+paracetamol, taken for post-surgical pain, pruritic lesions appeared. The patient in case 13 had experienced pustular eruptions twice before. The first time, valaciclovir was one of four drugs taken, but no allergy tests were made. The second time, amoxicillin and interferon were deemed causative after positive allergy tests. The third time, valaciclovir was introduced and the eruptions appeared within two days.

Literature and labelling

AGEP is not labelled for either aciclovir or valaciclovir. Erythema multiforme (EM) and SJS/TEN are labelled with the frequency "Not known" for aciclovir 200 mg tablets from Wockhardt UK Ltd, and "Rare" for aciclovir 800 mg tablets from Accord.[1,8] However, in labels for other formulations, no mention is made of severe skin reactions.[9,10] The valaciclovir labels in the UK do not mention SCARs.[2]

In aciclovir labels from the US, EM, SJS and TEN are mentioned frequently.[11,12] However, the reaction is typically not mentioned in topical formulations. In labels for valaciclovir, only EM is mentioned.[13] EM is not a SCAR but it is important to note as it is often caused by herpes simplex virus, and may not be clearly distinguishable from AGEP in its early stage.[5]

Two of the cases in the series for aciclovir have been published in the literature. The first concerns case 1 in Table 1 where solifenacin is suspected to be the causative drug.[14] The second corresponds with case 9, and describes in detail the diagnosis where a biopsy revealed typical characteristics of AGEP. Aciclovir was suspected and replaced, and the reaction abated. Two months later, the exclusion of other potential causative agents than aciclovir was made, using patch tests.[15]

An additional published case report from Finland, not corresponding to any in the case series, describes a 44-year-old woman developing pustules after treatment with aciclovir against labial herpes. The diagnosis of AGEP secondary to aciclovir therapy was confirmed by positive patch testing.[16]

Case 1 in Table 2 is described in the literature, mentioning acute localised exanthematous pustulosis (ALEP) as the reaction, though the term reported to VigiBase was AGEP. The case report presents an antibiotic as the cause of the reaction and valaciclovir as a treatment of an assumed diagnosis of shingles.[17]

Discussion

Aciclovir case reports that strongly implicate aciclovir as the cause of AGEP, include two published cases where the causative drug was confirmed by patch test, and two unconfounded reports with good narratives (cases 2 and 4). Case 7, describing an aggravated skin reaction after discontinuation of confounding drugs also indicates aciclovir as the causative drug.

Most aciclovir reports (n=7) have a time to onset of between one and four days, consistent with the expected onset time for the reaction, and two reports have 11 and 21 days between drug intake and reaction onset. However, the report where it took 21 days to develop the reaction is the published case with patch test confirmation (case 9). It seems that there are circumstances where the reaction is delayed, and in this particular case, the concomitant administration of a corticosteroid is mentioned as one suspected cause of the delay, together with the absence of prior exposure to aciclovir and the "low sensitizing potential of the drug". Interestingly, in the aciclovir case where time to onset was reported as 11 days, an oral corticosteroid is reported to have been taken concomitantly. For valaciclovir, TTO ranged between one day and six months. However, the latter

case is unusual, and if excluding it as an outlier, the longest TTO in the case series was 14 days.

Case reports that strongly implicate valaciclovir as the cause of AGEP include cases 12 and 13 where the narratives describe clinical scenarios where the patient took valaciclovir and developed pustular eruptions shortly after. The patient in case 12 is was treated with codeine+paracetamol before the eruption of a temporal lesion, and paracetamol has been implicated as a cause of AGEP. However, the treatment only continued for three days, which means that it was stopped well before the temporal lesion emerged some days later. The lesion was suspected to be herpes zoster and treated with "bétadine" and valaciclovir, and after three more days, pruritic lesions appeared. The patient in case 13 had experienced pustular eruptions twice before. The third time, valaciclovir was introduced and the eruptions appeared within two days.

Most valaciclovir cases are co-reported with one or more antibiotics labelled to cause AGEP or a different SCAR, and in some of the reports, it seems more likely that a different drug was the cause of the reaction. In three cases (1, 8 and 9), an antibiotic is confirmed or strongly suspected as the cause, and in one case (11), it is more likely that the causative drug was the vaccine which was administered nine days before onset, alternatively an ongoing infection, while valaciclovir had been taken for six months. In case 14, the eruptions appeared some time into the treatment for leukaemia the patient was undergoing. All drugs were withdrawn, however bortezomib was re-introduced without the eruptions reappearing. Therefore, thalidomide, valaciclovir and amlodipine were still all suspects, although the reporter mentions a "low extrinsic imputability" of valaciclovir.

The fact that there are few reports where one or more co-reported drugs do not have a SCAR in the label, usually SJS/TEN but sometimes AGEP, as found in trials or as post-marketing experience, is the most important possible confounder for both case series. Overlap between SJS/TEN and AGEP does occur but this is rare,[18] so it is not clear if this would increase the possibility of aciclovir or valaciclovir causing AGEP, despite related mechanisms.

However, diagnostic confusion between SCARs can occur in the early stages[18] and also between severe AGEP, especially with mucous membrane involvement and SJS/TEN.[4] The latter might not have greatly impacted the case series as it is more likely that AGEP would be diagnosed as SJS/TEN than the reverse because of the characteristic pustules. However, a limitation of the case series is the absence of histopathology which clearly distinguishes between the SCARs.

Finally, it is important to note that AGEP might be confused with a herpes eruption, and two reports mention that aciclovir/valaciclovir was used as treatment for the eruptions (case 1 in Tables 1 and 2). In addition, a literature report not in the series described a case where AGEP was confused with a herpes eruption.[19]

Conclusion

In these case series, there are several cases where aciclovir and, though to a lesser extent, valaciclovir, can be strongly suspected to have been the cause of AGEP, and in two literature reports, this was confirmed by patch tests. Since the condition can be confused with a herpes eruption, it seems important to warn that also aciclovir could potentially cause the skin reaction.

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Table 1. Characteristics of case reports in VigiBase of AGEP in association with aciclovir

Case	Age/ Sex	Suspected (S) or concomitant (C) drugs	Reactions (MedDRA PT)	Biopsy or patch test result	TTO	Action taken with drug	Outcome	Comment
1	75/M	Aciclovir*, Solifenacin* (S) *Concomitant lisinopril, nitrendipine, solifenacin; tamsulosin mentioned in the published case report*	AGEP, Erythema, Swelling	Skin biopsy proved drug induced reaction	-	Drug withdrawn/ *unknown outcome*	Unknown	Published case report describes aciclovir as treatment for the reaction and points to solifenacin as prime suspect
2	68/F	Aciclovir* (S) Alprazolam, Budesonide; Formoterol, Lercanidipine, Metformin, Simvastatin, Venlafaxine* (C)	AGEP	-	1 days	-	Recovering	TTO seems to have been 2 days. No dates reported for concomitant drugs
3	70/M	Aciclovir*, Benzylpenicillin, Gabapentin*, Olanzapine (S)	AGEP	-	3 days	-	Recovering	Both benzylpenicillin and gabapentin were started after aciclovir (TTO 1 and 0 days).
4	26/F	Aciclovir* (S), Dexamethasone (C) *Concomitant ranitidine and calcium mentioned in narrative*	AGEP	-	11 days	Drug withdrawn/ Reaction abated	Recovering	TTO probably shorter since narrative states that eruptions appeared before admission to ICU and reaction start date reported to be day after admission.
5	73/F	Aciclovir*, Cefotaxime*, Dexamethasone (S) Duloxetine*, Ofloxacin**, Omeprazole*, Perindopril*, Pregabalin*, Valproic acid* (C)	AGEP	-	4 days	Drug withdrawn/ Reaction abated	Recovered	Cefotaxime and dexamethasone were started 11 days before (TTO=15 days) but discontinued together with aciclovir according to narrative
6	61/F	Aciclovir*, Cilastatin; Imipenem*, Ciprofloxacin*, Vancomycin** (S) Cytarabine, Daunorubicin, Gemtuzumab (C)	AGEP	Biopsy indicated AGEP	4 days	Drug withdrawn/ Reaction abated Rechallenge/No recurrence	Recovered	According to narrative, the patients journal vaguely states macular eruptions 3-4 months prior to reported event. TTO=22 days for co-suspected drugs.
7	20/F	Acetylcysteine; Benzalkonium; Tuaminoheptane***, Aciclovir*, Amoxicillin**, Biclotymol (S)	AGEP, Rash	-	3 days	Drug withdrawn/ *unknown outcome*	-	Antibiotic was discontinued but aciclovir was continued, together with a topical corticosteroid. The day after, the reaction was aggravated
8	50/M	Aciclovir* (S) Drug name/s under assessment for who-dd (herbal remedy) (C)	AGEP	-	-	Drug withdrawn/ Reaction abated	Recovered	Treatment duration = 2 days. However, not much information in report
9	53/M	Aciclovir* (S) Methylprednisolone (C)	AGEP	Biopsy confirmed AGEP. Positive patch test for aciclovir	21 days	Drug withdrawn/ Reaction abated Rechallenge/ Reaction recurred	Recovered	Published case report.

10	96/M	Aciclovir* (S) Piperacillin;Tazobactam** (S)	AGEP	-	3 days	Drug withdrawn/ Reaction abated	Recovered	Antibiotics started and stopped on the same day as the reaction occurred. Aciclovir continued for an additional 6 days.

** SJS, TEN, or Erythema multiforme (EM) labelled in an SmPC from the Electronic Medicines Compendium https://www.medicines.org.uk/emc*

*** AGEP + SJS, TEN or EM labelled in an SmPC from the Electronic Medicines Compendium https://www.medicines.org.uk/emc*

**** SJS, TEN or EM reported but only with other drugs*

Table 2. Characteristics of case reports in VigiBase of AGEP in association with valaciclovir

Case	Age/ Sex	Suspected (S) or concomitant (C) drugs	Reactions (MedDRA PT)	Biopsy or patch test result	TTO	Action taken with drug	Outcome	Comment
1	33/F	Amoxicillin; Clavulanic acid**, Ampicillin; Sulbactam, Co-trimoxazole*, Valaciclovir, Vancomycin** (S)	AGEP	Skin biopsy confirmation. Positive patch test for amoxicillin; clavulanic acid	-	Drug withdrawn/ Reaction abated	Recovered	Published case report. Valacoclovir used as treatment for eruptions
2	52/M	Paracetamol, Valaciclovir (S) Ceftriaxone**, Minocycline* (C)	AGEP	-	5 days	Drug withdrawn/ Reaction abated Rechallenge/ *unknown outcome*	Recovered	Negative rechallenge reported for Paracetamol. No dates reported for ceftriaxone or minocycline. Ceftriaxone was also withdrawn
3	-/M	Doxorubicin, Folinic acid, Gemcitabine*, Metoclopramide, Ondansetron, Sulfamethoxazole; Trimethoprim*, Valaciclovir, Vinorelbine (S)	AGEP	-	2 days	Drug withdrawn/ Reaction abated	Recovered	All drugs (except metoclopramide) started on the same day and were withdrawn. Dose reportedly not changed for metoclopramide
4	-/F	Ceftriaxone**, Valaciclovir (S)	AGEP	-	2 days	Drug withdrawn/ Reaction abated	Recovered	TTO for ceftriaxone: 5 days
5	43/F	Valaciclovir (S)	AGEP	-	-	Drug withdrawn/ *unknown outcome*	Unknown	Reporter: Other Health Professional, Consumer/Non-Health Professional
6	86/M	Valaciclovir (S)	AGEP, Syncope	-	1 days	-	Not recovered	Treatment continued 5 days after onset of AGEP. Syncope outcome also reported as not recovered

7	76/F	Naproxen*, Valaciclovir (S) Amlodipine; Atorvastatin*, Mecobalamin, Phenol;Zinc, Teprenone (C)	AGEP, Acute kidney injury	-	2 days	Drug withdrawn/ Reaction abated	Recovered	TTO = 2 days for naproxen, mecobalamin, teprenone and phenol;zinc. Amlodipine;atorvastatin treatment ongoing since several years
8	75/M	Dexamethasone, Lenalidomide*, Phenoxymethylpenicillin, Sulfamethoxazole; Trimethoprim*, Valaciclovir (S)	AGEP	Patch test positive for amoxicillin	5 days	Drug withdrawn/ Reaction abated	Recovered	All drugs started and stopped on the same day. Phenoxymethylpenicillin was the only drug the patient had not taken before
9	68/F	Cefpodoxime, Piperacillin; Tazobactam**, Valaciclovir (S) Glimepiride, Metformin, Pioglitazone, Torasemide* (C)	AGEP, Biopsy skin abnormal, C-reactive protein increased, Leukocytosis, Lymphopenia, Neutrophilia, Pyrexia, Skin exfoliation	AGEP was biopsy confirmed on two occasions	2 days	Drug withdrawn/No effect observed	Not recovered	According to the narrative, cefpodoxime was primary suspect drug, but valaciclovir or an infectious cause were not excluded as alternative explanations. Piperacillin;tazobactam was administered about 20 days after first onset of AGEP, and this resulted in new eruptions, erythroderma and circulatory collapse requiring intensive care.
10	62/M	Amoxicillin**, Carbamazepine**, Valaciclovir (S)	AGEP	-	14 days	Drug withdrawn/ Reaction abated Rechallenge/ *unknown outcome*	Recovered	Reported drug start date for amoxicillin is after reported reaction start. However, it is included in the "dose regimen" described in the narrative and the nature of the date could suggest an error in reporting
11	81/M	Influenza vaccine (Vaxigrip), Sulfamethoxazole; Trimethoprim*, Valaciclovir (S)	AGEP	The biopsy was in favour of a post-viral or medically induced reaction.	6 months	Dose not changed/ No effect observed Rechallenge/ *unknown outcome*	Not recovered	TTO vaccine: 9 days Eruptions are reported to have started "at the same time as a pharyngitis".
12	81/F	Valaciclovir (S), *Ebastine, Monotildiem, Co Aprovel, Elisor, Inexium are mentioned as ongoing treatment in narrative*	AGEP	Two biopsies, taken on thigh and arm, indicated a drug induced SCAR-type reaction	3 days	Drug withdrawn/ Reaction abated	Recovering	Narrative mentions codeine;paracetamol taken during three days about 8 days before eruption of temporal lesions which in turn was treated with valaciclovir since herpes zoster was suspected. Patient had taken topical aciclovir before without any problem.

13	50/M	Valaciclovir (S)	AGEP	Biopsy indicate drug induced reaction	2 days	Drug withdrawn/ Reaction abated	Recovered	Patient experienced pustular eruptions twice before current event. Allergologic work up then positive for amoxicillin and Introna® (Interferon alfa-2b). No work up performed for valaciclovir after most recent event.
14	64/F	Amlodipine*, Bortezomib*, Dexamethasone, Enoxaparin, Thalidomide*, Valaciclovir (S)	AGEP, Rash pustular, Urticaria	Biopsy showed leukocytoclastic vasculitis with secondary epidermal lesions	12 days	Drug withdrawn/ Reaction abated	Recovered	TTO urticaria/AGEP suspicion: Thalidomide: 7/11 days Amlodipine: 19/24 days Valaciclovir: 8/12 days Bortezomib: 7/11 days Dexamethasone: -1/3 days Enoxaparin: -4/0 days Reporter mentions low extrinsic imputability for valaciclovir

** SJS, TEN, or EM labelled in an SmPC from the Electronic Medicines Compendium https://www.medicines.org.uk/emc*

*** AGEP + SJS, TEN or EM labelled in an SmPC from the Electronic Medicines Compendium https://www.medicines.org.uk/emc*

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.

WHO Collaborating Centre for International Drug Monitoring
Box 1051, S-751 40, Uppsala, Sweden
Tel: +46 18 65 60 60 www.who-umc.org

Uppsala Monitoring Centre

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.

WHO Collaborating Centre for International Drug Monitoring
Box 1051, S-751 40, Uppsala, Sweden
Tel: +46 18 65 60 60 www.who-umc.org