Fluorouracil and Bradycardia – national signal from Peru with potential global relevance

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Summary

Fluorouracil is the third most used chemotherapeutic agent in the treatment of solid malignant tumours worldwide. It has many side effects, including on the cardiovascular system. In a signal detection workshop focussing on Latin American data in VigiBase, the WHO global database of individual case safety reports, a signal related to fluorouracil and bradycardia was detected from Peruvian data using quantitative signal detection methods. Thirteen cases were observed where only 0.3 were statistically expected to be seen. The review found that although bradycardia has been described as an adverse reaction in literature reports, it is not included in the summary of product characteristics (SmPC) or national fact sheets in Peru, nor in those of regulatory agencies in the USA, Spain, or Canada. The more general term of arrythmia is mentioned in some SmPCs, and tachycardias sometimes appear. The literature, including an observational study and a case series, supports the finding of bradycardia in patients undergoing chemotherapy. To summarise, in Peru we have suggested including bradycardia in the sections on adverse reactions, warnings and precautions in our national drug fact sheet for the product, and here we share this information with the global network for consideration.

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Introduction

Fluorouracil belongs to a class of drugs called antimetabolites. It is administered intravenously and acts by reducing or stopping the growth of cancerous cells in the body. Fluorouracil is generally used in combination with other chemotherapeutic drugs to treat cancer of the colon or rectum, certain types of breast cancer, pancreatic cancer, and stomach cancer, where the dosing varies between one and five days, often once monthly.[1]

Among listed adverse events associated with the use of fluorouracil are diarrhoea, hand-foot syndrome (a.k.a. palmar-plantar erythrodysesthesia), myelosuppression, mucositis, and cardiotoxicities.[2] Among listed cardiac side effects are chest pain, myocardial infarction, sudden cardiac death, pericarditis, and changes in the ECG, e.g. ST-T changes and arrhythmia, sometimes specified as atrial fibrillation or tachycardia.[3] The appearance of the specific term bradycardia is not listed among the adverse effects associated with fluorouracil in the summary of product characteristics of fluorouracil in the USA or the UK. Bradycardia means a slow heart rhythm, often defined as a frequency of less than 60 beats per minute.[4]

VigiBase reports

The combination of bradycardia and fluorouracil was identified in a signal detection workshop focussing on Latin American data in VigiBase, carried out in May 2019. It was detected using disproportionality analysis where the expected number of cases in Peru was calculated to be 0.3 while the number observed was 13 (IC_{025}: 3.2). The data referred to in Table 1 includes the characteristics of all the 13 Peruvian reports which formed the basis of the signal analysis.

Table 1 includes four reports (1, 2, 3 and 4) that give fluorouracil as the only administered drug; the diagnoses for which fluorouracil was administered were in these cases colon adenocarcinoma, colon cancer and gastric cancer.

Some of the other cases mention concomitantly used drugs which potentially could have caused or contributed to the event: Four other reports describe the concomitant administration of oxaliplatin, a drug with the capacity to cause adverse cardiac effects.[5,6,7,8,9] In the case of oxaliplatin the development of bradycardia associated with overdose is noted in the prescribing information.[8,9] One of the four reports (Case 5) described concomitant administration of calcium folinate, and two other (11 and 12) included docetaxel, neither of which give bradycardia as an acknowledged adverse drug reaction.[10,11,12,13,14,15] One of the four reports described the concomitant administration of ondansetron, and development of bradycardia as an infrequent adverse reaction.[16,17] The information shown in the reports indicates that administration of fluorouracil and its concomitants (oxaliplatin, ondansetron) was on the same day, but not specifying a more detailed time for each one in relation to the event.

Four reports included the administration of cisplatin, which in its labelling has bradycardia as an adverse reaction,[18] and in two of these, docetaxel was also administered. In three of the four reports fluorouracil and the concomitant drugs were administered on the same day, but the exact hour of administration of each drug is not specified. In two of the four reports the bradycardia occurred on the same day that administration of fluorouracil and the concomitant drugs was started; equally, in the other two reports the bradycardia started three days after administration of fluorouracil began. In addition, in these four cases fluorouracil was the only drug reported as suspected.

Case 13 in Table 1 had concomitant administration of irinotecan and fluorouracil. The information in the fact sheet for irinotecan describes the appearance of bradycardia in the section on adverse reactions.[19] The report only states that the administration of both drugs was carried out on the same day but does not specify the exact time of administration.

Onset of bradycardia was on day 1-3 in all the Peruvian cases. None of the cases give any ECG findings. In three cases (1, 3 and 11) the level of bradycardia ranged between 40 and 54 beats per minute. No cases reported additional symptoms of the bradycardia and only three cases (7, 8 and 11) gave any additional adverse drug reaction: headache, hypertension and peripheral neuropathy.

Five of the Peruvian reports (Cases 6, 7, 8, 12 and 13) came from the same doctor while each of the others came from a different reporter.

In VigiLyze, the combination bradycardia-fluorouracil results in 139 reports from 23 countries worldwide,

Table 1 Patient characteristics of the 13 Peruvian case reports which formed the basis of the signal analysis.

N°	Age (years)	Sex	Indication	Drugs	Doses mg	ADRs reported	Time to onset (days)	Positive dechallenge	Positive Rechallenge
1	66	F	Colon adenocarcinoma	Fluorouracil (S)	960mg	Bradycardia	0	Yes	Yes
2	76	M	Colon cancer	Fluorouracil (S)	-	Bradycardia	1	No	-
3	56	M	Gastric cancer	Fluorouracil (S)	-	Bradycardia	1	Yes	-
4	56	F	Gastric cancer	Fluorouracil (S))	-	Bradycardia	1	Yes	Yes
5	30	F	Rectal cancer	Fluorouracil (S) Oxaliplatin (C) Calcium folinate (C)	500 mg 130 mg 250 mg	Bradycardia	2	Yes	-
6	55	M	Gastric malignant neoplasm	Fluorouracil (S) Oxaliplatin (C)	1650 mg 114 mg	Bradycardia	0	Yes	-
7	69	M	Malignant neoplasm of the colon	Fluorouracil (S) Oxaliplatin (C)	3440 mg 280 mg	Bradycardia Peripheral neuropathy	1	-	-
8	89	M	Malignant neoplasm of the colon	Fluorouracil (S) Oxaliplatin (C) Ondansetron (C)	1000 mg 85 mg 24 mg	Bradycardia Hypertension	1	-	-
9	63	F	Malignant neoplasm of the vagina	Fluorouracil (S) Cisplatin (C)	1000 mg 100 mg	Bradycardia	3	Yes	-
10	68	M	Gastric malignant neoplasm	Fluorouracil (S) Cisplatin (C)	900 mg -	Bradycardia	0	-	-
11	42	F	Gastric cancer	Fluorouracil (S) Cisplatin (C) Docetaxel (C)	1580 mg 58 mg 75 mg	Bradycardia Headache	0	Yes	Yes
12	53	F	Gastric malignant neoplasm	Fluorouracil (S) Cisplatin (C) Docetaxel (C)	3920 mg 98 mg 98 mg	Bradycardia	3	Yes	-
13	58	M	Malignant neoplasm of the cecum	Fluorouracil (S) Irinotecan (C)	3060 mg 220 mg	Bradycardia	1	Yes	-

with Peru third after the USA (34 reports) and India (18 reports). Table 2 shows the main characteristics of these cases (including the ones from Peru).

There were 13 global reports with a VigiBase completeness score of 1.00; here we illustrate four of these cases:

1. France: a male patient aged 53 was administered fluorouracil intravenous 6300 mg/cycle to treat oropharyngeal cancer. On the third day of treatment the patient presented with bradycardia, hypotension, bradypnea and allergic shock. The report indicates that the patient recovered after the suspension of the treatment.

2. India: a 20-year-old, 52 kg male patient was given 900 mg/24 hr intravenously for a diagnosis of nasopharynx malignancy; with only fluorouracil administration reported. On the second day of treatment the patient presented with bradycardia, observing recovery two days later, without having reported any suspension of treatment.

Table 2. Case series characteristics of 139 global reports on bradycardia with fluorouracil in VigiBase

Feature	N° of reports (%)
Male / Female/ Information missing	80 (58) / 52 (37) / 7 (5)
0-17y /18-44y / 45-64y /65-74 y / 75+y/ information missing	1 (1) / 26 (19) / 50 (36) / 40 (29) / 9 (6) / 13 (9)
Serious case*	71 (51)
Fatal outcome	6 (4)
Sole reported drug	31 (22)
Time to onset 0-7 days / > 7 days/ information missing	77 (55) / 26 (19) / 36 (26)
Positive dechallenge / Positive rechallenge	41 (29) / 4 (3)

**Some countries cannot report seriousness to VigiBase due to limitations in their reporting format, so the true proportion of serious cases may be higher.*

3. India: a 36-year-old male patient, 54 kg, who was given intravenous fluorouracil 1000 mg/24 hr for nasal cavity neoplasia. The patient presented with bradycardia on the fifth day after administration, with recovery being observed the same day. The report only indicates the administration of fluorouracil.

4. India: a 41-year-old male patient, 68 kg and 168 cm, who was given 750 mg/24 hr fluorouracil intravenously for a diagnosis of an unknown neoplasm. The patient presented with bradycardia on the third day of administration, so the treatment was discontinued, with the patient's recovery being observed. The report only indicates the administration of fluorouracil.

An expanded search was performed in VigiBase to retrieve additional cases of bradycardia but coded otherwise. Among the terms considered were atrioventricular block (complete, first degree and second degree), cardiac arrest, abnormal electrocardiogram, sudden death. The few additional cases retrieved were, after assessment, not considered relevant for the signal.

Literature and Labelling

The information sheets/labelling of some international regulatory agencies set out information on heart disorders or events associated with the use of fluorouracil. However, bradycardia is not listed in the section of adverse drug reactions, nor warnings and precautions in the country sources that were checked, such as the USA (Food and Drug Administration - FDA), Spain (Agencia Española de Medicamentos y Productos Sanitarios - AEMPS) and Canada (Health Canada).

Three peer-reviewed publications describing cases or case series of bradycardia in relation to fluorouracil use were found:

Talapatra K *et al* [20] discussed a series of cases of six patients (aged 38-59 years) who developed transient asymptomatic bradycardia (heart rate ≤50/ minute) in a group of 207 patients who received chemotherapy with injectable fluorouracil and cisplatin (dose: cisplatin 75-100 mg/m^2 and injectable 5-fluorouracil 750-1000 mg/m^2 day one and with continued 5-fluorouracil infusion during day 2-5 of the treatment). None of the six patients had any comorbidities, except one with hypertension. The assessment of the six patients indicated that there were no associated symptoms, such as chest pain, giddiness or sweating at the time of the bradycardia. The serum electrolytes were checked in the patients during the episodes of bradycardia, observing normal results. The authors concluded that the case series shows a tendency for the development of asymptomatic bradycardia in patients undergoing treatment with infusion of fluorouracil. It may be argued that cisplatin and hydration of the patient had a part to play in the development of bradycardia but since the development of bradycardia appeared after the third day in all the patients, the authors consider that this makes it likely that fluorouracil was a more plausible cause.

Nakajima T *et al* [21] described a male patient of Japanese origin, aged 78 years with a medical history that included hypertension, and diagnosed with stage III oesophageal cancer, who received a combination of cisplatin and fluorouracil. The patient experienced episodes of bradycardia on the first day after cisplatin administration, and due to it being asymptomatic

it was decided to continue the planned 2-5 days of continuous infusion of fluorouracil. On treatment day 4 his heart rate fell to 22 beats/min without other objective findings or subjective symptoms. With atropine treatment the rate temporarily improved. The treatment was interrupted, and a gradual improvement of the patient's heart rate ensued. Within two days of stopping the treatment the rate had returned to normal. The authors discuss the pharmacokinetics of the two drugs and speculate that the second phase of a biphasic elimination curve of the cisplatin with a half-life of >100 hours could have acted synergistically with fluorouracil to adversely affect cardiomyocytes and the cardiac conduction system resulting in the bradycardia observed during its infusion. They conclude that while the combination chemotherapy is a useful treatment for this type of cancer it may induce severe bradycardia and point out the need for carefully monitoring patients.

Khan MA *et al* [22] carried out research on cardiotoxicities, especially bradycardia, in cancer patients treated with chemotherapy regimens based on fluorouracil in the Pakistani population. Symptomatic cardiotoxicity was noted in 60 (19.9%) out of 301 patients. Bradycardia was the most common cardiotoxicity and was observed in 36 (12.0%) of the patients. The incidence of cardiotoxicity was not significantly different between patients with or without pre-existing cardiovascular disease (p = 0.095). Cardiotoxicities were more common with continuous infusion of fluorouracil, when radiotherapy was given concurrently with fluorouracil, and when fluorouracil was used in combination with cisplatin.

Discussion and Conclusion

There is a variety of probable causes for the appearance of *cardiotoxicity in general* associated with the use of fluorouracil, among which are the dose and method of administration, use of concomitant chemotherapeutic agents with cardiotoxic potential, and concurrent radiotherapy. Moreover, the clinical characteristics of the patients (presence of pre-existing coronary lesions, arterial disease, or traditional cardiovascular risk factors) and variability in the definitions of cardiotoxicity should be considered. Cardiotoxicity with fluoropyrimidines tends to occur in association with the first cycle of administration. An average time of onset of symptoms is observed up to 12 hours after the start of the infusion, although heart conditions may occur at any time during the infusion or even up to 1-2 days after the infusion, as observed in the cases reported for bradycardia in Peru (84.6%) and globally (39.5%).[23]

The cardiotoxicity associated with the use of fluorouracil is well known and has been reported: atrial fibrillation, ST-T changes and chest pain being the most frequently observed symptoms. Cardiotoxicity in relation to the use of fluorouracil requires close clinical supervision and, if it occurs, treatment may require suspension of the drug. The effect of fluorouracil withdrawal (positive dechallenge) is evidenced in the cases of bradycardia reported in Peru (62%), as well as worldwide (29%).[24]

Khan *et al*. concluded that bradycardia events were more common with a continuous infusion of fluorouracil, radiotherapy concurrent with fluorouracil, and when fluorouracil was used in combination with cisplatin.[22]

While information on adverse cardiac reactions is found in the fact sheets of countries such as the USA (Food and Drug Administration - FDA), Spain (Agencia Española de Medicamentos y Productos Sanitarios - AEMPS) and Canada (Health Canada)[5,6,7] including in some cases information on increased heart rate, tachycardia; they do not describe bradycardia in the sections on adverse reactions, warnings and precautions.

Cisplatin, ondansetron, oxaliplatin and irinotecan, which were observed as concomitant drugs in some of the Peruvian cases, include information about the development of bradycardia, notably for oxaliplatin and irinotecan, only in association with overdose cases[8,9] or as part of the appearance of cholinergic diarrhoea or reaction.[19]

The administration of fluorouracil and the concomitant drugs is performed cyclically in different doses and ways.[25] However, in the Peruvian cases, the information regarding the exact moment of administration of each drug in relation to the event is not clear, making it difficult to fully assess the causal relationship of each individual drug to the adverse reaction.

Capecitabine, another anticancer agent, is a prodrug to fluorouracil which is metabolised to fluorouracil in the body.[26] International regulatory agencies

(eg. FDA, AEMPS and EMA) include information referring to the development of bradycardia with the administration of capecitabine.[27,28,29] Taking this into account, it is relevant to consider including bradycardia as an adverse reaction associated with the use of fluorouracil in relevant drug information documents.

Peru has 10 registered pharmaceutical products that contain fluorouracil, none of which include bradycardia as an adverse reaction or a warning. It is therefore suggested to include in Peru bradycardia in the sections on adverse reactions, warnings and precautions in the national drug fact sheet, and we would like to inform the global network for consideration at national level.

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References

1. MedlinePlus [Internet]. U.S. National Library of Medicine. [updated 30 December 2019]. Fluorouracil Injection. Available at: https://medlineplus.gov/druginfo/meds/a682708.html

2. Dailymed [Internet]. U.S. National Library of Medicine. [updated 23 February 2017]. Label: Fluorouracil injection, solution. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=66d451fe-2436-494c-80c5-4528c8e34369#L8a71c005-1a49-46d2-a01a-0786b921dc76

3. Medicines & Healthcare products Regulatory Agency – MHRA [Internet]. SUMMARY OF PRODUCT CHARACTERISTICS- Fluorouracil 25 mg/ml Injection. [updated 12 April 2019]. Available at: http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1555647114072.pdf

4. UpToDate [Internet]. Sinus bradycardia. [23 January 2019]. Available at: https://www.uptodate.com/contents/sinus-bradycardia

5. Agencia Española de Medicamentos y Productos Sanitarios-AEMPS [Internet]. Fluorouracilo Accord 50 mg/ml solución inyectable o para perfusión EFG. [updated February 2019]. Available at: https://cima.aemps.es/cima/dochtml/ft/71868/FT_71868.html

6. Health Canada [Internet]. Product monograph: Fluorouracil Injection USP 50 mg/mL (5 g/100 mL). [updated 17 April 2018]. Available at: https://pdf.hres.ca/dpd_pm/00044861.PDF

7. Dailymed [Internet]. LABEL: FLUOROURACIL-fluorouracil injection, solution. [updated 23 February 2017]. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=66d451fe-2436-494c-80c5-4528c8e34369

8. Health Canada [internet]. Product monograph: PrOXALIPLATIN Oxaliplatin Injection, Pfizer Standard 5 mg/mL oxaliplatin. [updated 19 November 2018]. Available at: https://pdf.hres.ca/dpd_pm/00048594.PDF

9. Food and Drug Administration – FDA [Internet]. ELOXATIN (oxaliplatin) injection for intravenous use. [updated September 2018]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021759s019lbledt.pdf

10. Agencia Española de Medicamentos y Productos Sanitarios-AEMPS [Internet]. FOLINATO CÁLCICO NORMON 50 mg Polvo y disolvente para solución inyectable EFG / FOLINATO CÁLCICO NORMON 350 mg Polvo para solución inyectable EFG. Available at: https://cima.aemps.es/cima/dochtml/ft/70340/FT_70340.html

11. Food and Drug Adminsitration-FDA [internet]. LevoLeucovorin injection. [updated November 2013]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/203563Orig1s000lbl.pdf

12. Health Canada [Internet]. Product monograph: PRODUCT MONOGRAPH LEUCOVORIN CALCIUM INJECTION 10 mg/mL USP. [updated August 2018]. Available at: https://pdf.hres.ca/dpd_pm/00046849.PDF

13. Agencia Española de Medicamentos y Productos Sanitarios-AEMPS [Internet]. Docetaxel Hospira 10 mg/ml concentrado para solución para perfusión. [updated September 2018]. Disponible en: https://cima.aemps.es/cima/dochtml/ft/71799/FT_71799.html

14. Food and Drug Administration – FDA [Internet]. DOCETAXEL INJECTION, for intravenous use. [updated September 2018]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022234s011,202356s003lbl.pdf

15. Health Canada [Internet]. Product monograph: PrDOCETAXEL INJECTION USP 10 mg/mL Sterile Solution. [updated June 2019]. Available at: https://pdf.hres.ca/dpd_pm/00045702.PDF

16. Health Canada [Internet]. Product monograph: PrJAMP-ONDANSETRON ONDANSETRON INJECTION, USP 2 mg/mL ondansetron (as ondansetron hydrochloride dihydrate). [updated 17 March 2015]. Available at: https://pdf.hres.ca/dpd_pm/00029958.PDF

17. Agencia Española de Medicamentos y Productos Sanitarios-AEMPS [Internet]. Ondansetrón Accord 2 mg/ml solución inyectable EFG. [updated February 2018]. Available at: https://cima.aemps.es/cima/dochtml/ft/72117/FT_72117.html

18. Food and Drug Adminsitration – FDA [Internet]. CISPLATIN for injection, for intravenous use. [updated February 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/018057s089lbl.pdf

19. Health Canada [Internet]. Product monograph: PrIRINOTECAN irinotecan hydrochloride trihydrate for injection 20 mg/mL. [updated 06 March 2019]. Available at: https://pdf.hres.ca/dpd_pm/00049996.PDF

20. Talapatra K, Rajesh I, Rajesh B, Selvamani B, Subhashini J. Transient asymptomatic bradycardia in patients on infusional 5-fluorouracil. J Can Res Ther 2007; 3:169-71

21. Nakajima T, Kawamori H, Ohno M, Kusunoki N, Yamazaki Y, Takase S. A Case of Severe Bradycardia Induced by Combination Chemotherapy with Cisplatin and 5-Fluorouracil [Abstract]. Gan To Kagaku Ryoho. 2015 Nov;42(11):1415-8.

22. Khan MA, Masood N, Husain N, Ahmad B, Aziz T, Naeem A. A retrospective study of cardiotoxicities induced by 5-fluorouracil (5-FU) and 5-FU based chemotherapy regimens in Pakistani adult cancer patients at Shaukat Khanum Memorial Cancer Hospital & Research Center. 2012 May, Volume 62, Issue 5: 430-4.

23. Jaskanwal D. Sara, Jasvinder Kaur , Ryan Khodadadi , Muneeb Rehman , Ronstan Lobo , Sakti Chakrabarti , Joerg Herrmann , Amir Lerman y Axel Grothey. 5-fluorouracil and cardiotoxicity: a review. Ther Adv Med Oncol. 2018 June, Vol 10: 1 - 18.

24. Eskilsson J1, Albertsson M, Mercke C. Adverse cardiac effects during induction chemotherapy treatment with cis-platin and 5-fluorouracil. Radiother Oncol. 1988 Sep;13(1):41-6.

25. Instituto Nacional de Enfermedades Neoplásicas – INEN. Guía de Práctica Clínica de Cáncer de Colon. Lima – Perú 2013. Available at: http://www.inen.sld.pe/portal/documentos/pdf/normas_tecnicas/2013/08072014_GU%C3%8DAS_DE_PR%C3%81CTICA_CL%C3%8DNICA_DE_C%C3%81NCER_DE_COLON.pdf

26. Dailymed [Internet]. LABEL: CAPECITABINE 150MG- capecitabine tablet, film coated. [updated 22 February 2019]. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7f555b6b-60db-45e2-a61e-537e57f43fdc

27. Food and Drug Administration – FDA [Internet]. Highlights of prescribing information XELODA (capecitabine) tablets, for oral use. [updated February 2019]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020896s042lbl.pdf

28. Agencia Española de Medicamentos y Productos Sanitarios – AEMPS [Internet]. Anexo I: Ficha técnica o resumen de las características del producto. Capecitabina Accord. [updated 09 January 2017]. Available at: https://cima.aemps.es/cima/pdfs/ft/112762023/FT_112762023.pdf

29. European Medicines Agency – EMA. EPAR summary for the public – Xeloda (Capecitabina). [updated April 2019]. Available at: https://www.ema.europa.eu/en/documents/overview/xeloda-epar-summary-public_es.pdf

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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