Signal

Nintedanib and ischaemic colitis

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Summary

Nintedanib is a small molecule protein kinase inhibitor approved for the treatment of idiopathic pulmonary fibrosis, a rare and progressive disease with a median survival of only several years after diagnosis. Statistical screening of VigiBase, the WHO global database of individual case safety reports, identified disproportional reporting of the MedDRA Preferred Term (PT) "colitis" with nintedanib. Review of published literature and further exploration allowed for refinement of the signal from the non-specific term of "colitis" to the more specific clinical scenario of ischaemic colitis. A number of Bradford Hill criteria, including strength of association, specificity, consistency, analogy and plausibility, are discussed to support the hypothesis of a causal relationship between nintedanib and ischaemic colitis. Communication of this signal is considered warranted, as early identification of ischaemia may prevent progression to the serious, life-threatening event of gastrointestinal perforation. Given that the most commonly occurring gastrointestinal adverse reaction for nintedanib is diarrhoea, which can be a symptom of ischaemic colitis, it could be important to inform health care providers to rule out ischaemia prior to the recommended symptomatic treatment of diarrhoea with loperamide.

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Introduction

The drug

Nintedanib is a small molecule receptor tyrosine kinase inhibitor (TKI) blocking vascular endothelial growth factor receptors (VEGFR 1-3), fibroblast growth factor receptors (FGFR 1-3) and platelet-derived growth factor receptors (PDGFR) α and β kinase activity. In pre-clinical studies, nintedanib was found to inhibit the proliferation and transformation of human lung fibroblasts and showed antifibrotic and anti-inflammatory activity in two animal models of pulmonary fibrosis.[1]

Idiopathic pulmonary fibrosis (IPF) is a rare disease of unknown aetiology that is characterised by an excess of fibroblasts, leading to fibrosis of the interstitium of the lung. The fibrosis is a progressive process, leading to decreased lung volume and ultimately, respiratory failure. Median survival, as described across a range of studies, is only two to five years after diagnosis. IPF is an uncommon disease with a prevalence of 3 per 10,000, and it is most prevalent in middle-aged and elderly patients.[1]

Nintedanib was licensed for use in the treatment of IPF by both the European Medicines Agency (EMA) and the United States Food and Drug Administration (US FDA) in 2014. In two pivotal clinical trials, benefit with nintedanib was measured by a reduction in the decline of a measure of lung function, the forced vital capacity (FVC), by approximately 94 mL/year and 125 mL/year respectively. It has also been licensed by the EMA for use in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.[1] Additionally, given its anti-angiogenic effects as a VEGFR-inhibitor, it is being tested in clinical trials for other oncology indications.

Ischaemic colitis

Ischaemic colitis is a condition caused by insufficient blood flow to the large intestine which results in mucosal ulceration, inflammation and haemorrhage. Causes can be either physiological (hypotension, secondary to embolus/thrombosis) or iatrogenic (secondary to medicines, surgery). Ischaemic colitis clinically manifests with diarrhoea, colicky abdominal pain, and rectal bleeding. It can be difficult for clinicians to differentiate ischaemic colitis from infective and inflammatory colitis. With its high mortality rate, patients with ischaemic colitis should be recognised quickly, as colonoscopic evaluation is recommended within 48 hours of symptom onset. Colonoscopy can distinguish those cases that may be treated with conservative management from those that require emergency resection. The complications which can arise from ischaemic colitis include obstruction, necrosis, and perforation.[2]

Reports in VigiBase

The drug-ADR combination of nintedanib-colitis was identified as a statistical signal during a screening of VigiBase, the WHO global database of individual case safety reports, performed in December 2018. The original case series included 25 cases which, upon review, described either different specific types of colitis, such as ischaemic or inflammatory, or were unspecified. Given that nintedanib acts upon the VEGF-receptor, a decision was taken to explore the association between nintedanib and the more specific clinical concept of "ischaemic colitis".

One case with the original MedDRA Preferred Term (PT) "colitis" was considered to have information sufficient to be considered as "ischaemic colitis" (colonscopy results were provided). Subsequent exploration within VigiBase used the MedDRA Standardised Medical Query (SMQ), "ischaemic colitis (narrow)". Nine additional cases were identified through this search strategy. The final case series consists of 10 cases: five reporting colitis ischaemic, two reporting intestinal ischaemia, one with both colitis ischaemic and intestinal ischaemia, one intestinal infarction and one colitis.

Illustrative case report

A 56-year-old female with a medical history of bronchial carcinoma and hypothyroidism. Therapy for bronchial carcinoma was initiated with nintedanib at 400 mg per day, and the patient was treated for 20 days. Twenty-five days after initiation of nintedanib, the patient experienced intestinal ischaemia and gastrointestinal necrosis. She underwent surgical resection of the descending portion of the large intestine. Pathology revealed: "from the colon descendens, sigmoideum and upper rectum with intense and distinct ischaemic necrosis of gut wall,

Table 1. Disproportionality analysis (VigiBase data up to 5 May 2019)

Substance	Reaction	$N_{observed}$	$N_{expected}$	IC	IC_{025}
Nintedanib	Colitis (PT)	30	9.23	1.65	1.09
Nintedanib	Ischaemic colitis SMQ (narrow)			1.77	1.14
	Colitis ischaemic (PT)	6	1.56	1.65	0.28
	Intestinal ischaemia (PT)	3	1.10	1.13	-0.92
	Intestinal infarction (PT)	1	0.21	1.07	-2.72

inclusion of max. 2.3 cm polyp, without evidence of vital mucosa. Beside a 0.9 cm tubular adenoma with slight intraepithelial neoplasia (low-grade adenoma following WHO-classification)". Transmural haemorrhagic necrosis (reaching out up to the resection area) of gut wall without inflammation, as appropriate for ischaemia. Tumour-free resection of vessels and gut sections. The patient was subsequently initiated on docetaxel about one month after the event of gastrointestinal ischaemia.

Case series

Of the 10 reports in the case series, there was a predominance of males: seven reports compared to reports for females (table 2). Ages ranged between 53 and 78; age was not given in one report. Reports originated from five countries (one country in the Americas, three in Europe, one in Asia). Time to onset ranged from three days to five months. In seven cases, the indication for use of nintedanib was idiopathic pulmonary fibrosis; in the three other cases, non-small cell lung cancer, bronchial carcinoma and glioblastoma. Diagnostic results were given in three cases (6, 8, and 10). Fatal outcomes were reported in four cases. Very limited information regarding the individual cases was available for most cases given that narratives had not been entered into VigiBase. Potential confounding factors/risk factors for ischaemic colitis was advanced age for many of the cases, concomitant use of corticosteroids in two cases (1 and 5) and the medical history of hyperlipidaemia in two cases (2 and 5).

Literature and labelling

Product labelling for nintedanib includes warnings for diarrhoea and gastrointestinal perforation in section 4.4 of the Summary of Product Characteristics. There is also information regarding management options for serious cases of diarrhoea including hydration, anti-diarrhoeal products, and dose reduction and information regarding potential risk factors for gastrointestinal perforation, such as previous abdominal surgery or peptic ulceration, and diverticular disease and concomitant use of corticosteroids or NSAIDs. Included in the list of ADRs in section 4.8 are nausea, vomiting, diarrhoea, abdominal pain and pancreatitis.[3]

Within the risk management plan were the identified risks of diarrhoea and liver function abnormalities as important identified risks and "perforation" as an important potential risk; there were no planned post-authorisation safety studies to further characterise any risks for the gastrointestinal system.[4]

Discussion

The aim of this signal assessment is to argue for a potential causal relationship between nintedanib and ischaemic colitis. Five of the Bradford Hill criteria can be used to support this causal hypothesis, including strength of association, specificity, consistency, biological plausibility, and analogy.[5]

The strength of association has been explored with various approaches to analysing disproportionality in VigiBase. The initial drug-ADR combination identified by statistical screening of the database using the vigiRank algorithm for combination prioritisation was nintedanib-colitis. Colitis, being a general term meaning "inflammation of the colon", provides no specificity as to the cause of the pathology. Within the MedDRA hierarchy, the PT colitis is located within an HLT colitis (excluding infectious); other PTs included within this HLT reflect the diversity of etiology of colitis: examples include autoimmune colitis, colitis ulcerative, necrotizing colitis, colitis ischaemic, colitis microscopic. Within this HLT, only two PTs were noted to exhibit significant disproportionality, colitis (IC_{025} 0.89) and colitis ischaemic (IC_{025} 0.32). To explore the potential to improve the specificity of the association, a subsequent search was performed utilising the

SMQ ischaemic colitis (narrow); disproportionality analysis at this drug-SMQ level revealed an IC_{025} 1.14. PTs included within this SMQ exhibiting increased disproportionality (observed > expected, although not all significantly enough to result in $IC_{025} > 0$) were large intestine perforation (IC_{025}1.48), large intestinal haemorrhage (IC_{025}-0.34), colitis ischaemic (IC_{025} 0.28), intestinal ischaemia (IC_{025} -0.92), gastrointestinal necrosis (IC_{025} -1.50), and intestinal infarction (IC_{025} -2.72). The clinical concepts of perforation and haemorrhage are already included as warnings in the product labelling.

Consistency of the association is exhibited in the case series in the description of the clinical scenario of ischaemic colitis, albeit being coded to various MedDRA PTs, from several countries throughout the world.

The biologic plausibility of an association between nintedanib and ischaemic colitis is based upon its inhibitory action of the VEGF-receptor. VEGF is a protein which mediates multiple functions within the vascular system, including endothelial cell proliferation as well as vascular permeability and vasodilation.[6] A mouse model has shown that inhibition of VEGF signalling resulted in regression of capillaries of intestinal villi[7] and it has been hypothesised that VEGF inhibition contributes directly to GI perforation by inducing regression of normal blood vessels in the GI tract[8] (presumably via an intermediate step of ischaemia). Furthermore, VEGF mediates release of nitric oxide, and its inhibition causes vasoconstriction[6]; indeed, hypertension is a well-characterised ADR for all anti-VEGF agents. Additionally, the labelling for anti-VEGF agents include a warning for arterial thromboembolism; the label for nintedanib specifically cautions for acute myocardial ischaemia in the treatment in patients at higher cardiovascular risk including known coronary artery disease.[3]

Given its inhibitory effect on the VEGF receptor, the ADR profile for nintedanib can be considered analogous to other anti-angiogenic agents which antagonise VEGF (aflibercept, bevacizumab) or inhibit the VEGF-receptor (regorafenib, sorafenib). Indeed, the labels for all products contained harmonised wording regarding the risk of gastrointestinal perforation, and all also lack the inclusion of ischaemic colitis. However, literature review reveals case reports of ischaemic colitis with other VEGF-receptor antagonists, specifically, aflibercept (intravitreal administration)[9] and bevacuzimab,[10] both of which were administered intravitreally. Data mining within VigiBase reveals evidence of disproportional reporting of MedDRA PT within the "ischaemic colitis" SMQ for a number of other anti-angiogenic agents (bevacizumab: intestinal ischaemia IC_{025} 2.23; colitis ischaemic IC_{025} 2.24; aflibercept: colitis ischaemic IC_{025} 0.62; midostaurin: intestinal ischaemia IC_{025} 0.38; ranibizumab: intestinal ischaemia IC_{025} 0.36; sunitinib: intestinal ischaemia IC_{025} 0.22; sorafenib: colitis ischaemic IC_{025} 0.18).

Given that both diarrhoea and gastrointestinal perforation are included in the label, it is relevant to consider the possibility that gastrointestinal ischaemia is the underlying pathology for each of these "known" ADRs. Small perturbations of blood flow by VEGF inhibition can lead to rapid metabolic changes in the intestinal mucosa characteristic of hypoxia and ischaemia.[11] Epithelial hypoxia is clinically associated with diarrhoea,[12] and changes in the bowel mucosa are consistent with ischaemic colitis.[13] A small study of 10 patients aimed to examine the underlying pathophysiologic mechanism of diarrhoea. Sigmoidoscopy revealed no evidence of ischaemia in any of the 10 subjects; however, gastroduodenoscopy revealed mucosal abnormalities in 8 patients.[14] There is better knowledge on the role of ischaemia in gastrointestinal perforation, as perforation is a known complication of gastrointestinal ischaemia. However, the labelling currently describes other risk factors for perforation such as concomitant corticosteroid use and prior history of abdominal surgery without mention of gastrointestinal ischaemia.

Taking all of the presented evidence together, it is considered that there is a reasonable possibility that nintedanib can cause ischaemic colitis.

Conclusions

Screening of VigiBase has identified a signal of disproportional reporting of colitis with nintedanib, a small molecule tyrosine-kinase inhibitor. Given that nintedanib blocks VEGF receptors, the initial signal was further explored in VigiBase and refined to the more specific clinical phenomenon of "ischaemic colitis". The case series supporting this signal consists of 10 cases, captured under several MedDRA PTs including "colitis", "colitis ischaemic", "intestinal ischaemia" and "intestinal infarction". Assessment

of the signal demonstrated the data support of the Bradford Hill criteria has resulted in a conclusion of a reasonable possibility of a causal relationship between nintedanib and ischaemic colitis.

It appears prudent to consider the addition of ischaemic colitis to the product labelling for nintedanib. Furthermore, given that the most commonly occurring gastrointestinal adverse reaction is diarrhoea, which can be a symptom of ischaemic colitis, it could be important to inform health care providers to rule out ischaemia prior to the recommended symptomatic treatment of diarrhoea with loperamide.

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Table 2. Cases identified as representing the clinical scenario of "ischaemic colitis". The cases within this table have been identified from VigiBase review of number MedDRA PTs, including colitis ischaemic, intestinal ischaemia, intestinal infarction, and the originally signalled PT, colitis.

Case	Age/ Sex	Drugs	Indication	ADR	Dosage	TTO	Outcome	Notes
1	78y/M	Nintedanib (S) Prednisolone (S) Acetylcysteine (C) Dimemorfan (C) Drug not accepted in WHODrug (C)	Idiopathic pulmonary fibrosis	Ischaemic enterocolitis	300 mg qd x 2 months, followed by 200 mg qd (duration un-known)	15 days	Recovered	55 kg, 159 cm Report from study
2	74y/M	Nintedanib (S) Vonoprazan (C) Irbesartan; Trichlormethiazide (C) Atorvastatin (C) Acetylsalicylic acid (C)	Idiopathic pulmonary fibrosis	Colitis ischaemic Pneumonia bacterial	300 mg qd x 11 months 200 mg x qd x 2 months	3 days	Recovered	62.9 kg, 165 cm Report from study
3	65y/F	Nintedanib (S) Alfacalcidol (C) Levothyroxine (C) Ascorbic acid; pantothenic acid (C) Minodronic acid (C) Drug not accepted in WHODrug (C)	Idiopathic pulmonary fibrosis	Colitis ischaemic	300 mg qd x 10 months	4 months	Not recovered	50.5 kg, 161 cm Report from study
4	77y/M	Nintedanib (S) Insulin (C)	Idiopathic pulmonary fibrosis	Colitis ischaemic Abnormal loss of weight Septic shock Decreased appetite Vomiting Nausea Diarrhoea	150 mg 2 per day		Died	
5	77y/F	Nintedanib (S) Tacrolimus (C) Prednisolone (C) Trimethoprim / sulfamethaxazole (C) Warfarin (C) Alfacalcidiol (C) Rabeprazole (C) Loperamide (C) Drug not accepted in WHODrug (C) Drug not accepted in WHODrug (C) Drug not accepted in WHODrug (C) Drug not accepted in WHODrug (C)	Idiopathic pulmonary fibrosis	Ischaemic enterocolitis	200 mg qd x 5 months	5 months	Died sec-ondary to ischaemic entercolitis and lower gastroin-testinal perforation	36 kg, 153 cm Report from study. History of hyperlipidemia, osteoporosis, gastroesophageal reflux disease, venous thrombosis, constipation, insomnia, chronic gastritis, breast cancer

Case	Age/ Sex	Drugs	Indication	ADR	Dosage	TTO	Outcome	Notes
6	53y/M	Nintedanib (S)	Glioblas-toma	Mesenteric ischaemia Colitis ischaemic Obstipation Stomach pain Thrombo-embolic event Ischaemia peripheral Wound healing delayed Wound infection	400 mg per day	27 days	Died	185 cm Report from study. Patient presented with abdominal pain 27 days after initiation on nintedanib. Admitted to hospital, diagnosed with ischaemic colitis (grade 2), and treated with mesalazin. Five days later, the patient experienced obstipation. Ten days later, the patient had stomach pain (grade 3), acute mesenteric ischaemia (grade 4), thromboembolic event (grade 4), and peripheral ischaemia (grade 3). Had thromobectomy of arteria mesenterica superior, explorative laparotomy and small intestinal segment resection. Hospitalisation complicated by wound healing disorder which led to cardiovascular failure, sepsis and death.
7	- /M	Nintedanib (S) Omeprazole (S) Indacaterol (C) Olmesartan (C) Salbutamol (C) Lercanidipine (C)	Fibrosis lung	Bowel ischaemia Vein thrombosis mesenteric	2 DF per day		Recovering	

Case	Age/ Sex	Drugs	Indication	ADR	Dosage	TTO	Outcome	Notes
8	56y/F	Nintedanib (S) Docetaxel (S) Zoledronic acid (C) Levothyroxine (C)	Bronchial carcinoma	Intestinal ischaemia Bowel ischaemia Gastro-intestinal necrosis Necrosis bowel	400 mg per day	25	Unknown	Surgery preparation of colon descendens, sigmoideum and upper rectum with intense and distinct ischaemic necrosis of gut wall, inclusion of max. 2.3 cm polyp, without evidence of vital mucosa. Beside a 0.9 cm in sano resected tubular adenoma with slight intraepithelial neoplasia (low-grade adenoma following WHO-classification). Transmural haemorrhagic necrosis (reaching out up to the resection area) of gut wall without inflammation, as appropriate for ischaemia.
9	74y/M	Nintedanib (S) Lansoprazole (C)	Idiopathic pulmonary fibrosis	Intestinal infarction			Died	69 kg

Case	Age/ Sex	Drugs	Indication	ADR	Dosage	TTO	Outcome	Notes
10	57y/M	Nintedanib (S) Ipratropium (C) Acetylsalicyclic acid (C) Glyceryl trinitrate (C) Fluvastatin (C) Torasemide (C) Lormetazepam (C) Metamizole (C) Omeprazole (C)	Non-small cell lung cancer	Colitis Diarrhoea Vomiting Nausea Mucositis Anorexia Respiratory failure	400 mg once per day	9 days		Serious. Clinical trial patient. Died, cause of death "respiratory failure" Medical history: Idiopathic cardiomyopathy Bronchial disorder Insomnia Pain Smoker Alcohol abuse Patient experienced diarrhoea and vomiting which required hospitalisation 10 days after initiation of drug. CT scan of abdomen on day of admission with probably stenosis lesion of the sigmoid colon and proximal colonic dilation and loops of small bowel. Colonoscopy 11 days after discontinuation of drug revealed ischaemic colitis. Repeat CT 16 days after discontinuation revealed no evidence of obstruction. Investigator considered that there is a causal relationship between the drug and GI symptoms and signs.

Response from Boehringer Ingelheim AB

The opportunity to comment on the signal of 'ischaemic colitis' for nintedanib identified by the Uppsala Monitoring Center (UMC) is acknowledged

Nintedanib is authorised in 2 indications:

- treatment of Idiopathic Pulmonary Fibrosis (IPF) and to slow disease progression (Ofev)
- treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first line chemotherapy (Vargatef)

In the indication IPF, nintedanib is administered as monotherapy (starting dose 150 mg bid). In the indication NSCLC nintedanib is administered in combination with docetaxel (starting dose of 200 mg bid). The dose of nintedanib can be reduced for the management of adverse reactions.

Diarrhoea, vomiting, nausea, abdominal pain, pancreatitis and bleeding are included in the list of ADRs of nintedanib. Diarrhoea and bleeding are important identified risks. For Vargatef perforation, mucositis and venous thromboembolism (VTE) are also ADRs. Perforation is an important identified risk. Arterial thromboembolism is an important potential risk of nintedanib and perforation and VTE are important potential risks for Ofev. These conditions are regularly monitored.

Stomatitis, diarrhoea, nausea, vomiting, constipation as well as enterocolitis, colitis, ischaemic colitis, and neutropenic enterocolitis are known ADRs of docetaxel.

The signal of 'colitis' has been evaluated for nintedanib with DLP 15 Oct 2018 based on HLT 'colitis, excluding infective'. In the next version of the EU SmPC 'colitis' will be included as ADR of nintedanib.

In order to appropriately address all comments by the UMC, it has been decided to evaluate data from all sources with regard to ischaemic colitis under treatment with nintedanib.

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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