Descriptive analysis of COVID-19-related spontaneous reports from VigiBase: interim results

Report from the WHO Collaborating Centre for International Drug Monitoring

Report date: 2020-08-26

This eleventh review of global reporting of ADRs for drugs used to treat COVID-19 is as before mainly descriptive in nature. It includes reviews for the drugs that were initially included in WHO Solidarity trial to find an effective COVID-19 treatment and other drugs used for a COVID-19 indication where the number of reports in VigiBase exceeds 100.

Regarding remdesivir, a major increase in reports was seen in this review. Notable numbers of reports for several non-labelled ADR terms have been shared within the system, described in the remdesivir section of the document.

Concerning the other drugs reviewed, ADR-patterns are consistent with those described in earlier reports and mostly within the labelling for the respective drugs.

Reports have been shared from all WHO regions, with the largest number now originating in the WHO region of the Americas with 45% of the shared reports (Table 2).

WHO has announced the discontinuation of the hydroxychloroquine (HCQ) and lopinavir;ritonavir arms of the Solidarity trial as per the recommendation from the international steering committee[1]. The decision applies only to the conduct of the Solidarity trial in hospitalized patients and does not affect the possible evaluation in other studies of hydroxychloroquine or lopinavir;ritonavir in non-hospitalized patients or as pre- or post-exposure prophylaxis for COVID-19.

Contents

Reports in VigiBase

The search methodology is with one exception the same in this tenth review, as in the ninth. Reports were screened for drugs given on a corona or COVID-19 indication, by relevant free-text terms and laboratory tests. Reports were considered for inclusion if they were received at the National Centres between November 1st 2019 and August 17th 2020 and were reported to VigiBase no later than August 17th.* Reports were considered for inclusion when they reported as suspected/interacting drugs initially included in the Solidarity trial or drugs considered clinically relevant based on medical-expertise and reported to VigiBase on a Corona or COVID-19 indication, see Table 4.

There is country-specific reporting delay after receipt of reports at National Centres and thus the reporting date to VigiBase should not be considered as proxy for reporting date to National Centres or the date of adverse events. See Figure 1 for a visualisation of the arrival dates at National Centres for this reviewing period.

Assessment of causality in individual cases is for all COVID-19 drugs difficult due to the background disease, the limited data on the drugs as used in this disease and the relatively large proportion of multiple concomitant other COVID-19 treatments and has therefore in most cases not been performed.

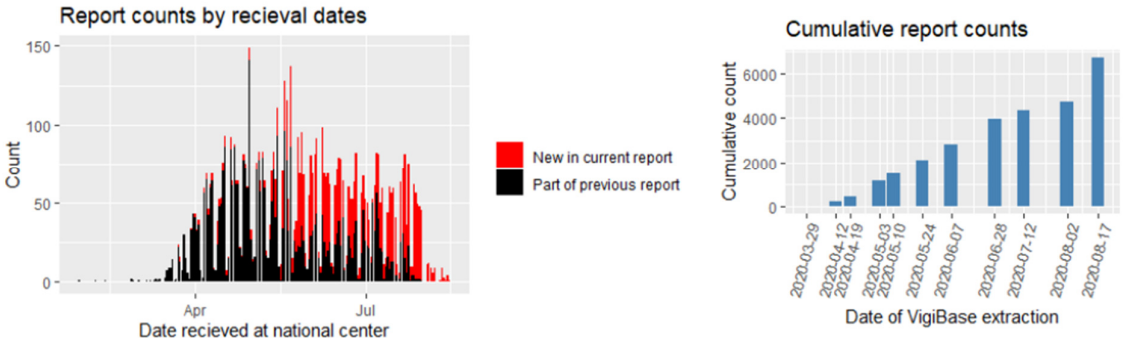


Figure 1. Number of reports by dates received at national center (left), and cumulative number of reports in VigiBase at the dates of extractions for reports. The rightmost bar (right panel) shows the total number of reports received so far.

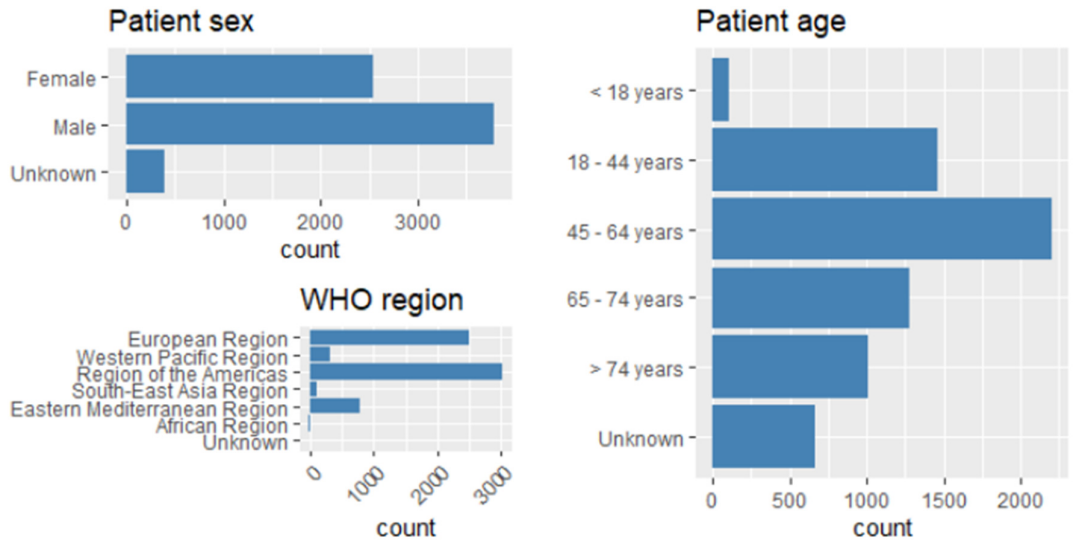
* If the arrival date at the National Center was not reported, the date of latest update at the National Center was used instead. Reports referred to as "new" during the current time interval may be reports with an initial entry into Vigibase during the time interval or an update of a report which had been previously received into the database prior to the current reporting period.

Overview of patient characteristics

Since the last analysis, 2623 new case reports have been identified using the selected search strategy (Table 1). Cumulatively, a total of 6718 reports have been shared from all WHO regions with the majority now originating from the Americas (45%). 58.5% of the reports were classified as "serious" (Table 2) but not all reporting standards include seriousness (e.g. INTDIS). Males accounted for 56.4% of the reports and females for 37.7%.

To high extent reports describe at least one drug originally included in the WHO Solidarity trial, i.e. with hydroxychloroquine (in some regions replaced by chloroquine), azithromycin, remdesivir and lopinavir;ritonavir reported as either suspected or interacting. Additionaly, reports describing other drugs used in the treatment of COVID-19 disease and reported more than 100 times into the database have been included in the more detailed review. These currently include tocilizumab, oseltamivir, enoxaparin and sarilumab. Overall reporting demographics for the drugs are shown in Figure 2. In line with males being more affected by COVID-19 infection globally, all drugs except chloroquine and oseltamivir are more reported for men than women. Patient ages are similar between drugs, with oseltamivir appearing to have the lowest median age.

A)



B)

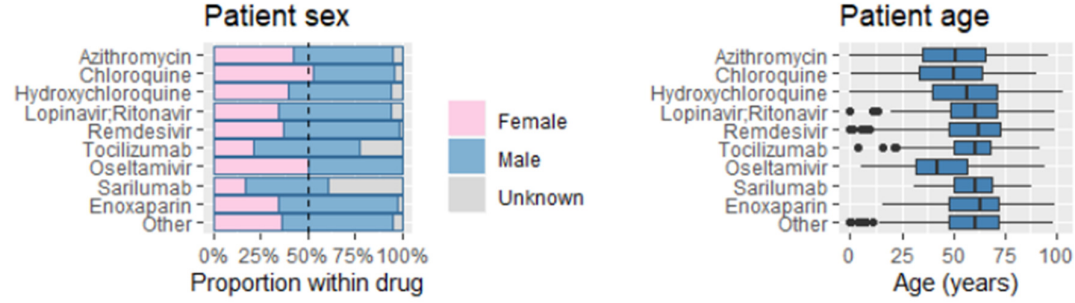


Figure 2. Overall demographics of case safety reports sent into VigiBase in treatment of COVID-19. A) All reports. B) Reports by drug. The B) graphs rely on counts of reports which include each drug as suspected or interacting. Reports including several drugs will be counted once for each reported drug. Patient age boxes show medians and interquartile ranges.

Characteristics of the reports on drugs shared more than 100 times into VigiBase

Hydroxychloroquine alone or in combination with azithromycin

There were 338 new reports for hydroxychloroquine during this time period, adding to a cumulative total of 2412 reports. The new reports included 141 men, 118 women and 79 with unknown sex. The new reports originated from Eastern Mediterranean Region (15), European Region (75), Region of the Americas (241) and South-East Asia Region (seven). In the new reports the median age was 60 years (85 reports had age unreported). For the new reports, hydroxychloroquine was a single suspected drug in 114 cases. An overview of the cumulative reporting demography is shown in Figure 3.

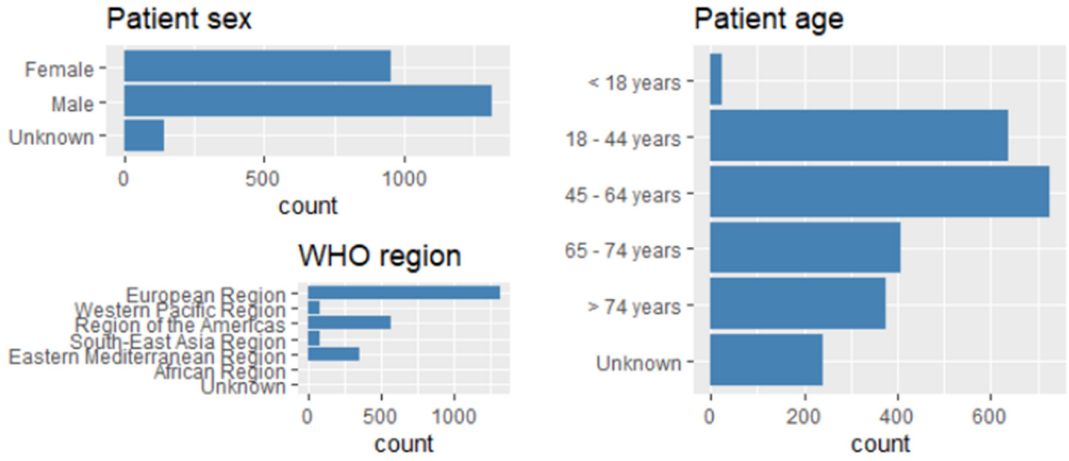


Figure 3. Demography of VigiBase reports received cumulatively so far on hydroxychloroquine as suspected or interacting drug.

Adverse events

During this iteration, reports from the Region of the Americas relating to administration during pregnancy and foetal exposures began to appear in VigiBase. The MedDRA PTs that relate to these circumstances were: Apgar score low (two reports), exposure during pregnancy (three reports), foetal death (one report), foetal exposure during pregnancy (eight reports), low birth weight baby (four reports), premature baby (four reports), premature delivery (seven reports), pulmonary haemorrhage neonatal (one report). These terms were distributed across 13 reports in total, most of which could be traced back to a single published case report describing the successful pre-term caesarean delivery of twins.[2] This case report does not appear to describe pre-term delivery as a direct consequence of her treatment with hydroxychloroquine, azithromycin and ceftriaxone, but as a procedure adopted to improve the progressively worsening condition of the mother after COVID-19 infection. One report remains, which refers to a woman who was exposed during pregnancy to hydroxychloroquine, azithromycin and ceftriaxone: the patient, in advanced maternal age, experienced foetal death and haemolysis, with thrombocytopenia, acute kidney injury and abnormal hepatic enzymes. No further information is available. The European SmPC currently reports that prospective studies in long-term use of hydroxychloroquine have not observed increased risks of congenital malformations or poor pregnancy outcomes.[3]

Four reports include new terms of infections: candida sepsis, cardiac infection, enterocolitis haemorrhagic and staphylococcal bacteraemia; two of these co-reported either tocilizumab or sarilumab, one co-reported treatment for hypertension and back pain, while one included hydroxychloroquine alone. The latter, a fatal case, further features the term “SARS-CoV-2 test negative”, though the indication of hydroxychloroquine was “COVID-19”. With no information on

the dates of onset of the reactions, it is unclear whether the test result was produced before, during, or after the treatment.

Other serious and new terms in VigiBase include: ear pain with otorrhoea, skin necrosis (with heparin-induced thrombocytopenia) and stress cardiomyopathy with hypermagnasaemia. Mosts of these reports were fairly incomplete and no further conclusions could be drawn. Perhaps of note was the occurrence of hypermagnasaemia in a woman with a history of rheumatoid arthritis treated with azithromycin and hydroxychloroquine for severe COVID-19: the full case report has been published,[4] this adverse event is unlisted on the SmPC.

The remainder of the adverse events with hydroxychloroquine reported to VigiBase was in line with previous iterations.

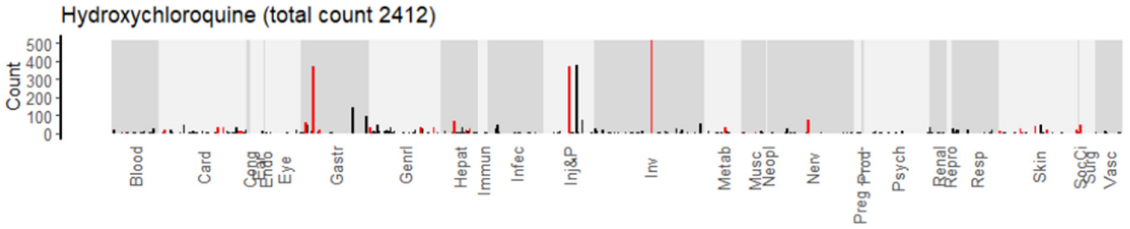


Figure 4. Cumulative report counts for hydroxychloroquine in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table 6). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

Chloroquine

During this reviewing period, 11 new reports in which chloroquine was reported as suspecting or interacting drugs were reviewed. These concerned eight male and two female patients; median age of patients described in the new reports was 68 years (two reports had age unreported). The new reports originated from European Region (nine) and Region of the Americas (two). An overview of the cumulative reporting demography is shown in Figure 5.

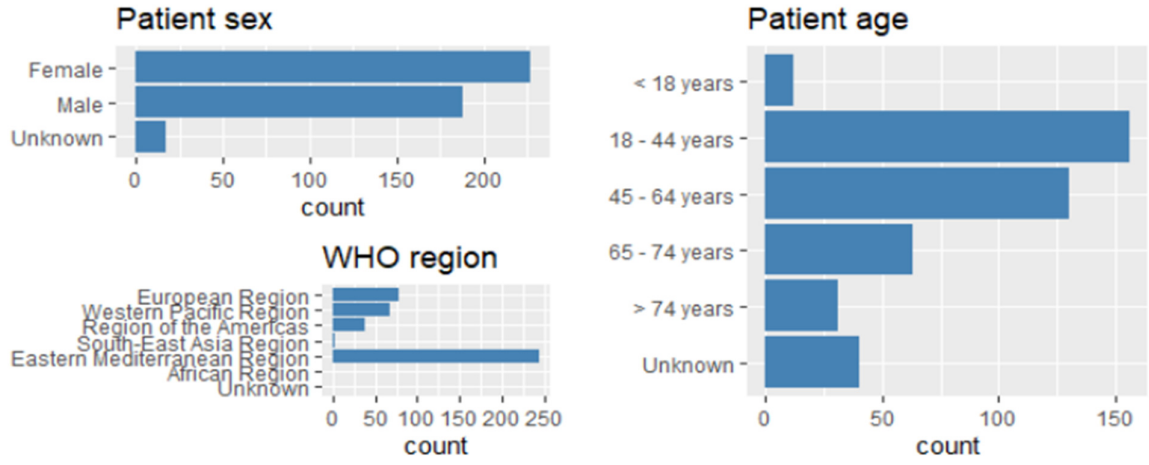


Figure 5. Demographics of VigiBase reports received cumulatively so far for chloroquine as suspected or interacting drug.

Adverse events

The profile of chloroquine continues to be in line with the previous iterations and included in the labelling[5], with cardiac (Electrocardiogram QT prolonged), gastrointestinal (Diarrhoea, vomiting, abdominal pain upper), psychiatric (Insomnia, Hallucination) and eye disorders (Vision blurred) composing the majority of the reports in VigiBase.

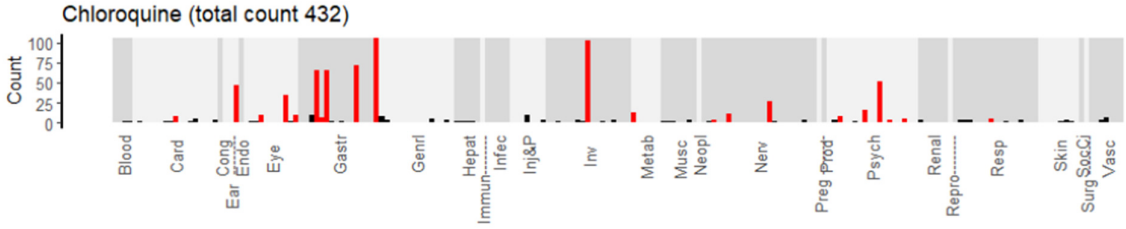


Figure 6. Cumulative report counts for chloroquine in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table 6). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

Azithromycin

Azithromycin is to a high extent reported from the Eastern Mediterranean region. The 124 new reports including azithromycin are largely reviewed in the sections of hydroxychloroquine or lopinavir;ritonavir as it is mostly reported in combination with these drugs. Statistics regarding co-medications used with azithromycin are presented in Table 5 where the most common co-reported drug by far is hydroxycholoquine, followed by the heparin like drugs and remdesivir as the third most common.

Using disproportionality analysis with COVID-19 drugs in VigiBase as the background (see also remdesivir section) no PTs were detected with a positive IC_{025} value ie, simplified no terms have been disproportionately more often reported in relation to azithromycin than compared to other COVID-19 drugs in VigiBase. Among clinical terms reported for the first time within this review the highest numbers were observed for cardiomyopathy (cumulatively four reports, all new), hypothemia (cumulatively two reports, both new) and electrocardiogram T wave abnormal (cumulatively three reports, all new).

An overview of the cumulative reporting demography is shown in Figure 7.

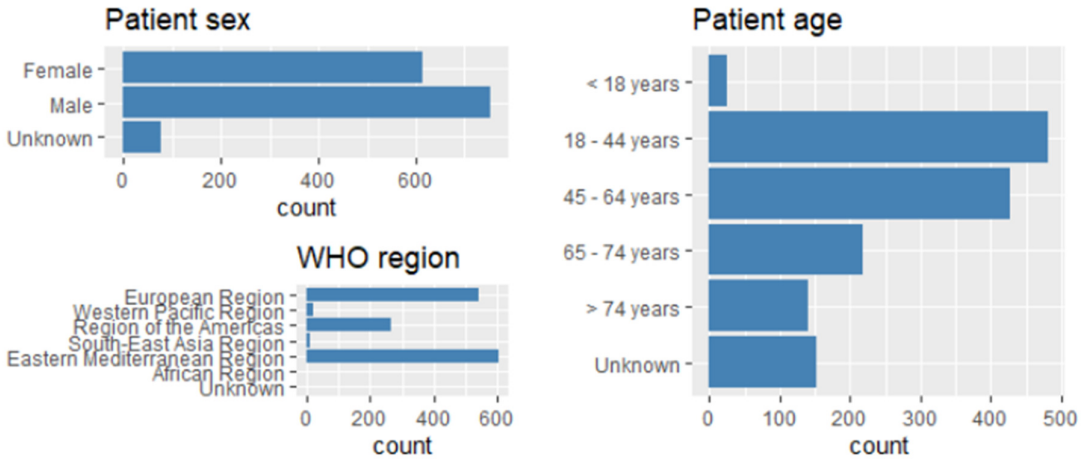


Figure 7. Demography of VigiBase reports received cumulatively so far on azithromycin as suspected or interacting drug.

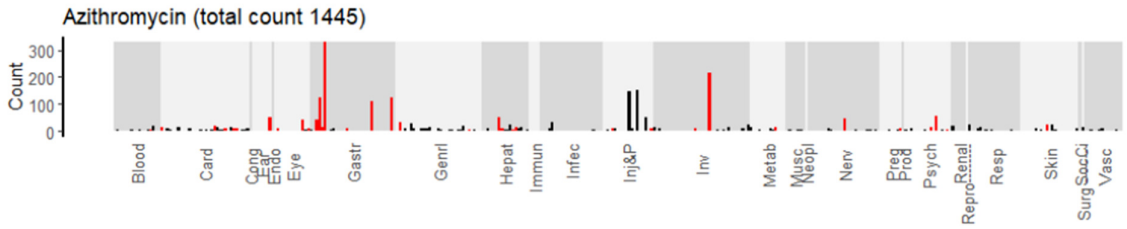


Figure 8. Cumulative report counts for azithromycin in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table 6). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

Lopinavir;ritonavir

During this reviewing period, 66 new reports in which lopinavir;ritonavir were reported as suspecting or interacting drugs were reviewed. These concerned 29 male and 28 female patients; median age of patients described in the new reports was 59 years (nine reports had age unreported).

The new reports originated from Eastern Mediterranean Region (five), European Region (39) and Region of the Americas (22). An overview of the cumulative reporting demography is shown in Figure 9.

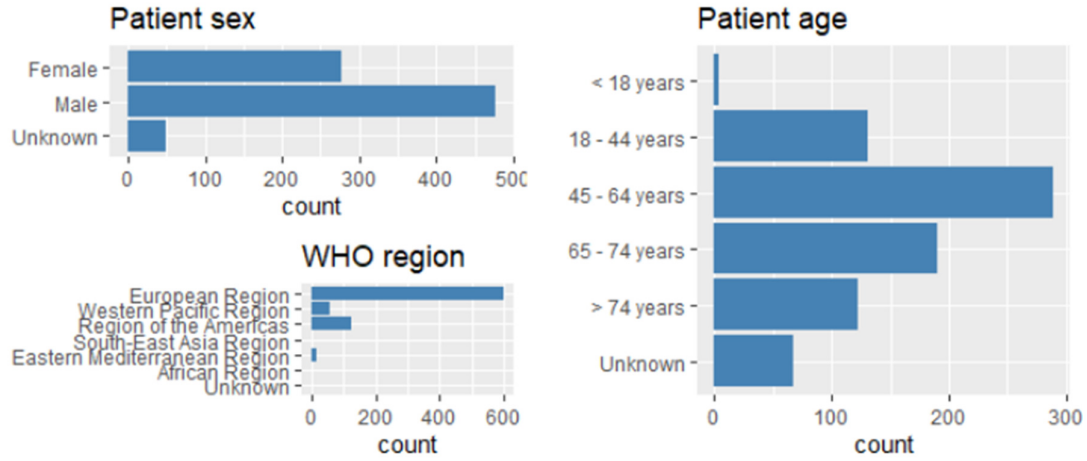


Figure 9. Demographics of VigiBase reports received cumulatively so far for lopinavir;ritonavir as suspected or interacting drug.

Adverse events

The most commonly reported ADRs continued to be those which are included on the product labelling for lopinavir;ritonavir.[6]

The most commonly reported ADRs during the review period were diarrhoea (13 reports/220 cumulative), COVID-19 (11/13), renal failure (9/16), transaminases increased (8/24), and multiple organ dysfunction syndrome (7/7).

The most commonly reported ADRs cumulatively are: diarrhoea (220 reports), nausea (69 reports), electrocardiogram QT prolonged (62 reports), hepatocellular injury (56 reports), and hypertriglyceridemia (52 reports).

Off-label use was reported as an ADR in 19 reports during the review period and in 181 reports cumulatively.

Drug interaction was reported as an ADR in 15 reports during the review period and in 48 reports cumulatively. 14 of the 15 reports reported an interaction between lopinavir;ritonavir and

tacrolimus. 11 of the 15 reports co-reported the ADR term “immunosuppressant drug level increased”. This interaction is included in the labelling for lopinavir;ritonavir.

Notable new ADR terms include Pneumocystis jirovecii pneumonia (five reports) and BK virus infection (two reports). The five reports of pneumonia appear to be one case with four duplicate reports of a 59 year old woman on immunosuppressant treated with tacrolimus and mycophenolic acid as well as lopinavir;ritonavir who experienced a fatal outcome. The reports of BK virus infection appears to be also one case with one duplicate report of a 61 year old treated also with tacrolimus and mycophenolic acid as well as lopinavir;ritonavir.

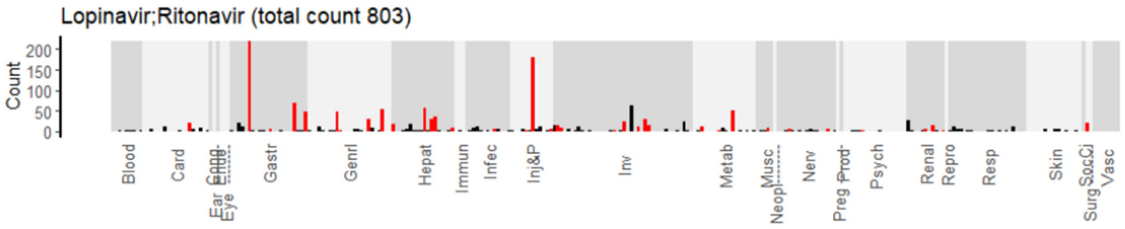


Figure 10. Cumulative report counts for lopinavir;ritonavir in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table 6). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

Remdesivir

The antiviral substance remdesivir has during the pandemic been authorized with the indication of COVID-19 in several countries. Publicly available information on its side effects and precautions for its use are therefore still limited and includes hypersensitivity including infusion-related and anaphylactic reactions (frequency designated as rare for both), transaminase elevations (very common), nausea (common), headache (common), rash (common) and renal impairment (precaution) and interactions including risk of decreased antiviral activity when co-administered with hydroxychloroquine and chloroquine.[7]

There was at the time of the data lock point a total of 1977 reports of remdesivir in VigiBase being suspected to have caused or contributed to an adverse reaction. During this reviewing period, 1806 new or updated remdesivir reports were shared, of which in 1763 the drug was reported as single suspected. These concerned 1099 female and 689 male patients as well as 18 patients of unknown sex. The new reports originated from African Region (two), European Region (45), Region of the Americas (1750), South-East Asia Region (three) and Western Pacific Region (six). An overview of the cumulative number of reports up until the previous period is available in the previous report.

An overview of the cumulative reporting demography is shown in Figure 11 where middle aged and men are still with the large increase in reports the most commonly reported catergories. A cumulative overview of other COVID-19 drugs co-administrated with remdesivir is available in Table 5 where, the most commonly reported at this point are: heparin-like substances (>700) , corticosteroids (>400), azithromycin (315), Ascorbic acid (145), Toclizumab (138), Zinc (134).

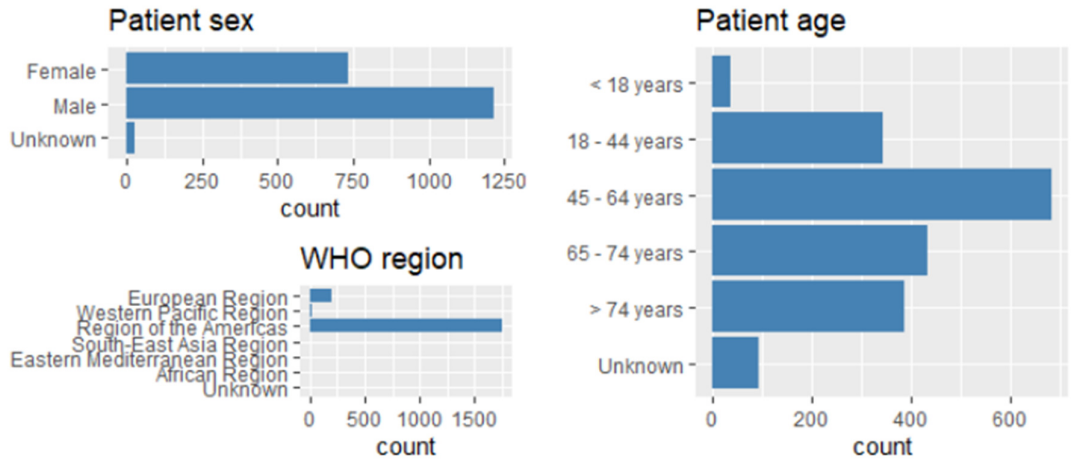


Figure 11. Demographics of VigiBase reports received cumulatively so far for remdesivir as suspected or interacting drug.

Adverse events

The new reports for remdesivir in a suspect or interacting role in this review comprise 76% of the cumulative total of reports; adding the updated reports since the last review this number increases to 91%. For resource reasons the review of the cases has been strictly limited to overviews. Disproportionality analysis using the other COVID-19 drug reporting as a background as well as the whole database has been used for evaluating reported terms belonging to SOCs where no ADRs are currently included in the labelling. Using the therapeutic area as a background has previously been validated and shown valuable in reducing background noise and disease spillover in coding[8] and is being used here in the COVID-19 situation.

In previous UMC COVID-19 reviews, reporting of kidney and liver function disturbances and skin reactions were common for remdesivir. At this point the reporting spectrum has changed and widened.

Hepatobiliary disorders and related investigational terms ("liver-related terms")

With the large increase in reports for this review transaminase-related PTs are the top reported terms with several hundred new reports and reports in total which appear in line with the labelling for the drug as mentioned above. All liver-related terms reported more than eight times are also disproportionately often reported both comparing to the database as a whole *and* compared to all the other COVID-19 drugs potentially indicating that they occur more frequently in remdesivir-treated patients. There may be other explanations for the disproportionality noted e.g. that the majority of the remdesivir reports come from one country where differences in coding practice compared to other countries and differences in co-treatment may influence the calculations.

Liver-related terms currently not in the labelling and reported cumulatively at least five times include the unspecific terms liver function test increased (151 new reports/159 in total), hepatic enzyme increased (50/62), and the more specific terms blood bilirubin increased (32/34), blood alkaline phosphatase increased (31/31), international normalised ratio increased (22/23), ischaemic hepatitis (9/9), hepatotoxicity (6/7), heaptic failure (5/6), acute hepatic failure (5/8), liver injury (4/5), and hepatitis (3/7).

Among hepatic terms reported less than five times in total, terms of note are hepatic steatosis (3/3), cholelithiasis (2/2), cholecystitis (1/1), cholestasis(1/1), hepatic cirrhosis (1/1), jaundice (1/1), non-alcoholic fatty liver (1/1).

A vast majority of the reports which included hepatic terms mentioned above were coded as serious. Except for reports on cases reported with a fatal outcome, most of these hepatic terms were fatal only in a minority (<10%) of reported cases. Notable exceptions are hepatic failure and acute hepatic failure where 37% and 67% of cases respectively were fatal.

Renal and urinary disorders and related investigational terms

As already mentioned no renal terms are included as acknowledged ADRs in the EU SmPC for remdesivir.[9] Investigational terms dominate the collection of reports of kidney related terms with in falling order and with more than five reports; blood creatinine increased (171 new reports/174 reports in total), glomerular filtration rate decreased (67/70), creatinine clearance decreased (23/23), blood urea increased (14/14), renal tubular necrosis (9/9), glomerular filtration rate increased (8/8), urine output decreased (8/8), nephropathy toxic (7/7), oliguria (6/6). All of these terms were disproportionately more often reported both in comparison to the other COVID-19 drugs and to the database as a whole, potentially indicating that they occur more frequently in remdesivir-treated patients. There may be other explanations for the disproportionality noted e.g. that the majority of the remdesivir reports come from one country where differences in coding practice compared to other countries and differences in co-treatment may influence the calculations.

Among kidney related terms reported less than five times in total, terms of note are anuria (4/4), azotaemia (3/4), ammonia increased (3/3), renal injury (3/3), end stage renal disease (2/2), hydronephrosis(2/2), prerenal failure (2/2), urinary casts (1/1), bladder calculus (1/1), crystal nephropathy (1/1).

The majority of the reports of the renal terms were coded as serious and a smaller proportion of the reports were coded as having a fatal outcome.

Skin and subcutaneous tissue disorders

Rash is the only term in this SOC labelled in the EU SmPC with a frequency of common. Different kinds of rashes account for most of the reporting within the SOC. Terms cumulatively reported at least five times are: rash (12 new reports, 23 reports in total), hyperhidrosis (10/10), angioedema (6/6), erythema (5/6), pruritus (6/6), rash papular (5/6), rash erythematous (4/5), rash maculopapular (2/5). None of the reports were disproportionately often reported compared to the COVID-19 drugs or VigiBase as a whole. Among skin terms reported less than five times in total, terms of note are urticaria (2/3), subcutaneous emphysema(2/2), ecchymosis (1/1), red man syndrome (1/1). Generally reports where these terms occurred were reported as serious. Of the terms mentioned only the two cases where subcutaneous emphysema was included were fatal.

Immune system disorders; hypersensitivity reactions and infusion related reactions are labelled for remdesivir, both with a frequency of rare. Terms reported within the Immune system disorders SOC are hypersensitivity (7 new reports/8 reports in total), anaphylactic reaction (2/2), anaphylactic shock (1/1), drug hypersensitivity (1/1). Nearly all reports including these terms were coded as serious and the case of anaphylactic shock was fatal. Within the general disorders SOC further relevant terms related to what is described in the labelling were reported such as infusion site swelling (7/7) and erythemata (6/6).

Reported terms belonging to SOCs where **no** ADR term currently is labelled: 667 different such PTs were reported and for all but 18 of these, new or updated reports were included in the review. A disproportionality analysis using the therapeutic area COVID-19 as the background produced 47 terms reaching an IC_{025} >0 for analysis (where new or updated reports were present). Among the non-organ specific terms were noted death (126 new or updated reports /127 in total), product preparation error (31/32), product administration error (18/18), product preparation issue (18/18), product dispensing error (13/14), product storage error (9/9) and medication error (6/8).

Among organ specific terms, the terms in the table on next page were detected (sorted by their IC_{025} value in falling order and with the second column representing the cumulative number of reports the term is included in and the third column, the number of new or updated reports where the term is included). Many terms are plausibly related to the background disease. No further assessment of this was feasible to finalise for the report.

Preferred term reported	Cumulative number	New or updated number
Hypotension	76	73
Respiratory failure	82	72
Cardiac arrest	70	67
Bradycardia	57	57
Hypoxia	53	52
Dyspnoea	42	42
Pulseless electrical activity	31	31
Cardio-respiratory arrest	25	24
Shock	21	21
Sepsis	18	17
Respiratory distress	16	16
Respiratory arrest	12	11
Disseminated intravascular coagulation	11	11
Respiratory disorder	11	11
Unresponsive to stimuli	10	10
Acute myocardial infarction	9	9
Mental status changes	8	8
Haemodynamic instability	8	8
Dysphagia	8	8
Fluid overload	7	7
Shock haemorrhagic	8	7
Lethargy	7	7

Among terms not being disproportionately more reported for remdesivir than for the COVID-19 background *and* not previously mentioned *and* reported more than once are especially noted: ventricular tachycardia (11 new or updated reports/12 cumulative total), seizure (9/10), haemoglobin decreased (8/8), hyperkalemia (7/11), rhabdomyolysis (7/7), flushing (6/6), ventricular fibrillation (6/7), burning sensation (5/5), myasthenia gravis crisis (2/2), musculoskeletal stiffness (2/2). The reported reactions and their level of seriousness are all cumulatively and for this period.

Remdesivir reported in relation to pregnancy: Relevant ADR Terms reported (not representing the number of pregnancies as more than one term is often included per report) include: maternal exposure during pregnancy (7 new or updated reports/ 11 reports cumulatively), maternal drugs affecting foetus (1/1), maternal exposure timing unspecified (1/1), foetal death (2/2), foetal exposure during pregnancy (2/2 including one reported as fatal), exposure during pregnancy (1/1), premature labour (1/1).

As noted above, a wide variety of currently non-labelled ADR terms[9] have been reported in relation to the use of remdesivir in non-negligible numbers. Detailed analysis of the reports and signal assessment of the combinations to discern whether any of them would be relevant to consider being true, ADRs of remdesivir has not been performed by the UMC. As the drug has just relatively recently been approved under special circumstances and procedures by some drug agencies, labelling is expected to be updated. The general pattern of reported ADRs cannot however be considered to lie within what is currently labelled for the drug. Reports for remdesivir in VigiBase are currently exclusively reported with the indication of COVID-19. Hence statistics and data on such reports for all preferred terms reported in relation to remdesivir are easily retrievable for users of VigiBase.

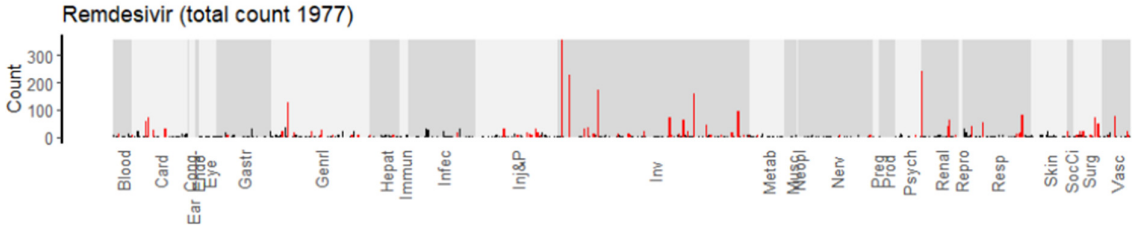


Figure 12. Cumulative report counts for remdesivir in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table 6). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

Tocilizumab

Tocilizumab is a monoclonal antibody against the interleukin-6 receptor used in COVID-19 to alleviate the inflammatory cytokine storm, seen in severe cases as part of a response to the viral infection. Among approved indications is cytokine release syndrome (CRS).[11]

During this reviewing period there were 151 new or updated reports in which tocilizumab was reported as suspected or interacting adding up to a total cumulative number of 547 reports. The new reports concerned 82 males, 41 females and 28 where sex was not reported; median age of the patients was 60 (with 37 reports lacking information on age). The new reports were shared from the African Region (six), Eastern Mediterranean Region (one), European Region (20), Region of the Americas (122) and Western Pacific Region (two).

A cumulative overview of other COVID-19 drugs co-administrated with tocilizumab is available in Table 5. The most common COVID-19 drugs co-adminstrated with toclilzumab are hydroxychloroquine/chloroquine (230), heparin class drugs (169), azithromycin (149), remdesivir (138) and corticosteroids (138). An overview of the cumulative reporting demography is shown in Figure 13; toclizumab is reported in males more than twice as often as in females.

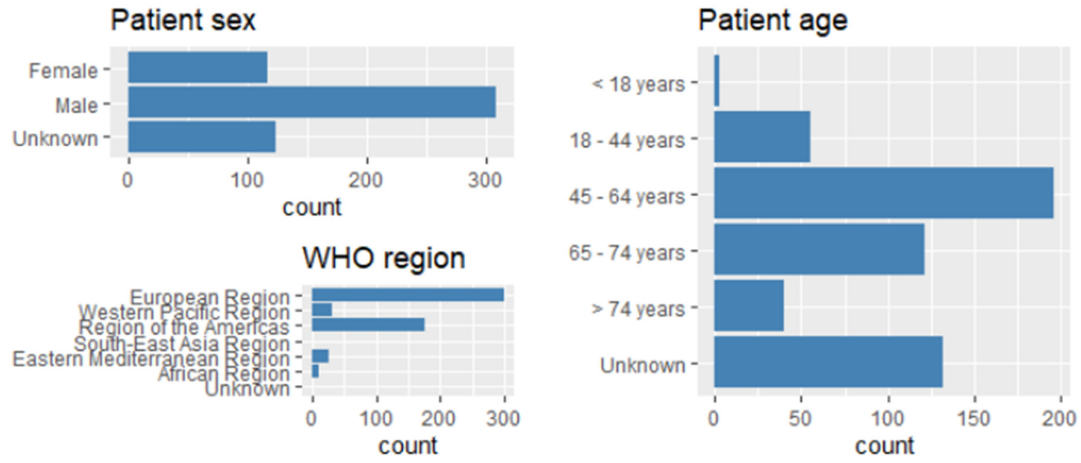


Figure 13. Demographics of VigiBase reports received cumulatively so far for tocilizumab as suspected or interacting drug.

Adverse events

New or updated reports in this review comprise 28% of the cumulative number of reports for tocilizumab.

The widespread ADR reporting pattern remains similar to what has been seen in previous reviews. A visualization of this is visible in figure 14; the highest bars within the Injury, poisoning and procedural complications SOC in the figure representing coding of off-label use and similar codes. Hepatic reactions and related investigational terms are being reported dominated by terms

representing transaminase increase (27 new cases/60 cumulative total of cases) and hepatitis (1/37), the latter acknowledged in the labelling as a rare side effect for tocilizumab. Within the cardiac SOC new reports in this review include cardiac arrest (4/9), bradycardia (4/5), pulseless electrical activity (3/3), A-V-block (2/2). The tocilizumab labelling does not include any cardiac reactions.

Gastrointestinal ADRs including perforations and gastrointestinal haemorrhages continue to be reported to a disproportionate level compared to other COVID-19 drugs and compared to the database in general; examples are gastrointestinal haemorrhage (2/4), intestinal perforation terms (3/14), pneumatosis intestinalis (1/1), pneumoperitoneum (1/1).
Mouth ulceration, Gastritis, Stomatitis and Gastric ulcer are included in the tocilizumab label but not perforations and haemorrhages per se other than as a complication of diverticulitis; there is a warning regarding treating patients at risk of perforation.

The risk of infections is labelled for tocilizumab and a large proportion of reports for tocilizumab contain infection-related terms (other than COVID-19 per se) representing numerous infectious agents.

Among terms disproportionately more reported for tocilizumab than for the COVID-19 background and not previously mentioned in detail and reported more than once are especially noted: hypofibrinogenaemia (no new reports/cumulative number 15), neutropenia (4/16), candida infection (2/5), pulmonary embolism (2/11).

Among terms not disproportionately reported (and not mentioned above) most have been reported in very low numbers. Noted terms here are hypothermia (4 new reports/4 in total), acute kidney injury (4/6), renal failure (2/6), platelet count decreased (3/3), catatonia (2/2),

The pattern of reported ADRs for lies largely within what is labelled for the drug except still for the cardiac events and regarding their seriousness, the gastrointestinal events.[11]

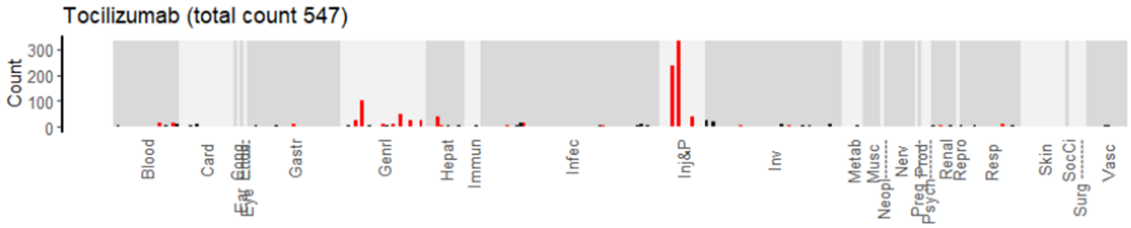


Figure 14. Cumulative report counts for tocilizumab in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table 6). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

Oseltamivir

During this reviewing period there were 9 new reports in which oseltamivir was reported as suspected or interacting adding up to a total cumulative number of 175 reports. The new reports concerned two males and seven females; median age of the patients was 59. The new reports were shared from the Eastern Mediterranean Region (four) and Region of the Americas (five). An overview of the cumulative reporting demography is shown in Figure 15.

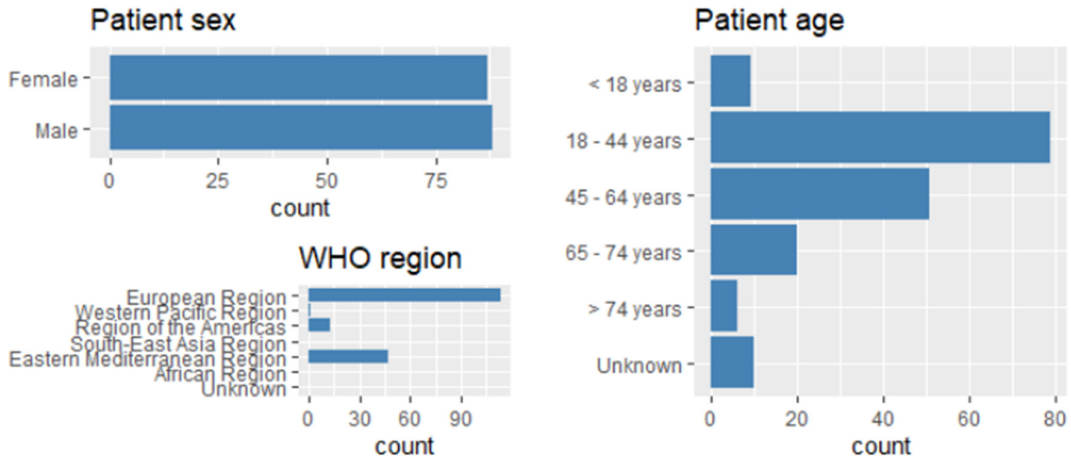


Figure 15. Demographics of VigiBase reports received cumulatively so far for oseltamivir as suspected or interacting drug.

Adverse events

The most commonly reported ADRs are those which are in line with the product labelling for oseltamivir.[12]

The most commonly reported ADRs during the review period were abdominal pain upper (2 reports/ 11 cumulative), pruritus (1/12), and rash (1/12), multiple organ dysfunction syndrome (1/1), and COVID-19 (1/1).

The most commonly reported ADRs cumulatively are: nausea (35 reports), diarrhoea (27 reports), vomiting (24 reports), abdominal pain (23 reports), and pruritus (12 reports) and rash (12 reports).

There were no new notable ADRs during the reporting period.

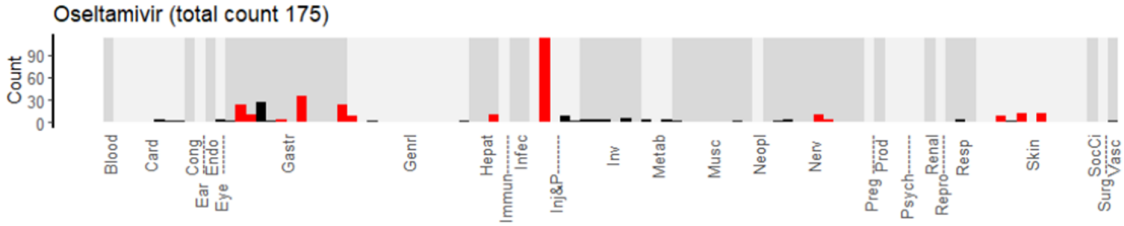


Figure 16. Cumulative report counts for oseltamivir in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table 6). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

Enoxaparin

During this reviewing period there were 15 new reports in which enoxaparin was reported as suspected or interacting adding up to a total cumulative number of 141 reports. The new reports concerned seven males, six females and two where sex was not reported; median age of the patients was 72 (with five reports lacking information on age). The new reports were shared from the Eastern Mediterranean Region (two), European Region (three) and Region of the Americas (10).

An overview of the cumulative reporting demography is shown in Figure 17. Enoxaparin was in a majority of cases co-reported with at least two other drugs and hence there is an overlap between enoxaparin and other drugs that have already been covered in the report, e.g. remdesivir, tocilizumab, lopinavir;ritonavir, azithromycin and hydroxychloroquine. Apart from this the ADRs reported correspond largely to what is known for enoxaparin.[13]

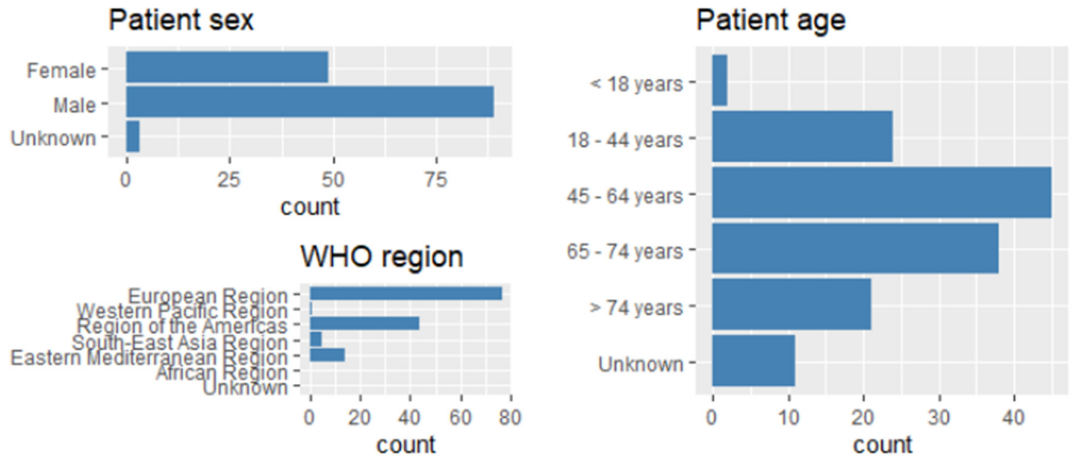


Figure 17. Demographics of VigiBase reports received cumulatively so far for enoxaparin as suspected or interacting drug.

Adverse events

The 15 new reports included 23 serious preferred terms not previously reported. These largely showed a similar pattern to previous periods and mainly contain what would be expected for this drug or the underlying Covid-infection or its treatment with concomitant medicines. After removal of two duplicate reports only septic shock was reported more than once (3 in total). Overall the most serious reports could be classified mainly as haemorrhagic or immune-related. These included serious outcomes of haemorrhage reported for the first time (retroperitoneal haematoma and retroperitoneal haemorrhage, intra-abdominal haemorrhage). There were also two additional reports this period of haemorrhagic shock out of a total of three and an additional report of disseminated intravascular coagulation (DIC) in addition to one already entered. Other new serious PTs described immune magnification or suppression (cytokine storm, candida sepsis, pneumonia, septic shock) which could have been attributable to COVID-19 infection or concomitant immunosuppressants such as tocilizumab and corticosteroids.

Some reports showed serious haemorrhagic and immune or septic adverse effects reported for the first time and occurring together. For example one fatal report of DIC included also septic shock, retroperitoneal haemorrhage and intra-abdominal haemorrhage and the other DIC report included retroperitoneal haematoma, haemorrhagic shock, pneumonia, lactic acidosis, cytokine storm, liver injury and hyperkalaemia demonstrating how the haemorrhagic ADRs with enoxaparin add to the existing burden of COVID-19 related disease and its treatment. The reports of DIC did not show evidence of excessive use of enoxaparin. For one patient heparin was listed as concomitant but there were no administration dates. No other additional medicines that might have increased the risk of bleeding were listed. However, pre-treatment renal function, which should have determined enoxaparin dose, was not specifically mentioned.

Dyshidrotic eczema and eczema were new PTs in one report but there were no administration dates for enoxaparin. Other suspects were tocilizumab, lopinavir;ritonavir and hydroxychloroquine all of which had been recently discontinued.

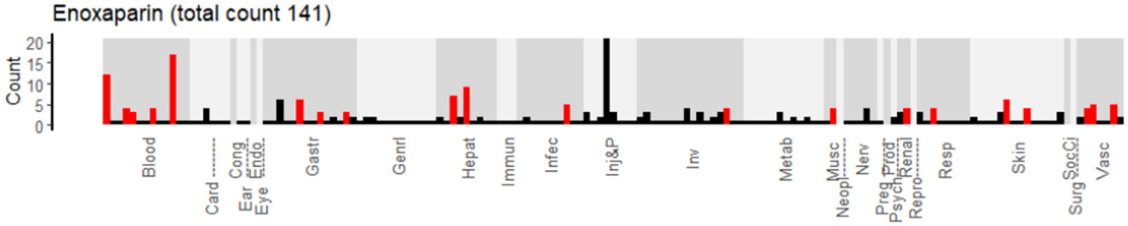


Figure 18. Cumulative report counts for enoxaparin in one bar for each preferred term, sorted by SOC.

Sarilumab

During this reviewing period there were 118 new reports in which sarilumab was reported as suspected or interacting adding up to a total cumulative number of 158 reports. The new reports concerned 41 males, 15 females and 62 where sex was not reported; median age of the patients was 61 (with 62 reports lacking information on age). The new reports were shared from the European Region (eight) and Region of the Americas (110). An overview of the cumulative reporting demography is shown in Figure 19.

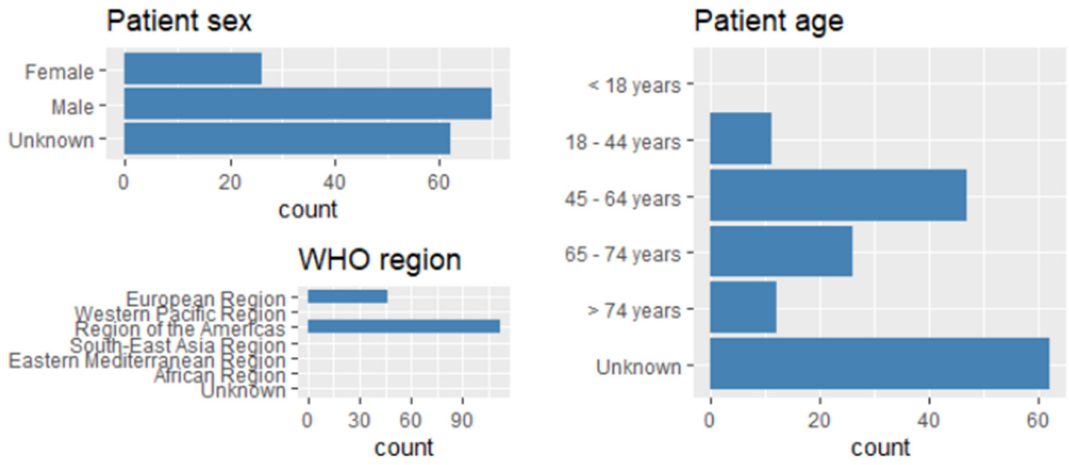


Figure 19 Demographics of VigiBase reports received cumulatively so far for sarilumab as suspected or interacting drug.

Adverse events

The most commonly reported ADRs are those which are in line with the product labelling for sarilumab.[14]

The most commonly reported ADRs during the review period were ALT increased (31 reports), AST increased (29 reports), transaminases increased (19 reports), pneumonia bacterial (18 reports) and hypotension (14 reports).

The most commonly reported ADRs cumulatively are: ALT increased (32 reports), AST increased (30 reports), transaminases increased (19 cumulative), pneumonia bacterial (18 reports), and hypotension (14 reports).

In previous reviews were mentioned two ADRs that are not included in the sarilumab labelling: acute kidney injury and deep vein thrombosis / pulmonary embolism. There appear to be only updates of previously received reports during this review period.

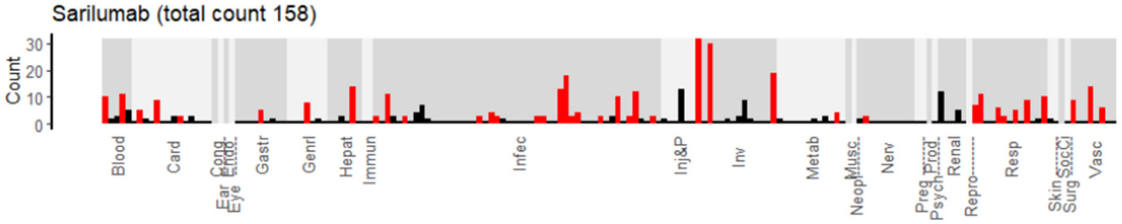


Figure 20. Cumulative report counts for sarilumab in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table 6). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

Drugs for use in COVID-19 reported less than 100 times into VigiBase

Besides reports for WHO Solidarity trial drugs, some of which have since been discontinued from the trial, many ADR reports describe the use of other drugs for the treatment of COVID-19. As ADR data accumulate for such substances, treatment and patterns of reported adverse events for them are being reviewed once the number of reports for a drug exceeds 100. The rest of the drugs identified as being used are presented as “other” (Table 4).
For the non-solidarity drug reports (marked as “other” in the table) individual case validation has not been performed.

Disclaimer

Data in the reports are not complete and only a subset of the reports in the analysis unfortunately contained narratives precluding quality causality assessment. With limited data available at this stage of the pandemic and the uncertainty over other confounders (such as the underlying disease), this report is no more than a preliminary overview of cases and reported ADRs. No automated deduplication method was used. Any signals detected from this monitoring will be communicated separately.

An error in the Report counts by dates received in previously submitted reports:

By mistake, the counts in the left panel of Figure 1 in previously submitted reports, counted the number of reportings of any drug, not acknowledging that some drugs were reported on the same case report, so the actual number of reports was smaller. As far as we can see, it does not make a tangible difference to the "impression" given by the figure, but there is indeed a change in the numbers on the Y axis. The error is corrected in this report and onwards, which is why the Y axis of this report spans a narrower range than in previously submitted reports.

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Appendix

Drug group	N_old	N_new	N_total
Azithromycin	1268	177	1445
Chloroquine	421	11	432
Hydroxychloroquine	2074	338	2412
Lopinavir;ritonavir	737	66	803
Remdesivir	171	1806	1977
Tocilizumab	396	151	547
Oseltamivir	166	9	175
Enoxaparin	126	15	141
Sarilumab	40	118	158
Other drugs	618	266	884
Unique reports	4095	2623	6718

Table 1. N_old display reports described in previous reports, which included reports received to VigiBase no later than the 2nd of August. N_new includes reports received to VigiBase no later than the 17th of August. Other drugs are selected from medical expertise from the set of corona virus indicated drugs reported to VigiBase, see Table 3. Counts include suspected or interacting drugs. As one report may contain several drugs, rows are not mutually exclusive.

		Azithromycin		Chloroquine		Hydroxychloroquine		Lopinavir;Ritonavir		Remdesivir		Tocilizumab		Oseltamivir		Enoxaparin		Sarilumab		Other		Unique reports	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Report characteristics																							
	Total N	1445	100	432	100	2412	100	803	100	1977	100	547	100	175	100	141	100	158	100	884	100	6718	100
	Single Susp.	187	12.9	163	37.7	957	39.7	295	36.7	1895	95.9	371	67.8	32	18.3	27	19.1	138	87.3	456	51.6	4521	67.3
	Serious	630	43.6	134	31	1261	52.3	392	48.8	1521	76.9	422	77.1	49	28	105	74.5	151	95.6	512	57.9	3928	58.5
	Fatal	72	5	10	2.3	156	6.5	51	6.4	431	21.8	194	35.5	5	2.9	16	11.3	50	31.6	170	19.2	957	14.2
Sex																							
	Female	613	42.4	227	52.5	953	39.5	276	34.4	735	37.2	116	21.2	87	49.7	49	34.8	26	16.5	307	34.7	2534	37.7
	Male	753	52.1	188	43.5	1316	54.6	477	59.4	1217	61.6	308	56.3	88	50.3	89	63.1	70	44.3	514	58.1	3788	56.4
	Unknown	79	5.5	17	3.9	143	5.9	50	6.2	25	1.3	123	22.5			3	2.1	62	39.2	63	7.1	396	5.9
Age																							
	Median (Q1-Q3)	51 (35-65)		50 (33-64)		57 (40-71)		61 (49-71)		62 (48-73)		61 (50-68)		42 (32-57)		63 (48-72)		60 (50-69)		60 (47-70)		59 (44-70)	
	< 18 years	26	1.8	12	2.8	25	1	4	0.5	35	1.8	3	0.5	9	5.1	2	1.4	0	0	11	1.2	102	1.5
	18 - 44 years	481	33.3	156	36.1	638	26.5	131	16.3	343	17.3	55	10.1	79	45.1	24	17	11	7	157	17.8	1465	21.8
	45 - 64 years	426	29.5	130	30.1	726	30.1	289	36	684	34.6	196	35.8	51	29.1	45	31.9	47	29.7	305	34.5	2203	32.8
	65 - 74 years	219	15.2	63	14.6	408	16.9	190	23.7	435	22	121	22.1	20	11.4	38	27	26	16.5	187	21.2	1277	19
	> 74 years	140	9.7	31	7.2	376	15.6	122	15.2	387	19.6	40	7.3	6	3.4	21	14.9	12	7.6	117	13.2	1008	15
	Unknown	153	10.6	40	9.3	239	9.9	67	8.3	93	4.7	132	24.1	10	5.7	11	7.8	62	39.2	107	12.1	663	9.9
WHO region																							
	African Region	2	0.1	0	0	2	0.1	0	0	2	0.1	10	1.8	0	0	0	0	0	0	3	0.3	15	0.2
	Eastern Mediterranean Region	606	41.9	245	56.7	357	14.8	18	2.2	0	0	27	4.9	47	26.9	14	9.9	0	0	23	2.6	777	11.6
	European Region	543	37.6	78	18.1	1320	54.7	601	74.8	203	10.3	301	55	114	65.1	77	54.6	46	29.1	455	51.5	2491	37.1
	Region of the Americas	264	18.3	38	8.8	570	23.6	127	15.8	1755	88.8	177	32.4	13	7.4	44	31.2	112	70.9	316	35.7	3023	45
	South-East Asia Region	9	0.6	3	0.7	83	3.4	0	0	3	0.2	0	0	0	0	5	3.5	0	0	10	1.1	108	1.6
	Western Pacific Region	21	1.5	68	15.7	80	3.3	57	7.1	14	0.7	32	5.9	1	0.6	1	0.7	0	0	77	8.7	304	4.5
	Unknown	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 2. Counts are cumulative and include suspected and interacting drugs. As one report may contain several drugs, columns are not mutually exclusive. Other drugs are selected from medical expertise from the set of corona virus indicated drugs reported to VigiBase, see Table 3. Single susp. = Drug was reported as single suspected or interacting drug, Q1-Q3 = First to third quartile.

Last updated: August 25, 2020

Drug	N	%
Unique reports	175	100
Favipiravir	81	46.3
Methylprednisolone	73	41.7
Prednisone	67	38.3
Ivermectin	65	37.1
Dexamethasone	58	33.1
Heparin	47	26.9
Eculizumab	46	26.3
Ritonavir	45	25.7
Ruxolitinib	36	20.6
Anakinra	35	20
Plasma	32	18.3
Atazanavir	29	16.6
Darunavir	27	15.4
Baricitinib	20	11.4
Apixaban	19	10.9
Interferon beta-1b	19	10.9
Hyperimmune plasma Covid-19	16	9.1
Canakinumab	15	8.6
Epoprostenol	14	8
Ribavirin	13	7.4
Lopinavir	12	6.9
Montelukast	12	6.9
Rituximab	12	6.9
Hydrocortisone	11	6.3
Immunoglobulin human normal	11	6.3
Maraviroc	11	6.3
Metamizole	11	6.3
Baloxavir marboxil	10	5.7
Alteplase	9	5.1
Ascorbic acid	9	5.1
Cobicistat;Darunavir	9	5.1
Prednisolone	9	5.1
Colecalciferol	8	4.6
Itolizumab	8	4.6
Warfarin	8	4.6
Zinc	8	4.6
Aciclovir	7	4
Colchicine	7	4
Siltuximab	5	2.9
Interferon beta	4	2.3
Investigational drug	4	2.3
Nitazoxanide	4	2.3
Tinzaparin	4	2.3
Valaciclovir	4	2.3
Apremilast	3	1.7
Interferon	3	1.7

Note that table 3 continues on the next page.

Interferon beta-1a	3	1.7
Selinexor	3	1.7
Ciclosporin	2	1.1
Cobicistat	2	1.1
Darunavir;Ritonavir	2	1.1
Infliximab	2	1.1
Octreotide	2	1.1
Peginterferon alfa-2a	2	1.1
Tofacitinib	2	1.1
Acalabrutinib	1	0.6
Ademetionine	1	0.6
Allogenic mesenchymal stem cells nos	1	0.6
Almitrine	1	0.6
Bcg vaccine	1	0.6
Beractant	1	0.6
Bevacizumab	1	0.6
Bromhexine	1	0.6
Daclatasvir	1	0.6
Icatibant	1	0.6
Iloprost	1	0.6
Mefloquine	1	0.6
Sofosbuvir	1	0.6

Table 4 continued. Drugs included in the Other drugs-category. Counts are cumulative and include drugs reported as suspected or interacting. As one report may contain several drugs, rows are not mutually exclusive.

	Azithromycin	Chloroquine	Hydroxychloroquine	Lopinavir;Ritonavir	Remdesivir	Tocilizumab	Oseltamivir	Sarilumab	Enoxaparin
Total (S/I/C)	2151	458	2834	907	1995	713	269	159	1165
Single suspected	809	183	1312	383	1908	513	96	139	764
Azithromycin		273	1292	220	315	149	138	60	461
Chloroquine	273		8	31	3	13	6	2	19
Hydroxychloroquine	1292	8		454	80	223	217	80	485
Lopinavir;Ritonavir	220	31	454		20	87	17	1	134
Remdesivir	315	3	80	20		138	3	6	525
Tocilizumab	149	13	223	87	138		11	4	123
Oseltamivir	138	6	217	17	3	11			64
Sarilumab	60	2	80	1	6	4			35
Enoxaparin	461	19	485	134	525	123	64	35	
Acalabrutinib	1				1				1
Aciclovir	3		9	3	5	1			4
Almitrine								1	
Alteplase	9		7		1	6	1	1	5
Anakinra	19		21	2	7	7	1	4	9
Apixaban	12	2	23	10	46	8	2	4	5
Apremilast	2		2		1	1			3
Ascorbic acid	143	14	112	13	145	27	22	8	148
Atazanavir			33	3			2		3
Baloxavir marboxil							1		
Baricitinib	6		6	25	6	1			1
Bromhexine	1	1	11		1		6		6
Canakinumab			2		1				1
Ciclosporin	1		7	2	2	1			1
Cobicistat			2	1					
Cobicistat;Darunavir	7		12	3	1	3			4
Colchicine	6		14	3	4	5	1		9
Colecalciferol	67	3	46	2	78	10	1	3	53
Darunavir	6	4	26	3	2	8			12
Darunavir;Ritonavir			3						
Dexamethasone	142		52	15	348	45	2	3	182
Eculizumab	6		8	3	1	1			7
Epoprostenol	16		5		29	11		2	13
Favipiravir	43		73	3	1	12	23		41
Ganciclovir	2			2		1	1		
Heparin	85	3	82	30	209	46	9	26	68
Hydrocortisone	23	1	26	9	42	10	6	5	29
Iloprost					1				1
Immunoglobulin human normal	4		7	2	2	6		1	2
Immunoglobulins nos			3	1		1	1		
Infliximab	1		1				1		
Interferon	2		4	1					1
Interferon beta	4		4	5		1			1
Interferon beta-1a			1	4					1
Interferon beta-1b	16	2	30	30		6	2		10
Investigational drug					1				
Ivermectin	32	1	18	13	4	5	1	1	21
Lopinavir	5		17	1		2			5
Maraviroc			10		2				
Metamizole	31	1	47	17	14	5	8		28
Methylprednisolone	129	8	133	43	160	64	3	36	186
Montelukast	11		2	2	24	2			14
Nitazoxanide	5		1	5			2		1
Peginterferon alfa-2a	1		1						
Plasma	4	1	6		7	5		4	2
Prednisolone	5	3	5	10	8	2			5
Prednisone	54	1	82	14	31	17	2	11	32
Ribavirin	16		10	51	2	3	1	1	4
Ritonavir	11		69	6	1	6	2		19
Rituximab	4		6	1	1	6	1		
Ruxolitinib	5	1	14	5	2	3	1		11
Selinexor	2				5				3
Siltuximab			1	1					1
Tinzaparin	8	2	5	7	3				
Umifenovir				1			1		
Valaciclovir	1		3	1	3			1	4
Warfarin	6		8	2	10	2	4	1	6
Zinc	112	8	74	7	134	22	7	7	117
Other	1122	110	1358	511	1223	297	155	122	1032

Table 5. Co-medication frequencies. First row gives total number of reports including a drug irrespectively of drug role (suspected/interacting/concomitant). Second row gives number of reports on which the drug was the single suspected or interacting drug. Remaining rows give frequencies of co-reporting of a drug pair, irrespectively of drug role.

SOC_ABBREV	SOC
Blood	Blood and lymphatic system disorders
Card	Cardiac disorders
Cong	Congenital, familial and genetic disorders
Ear	Ear and labyrinth disorders
Endo	Endocrine disorders
Eye	Eye disorders
Gastr	Gastrointestinal disorders
Genrl	General disorders and administration site conditions
Hepat	Hepatobiliary disorders
Immun	Immune system disorders
Infec	Infections and infestations
Inj&P	Injury, poisoning and procedural complications
Inv	Investigations
Metab	Metabolism and nutrition disorders
Musc	Musculoskeletal and connective tissue disorders
Neopl	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Nerv	Nervous system disorders
Preg	Pregnancy, puerperium and perinatal conditions
Prod	Product issues
Psych	Psychiatric disorders
Renal	Renal and urinary disorders
Repro	Reproductive system and breast disorders
Resp	Respiratory, thoracic and mediastinal disorders
Skin	Skin and subcutaneous tissue disorders
SocCi	Social circumstances
Surg	Surgical and medical procedures
Vasc	Vascular disorders

Table 6. Abbreviations used for SOCs displayed in the reaction overview bar charts

CAVEAT DOCUMENT

2018-11-20

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.