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

Report from the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre

Report date: 2020-07-01

This eighth report of global reporting of ADRs for drugs used to treat COVID-19 is mainly descriptive in nature. It includes reviews for the drugs in the 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.

Reports have so far been shared from five of the six WHO regions, with the largest number still originating in the WHO European Region.

On 17 June 2020, WHO announced that inclusion of new patients into the hydroxychloroquine (HCQ) arm of the Solidarity Trial was being stopped.[1] The decision applies only to the conduct of the Solidarity trial and not to the use or evaluation of hydroxychloroquine in pre- or post-exposure prophylaxis in patients exposed to COVID-19.

NEWS in this report are A) summaries of reports for sarilumab and enoxaparin which have been reported more than 100 times in to the VigiBase and B) visualising figures on the adverse drug reaction spectrum of each drug sorted per SOC and PT with information on whether the terms are disproportionally reported or not. These visualisations are presented for each of the drugs reviewed as in Figure 4.

Reports in VigiBase

The methodology of search is with one exception the same in this eighth review, as in the seventh. 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 and June 28st 2020 and were reported to VigiBase no later than June 28st.* Foreign reports, i.e. reports originating from another country than the one sharing them into VigiBase accounted for 1.2% in the last (seventh) report. With incoming data from a larger number of countries this proportion increased to 13% for this review. A decision was made to exclude the foreign reports, which to a great extent are duplicates, from this report onwards. This means data in tables may in some instances appear to have decreased. Reports were considered for inclusion when they reported as suspected/interacting drugs 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 3) in appendix.

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

* If the arrival date at the National Center was not reported, the date of latest update at the National Center was used instead.

performed.

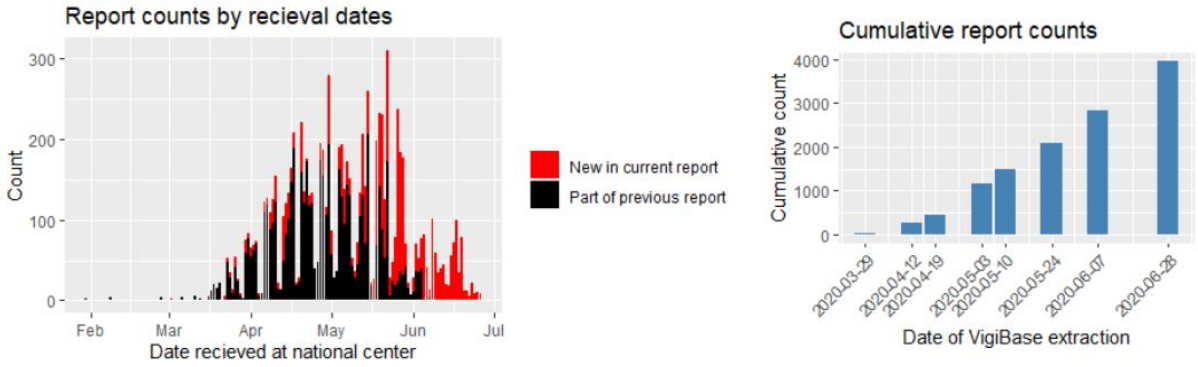


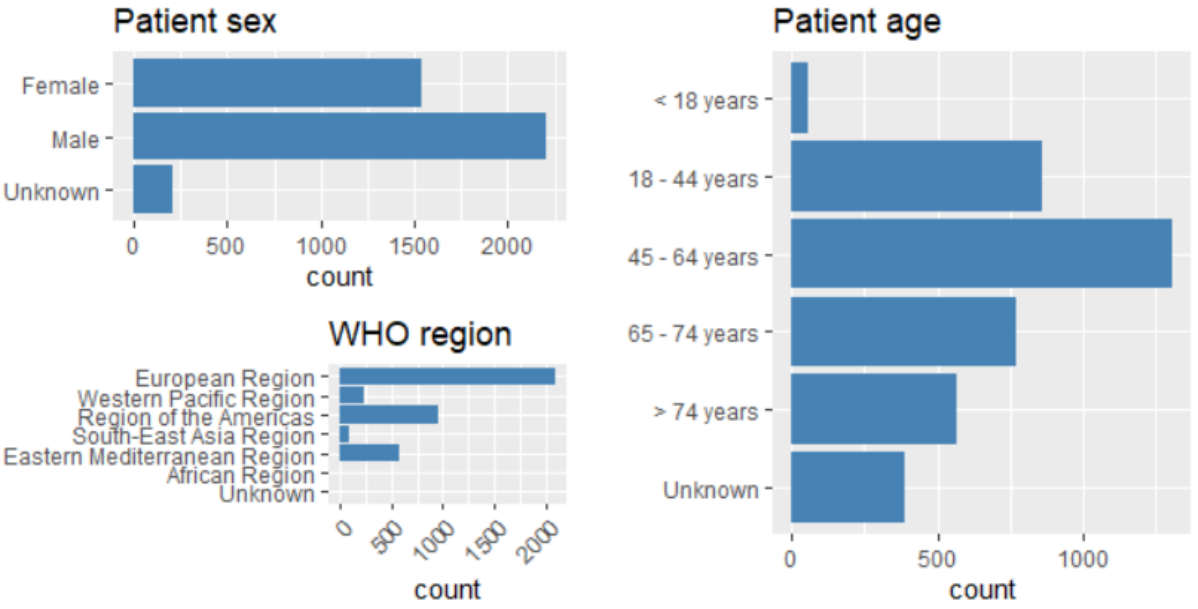
Figure 1. Number of reports by dates received at national center (left), and cumulative number of reports in VigiBase at the dates of extractions for reports. The rightmost bar (right panel) shows the total number of reports received so far.

Overview of patient characteristics

Since the last analysis, 1346 new case reports have been identified using the selected search strategy (Table 1). Cumulatively, there have been a total of 3946 reports from six WHO regions, the majority from the European region (53.1 %). 55 % of the reports were classified as "serious" (Table 2) but not all reporting standards used (e.g. INTDIS) record seriousness. Males accounted for 55.9 % of the reports and females 38.9 %.

Most of the reports describe at least one drug or substance in the WHO Solidarity trial, i.e. hydroxychloroquine (in some regions replaced by chloroquine, and from now no longer part of the trial, as described above), azithromycin, remdesivir and lopinavir;ritonavir reported as either suspected or interacting. The search also identified additional reports describing other drugs used in the treatment of COVID-19 disease. Among these, tocilizumab, oseltamivir, enoxaparin and sarilumab were reported more than 100 times into the database and were included in the more detailed descriptive analysis. Overall reporting demographics are shown in Figure 2. In line with males being more affected by COVID-19 infection globally, all drugs except chloroquine and oseltamivir are reported more for men than women. Patient ages are similar between drugs, although oseltamivir has the lowest median age.

A)



B)

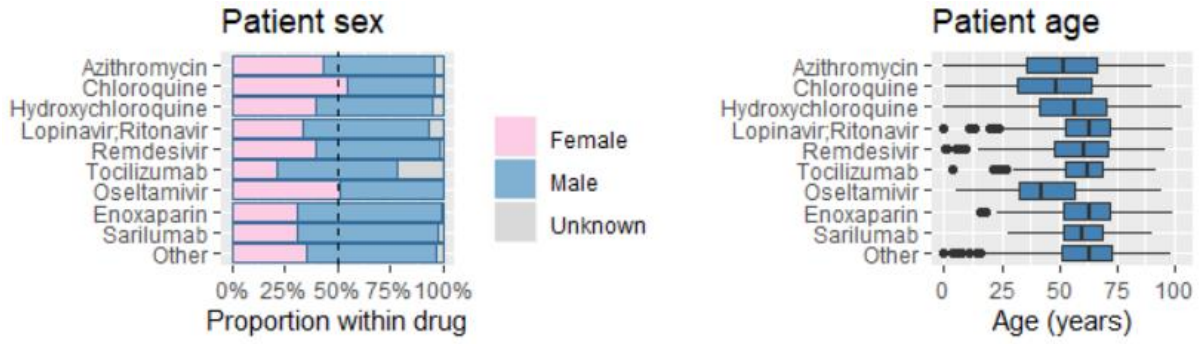


Figure 2. Overall demographics of case safety reports sent into VigiBase in treatment of COVID-19. A) All reports. B) Reports by drug. The B) graphs rely on counts of reports which include each drug as suspected or interacting. Reports including several drugs will be counted once for each reported drug.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

Characteristics of the reports on WHO Solidarity trial drugs, and drugs reported more than 100 times into VigiBase

Hydroxychloroquine alone or in combination with azithromycin

There were 486 new reports for hydroxychloroquine during this time period, adding to a cumulative total of 1932 reports. The new reports included 267 men, 184 women and 35 with unknown sex. The new reports originated from Eastern Mediterranean Region (93), European Region (196), Region of the Americas (146), South-East Asia Region (19) and Western Pacific Region (32). In the new reports the median age was 58 years (78 reports had age unreported). For the new reports, hydroxychloroquine was a single suspected drug in 224 cases. An overview of the cumulative reporting demography is shown in Figure 3.

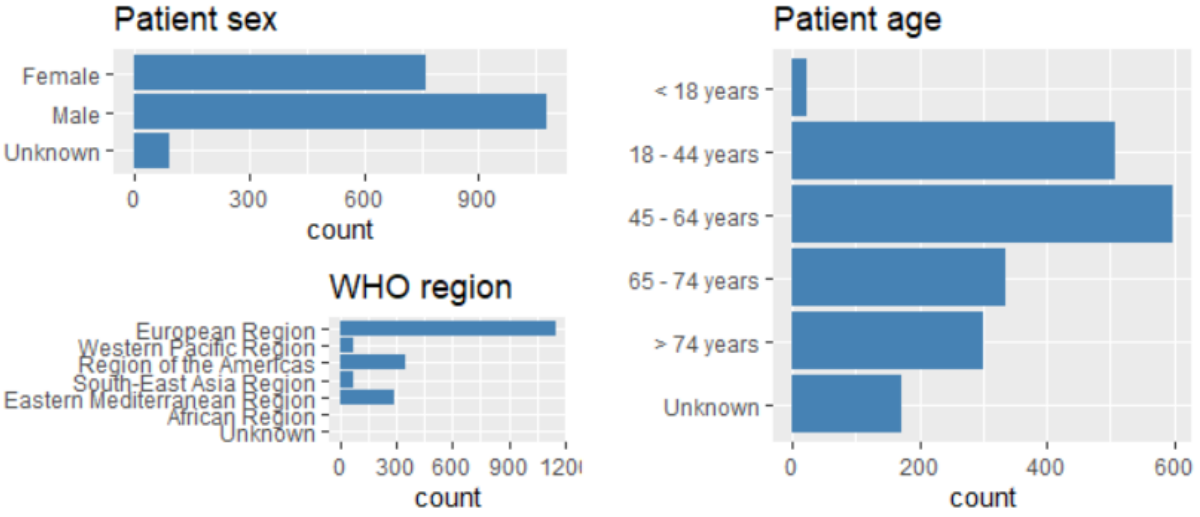


Figure 3. Demography of VigiBase reports received cumulatively so far on hydroxychloroquine as suspected or interacting drug.

Adverse events

The adverse drug event pattern for hydroxychloroquine seems to follow previously weeks observations with electrocardiogram QT prolonged, hepatic related events and gastrointestinal ADRs such as vomiting, nausea, diarrhoea among the top reported ADRs during this period. These terms are labelled for the drug[2] or for the concomitant drugs that have been administered together with hydroxychloroquine.

One serious event that had a large increase this period was the event "death" with eight new cases for this period, cumulatively 10. The cases have been shared from three different countries describing patients (one female, three males and four unknown gender) taking hydroxychloroquine with azithromycin in six cases, ceftriaxone in three cases, tocilizumab and lopinavir/ritonavir in two cases each. There was no clear explanation to why the patients died more than that the term *drug ineffective* had been co-reported in several of the reports. Acute kidney injury and transaminase increased were two terms with a high proportional increase (> 100%), both terms related to either hydroxychloroquine itself or the concomitantly taken drugs lopinavir/ritonavir and azithromycin.

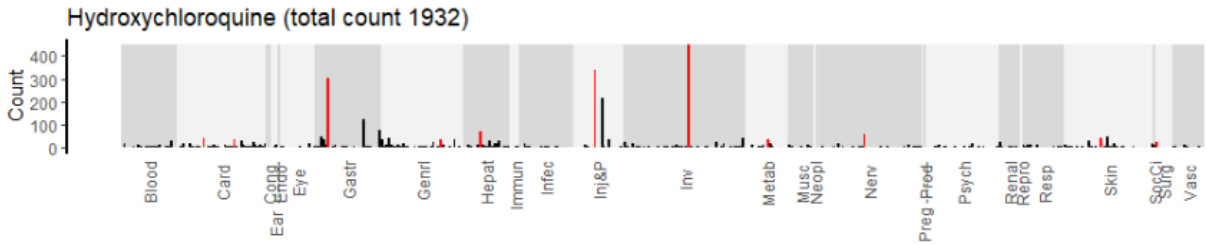


Figure 4. Cumulative report counts for hydroxychloroquine in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table 5). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

Chloroquine

During this reviewing period 40 new reports in which chloroquine was reported as suspecting or interacting drugs were reviewed. These concerned 17 male and 23 female patients; median age of patients described in the new reports was 42 years (three reports had age unreported). The new reports originated from Eastern Mediterranean Region (24), European Region (six), Region of the Americas (nine) and Western Pacific Region (one). An overview of the cumulative reporting demography is shown in Figure 5.

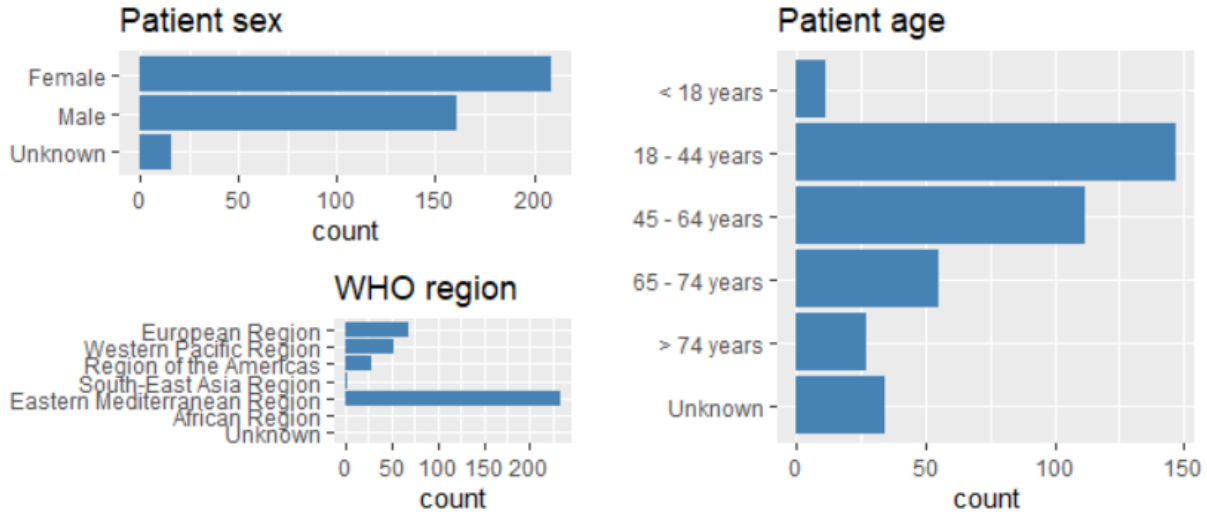


Figure 5. Demographics of VigiBase reports received cumulatively so far for chloroquine as suspected or interacting drug.

Adverse events

The 10 most frequently reported MedDRA Preferred Terms were: Vomiting (13 reports), followed by abdominal pain upper (11 reports), nausea (seven reports), diarrhoea (seven reports), vertigo (six reports), electrocardiogram QT prolonged (five reports), insomnia (five reports), headache (four reports), malaise (three reports), off label use (three reports), hallucination (three reports), seizure (two reports), dizziness (two reports), tachycardia (two reports), abdominal pain (two reports), agitation (two reports).

Of the 11 serious reports, a minimum of two reports included at least one of the following Preferred Terms: Vomiting (four reports), Nausea (two reports), Electrocardiogram QT prolonged (two reports), Off label use (two reports), Abdominal pain upper (two reports), Malaise (two reports), Blindness (two reports).

One of the blindness reports was accompanied by overdose owed to 1g of chloroquine per day, together with hypoaesthesia, energy increased, orthostatic hypotension and an unspecified cardiovascular disorder. The patient was recovering at the time of reporting. The second report of blindness describes a patient taking chloroquine 500mg twice per day for four days. Time to onset was three days. The patient was recovering at the time of reporting.

Another two serious report were fatal. One describes a patient with rheumatoid arthritis treated with methotrexate and corticosteroids with severe COVID-19. The patient experienced an increase in hepatic enzymes and an unevaluable event under treatment with chloroquine and azithromycin. The second fatal report describes a patient treated with chloroquine, azithromycin, lopinavir;ritonavir who experienced long QT syndrome

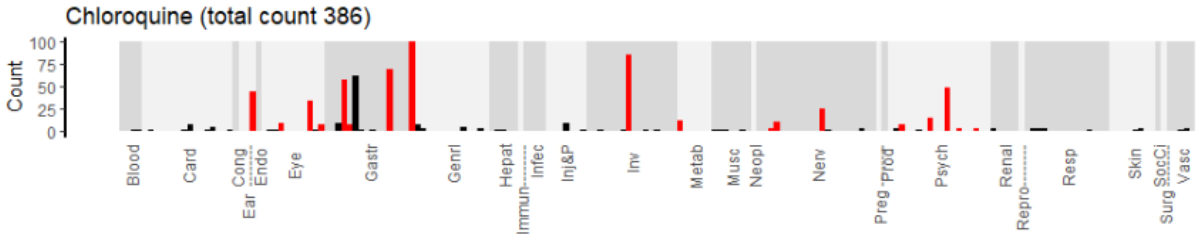


Figure 6. Cumulative report counts for chloroquine in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table 5). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

Azithromycin

Reports including azithromycin are largely described in the sections of chloroquine, hydroxychloroquine or lopinavir;ritonavir.

Azithromycin reported as the single drug for COVID-19: 16 new cases (64 cumulatively). The reports have been shared from five different countries involving 60% male and 40% females between the ages of 18-44y (40% of the cases), 45-64y (20% of the cases) and 65-74y (10% of the cases). A proportion of 30% of the submitted cases where noted as serious. The gastrointestinal events abdominal pain, diarrhoea and nausea can be found among the top reported reactions during this period as well as electrocardiogram QT prolonged, similarly as previously. All events are labelled for azithromycin.

All the reported reactions and their level of seriousness are (cumulatively and for this period) available on an HLGT level in attachment 1 [separate file]. An overview of the cumulative reporting demography is shown in Figure 7.

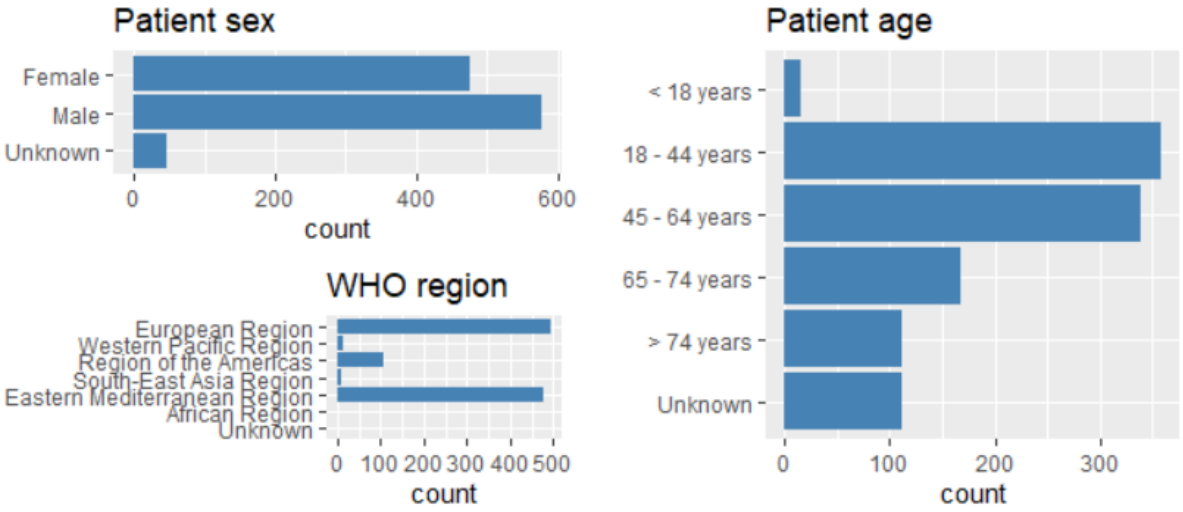


Figure 7. Demography of VigiBase reports received cumulatively so far on azithromycin as suspected or interacting drug.

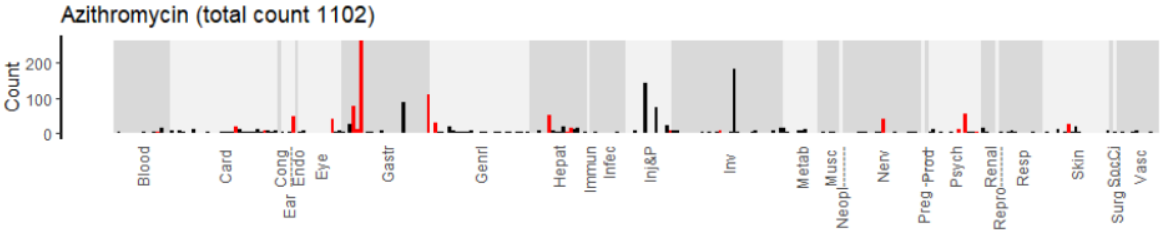


Figure 8. Cumulative report counts for azithromycin in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table 5). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

Lopinavir;ritonavir

During this reviewing period 120 new reports in which lopinavir;ritonavir were reported as suspecting or interacting drugs were reviewed. These concerned 71 male and 46 female patients; median age of patients described in the new reports was 62 years (three reports had age unreported). The new reports originated from Eastern Mediterranean Region (three), European Region (77), Region of the Americas (10) and Western Pacific Region (30). An overview of the cumulative reporting demography is shown in Figure 9.

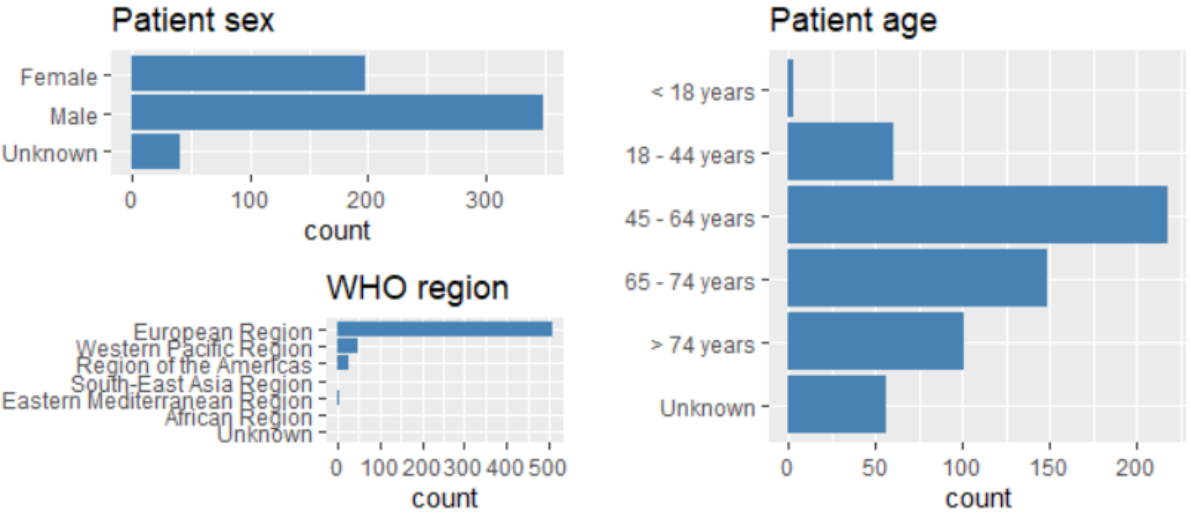


Figure 9. Demographics of VigiBase reports received cumulatively so far for lopinavir;ritonavir as suspected or interacting drug.

Adverse events

The most commonly reported ADRs continued to be those which are included on the product labelling for lopinavir;ritonavir.[3]

The most commonly reported ADRs during the review period were diarrhoea (30 reports, 156 cumulative), electrocardiogram QT prolonged (15 reports, 43 cumulative), increased bilirubin (nine reports, 30 cumulative), hypertransaminasemia (8 reports, 35 cumulative), and transaminases increased (eight reports, 14 cumulative).

The most commonly reported ADRs cumulatively are: diarrhoea (156 reports), nausea (54 reports), therapeutic response unexpected (51 cumulative), hepatocellular injury (47 reports), and electrocardiogram QT prolonged (43 reports).

Off-label use has been reported as an ADR in 27 reports during the review period and in 148 reports cumulatively.

Other newly reported ADRs of interest include: serotonin syndrome (two reports), flight of ideas (one report), logorrhea (one report), and hallucination, auditory (one report).

There were two additional cases of rhabdomyolysis received in the current period, bringing the cumulative total to eight. One of the two new cases had atorvastatin listed as a concomitant medication. Interaction with lopinavir;ritonavir and atorvastatin is described in the label.

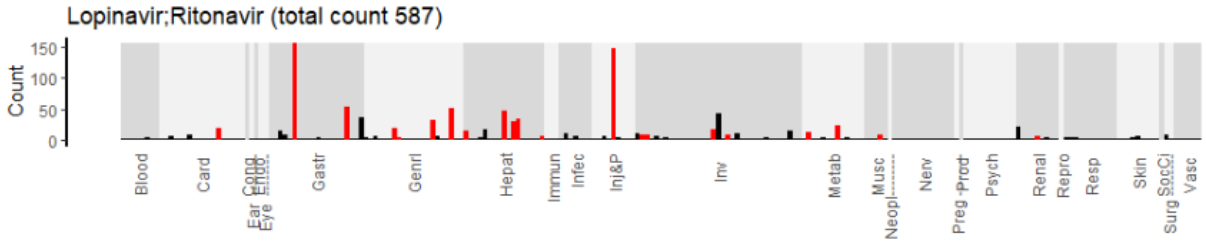


Figure 10. Cumulative report counts for lopinavir;ritonavir in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table 5). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

Remdesivir

Remdesivir is an antiviral substance against RNA viruses including SARS-CoV-2. It has been authorized for emergency use in several countries during the pandemic. Publicly available information on its side effects is still limited and includes hypersensitivity reactions, transaminase elevations and risk of decreased antiviral activity when co-administered with hydroxychloroquine and chloroquine.

There is a total of 404 reports of remdesivir in VigiBase. During this reviewing period, 328 new remdesivir reports were shared, of which in 315 the drug was reported as single suspected. These concerned 183 female and 144 male patients as well as one patient of unknown sex. The new reports originated from European Region (36), Region of the Americas (291) and Western Pacific Region (one).

An overview of the cumulative reporting demography is shown in
Figure 11 and an overview of other COVID-19 drugs co-administrated with remdesivir is available in Table 4 where, enoxaparin, hydroxychloroquine, methylprednisolone and heparin are the most common ones.

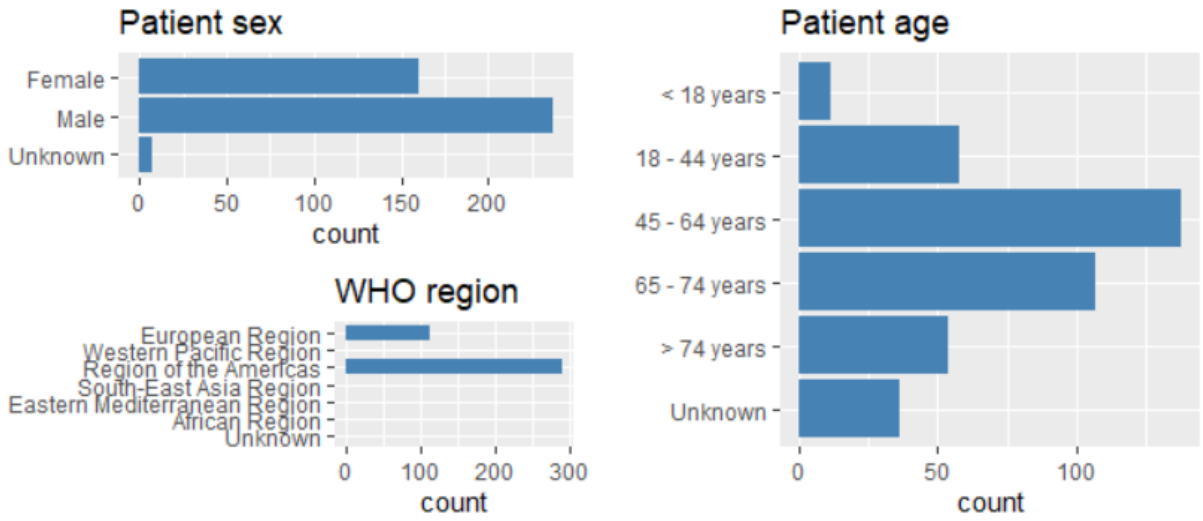


Figure 11. Demographics of VigiBase reports received cumulatively so far for remdesivir as suspected or interacting drug.

Adverse events

The new reports in this review comprise 81% of the cumulative total of reports.
In previous UMC COVID-19 reviews reporting of kidney and liver function disturbances and skin reactions were common for remdesivir.

The pattern of reporting has mainly stayed within the same dominant system organ classes (MedDRA SOCs) as previously. The reported reactions and their level of seriousness are all (cumulatively and for this period) available on an HLGT level in attachment 1 [separate file].

The largest increases in reporting relates to the hepatobiliary disorders and related investigations, renal and urinary disorders and related investigations. When performing disproportionality analyses using the full database or other COVID-19 drugs as a background the most disproportionately reported terms in both cases also belong to the hepatobiliary and kidney terms including investigational terms with a few non-clinical terms interspersed such as clinical trial participant and therapy interrupted.

Included in the Information for compassionate use in Europe[4], information on liver reactions are mentioned such as transient elevations in ALT and AST and mild reversible PT prolongation but without any clinically relevant change in INR or other evidence of hepatic effects. In the same document kidney-related reactions are not recognized in humans yet but "In nonclinical animal studies, toxicity findings were consistent with dose-dependent and reversible kidney injury and dysfunction". The most common liver-related reactions reported are in descending order the ones gathered under the HLTs, liver function analyses (n=122; whereof 95 new this period), hepatocellular damage and hepatitis NEC (n=6; 2) and hepatic failure and associated disorders (n=5; 5). The most common kidney-related reactions belong to the HLT renal failure and impairment (n= 81; whereof 70 new this period), renal function analyses (n=57; 52) and renal vascular and ischaemic conditions (n=6; 6).

Among new MedDRA PTs of note reported this period and not part of the above areas and not being recognised as side effects for remdesivir in the product information are:

- four cases of disseminated intravascular coagulation which all, based on co-reported terms and drugs paint a picture of severe COVID-19 disease and risk factors for severe disease,
- six cases of pulseless electrical activity (Cardiac SOC), in most cases with very limited clinical data in the reports,
- four cases of maternal exposure during pregnancy and one of caesarean section. Foetal heart rate abnormal was co reported in the case reporting the caesarean section. None of the cases were reported as fatal and no information on the outcome of the pregnancy or symptoms of the foetus during the pregnancy was provided in any of the cases.

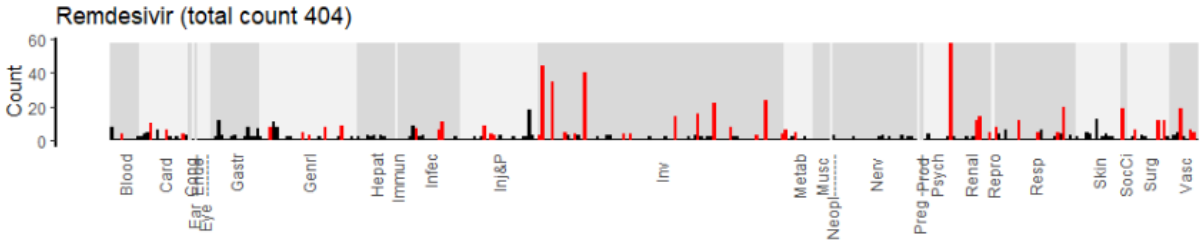


Figure 12. Cumulative report counts for remdesivir in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table 5). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

Tocilizumab

Tocilizumab is a monoclonal antibody against the interleukin-6 receptor. Approved indications are all non-infectious in nature and among them and most relevant for its use in COVID-19, is cytokine release syndrome (CRS).[5,6] The drug is used in COVID-19 to alleviate the inflammatory cytokine storm, seen in severe cases as part of a severe inflammatory response to the viral infection.
During this reviewing period there were 131 new reports in which tocilizumab was reported as suspected or interacting adding up to a total cumulative number of 377 reports. The new reports concerned 84 males, 30 females and 17 where sex was not reported; median age of the patients was 62 (with 24 reports lacking information on age). The new reports were shared from the Eastern Mediterranean Region (6), European Region (56), Region of the Americas (61) and Western Pacific Region (8).
An overview of other COVID-19 drugs co-administrated with tocilizumab is available in Table 4 where hydroxychloroquine, enoxaparin and the combination drug lopinavir;ritonavir are the three most common ones. An overview of the cumulative reporting demography is shown in Figure 13.

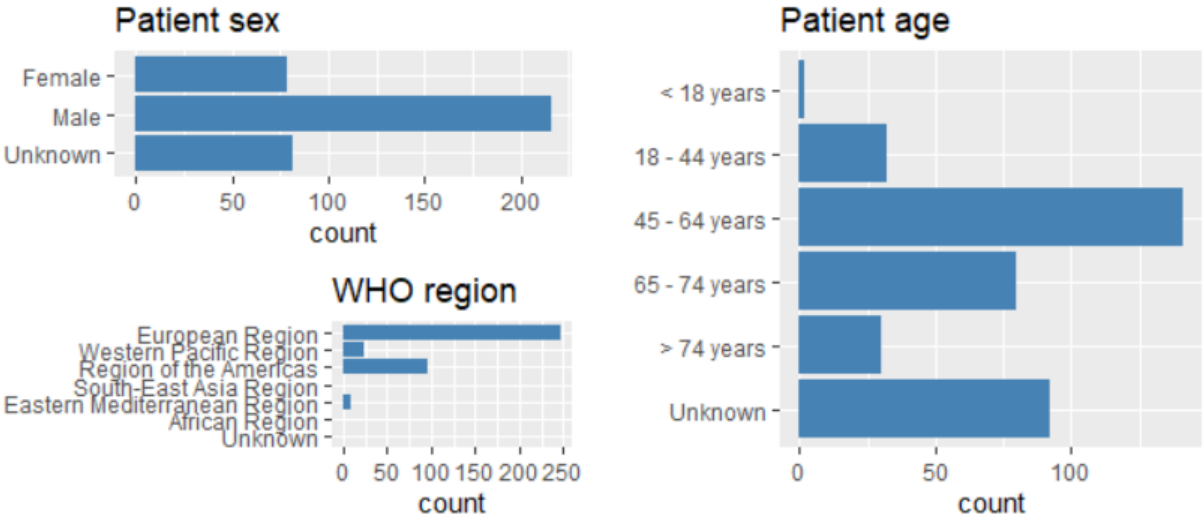


Figure 13. Demographics of VigiBase reports received cumulatively so far for tocilizumab as suspected or interacting drug.

Adverse events

All the reported reactions and their level of seriousness are (cumulatively) available on HLGT level in attachment 1 [separate file].
The most common reported terms for tocilizumab are those gathered under the “administrative” MedDRA HLTs off-label use and intentional product use issues, which are also those reported most during the period of this latest review. Among other similar terms that also continue to be reported, are HLTs adverse effect absent, medication errors, product use errors and issues NEC and product prescribing errors and issues.

As before the ADR reporting spectrum is widespread for the drug. Closer assessment of causality in individual cases has (as for all COVID-19 drugs) been difficult due to the background disease, the limited data on the drug used in this indication and relatively large proportion of multiple concomitant other COVID-19 treatments.

Hepatic reactions and related investigational terms continue to be among the most reported where the HLT Hepatocellular damage and hepatitis NEC gathering the most reports (n=51 ; whereof four in the latest period) followed by HLT Liver function analyses (n=29; 14). Hepatitis is acknowledged in the labelling as a rare side effect for tocilizumab.[5,6]

Reports from the Cardiac disorders SOC continue to arrive, e.g. within but not exclusively so the HLT Ventricular arrhythmias (n=8 ; whereof five in the latest period). The tocilizumab labelling does not include any cardiac events[5,6.]

Intestinal perforations and gastrointestinal haemorrhages also continue to be reported where the HLT intestinal Ulcers and perforations has increased by three to a total of nine reports. Mouth ulceration, Gastritis, Stomatitis and Gastric ulcer are included in the tocilizumab label[5,6] but not colitis, 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 infections continue to be reported on a large scale with 42 new reports adding up to a total of 58. Most of the new reported MedDRA PTs this period concern different forms of infections and related investigations. Seventeen of these cases report COVID-19 as the ADR. They are a mix of indication spill-over miscoding i.e. the indication being reported as the ADR, several published case series of patients already treated with tocilizumab for an underlying disease and becoming infected with COVID-19, patients treated w tocilizumab for COVID-19 with or without underlying severe disease and with or without ADRs being reported. Interestingly none of the published case series seem to have resulted in more than one case report each.

When performing disproportionality analyses using the full database or the other COVID-19 drugs as a background the most disproportionately reported terms in both cases are those that have been discussed previously in these reviews, such as hypofibrinogenemia, and the general terms death and treatment failure. There are, based on the drug and the disease under treatment no new unexpected, unlabelled terms reported.

The pattern of reported ADRs for lies largely within what is labelled for the drug except for the cardiac events.[5,6]

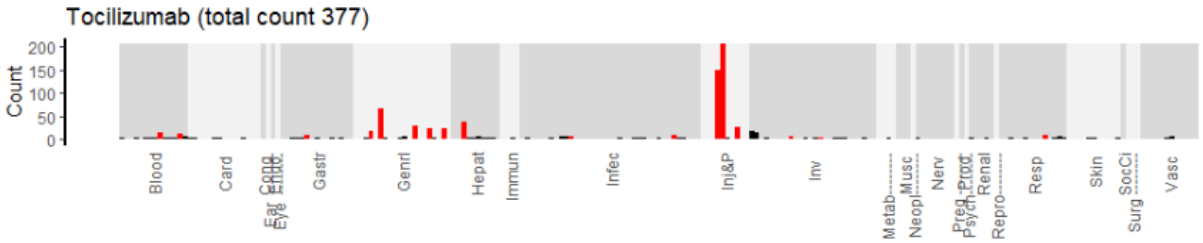


Figure 14. Cumulative report counts for tocilizumab in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table 5). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

Oseltamivir

During this reviewing period there were 28 new reports in which oseltamivir was reported as suspected or interacting adding up to a total cumulative number of 156 reports. The new reports concerned 11 males, 17 females; median age of the patients was 40 (with two reports lacking information on age). The new reports were shared from the Eastern Mediterranean Region (24), European Region (one) and Region of the Americas (three). An overview of the cumulative reporting demography is shown in Figure 15.

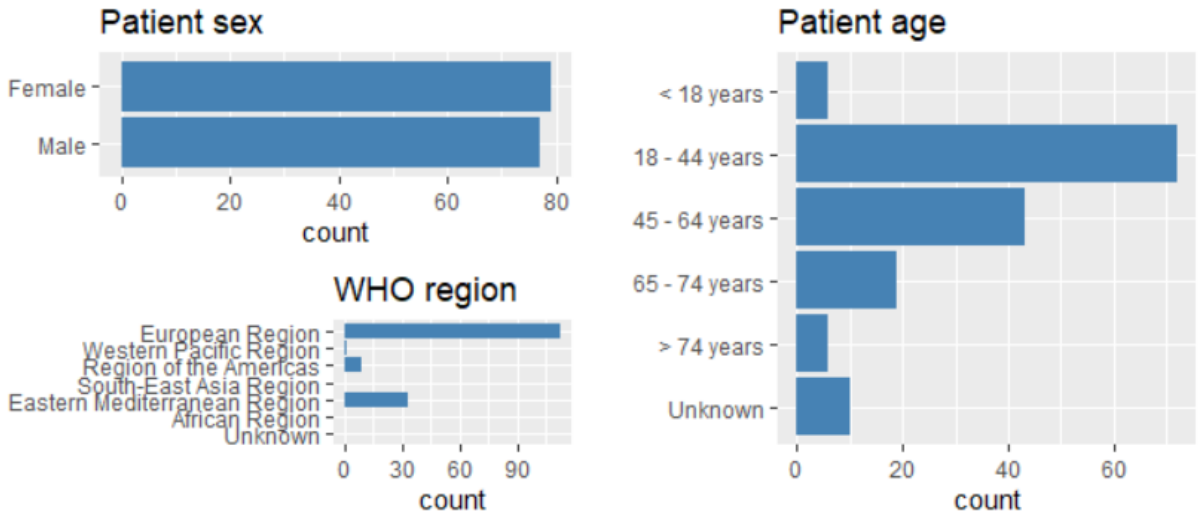


Figure 15. Demographics of VigiBase reports received cumulatively so far for oseltamivir as suspected or interacting drug.

Adverse events

The most commonly reported ADRs for oseltamivir for this period involves the similar terms as labelled for the drug[7] and that have been describe in previously published reports. Gastrointestinal events as abdominal pain (nine cases, 17 cumulatively), vomiting (seven cases, 22 cumulatively) and diarrhoea (seven cases, 26 cumulatively) were among the events that had a high increase in number of new reports during this period. There were no new cases of hepatotoxicity (11 cumulatively). Two death cases were reported with oseltamivir for the first time. One of the reports, a female diabetes-type II patient in her 70s from South America, was probably administered (dates unknown) oseltamivir together with three other drugs (tocilizumab, ceftriaxone and ivermectin). The patient died because of respiratory failure. The second patient, an elderly man also pre-diagnosed with diabetes was given oseltamivir concomitantly with hydroxychloroquine, dexamethasone, azithromycin, enoxaparin and vancomycin to treat COVID-19. The patient died five days after hospital admission as a consequence of his respiratory failure.

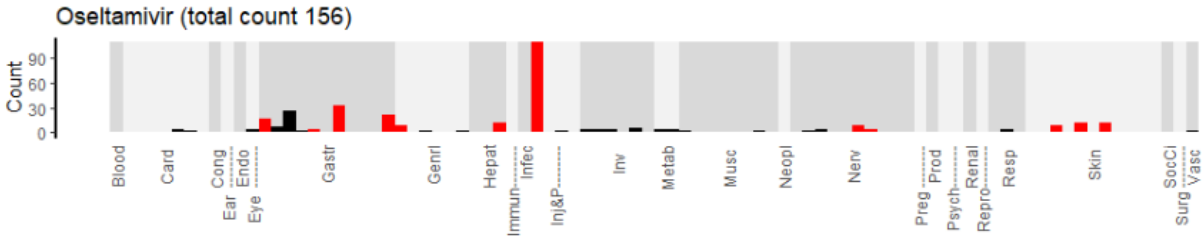


Figure 16. Cumulative report counts for oseltamivir in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table 5). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

Enoxaparin

During this reviewing period there were 37 new reports in which enoxaparin was reported as suspected or interacting adding up to a total cumulative number of 116 reports. The new reports concerned 23 males, 13 females and one where sex was not reported; median age of the patients was 62 (with seven reports lacking information on age). The new reports were shared from the Eastern Mediterranean Region (four), European Region (19), Region of the Americas (nine) and South-East Asia Region (five). 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, lopinavir;ritonavir, azithromycin and hydroxychloroquine. Apart from this the ADRs reported correspond largely to what is known for enoxaparin.

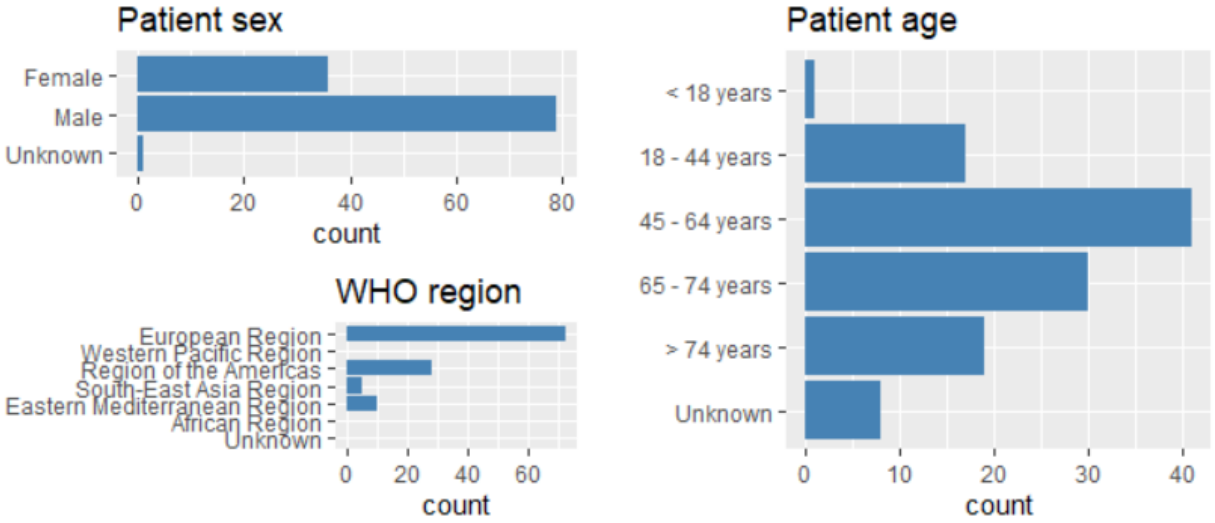


Figure 17. Demographics of VigiBase reports received cumulatively so far for enoxaparin as suspected or interacting drug.

Adverse events

Most of the 116 reports concerned the MedDRA PTs: off label use (19 reports), thrombocytopenia (12 reports), anaemia (11 reports), hepatocellular injury (nine reports), hepatitis (seven reports), gastrointestinal haemorrhage (six reports), diarrhoea (five reports), pruritus (five reports), hypofibrinogenaemia (four reports), haematoma muscle (four reports), haemorrhage (four reports). The following PTs occurred at least thrice: aspartate aminotransferase increased, electrocardiogram QT prolonged, platelet count increased, platelet count decreased, headache, haematuria, cough, erythema, rash maculo-papular, urticaria, haematoma, shock haemorrhagic.

Out of 116, 88 were serious. At least three reports included the following MedDRA PTs: off label use (16 reports), anaemia (11 reports), thrombocytopenia (seven reports), hepatocellular injury (seven reports), hepatitis (seven reports), gastrointestinal haemorrhage (six reports), hypofibrinogenaemia (four reports), haematoma muscle (four reports), haemorrhage (four reports), diarrhoea (three reports), pruritus (three reports), aspartate aminotransferase increased (three reports), electrocardiogram QT prolonged (three reports), platelet count increased (three reports), platelet count decreased (three reports), haematuria (three reports), haematoma (three reports) shock haemorrhagic (three reports).

Twelve reports had a fatal outcome. Most included haemorrhagic-related adverse events, such as anaemia, retroperitoneal haemorrhage, thrombocytopenia, shock haemorrhagic, intra-abdominal haemorrhage or hypofibrinogenaemia.

One report (duplicated), included disseminated intravascular coagulation together with remdesivir, as noted in the medicinal product's section of this communication.

Haemorrhagic events are known to occur with anticoagulants, such as enoxaparin[8]. Enoxaparin is further known to cause hepato-biliary disorders, however, in all reports where these were reported it was accompanied by other medicinal products known to affect the liver, such as azithromycin, lopinavir;ritonavir and hydroxychloroquine.

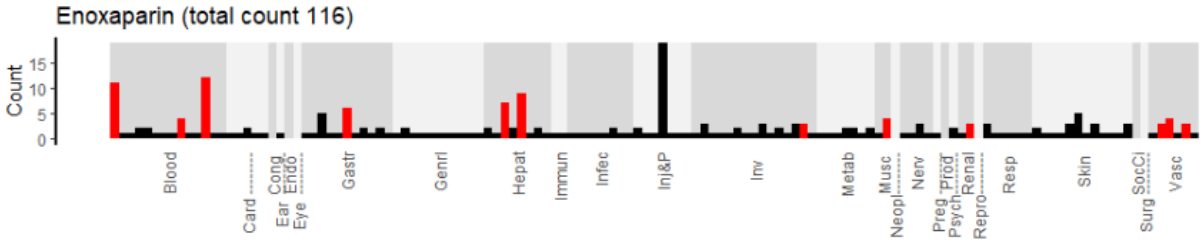


Figure 18. Cumulative report counts for enoxaparin in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table 5). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

Sarilumab

During this reviewing period there were 121 new reports in which sarilumab was reported as suspected or interacting adding up to a total cumulative number of 128 reports. The new reports concerned 81 males, 37 females and three where sex was not reported; median age of the patients was 60 (with three reports lacking information on age). The new reports were shared from the European Region (30) and Region of the Americas (91). An overview of the cumulative reporting demography is shown in Figure 19.

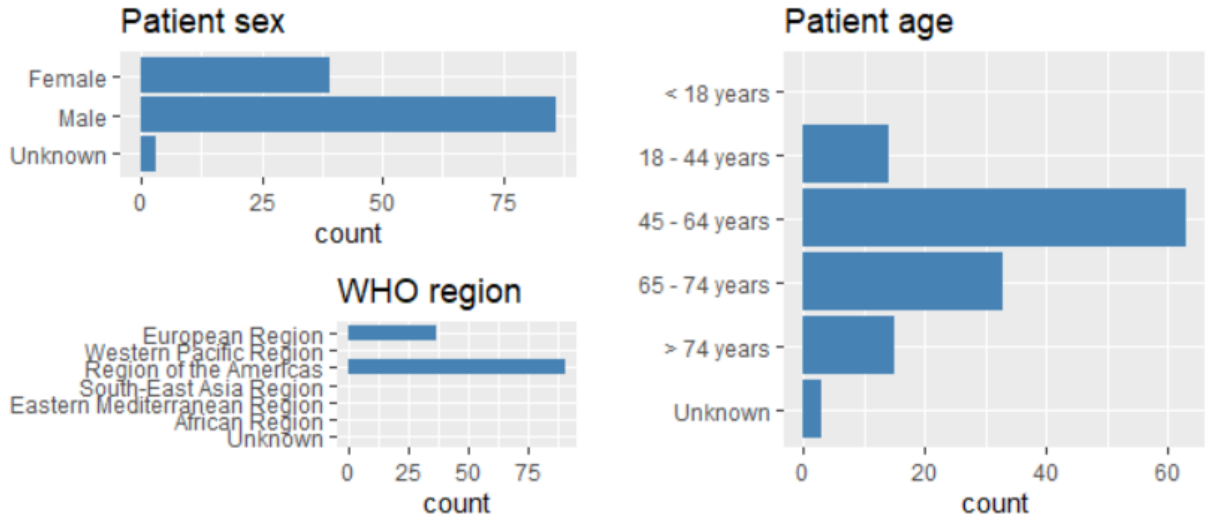


Figure 19 Demographics of VigiBase reports received cumulatively so far for sarilumab as suspected or interacting drug.

Adverse events

Given that this is the first review of sarilumab within the weekly report, it is a review of the ADRs reported for the cumulative total of 128 reports.

The most commonly reported ADRs are those which are in line with the product labelling for sarilumab and include ALT increased, AST increased, transaminases increased, hepatocellular injury, and pneumonia bacterial.

Regarding ADRs related to the hepatobiliary system, additional reported PTs were liver injury and hepatic failure. According to the Summary of Product Characteristics for sarilumab[9]: "Treatment with Kevzara was associated with a higher incidence of transaminase elevations. These elevations were transient and did not result in any clinically evident hepatic injury in clinical studies (see section 4.8). Increased frequency and magnitude of these elevations were observed when potentially hepatotoxic medicinal products (e.g., MTX) were used in combination with Kevzara."

Regarding ADRs related to infections, top additional reported PTs were bacteremia (nine reports), pneumonia (nine reports), staphylococcal infection (six reports), and septic shock (six reports). Multiple organisms are mentioned in the reported PTs, examples include: Pneumonia klebsiella (three reports), Pneumonia pseudomonal (three reports), Candida infection (three reports), Enterobacter pneumonia (two reports), Streptococcal bacteraemia (one report), Cytomegalovirus colitis (one report), Citrobacter infection (one report), Aspergillus infection (one report). According to the Summary of Product Characteristics for sarilumab[9] : "Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including Kevzara for RA. The most frequently observed serious infections with Kevzara included pneumonia and cellulitis (see section 4.8). Among opportunistic infections, tuberculosis, candidiasis, and pneumocystis were reported with Kevzara."

Also commonly reported were ADRs related to the blood disorders, such as neutropenia (10 reports), anaemia (five reports), and thrombocytopenia (four reports). According to the Summary of Product Characteristics for sarilumab[9], neutropenia is a very common ADR and thrombocytopenia is common.

Two ADRs of note given the total number of reports and the fact that there are no such events included in the sarilumab labelling are: acute kidney injury (10 reports) and deep vein thrombosis / pulmonary embolism (seven reports each). A high-level review of the cases reporting acute kidney injury reveals multiple concomitantly administered medications including hydroxychloroquine, various antibiotics and methylprednisolone; all cases co-reported ADRs consistent with liver injury. A high-level review of deep vein thrombosis and pulmonary embolism reveals the same pattern of concomitant drug use and co-reported ADRs of multiorgan failure/sepsis. All cases reviewed were from the region of the Americas.

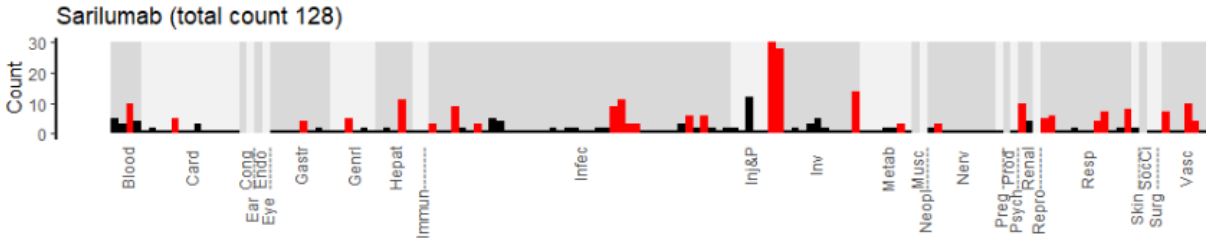


Figure 20. Cumulative report counts for sarilumab in one bar for each preferred term, sorted by SOC (which is abbreviated as in Table 5). Red bars reflect preferred terms significantly more reported with this drug than in the total set of COVID-19 reports covered in this report. The widths of the bars carry no meaning.

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

Besides reports for WHO-solidarity trial drugs, 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 3).
The reported reactions and their level of seriousness for all drugs (cumulatively and for this period) available in attachment 1 [separate file]. 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 contained narratives. 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.

References

1. World Health Organization. “Solidarity” clinical trial for COVID-19 treatments [Internet]. 2020 [cited 2020 Jul 1]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments

2. Electronic Medicines Compendium. Summary of product characteristics, Plaquenil-Hydroxychloroquine sulfate 200mg Film-coated Tablets [Internet]. 2020 [cited 2020 Jul 1]. Available from: https://www.medicines.org.uk/emc/product/1764/smpc

3. Electronic Medicines Compendium. Summary of product characteristics, Kaletra 200 mg/50 [Internet]. 2020 [cited 2020 Jul 1]. Available from: https://www.medicines.org.uk/emc/product/221/smpc

4. European Medicines Agency. Summary on compassionate use (Remdesivir, Gilead) [Internet]. 2020 [cited 2020 Jul 1]. Available from: https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf

5. European Medicines Agency. Summary of products characteristics for tocilizumab solution for infusion [Internet]. 2013. Available from: https://www.ema.europa.eu/en/documents/product-information/roactemra-epar-product-information_en.pdf

6. U. S Food and Drug Administration. Label for tocilizumab injection for intravenous or subcutaneous use [Internet]. 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125276s114lbl.pdf

7. Electronic Medicines Compendium. Tamiflu 6 mg/ml Powder for Oral Suspension - Summary of Product Characteristics (SmPC) - (emc) [Internet]. [cited 2020 Jul 1]. Available from: https://www.medicines.org.uk/emc/product/9108/smpc

8. Clexane pre-filled syringes - Summary of Product Characteristics (SmPC) - (emc) [Internet]. [cited 2020 Jul 1]. Available from: https://www.medicines.org.uk/emc/product/4499/smpc

9. Electronic Medicines Compendium. Kevzara 150 mg solution for injection in pre-filled syringe - Summary of Product Characteristics (SmPC) - (emc) [Internet]. [cited 2020 Jul 1]. Available from: https://www.medicines.org.uk/emc/product/762

World Health Organization

Appendix

Drug group	N_old	N_new	N_total
Azithromycin	882	220	1102
Chloroquine	346	40	386
Hydroxychloroquine	1446	486	1932
Lopinavir;ritonavir	467	120	587
Remdesivir	76	328	404
Tocilizumab	246	131	377
Oseltamivir	128	28	156
Enoxaparin	79	37	116
Sarilumab	7	121	128
Other drugs	311	214	525
Unique reports	2600	1346	3946

Table 1. N_old display reports described in previous reports, which included reports received to VigiBase no later than the 7th of June. N_new includes reports received to VigiBase no later than the 28st of June. Other drugs are selected from medical expertise from the set of corona virus indicated drugs reported to VigiBase, see Appendix. 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	1102	100	386	100	1932	100	587	100	404	100	377	100	156	100	116	100	128	100	525	100	3946	100
	Single Susp.	68	6.2	135	35	787	40.7	201	34.2	378	93.6	250	66.3	23	14.7	21	18.1	114	89.1	270	51.4	2247	56.9
	Serious	483	43.8	123	31.9	1004	52	318	54.2	310	76.7	282	74.8	41	26.3	90	77.6	122	95.3	315	60	2169	55
	Fatal	50	4.5	5	1.3	114	5.9	39	6.6	82	20.3	132	35	4	2.6	12	10.3	34	26.6	107	20.4	451	11.4
Sex																							
	Female	477	43.3	209	54.1	761	39.4	198	33.7	160	39.6	79	21	79	50.6	36	31	39	30.5	179	34.1	1535	38.9
	Male	578	52.5	161	41.7	1078	55.8	349	59.5	237	58.7	216	57.3	77	49.4	79	68.1	86	67.2	320	61	2205	55.9
	Unknown	47	4.3	16	4.1	93	4.8	40	6.8	7	1.7	82	21.8			1	0.9	3	2.3	26	5	206	5.2
Age																							
	Median (Q1-Q3)	52 (36-66)		49 (32-64)		57 (41-70)		63 (53-72)		61 (48-71)		62 (53-69)		42 (32-57)		63 (52-72)		60 (52-69)		62 (50-73)		59 (44-70)	
	< 18 years	15	1.4	11	2.8	22	1.1	3	0.5	11	2.7	2	0.5	6	3.8	1	0.9	0	0	8	1.5	57	1.4
	18 - 44 years	358	32.5	147	38.1	507	26.2	60	10.2	58	14.4	32	8.5	72	46.2	17	14.7	14	10.9	71	13.5	859	21.8
	45 - 64 years	338	30.7	112	29	598	31	218	37.1	138	34.2	141	37.4	43	27.6	41	35.3	63	49.2	185	35.2	1305	33.1
	65 - 74 years	167	15.2	55	14.2	335	17.3	149	25.4	107	26.5	80	21.2	19	12.2	30	25.9	33	25.8	122	23.2	768	19.5
	> 74 years	112	10.2	27	7	299	15.5	101	17.2	54	13.4	30	8	6	3.8	19	16.4	15	11.7	89	17	567	14.4
	Unknown	112	10.2	34	8.8	171	8.9	56	9.5	36	8.9	92	24.4	10	6.4	8	6.9	3	2.3	50	9.5	390	9.9
WHO region																							
	African Region	1	0.1	0	0	2	0.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0.1
	Eastern Mediterranean Region	479	43.5	234	60.6	285	14.8	4	0.7	0	0	9	2.4	33	21.2	10	8.6	0	0	11	2.1	570	14.4
	European Region	496	45	68	17.6	1156	59.8	510	86.9	112	27.7	248	65.8	113	72.4	73	62.9	37	28.9	375	71.4	2096	53.1
	Region of the Americas	105	9.5	29	7.5	347	18	26	4.4	291	72	97	25.7	9	5.8	28	24.1	91	71.1	87	16.6	964	24.4
	South-East Asia Region	8	0.7	3	0.8	72	3.7	0	0	0	0	0	0	0	0	5	4.3	0	0	1	0.2	85	2.2
	Western Pacific Region	13	1.2	52	13.5	70	3.6	47	8	1	0.2	23	6.1	1	0.6	0	0	0	0	51	9.7	229	5.8
	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 Appendix. Single susp. = Drug was reported as single suspected or interacting drug, Q1-Q3 = First to third quartile.

Drug	N	%
Unique reports	156	100
Favipiravir	67	42.9
Ritonavir	42	26.9
Eculizumab	40	25.6
Plasma	40	25.6
Methylprednisolone	35	22.4
Heparin	34	21.8
Anakinra	27	17.3
Dexamethasone	24	15.4
Ruxolitinib	24	15.4
Darunavir	23	14.7
Prednisone	19	12.2
Interferon beta-1b	18	11.5
Apixaban	13	8.3
Baricitinib	13	8.3
Canakinumab	12	7.7
Montelukast	12	7.7
Ivermectin	10	6.4
Immunoglobulin human normal	9	5.8
Lopinavir	9	5.8
Ascorbic acid	8	5.1
Cobicistat;Darunavir	8	5.1
Colecalciferol	8	5.1
Epoprostenol	8	5.1
Metamizole	7	4.5
Prednisolone	7	4.5
Ribavirin	7	4.5
Rituximab	7	4.5
Hydrocortisone	6	3.8
Warfarin	6	3.8
Alteplase	5	3.2
Siltuximab	5	3.2
Zinc	5	3.2
Colchicine	4	2.6
Interferon beta-1a	3	1.9
Valaciclovir	3	1.9
Aciclovir	2	1.3
Apremilast	2	1.3
Darunavir;Ritonavir	2	1.3
Interferon	2	1.3
Interferon beta	2	1.3
Nitazoxanide	2	1.3
Peginterferon alfa-2a	2	1.3
Tofacitinib	2	1.3
Acalabrutinib	1	0.6
Ademetionine	1	0.6
Allogenic mesenchymal stem cells nos	1	0.6
Almitrine	1	0.6
Bromhexine	1	0.6
Ciclosporin	1	0.6
Icatibant	1	0.6
Infliximab	1	0.6
Investigational drug	1	0.6
Maraviroc	1	0.6
Octreotide	1	0.6
Selinexor	1	0.6

Table 3. 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	Enoxaparin	Sarilumab
Total (S/I/C)	1427	405	2242	660	408	443	232	609	129
Single suspected	344	150	1047	259	382	299	75	305	115
Azithromycin		258	1013	150	40	89	126	261	47
Chloroquine	258		8	25	1	6	4	21	2
Hydroxychloroquine	1013	8		352	51	174	196	371	66
Lopinavir;Ritonavir	150	25	352		16	67	14	88	1
Remdesivir	40	1	51	16		32	2	119	4
Tocilizumab	89	6	174	67	32		9	68	2
Oseltamivir	126	4	196	14	2	9		51	
Enoxaparin	261	21	371	88	119	68	51		26
Sarilumab	47	2	66	1	4	2		26	
Aciclovir			3	3	2	1		3	
Almitrine									1
Alteplase	4		2			4		3	1
Anakinra	16		20	2	1	5		8	4
Apixaban	6	2	17	7	11	4		2	3
Apremilast	1		2					2	
Ascorbic acid	70	9	78	10	31	8	14	56	7
Baricitinib	2		5		2	1			
Bromhexine		1	4				4		
Canakinumab			2						
Ciclosporin			6	2					
Cobicistat;Darunavir	6		11	3	1	3		4	
Colchicine	4		9	1		3	1	4	
Colecalciferol	34	3	34	1	13	3	1	18	3
Darunavir	6		22	2	2	2		11	
Darunavir;Ritonavir			3						
Dexamethasone	14		35	7	10	16	2	23	2
Eculizumab	4		5	3		1		4	
Epoprostenol	2		2		5	1		2	1
Favipiravir	42		65	3	1	12	23	38	
Ganciclovir						1			
Heparin	30	2	54	25	50	23	3	33	20
Hydrocortisone	13		20	7	11	5	2	9	4
Iloprost					1			1	
Immunoglobulin human normal	2		6	1		2			
Immunoglobulins nos			1	1		1			
Infliximab	1		1				1		
Interferon	1		3	1					
Interferon beta	1		1	3		1			
Interferon beta-1a			1	4				1	
Interferon beta-1b	15	2	27	29		5	2	10	
Ivermectin	6	1	5	2		3	1	5	1
Lopinavir	3		13	1		2		5	
Maraviroc					1				
Metamizole	18	1	28	6	8	5	6	14	
Methylprednisolone	62	6	89	29	50	31	2	81	30
Montelukast	4		1	1	6	1		4	
Nitazoxanide	2		1						
Peginterferon alfa-2a	1		1						
Prednisolone	3	2	2	6	5			1	
Prednisone	16	1	35	10	10	6		17	7
Ribavirin	4		7	13	1	2	1	1	1
Ritonavir	10		52	6	1	4	1	17	
Rituximab			2	1		3			
Ruxolitinib	1		10	4	2	2		6	
Selinexor	1				2			1	
Siltuximab			1	1				1	
Umifenovir				1			1		
Valaciclovir	1		3	1	2			2	1
Warfarin	3		6	1	3	1	2	1	1
Zinc	49	7	45	3	27	5	1	38	7
Other	639	93	1017	353	267	160	127	514	96

Table 4. 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 5. Abbreviations used for SOCs displayed in the reaction overview barcharts.

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.