**Infection profile of immune-modulatory drugs used in autoimmune diseases: Analysis of summary of product characteristic data**

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**Abstract**

*Objective*

Serious infection remains a concern when prescribing immune-modulatory drugs for immune-mediated inflammatory diseases. The “summary of product characteristics” (SmPCs) provide information on adverse events e.g. infections, from clinical trials and post-marketing pharmacovigilance.

This review aimed to compare infection frequency, site and type across immune-modulatory drugs, reported in SmPCs.

*Methods*

The Electronic Medicines Compendium was searched for commonly-prescribed immune-modulatory drugs used for: rheumatoid arthritis, spondyloarthritis, connective tissue disease, autoimmune vasculitis, autoinflammatory syndromes, inflammatory bowel disease, psoriasis, multiple sclerosis and/or other rarer conditions.

Information was extracted on infection frequency, site and organisms. Frequency was recorded as per the SmPCs: very common(≥1/10); common(≥1/100 to <1/10); uncommon(≥1/1,000 to <1/100); rare(≥1/10,000 to <1/1,000); very rare(<1/10,000).

*Results*

39 drugs were included, across 20 indications: nine conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), six targeted synthetic DMARDs, 24 biologic (b)DMARDs.

Twelve infection sites were recorded. Minimal/no site information was available for most csDMARDs, certolizumab pegol and rituximab. Upper respiratory tract was the most common site, especially with bDMARDs. Lower respiratory, ear/nose/throat and urinary tract infections were moderately common, with clustering within drug groups.

Data for 27 pathogens were recorded, majority viruses, with herpes simplex and zoster and influenza most frequent. Variable/absent reporting was noted for opportunistic and certain high-prevalence infections e.g. Epstein-Barr.

*Conclusion*

Our findings show differences between drugs, and can aid treatment decisions alongside real-world safety data. However, data are likely skewed by trial selection criteria and varying number of trials per drug, and highlight the need for robust post-marketing pharmacovigilance.

**Key messages**

*What is already known about this subject?*

* Serious infection is a concern when prescribing immune-modulatory drugs for immune-mediated inflammatory diseases (IMIDs).
* The European Medicines Agency “summary of product characteristics” (SmPCs) data provides information on adverse events including infections; however, no comparison has been undertaken on reported infection frequencies across SmPCs for immune-modulators.

*What does this study add?*

* We undertook a summary analysis of the SmPCs using a novel methodological approach to help clinicians visualise infection risk patterns across treatment strategies.

*How might this impact on clinical practice?*

* Our findings can be used to visualise differences between drug infection risk profiles and aid treatment decisions, and highlights the need for robust post-marketing pharmacovigilance studies with real-world safety data.

**Introduction**

Serious infection remains a risk in people with immune-mediated inflammatory diseases (IMIDs). One of the great challenges of contemporary disease care is balancing risk and benefit of immune-modulatory therapies. For most patients, these drugs provide a safe and effective method of disease control (1). Advances in targeted therapies for autoimmune diseases have been accompanied by a growing awareness of the potential to change infection risk.

Quantifying the risk of serious infection can be challenging, as they are relatively rare events. Primary clinical trials are not scrutinised and long-term extension data rarely focus on safety. We instead rely on real-world data, such as registries. An example is the increased risk of serious infection in patients taking inhibitors of tumour necrosis factor (TNFis), demonstrated through studies of registry data in rheumatoid arthritis (RA), psoriasis and inflammatory bowel disease (IBD) (2–5). Similar infection risks have also been shown with non-TNFi biologics, such as rituximab and tocilizumab, the latter being associated with serious bacterial skin and soft tissue infections (6,7).

However, registry data are undermined by channelling bias and unmeasured confounding. Examining trial and long-term extension data combined would provide more power and overcome concerns around bias and confounding.

The European Medicines Agency (EMA) publishes a “summary of product characteristics” (SmPC) for each drug on the European market, produced by the drug manufacturer. Stringent guidelines exist on the format and content of SmPCs (8,9). EMA requires patient-level data from both clinical trials and long-term extension data to be submitted and reviewed. Data informing risk are also gathered from spontaneous reporting, directly by regulators or indirectly via the marketing authorisation holder (MAH). Altogether these inform risk profiling, as detailed in the SmPCs, through estimated event rates. (8). Information within the SmPCs is reviewed regularly (at least annually) and updated as and when new data becomes available. SmPCs are a crucial source of safety information for prescribers. However, to our knowledge, there has to date been no comparison undertaken on infection risk in immune-modulatory drug use, across SmPCs. Immune-modulatory drugs encompass conventional synthetic (cs), biologic (b) and targeted-synthetic (ts) disease modifying antirheumatic drugs (DMARDs).

We sought to undertake a summary analysis of the SmPCs using a novel methodological approach to help clinicians visualise infection risk patterns across treatment strategies.

The rationale for this work was to be able to compare the information, provided by regulators, as detailed in the SmPCs. SmPCs follow a common format and requirements, enabling comparability across agents.

**Methods**

The search question was as follows: What is the frequency and nature of infection in patients with IMIDs taking immunomodulatory medication, as reported in the SmPC literature?

*Participants*

An SmPC for a given drug was included if the drug is licensed in Europe for the treatment of an IMID. This comprised rheumatic diseases such as: inflammatory arthritis (including rheumatoid arthritis, axial spondyloarthropathy, psoriatic arthritis), gout, connective tissue disease (e.g. systemic lupus erythematosus, scleroderma, dermatomyositis), autoimmune vasculitis, autoinflammatory syndromes, juvenile idiopathic arthritis. Non-rheumatic diseases included: inflammatory bowel disease (Crohn’s and ulcerative colitis), psoriasis, multiple sclerosis, and other rarer conditions.

*Intervention*

The intervention is use of an immune-modulatory drug for the treatment of IMIDs. Information on infections as an adverse event secondary to the use of the drug, as described in the SmPC, was extracted and analysed.

*Comparator*

A comparator or control is not directly relevant to this review, although patients with an IMID and not taking the immune-modulatory drugs under study could be considered as such.

*Outcomes*

Infection risk and frequency based on each immunomodulatory drug under study were recorded, described by infection site (e.g. respiratory, urinary tract, skin etc), and by type (e.g. bacterial, viral, fungal etc).

**Study selection, data extraction and synthesis**

The Electronic Medicines Compendium (EMC) was searched for the most commonly-used immune-modulatory drugs in the treatment of IMIDs. The search and data extraction were performed on 28th September 2020.

Drugs were selected and agreed by all authors. Full length SmPC documents were manually searched for relevant information on infection risk and frequency, which was subsequently extracted from sections 4.4 and 4.8. Section 4.4, entitled “Special warnings and precautions for use,” includes data on serious adverse reactions, including infections, and consideration of at-risk groups. Section 4.8, “Undesirable effects,” contains details of infections from clinical trials, post-authorisation safety studies and spontaneous reporting, in which there is at least a reasonable possibility that these are as a consequence of the medicinal product. It is important to note that decisions on what is included in the SmPC can be subjective, and may be the result of a consensus decision determined by the relevant committee upon evaluation of the available data. In addition to in-depth data and description of these adverse events, details on frequency of subtypes of event (e.g. site and type of infection) were extracted.

25% of included SmPCs were screened and extracted by a second reviewer, using a purpose-built data extraction table. Disagreements were discussed until a consensus was agreed, with a third reviewer involved as needed. No papers, or additional data or supplementary material were required from authors.

Information on frequency of infection was recorded as per the convention in the SmPC documentation: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) (8). Of note, not all “very rare” infections may be included in a given SmPC- the threshold for inclusion may be subjective and be based, for example, on clinical importance of the infection. Any additional information was recorded within the extraction table with adequate referencing to the relevant SmPC. Information, where available, on infection site (e.g. respiratory, skin etc), type (e.g. bacterial, viral etc) and individual pathogenic organisms was also extracted.

**Results**

In total, 39 drugs were identified, used across 20 indications, including nine csDMARDs, six tsDMARDs (four Janus kinase [JAK] inhibitors, two sphingosine 1-phosphate receptor modulators) and 24 bDMARDs (17 cytokine-targeted and seven cell-targeted). All drugs are listed by DMARD category in Table 1. All included SmPCs had been updated within 18 months of the search date.

All SmPCs had areas of missing or unavailable data (i.e. not reported within the SmPCs), possibly due to the rarity of events or rarest events not being reported. For infection sites, this was most marked for cladribine, upadacitinib, certolizumab pegol, ravulizumab, natalizumab and dupilumab, which reported frequency of infection for a maximum of two sites. All drugs had large amounts of missing or unavailable data for frequencies of infection with pathogen groups (e.g. bacteria, fungi), aside from viruses, where there were no missing data. With regards individual organisms a large amount of missing data was noted for most pathogens, especially opportunistic infections, again due to low frequency of events. Infections were more likely to be listed by site than organism.

Twelve sites of infection were recorded. Minimal or no site information was available for most csDMARDs and siponimod, certolizumab pegol and rituximab. Figure 1 shows the most common sites of infection listed by drug group. Upper respiratory tract was the most common site of infection, especially with bDMARDs. Lower respiratory, ear/nose/throat (including sinusitis) and urinary tract infections were moderately common, with clustering within drug groups, especially TNFis. No drugs reported the risk of cardiac infections. The eye, musculoskeletal, neurological, oral and reproductive tract sites were the least commonly reported sites of infection.

Infection data for 27 distinct pathogens were recorded, the majority viruses, especially with bDMARD use. Supplementary figure 1 shows the most common pathogen subtypes by drug (where information was available). Specifically, herpes simplex and zoster were the most frequently listed pathogens (mainly with bDMARDs and tsDMARDs, most classed as “common” in frequency), followed by influenza virus (common to very common with the use of several drugs across all categories; very common with the use of fingolimod, canakinumab, infliximab and ocrelizumab). Common non-viral causes of infection were candida and tinea species.

Variable or absent reporting was noted for opportunistic infections and certain viruses with high prevalence in the general population e.g. Epstein-Barr. Infection frequencies for several opportunistic infections were reported, with variable amounts of missing data. Frequencies of infection with fungi- especially candida and tinea species- had the least missing data. Infection frequency for mycobacterium tuberculosis (TB) was reported for eight of the 39 drugs. Frequencies for other mycobacterial infections, including mycobacterium avium complex, were available for five drugs. Other opportunistic infections, including histoplasma, blastomyces and aspergillus had frequencies reported for three or fewer drugs. The full list of frequencies of infections with the individual pathogens, by drug, is found in Figure 2. Cells are left blank where there is no mention of the infection within the SmPC. Colours denote the frequency reported within the SmPC, including where it is reported as “unknown”.

**Discussion**

The SmPC literature reports differences in infection risk, by site and pathogen, between immune-modulatory drugs, albeit accounting for the lack of standardisation of reporting. The findings can be used to visualise risk estimates, in a format that is easily and quickly legible. However, some of the patterns we have shown lack face-validity to clinicians familiar with real-world safety data. Reasons for this include that the data are likely skewed in some cases by trial selection criteria, varying number of trials per drug, and quirks of individual study-reporting methodologies. In addition, data used to build SmPCs may fail to capture risk of rare infections, which may be detected in observational studies and real-world data.

To our knowledge, this is the first review comparing infection risk profile of immune-modulatory drugs, as detailed in the SmPCs. Previous studies have sought to compare other aspects of drug information reporting, such as drug interactions and contraindications in conditions other than the IMIDs (10–12). Similar to our findings, these also identified inconsistencies in reporting, especially when compared to real-world data, and potentially misleading information due to absent or contradictory information. All studies highlight the need to consult other sources prior to prescribing, and not relying solely on SmPC literature, e.g. outcomes from observational studies from large-scale datasets.

The lack of reporting on rarer events, missing or unavailable data may in part be due to a lack of use of spontaneous adverse event reporting systems, such as the MHRA yellow card system, especially after a drug has been on the market for a period of time, leading to the Weber effect (13). This is the phenomenon of increased reporting of adverse events for new drugs in their first years of approval.  The EMA guidance on the production of SmPCs requires information on adverse events to comprise both trial and real-world data (8,9). SmPCs for newer drugs are therefore likely to have their adverse event profile based upon trial data, whereas older drugs are more likely to have a greater real-world evidence base. Nonetheless, rarer infections may also be more likely to be reported with newer drugs such as tsDMARDs and IL-17 inhibitors, in comparison to drugs which have been on the market for longer and there is therefore awareness and management of risk, e.g. TNF inhibitors and tuberculosis.

With regards sites of infection, upper respiratory tract infections (URTIs) were noted to be common with all drugs, except cladribine, indicating this is a poor discriminator for drug choice. In contrast, urinary tract infections (UTIs) varied much more in frequency, with less frequent reporting for classes such as IL-17 inhibitors. There is also within-drug variation in the frequency of infections at different sites, e.g. for abatacept, gastrointestinal infections are classed as rare, compared to ENT and URTI which are very common. This is insightful as no studies to date have examined infection risk by site for a single drug. Abatacept overall appears to be associated with infections at all sites. The SmPC data would therefore suggest that it is not a good drug for patients at risk of infection. However, this is in contrast to registry data which has generally reported a good infection safety profile compared to other biologics such as the commonly-used TNF-inhibitors, although the EMA SmPC guidance stipulates that this data should be used in the production of SmPCs (7,14,15). The SmPC may report a greater number of infection sites for abatacept compared to other bDMARDs due to variations in trial data and reporting between drugs. This is a good example of the discordance between SmPCs and real-world registry data which will be familiar to clinicians prescribing biologic drugs in clinical practice. It is also important to note that target populations for patients taking abatacept may be different to those taking TNFi (e.g. rheumatoid arthritis vs psoriasis and inflammatory bowel disease) and this will affect infection rates- in this example, infection rates are overall higher in rheumatoid arthritis compared to psoriasis and inflammatory bowel disease. This reflects a limitation of the SmPCs, in that adverse events are not segregated by disease.

Variable or absent reporting was noted for most of the biologic DMARDs. This may be due to missing or unavailable data or due to numbers of patients being too low for very rare events to have occurred. It may also be the case that even if an event did occur, it simply was not reported in the SmPC document. Rituximab is a commonly-used medication for the management of IMIDs such as rheumatoid arthritis and ANCA-vasculitis. However, SmPC literature, based on pharmacovigilance data, was only able to provide information on respiratory tract infections and few organisms. In contrast, real-world registry data has been able to assess incidence ratios of infections, serious infections and hospitalisations with the use of this drug, as well as of individual infections (7,16). The same is true of other drugs with sparse infection frequency reporting in the SmPCs, such as abatacept, tocilizumab and anakinra (7,17). Interpretation of the SmPC data requires the user to appreciate that these could represent with no data or few data. For newer drugs, this is most likely explained by no or few events. For older drugs, it is likely to be due to true missing data, due to historical reporting methods in clinical trials and post-marketing pharmacovigilance. Of note, only two drugs, tofacitinib and abatacept, report “rare” sites of infections, for skin and gastrointestinal infections respectively.

Reporting of infection frequencies within the table of adverse events in the SmPCs is not within the context of individual IMIDs. Information within them therefore requires cautious interpretation or the details of trial data which can be found for some indications, but not all, within the document. For example, infections at all sites are reported as “very common” for canakinumab, a drug used in the treatment of periodic fever syndromes. The reported infection profile may reflect the underlying disease state, rather than the side-effect of the drug.

There is some face validity to the results described, e.g. the risk of lower respiratory tract infections (LRTI) and skin and soft tissue infections appear to be more frequent with TNF inhibitors, mirroring real-world data (2,3,18), whereas these infections are less common with the use of IL-23 inhibitors. However, some of the results from the SmPCs lack face validity. When considering individual pathogenic organisms (Figure 2), certain infections are overrepresented compared to the time spent managing them in clinical practice, e.g. candida. This may be due to certain infections being especially targeted or investigated, in comparison to infections with lower incidence. There is also no differentiation in this case as to whether this pertains to oral thrush or invasive candidiasis, two conditions with vastly different clinical features, management and prognosis. There are few missing data for organisms that are relatively prevalent, such as influenza, herpes zoster and herpes simplex. There is a relative underrepresentation of opportunistic infections, such as TB, given the importance of these for a patient’s clinical course and choice of immunosuppressant. There are also certain associations which appear to be absent from the SmPC data, e.g. natalizumab has association in clinical practice with progressive multifocal leukoencephalopathy (PML) secondary to JC virus. However, despite being discussed within the SmPC, its frequency is not reported as an adverse event. This is likely because the event is too rare. Similarly, trials on baricitinib included cryptococcus, but the frequency of this infection is not reported in the SmPC, although it is for tofacitinib. It may therefore be prudent in future for drugs of a similar type or target to have a standardised template by which to report events within the SmPCs. It is important to note that the SmPC guidelines specifically state that the section on undesirable events should “also inform on adverse reactions with very low frequency or with delayed onset of symptoms which may not have been observed in relation to the product, but which are considered to be related to the same therapeutic, chemical or pharmacological class. The fact that this is a class attribution should be mentioned” (8,9).

Finally, there is a discrepancy between reporting on sites of infection (Figure 1) and individual organisms (Figure 2). This is demonstrated by the C5 inhibitors, eculizumab and ravulizumab. While ravulizumab is reported as being strongly associated with ENT and URT infections, there is a lack of reporting on individual organisms. In contrast, eculizumab lists all sites of infection as uncommon or common, but only reports frequency data for six specific organisms.

There are several limitations to this work. This is a secondary analysis of the data. Therefore, if there is an error in the reporting of data within the SmPC by the EMA, it will be carried forward as we were unable to review the original data. Safety signals that have emerged post-licensing will not necessarily be listed on the SmPC documents as there may be a lag in updating them. The data within the SmPCs depend on the drug company and how the trials are designed to capture and report adverse events. While there are EMA guidelines on the format and content of the SmPCs, these are open to interpretation by drug companies producing them. SmPCs also report only generic drug information (i.e. not specific to certain patient demographics or subgroups), influenced by sampling bias of clinical trial recruitment. Patient numbers are not reported, so it is not possible to known the sample size upon which information on adverse events has been based. In addition, infection risk is affected by a number of factors including demographics such as age, the primary autoimmune diagnosis, as well as co-treatment with corticosteroids, which will be applicable to many patients taking these immune-modulatory drugs.

While it is useful to compare data across SmPCs, it is not possible to perform a “head-to-head” trial between them, due to the vast variation in trial designs and reporting methods. This will subsequently influence any between-drug differences. Nonetheless, our comparisons have potential use in clinical practice. For patients with recurrent infections at a given site, clinicians can use the charts for cross-drug comparison, as a point of reference to choose drugs with less frequent infections, albeit being mindful that absent or rare events may indicate less reporting of infection, not necessarily low frequency. Similarly, for patients with a history of infection with a specific organism or opportunism, visualisation of organism data can help select drugs with a weaker signal for these infections. However, to have sufficient face validity for comparisons between SmPCs to alter care, the EMA would need to ensure more detailed information on source data within the tables in the SmPCs, especially with regard adverse events with drug use in different diseases. Ultimately, drug choice is individualised, dependent on both patient and clinician.

In conclusion, the SmPC literature is an important source of information on infection frequency, including on individual types and infectious organism. Our comparison of SmPCs across immune-modulatory drugs show striking patterns, including the similarities and differences in infection, which can be used to guide prescribing decisions in this high-risk population. However, we have also highlighted the need for robust post-marketing pharmacovigilance studies, and the importance of using SmPC data alongside other sources when assessing infection risk.

**Competing interests:** none to declare.

**Contributorship**: MD undertook the analysis and drafted the manuscript. KB undertook the analysis. MD, KB and JG developed the methods. All authors actively contributed to the final content and structure of the manuscript.

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**Ethical approval**: not applicable

**Data sharing statement**: Data available upon request. Original data is contained within the European Medicines Agency Summary of Product Characteristics data which is freely available online.

**Patient and Public Involvement:** not applicable

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| --- | --- | --- | --- | --- |
| **Drug** | **Mode of action** | **IMID licensed indication(s)** | **Mode of administration** | **Date of last SmPC update at time of search** |
| **csDMARDs** |
| Azathioprine | Purine synthesis inhibitor | Crohn's, UC, RA | Oral | 03/12/2019 |
| Ciclosporin | Calcineurin inhibitor | UC, RA, PsO, atopic dermatitis | Oral | 10/03/2020 |
| Cladribine | Purine analog | MS | Oral | 21/01/2020 |
| Interferon beta | Unknown | MS | SC, IM | 23/10/2019 |
| Leflunomide | Pyrimidine synthesis inhibitor | RA, PsA | Oral | 15/08/2017 |
| Methotrexate | Dihydrofolate reductase inhibitor | Crohn's, RA, PsO | Oral, SC, IM | 23/01/2020 |
| Mycophenolate mofetil | Inosine-5′-monophosphate dehydrogenase inhibitor | nil IMID | Oral | 25/11/2020 |
| Sulfasalazine | Unknown | Crohn's, UC, RA | Oral | 15/10/2019 |
| Teriflunomide | Dihydro-orotate dehydrogenase inhibitor | MS | Oral | 18/09/2020 |
| **tsDMARDs** |
| Baricitinib | JAK1 and JAK2; limited inhibition of TYK2) | RA | Oral | 26/11/2019 |
| Filgotinib | JAK1 | RA | Oral | 24/09/2020 |
| Tofacitinib | JAK3 and JAK1; some affinity for JAK2; limited affinity for TYK2 | RA | Oral | 06/02/2020 |
| Upadacitinib | JAK1 | RA | Oral | 01/04/2020 |
|  |  |  |  |  |
| Fingolimod | Sphingosine 1-phosphate receptor modulator | MS | Oral | 16/01/2020 |
| Siponimod | Sphingosine 1-phosphate receptor modulator | MS | Oral | 24/04/2020 |
| **bDMARDs** |
| *Cytokine/Enzyme-targeted* |
| Adalimumab | TNFα inhibitor | Crohn's, UC, RA, PsO, axSpA, nr-axSpA | SC | 04/09/2020 |
| Anakinra | IL-1 receptor antagonist | RA, CAPS, Still's | SC | 28/05/2020 |
| Canakinumab | IL-1β inhibitor | Gout, autoinflammatory syndromes, Still's | SC | 13/03/2020 |
| Certolizumab pegol | TNFα inhibitor | RA, PsO, axSpA, PsA | SC | 12/08/2020 |
| Dupilumab | IL-4 receptor antagonist | Mod-severe atopic dermatitis, severe asthma | SC | 26/09/2017 |
| Eculizumab | C5 complement inhibitor | PNH | IV | 29/06/2020 |
| Etanercept | TNFα inhibitor | RA, PsO, PsA, AS, nr-axSpA | SC | 14/09/2020 |
| Golimumab | TNFα inhibitor | UC, RA, PsO, AS, nr-axSpA | SC, IV | 12/05/2020 |
| Guselkumab | IL-23 inhibitor | PsO | SC, IV | 29/06/2020 |
| Infliximab | TNFα inhibitor | Crohn's, UC, RA, AS, PsA, PsO | SC, IV | 28/10/2019 |
| Ixekizumab | IL-17A inhibitor | PsO, PsA | SC | 16/07/2020 |
| Mitoxantrone | Type II topoisomerase inhibitor | nil IMID | IV | 07/01/2020 |
| Ravulizumab | C5 complement inhibitor | PNH | IV | 28/09/2020 |
| Sarilumab | IL-6 receptor antagonist | RA | SC | 23/06/2017 |
| Secukinumab | IL-17A inhibitor | AS, PsA, PsO | SC | 19/08/2020 |
| Tocilizumab | IL-6 receptor antagonist | RA, GCA | IV | 02/09/2020 |
| Ustekinumab | IL-12/23 inhibitor | Crohn's, UC, PsO, PsA | SC | 27/02/2020 |
| *Cell-targeted* |
| Abatacept | CTLA-4 inhibitor | RA, PsA | SC, IV | 10/06/2020 |
| Alemtuzumab | CD52 antagonist | MS | IV | 16/09/2020 |
| Belimumab | B-cell activating factor | SLE | IV | 28/09/2020 |
| Natalizumab | α4β1 integrin inhibitor | MS | IV | 12/05/2020 |
| Ocrelizumab | CD20 inhibitor | MS | IV | 01/06/2020 |
| Rituximab | CD20 inhibitor | RA, autoimmune vasculitis, pemphigus vulgaris | IV | 08/04/2020 |
| Vedolizumab | α4β7 integrin inhibitor | Crohn's, UC | SC, IV | 15/05/2020 |

**Table 1**: Summary of immune-modulatory drugs included in this analysis, including date of last update to the summary of product characteristic (SmPC) document at the time of the search and data extraction.

**Figure legends**

Figure 1: Summary of common sites of infection for immune-modulatory drugs. Key: Very common ⬤ ; Common ⬤ ; Uncommon ⬤ ; Rare ⬤ ; Blank- no information available. Drugs with no frequencies reported for specific infection sites not included (azathioprine, ciclosporin, interferon beta, leflunomide, methotrexate, sulfasalazine, siponimod, certolizumab pegol, dupilumab).

Figure 2: Summary of infection frequency with specific organisms for immune-modulatory drugs. Key: Very common ⬤ ; Common ⬤ ; Uncommon ⬤ ; Rare ⬤ ; Very rare ⬤; Unknown ⬤; Blank- no information available.

Supplementary Figure 1: Summary of common infections by pathogen subtype. Key: Very common ⬤ ; Common ⬤ ; Uncommon ⬤ ; Rare ⬤ ; Blank- no information available. Drugs with no frequencies reported for specific infection sites not included (ciclosporin, interferon beta, leflunomide, methotrexate, sulfasalazine, siponimod, anakinra, dupilumab, mitoxantrone, ravulizumab, sarilumab, natalizumab).

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