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Data analysis report

Prevalence of immunocompromised patients with a diagnosis of cytomegalovirus infection

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1. Rationale and background

Cytomegalovirus (CMV) is the largest member of the virus family *Herpesviridae* and is a ubiquitous virus that infects almost all humans at some time in their lives, with the mean seropositive rate varying with location, race and socioeconomic status. It is estimated that between 40% and 100% of adults have this lifelong infection by adulthood. In healthy persons who acquire CMV after birth, the infection is usually asymptomatic.

In adults, CMV can be diagnosed by one or more of the following methods: (1) identification of CMV inclusion bodies or CMV antigen in infected tissue by using indirect immunofluorescence microscopy, (2) detection of the virus in cell culture monolayers inoculated with infected tissue or body fluids (for example, lung, kidney, bowel, liver, blood leukocytes, urine, throat washings, bronchoalveolar lung lavage fluid, or, rarely, cerebrospinal fluid), or (3) identification of an IgM-specific antibody in serum or a serial fourfold increase in IgG antibody to CMV in primary infection or a serial fourfold rise of IgG antibody to CMV in recrudescent infection.

Among immunocompromised individuals, especially those with suppression of T-lymphocyte function such as organ transplant recipients and patients with the acquired immunodeficiency syndrome (AIDS), CMV causes significant morbidity and mortality. Therefore testing for CMV is important when somebody has a weakened immune system. Treatment (i.e. prophylaxis) can be offered to immunocompromised individuals to prevent developing CMV or once diagnosed with CMV to treat it thereby decreasing the risk of morbidity and mortality. In patients receiving corticosteroids or cytotoxic drugs, discontinuation of the use of such drugs or tapering of the dose may help to control the infection.

The aim of this study was to generate more recent data on the prevalence of CMV in Europe in immunocompromised patients to support the regulatory discussions.

2. Research question and objectives

The primary objectives were to estimate the prevalence of:

a) immunocompromised patients, and

b) immunocompromised patients who were diagnosed with CMV.

3. Research methods

3.1. Study design

This was a descriptive study of yearly prevalence of immunocompromised individuals and those immunocompromised with CMV.

3.2. Setting and study population

The study population included patients ≥ 1 year of age visiting general practices in France and Germany between 2016 and 2020.

Measure of interest

Prevalence is defined as the number of previously diagnosed persons affected by a condition at a specified instant in time in a given population. Prevalence was assessed as number of patients per 100.000.

Event of interest

1) Immunocompromised patients

Immunocompromised patients at risk of complicated CMV infection are defined as patients that have at least one of these criteria:

- Solid organ transplant recipient
- HSCT/Bone marrow transplant recipient.
- HIV infection
- Primary immunodeficiencies
- Cancer patients (selected types) with solid tumours. If required the focus might shift to haematolgocial malignancies.

OR

- Patients treated with immunosuppressive therapy

Clinical codes to identify the above-mentioned criteria are defined in Annex 1.

2) Cytomegalovirus infection

Clinical codes to identify the infection are defined in Annex 1.

Infection in newborns (defined as <1 year of age) was considered a separate entity and excluded from the study population.

3.3. Data sources

The following databases were used: IQVIA™ Disease Analyzer France and IQVIA™ Disease Analyzer Germany. An overview of these databases used for this study can be found in Annex 2.

3.4. Statistical analysis

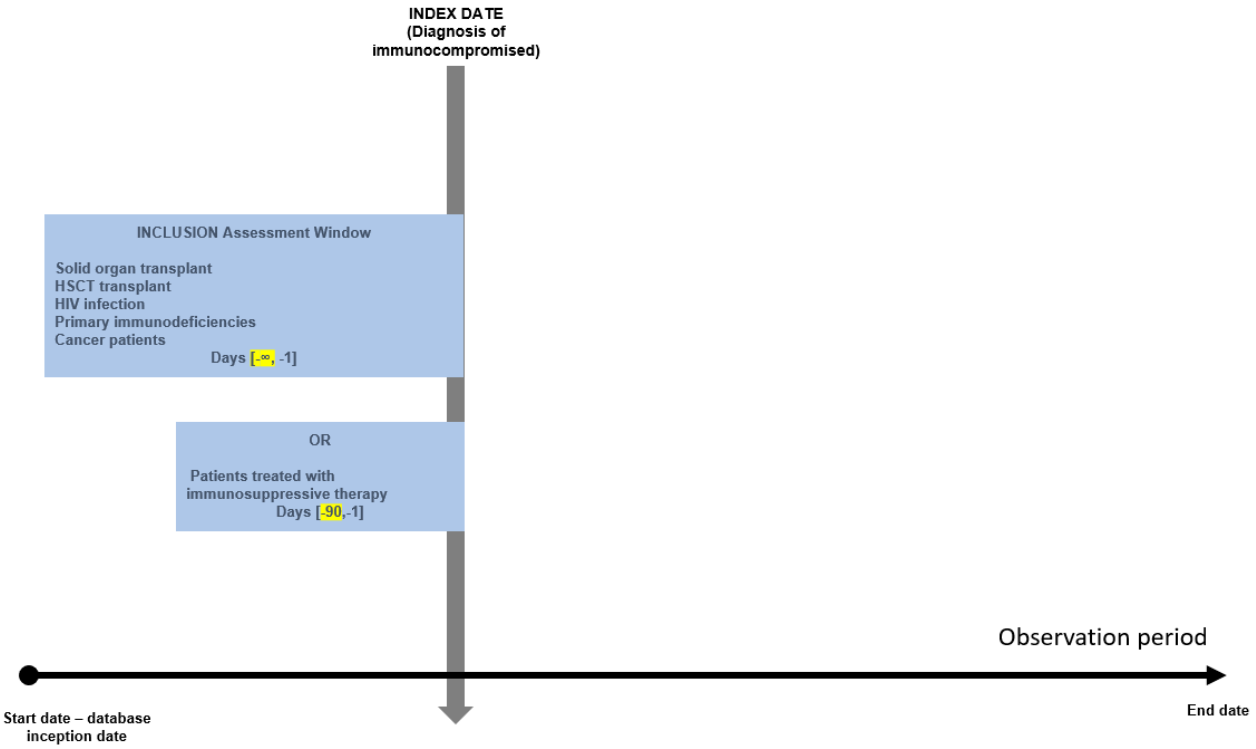
3.4.1. Main analysis

Two prevalence studies were performed.

Study 1. Prevalence of immunocompromised patients

- Numerator: The numerator consisted of patients that were immunocompromised, during the yearly time period. Patients with an underlying condition at any time prior or with a prescription of immunosuppressive therapy 90 days prior the assessment period were included.
- Denominator:The denominator consisted of patients that were observable for at least one day during the respective year. The observability for a patient started on the date of the first visit to the practice and ended on the date of the last visit to the practice.

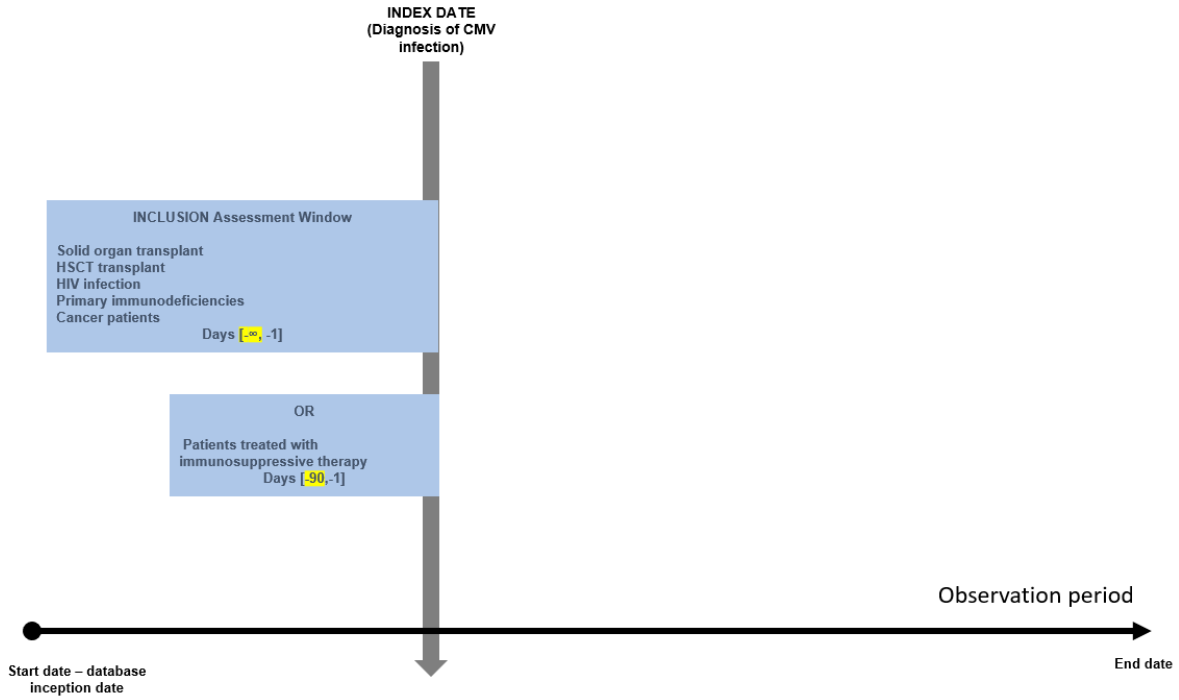
Assessment window prevalence of immunocompromised patients



Study 2. Prevalence of immunocompromised patients with CMV

- Numerator: The numerator consisted of patients that were immunocompromised and diagnosed with CMV during the yearly time period. Patients with an underlying condition any time prior the CVM diagnoses or with a prescription for immunosuppressive therapy 90 days prior the CMV diagnoses date were included.
- Denominator: The denominator consisted of patients that were observable for at least one day during the respective year. The observability for a patient started on the date of the first visit to the practice and ended on the date of the last visit to the practice.

Assessment window prevalence of immunocompromised patients with diagnosis of CMV



The statistical analyses where performed by EMA researchers using SAS Enterprise Guide version 7.15 and IHD (Instant Health Data platform).

3.4.2. Sensitivity analysis

Sentivity analyses were also performed including those patients that used corticosteroids. See Annex 1 for diagnostic codes.

3.5. Quality control

The study was conducted according to the ENCePP code of conduct (European Medicines Agency 2018).

Standard operating procedures or internal process guidance were adhered to for the conduct of the study. These procedures include rules for secure and confidential data storage, quality-control procedures for all aspects of the study from protocol development to the reporting of the results.

All documents underwent at least one round review by an experienced reviewer. Results from the statistical analysis were reviewed or checked via double coding.

The quality control of the data is the responsibility of the data holder.

4. Results

4.1.1. Descriptive data

Descriptive counts of observable persons (i.e., denominator), immunocompromised patients and immunocompromised patients with diagnosis of CMV are shown in Table 1 and Table 2. In Germany, the number of observable persons was more than 4.000.000 persons per year. In 2020, 350.096 and 12.161 were identified as immunocompromised in IQVIA™ Disease Analyzer Germany and IQVIA™ Disease Analyzer France respectively. The cohort of immucompromsed patients who were also diagnosed with CMV was small (<75 patients per year).

In France, the number of observable persons per year was significantly lower (roughly 775.000). This resulted also in a lower number of patients identified as immunocompromised (9000 to 12000 patients) or immunocompromised with diagnosis of CMV (0 to <10 patients). The study cohort increased substantially when including immunocompromised patients who used corticosteroids, which also led to the identification of a few patients who also had diagnosis of CMV (< 10 patients).

Table 1. IQVIA™ Disease Analyzer Germany

	2016	2017	2018	2019	2020
Denominator	4.321.019	4.527.585	4.534.403	4.441.801	4.037.396
Main analysis					
Numerator Immunocompromised	291.076	317.558	336.077	352.922	350.096
Numerator Immunocompromised and CMV	58	73	65	62	69
Sensitivity analysis					
Numerator Immunocompromised (incl. patients treated with corticosteroids)	398.159	440.337	462.446	481.180	458.771
Numerator Immunocompromised (incl. patients treated with corticosteroids) and CMV	62	79	76	68	77

Table 2. IQVIA™ Disease Analyzer France

	2016	2017	2018	2019	2020
Denominator	771.232	795.547	799.425	791.633	708.018
Main analysis					
Numerator immunocompromised patients	9.115	10.114	11.106	11.865	12.161
Numerator immunocompromised and CMV	<10	0	0	0	0
Sensitivity analysis					
Numerator immunocompromised (incl. patients treated with corticosteroids)	112.632	115.773	117.942	111.783	76.391
Numerator immunocompromised (incl. patients treated with corticosteroids) and CMV	<10	<10	<10	<10	0

4.1.2. Main analysis

In Germany, the prevalence of immunocompromised patients slightly increased over time from 6.736 per 100.000 in 2016 to 8.671 per 100.000 in 2020. A similar increasing pattern was observed for those immocompromised patients who also were diagnosed with CMV. However, the prevalence was signifincantly lower and varied from 1,34 per 100.000 in 2016 to 1,71 per 100.000 in 2020 (Table 3).

In France, the prevalence rate for those patients that were immunocompromised increased as well over time, from 1.182 per 100.000 in 2016 to 1.718 per100.000 in 2020. For those immunomcompromised patients with diagnosis of CMV, the prevalence was below 0,5 per 100.000 over time (Table 4).

4.1.3. Sensivity analysis

When also accounting for patients treated with corticosteroids in the 90 days prior assessment date, the prevalence of immunocompromised patients ranged from 9.124 per 100.000 in 2016 (36% increase compared to cohort without corticosteroids) to 11.363 per 100.000 in 2020 (31% increase compared to cohort without corticosteroids) in Germany (Table 5). The prevalence of those immocompromised patients with diagnosis of CMV slighly increased to 1,43 per 100.000 in 2016 and 1,91 per 100.000 in 2020 (Table 6).

In France, the number of patients treated with corticosteroids was considerably high, thereby increasing substantially the study cohort of immonucompromised patients. The prevalence of imumoncompromised patients decreased from 14.604 per 100.000 in 2016 to 10.789 per 100.000 in 2020 (Table 5). For those imumocompromised with diagnosed of CMV, the prevalence rate remained steady below 1 per 100.000 from 2016 to 2020 (Table 6).

Table 3. Yearly prevalence of immunocompromised patients per 100.000

Country	Immunocompromised patients per 100,000				
	2016	**2017**	**2018**	**2019**	**2020**
Germany	6736,28	7013,85	7411,71	7945,47	8671,33
France	1181,88	1271,33	1389,25	1498,80	1717,61

Table 4. Yearly prevalence of immunocompromised patients with diagnosis of CMV per 100.000

Country	Immunocompromised patients with diagnosis of CVM per 100,000				
	2016	**2017**	**2018**	**2019**	**2020**
Germany	1,34	1,61	1,43	1,40	1,71
France	0,13	0,00	0,00	0,00	0,00

Table 5. Yearly prevalence immunocompromised patients (incl. corticosteroids) per100.000

Country	Immunocompromised patients with (incl. corticosteroids) per 100,000				
	2016	**2017**	**2018**	**2019**	**2020**
Germany	9214,47	9725,65	10198,61	10832,99	11363,04
France	14604,17	14552,63	14753,35	14120,56	10789,41

Table 6. Yearly prevalence immunocompromised patients (incl. corticosteroids) with diagnosis of CMV per 100.000

Country	Immunocompromised patients with diagnosis of CVM (incl. corticosteroids) per 100,000				
	2016	**2017**	**2018**	**2019**	**2020**
Germany	1,43	1,74	1,68	1,53	1,91
France	0,13	0,50	0,13	0,13	0,00

5. Discussion

5.1. Key results

The yearly prevalence of immunocompromised patients visiting general practices varied from 7-9% in Germany to 1.2-1.7% in France. It was not possible to limit the analysis to patients with predominant suppression of T-cell function who would be considered to be at highest risk of developing CMV disease. In both countries, there was an increased risk in the prevalence in immunocomprised patients over time (Table 3.).

When including patients treated with corticosteroids (Table 5.), a similar pattern was observed in Germany. However, in France, the prevalence of immunocompromised patients was substantially higher when accounting for patients treated with corticosteroids.

In Germany, the prevalence of immunocompromised patients with diagnosis of CMV infection slightly increased but in France yearly prevalence were 0% (Table 4.). This finding remained after accounting for patients treated with cortisteroids (Table 6.).

In general, the number of immunocompromised patients with diagnosis of CMV infection as reported in the assessed primary health care databases are low and should be interpreted cautiously given the limitations of the data sources.

5.2. Limitations

This study was based on data from patients visiting primary care and denominators are not based on overall country population denominators. Information on patients not visiting primary care were not included in the data sources and then the study and this is the setting where most of the population at risk is expected to be diagnosed with immune deficiency, i.e. transplant centers, hospitals and specialist practices. Patients diagnosed and monitored only in secondary care (or higher) are likely to be missed. Most of the infections (if any) due to immune deficiency occur in the first months after transplantation during which the patients are likely to be still monitored in the tertiary centers involved.

In Germany, patients are not registered with a GP. This means that every time the individual visits a new practice he/she appears as a new patient in the database. As a result, for patients consulting different practices or different specialities (i.e. pediatrics), the same patient is counted multiple times. In addition, physicians in Germany have to document indications using ICD-10-GM (German Modification). In IQVIA Disease Analyzer Germany, the GM codes are converted to ICD-10-WHO codes. As the ICD-10-GRM is more granular, this conversion might result in loosing details on diagnosis.

Also, it should be noted that not all therapy codes (IDA Therapy Molecule) that have been listed in Annex 1 are registered in the German database and therefore this might result in an underestimation of the number of patients with immunosuppressive therapy.

Although both the German and French dataset are considered a representative sample of their respective population, it might be considered that they do not represent the overall European population. Additional data sources may be included in the future if deemed relevant and necessary.

6. References

Ross SA, Novak Z, Pati S, Boppana SB. Overview of the diagnosis of cytomegalovirus infection. Infect Disord Drug Targets. 2011 Oct;11(5):466-74. doi: 10.2174/187152611797636703.

Lancini D, Faddy HM, Flower R, Hogan C. Cytomegalovirus disease in immunocompetent adults. Med J Aust. 2014 Nov 17;201(10):578-80. doi: 10.5694/mja14.00183.

EMA Taskforce Data Analytics and Methods. Real-Word Data Analytics - Companion Booklet. https://analytics.emea.eu.int/rwd-companion-book/

Annexes

Annex 1 – Codelists

Codes used to identify CMV

WHO ICD-10 Codes
Cytomegalovirus

code	description
B20.2	HIV disease resulting in cytomegaloviral disease
B25	Cytomegaloviral disease
B27.1	Cytomegaloviral mononucleosis

Codes used to identify immunocompromised patients

Immunocompromised patients at risk of complicated CMV infection are defined as patients that have at least one of these criteria:

WHO ICD-10 Codes
Solid organ transplant recipient

code	description
N16.5	Renal tubulo-interstitial disorders in transplant rejection
T86.1	Kidney transplant failure and rejection
T86.2	Heart transplant failure and rejection
T86.3	Heart-lung transplant failure and rejection
T86.4	Liver transplant failure and rejection
Y83.0	Surgical operation with transplant of whole organ as the cause of abnormal reaction of the patient, or of later complication, without mention of misadventure at the time of the procedure
Z94.0	Kidney transplant status
Z94.1	Heart transplant status
Z94.2	Lung transplant status
Z94.3	Heart and lungs transplant status
Z94.4	Liver transplant status
Z94.5	Skin transplant status

HSCT transplant recipient (Stem Cell Transplant/Bone Marrow transplant)

code	description
T86.0	Bone-marrow transplant rejection
Z94.6	Bone transplant status

HIV infection

code	description
B20	Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases
B20.0	HIV disease resulting in mycobacterial infection
B20.1	HIV disease resulting in other bacterial infections
B20.2	HIV disease resulting in cytomegaloviral disease
B20.3	HIV disease resulting in other viral infections
B20.4	HIV disease resulting in candidiasis
B20.5	HIV disease resulting in other mycoses
B20.6	HIV disease resulting in Pneumocystis jirovecii pneumonia
B20.7	HIV disease resulting in multiple infections
B20.8	HIV disease resulting in other infectious and parasitic diseases
B20.9	HIV disease resulting in unspecified infectious or parasitic disease
B21	Human immunodeficiency virus [HIV] disease resulting in malignant neoplasms
B21.0	HIV disease resulting in Kaposi sarcoma
B21.1	HIV disease resulting in Burkitt lymphoma
B21.2	HIV disease resulting in other types of non-Hodgkin lymphoma
B21.3	HIV disease resulting in other malignant neoplasms of lymphoid, haematopoietic and related tissue

B21.7 HIV disease resulting in multiple malignant neoplasms
B21.8 HIV disease resulting in other malignant neoplasms
B21.9 HIV disease resulting in unspecified malignant neoplasm
B22 Human immunodeficiency virus [HIV] disease resulting in other specified diseases
B22.0 HIV disease resulting in encephalopathy
B22.1 HIV disease resulting in lymphoid interstitial pneumonitis
B22.2 HIV disease resulting in wasting syndrome
B22.7 HIV disease resulting in multiple diseases classified elsewhere
B23 Human immunodeficiency virus [HIV] disease resulting in other conditions
B23.0 Acute HIV infection syndrome
B23.1 HIV disease resulting in (persistent) generalized lymphadenopathy
B23.2 HIV disease resulting in haematological and immunological abnormalities, not elsewhere classified
B23.8 HIV disease resulting in other specified conditions
B24 Unspecified human immunodeficiency virus [HIV] disease

Primary immunodeficiencies

code description
D80 D80 Immunodeficiency with predominantly antibody defects [Non-Specific Code]
D80.0 Hereditary hypogammaglobulinemia
D80.1 Nonfamilial hypogammaglobulinemia
D80.2 Selective deficiency of immunoglobulin A [IgA]
D80.3 Selective deficiency of immunoglobulin G [IgG] subclasses
D80.4 Selective deficiency of immunoglobulin M [IgM]
D80.5 Immunodeficiency with increased immunoglobulin M [IgM]
D80.6 Antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia
D80.7 Transient hypogammaglobulinemia of infancy
D80.8 Other immunodeficiencies with predominantly antibody defects
D80.9 Immunodeficiency with predominantly antibody defects, unspecified
D81 D81 Combined immunodeficiencies [Non-Specific Code]
D81.0 Severe combined immunodeficiency [SCID] with reticular dysgenesis
D81.1 Severe combined immunodeficiency [SCID] with low T- and B-cell numbers
D81.2 Severe combined immunodeficiency [SCID] with low or normal B-cell numbers
D81.30 Adenosine deaminase deficiency, unspecified
D81.31 Severe combined immunodeficiency due to adenosine deaminase deficiency
D81.32 Adenosine deaminase 2 deficiency
D81.39 Other adenosine deaminase deficiency
D81.4 Nezelof's syndrome
D81.5 Purine nucleoside phosphorylase [PNP] deficiency
D81.6 Major histocompatibility complex class I deficiency
D81.7 Major histocompatibility complex class II deficiency
D81.8 D81.8 Other combined immunodeficiencies [Non-Specific Code]
D81.81 D81.81 Biotin-dependent carboxylase deficiency [Non-Specific Code]
D81.810 Biotinidase deficiency
D81.818 Other biotin-dependent carboxylase deficiency
D81.819 Biotin-dependent carboxylase deficiency, unspecified
D81.89 Other combined immunodeficiencies
D81.9 Combined immunodeficiency, unspecified
D82 D82 Immunodeficiency associated with other major defects [Non-Specific Code]
D82.0 Wiskott-Aldrich syndrome
D82.1 Di George's syndrome
D82.2 Immunodeficiency with short-limbed stature
D82.3 Immunodeficiency following hereditary defective response to Epstein-Barr virus
D82.4 Hyperimmunoglobulin E [IgE] syndrome
D82.8 Immunodeficiency associated with other specified major defects
D82.9 Immunodeficiency associated with major defect, unspecified
D83 D83 Common variable immunodeficiency [Non-Specific Code]
D83.0 Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
D83.1 Common variable immunodeficiency with predominant immunoregulatory T-cell disorders
D83.2 Common variable immunodeficiency with autoantibodies to B- or T-cells
D83.8 Other common variable immunodeficiencies
D83.9 Common variable immunodeficiency, unspecified

D84 D84 Other immunodeficiencies [Non-Specific Code]
D84.0 Lymphocyte function antigen-1 [LFA-1] defect
D84.1 Defects in the complement system
D84.81 Immunodeficiency due to conditions classified elsewhere
D84.82 D84.82 Immunodeficiency due to drugs and external causes [Non-Specific Code]
D84.821 Immunodeficiency due to drugs
D84.822 Immunodeficiency due to external causes
D84.89 Other immunodeficiencies
D84.9 Immunodeficiency, unspecified

Cancer patients with solid tumours

code description
C00 Malignant neoplasm of lip
C00.0 Malignant neoplasm: External upper lip
C00.1 Malignant neoplasm: External lower lip
C00.2 Malignant neoplasm: External lip, unspecified
C00.3 Malignant neoplasm: Upper lip, inner aspect
C00.4 Malignant neoplasm: Lower lip, inner aspect
C00.5 Malignant neoplasm: Lip, unspecified, inner aspect
C00.6 Malignant neoplasm: Commissure of lip
C00.8 Malignant neoplasm: Overlapping lesion of lip
C00.9 Malignant neoplasm: Lip, unspecified
C01 Malignant neoplasm of base of tongue
C02 Malignant neoplasm of other and unspecified parts of tongue
C02.0 Malignant neoplasm: Dorsal surface of tongue
C02.1 Malignant neoplasm: Border of tongue
C02.2 Malignant neoplasm: Ventral surface of tongue
C02.3 Malignant neoplasm: Anterior two-thirds of tongue, part unspecified
C02.4 Malignant neoplasm: Lingual tonsil
C02.8 Malignant neoplasm: Overlapping lesion of tongue
C02.9 Malignant neoplasm: Tongue, unspecified
C03 Malignant neoplasm of gum
C03.0 Malignant neoplasm: Upper gum
C03.1 Malignant neoplasm: Lower gum
C03.9 Malignant neoplasm: Gum, unspecified
C04 Malignant neoplasm of floor of mouth
C04.0 Malignant neoplasm: Anterior floor of mouth
C04.1 Malignant neoplasm: Lateral floor of mouth
C04.8 Malignant neoplasm: Overlapping lesion of floor of mouth
C04.9 Malignant neoplasm: Floor of mouth, unspecified
C05 Malignant neoplasm of palate
C05.0 Malignant neoplasm: Hard palate
C05.1 Malignant neoplasm: Soft palate
C05.2 Malignant neoplasm: Uvula
C05.8 Malignant neoplasm: Overlapping lesion of palate
C05.9 Malignant neoplasm: Palate, unspecified
C06 Malignant neoplasm of other and unspecified parts of mouth
C06.0 Malignant neoplasm: Cheek mucosa
C06.1 Malignant neoplasm: Vestibule of mouth
C06.2 Malignant neoplasm: Retromolar area
C06.8 Malignant neoplasm: Overlapping lesion of other and unspecified parts of mouth
C06.9 Malignant neoplasm: Mouth, unspecified
C07 Malignant neoplasm of parotid gland
C08 Malignant neoplasm of other and unspecified major salivary glands
C08.0 Malignant neoplasm: Submandibular gland
C08.1 Malignant neoplasm: Sublingual gland
C08.8 Malignant neoplasm: Overlapping lesion of major salivary glands
C08.9 Malignant neoplasm: Major salivary gland, unspecified
C09 Malignant neoplasm of tonsil
C09.0 Malignant neoplasm: Tonsillar fossa
C09.1 Malignant neoplasm: Tonsillar pillar (anterior)(posterior)
C09.8 Malignant neoplasm: Overlapping lesion of tonsil
C09.9 Malignant neoplasm: Tonsil, unspecified

C10 Malignant neoplasm of oropharynx
C10.0 Malignant neoplasm: Vallecula
C10.1 Malignant neoplasm: Anterior surface of epiglottis
C10.2 Malignant neoplasm: Lateral wall of oropharynx
C10.3 Malignant neoplasm: Posterior wall of oropharynx
C10.4 Malignant neoplasm: Branchial cleft
C10.8 Malignant neoplasm: Overlapping lesion of oropharynx
C10.9 Malignant neoplasm: Oropharynx, unspecified
C11 Malignant neoplasm of nasopharynx
C11.0 Malignant neoplasm: Superior wall of nasopharynx
C11.1 Malignant neoplasm: Posterior wall of nasopharynx
C11.2 Malignant neoplasm: Lateral wall of nasopharynx
C11.3 Malignant neoplasm: Anterior wall of nasopharynx
C11.8 Malignant neoplasm: Overlapping lesion of nasopharynx
C11.9 Malignant neoplasm: Nasopharynx, unspecified
C12 Malignant neoplasm of piriform sinus
C13 Malignant neoplasm of hypopharynx
C13.0 Malignant neoplasm: Postcricoid region
C13.1 Malignant neoplasm: Aryepiglottic fold, hypopharyngeal aspect
C13.2 Malignant neoplasm: Posterior wall of hypopharynx
C13.8 Malignant neoplasm: Overlapping lesion of hypopharynx
C13.9 Malignant neoplasm: Hypopharynx, unspecified
C14 Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
C14.0 Malignant neoplasm: Pharynx, unspecified
C14.1 Malignant neoplasm of laryngopharynx unspecified
C14.2 Malignant neoplasm: Waldeyer ring
C14.8 Malignant neoplasm: Overlapping lesion of lip, oral cavity and pharynx
C15 Malignant neoplasm of oesophagus
C15.0 Malignant neoplasm: Cervical part of oesophagus
C15.1 Malignant neoplasm: Thoracic part of oesophagus
C15.2 Malignant neoplasm: Abdominal part of oesophagus
C15.3 Malignant neoplasm: Upper third of oesophagus
C15.4 Malignant neoplasm: Middle third of oesophagus
C15.5 Malignant neoplasm: Lower third of oesophagus
C15.8 Malignant neoplasm: Overlapping lesion of oesophagus
C15.9 Malignant neoplasm: Oesophagus, unspecified
C16 Malignant neoplasm of stomach
C16.0 Malignant neoplasm: Cardia
C16.1 Malignant neoplasm: Fundus of stomach
C16.2 Malignant neoplasm: Body of stomach
C16.3 Malignant neoplasm: Pyloric antrum
C16.4 Malignant neoplasm: Pylorus
C16.5 Malignant neoplasm: Lesser curvature of stomach, unspecified
C16.6 Malignant neoplasm: Greater curvature of stomach, unspecified
C16.8 Malignant neoplasm: Overlapping lesion of stomach
C16.9 Malignant neoplasm: Stomach, unspecified
C17 Malignant neoplasm of small intestine
C17.0 Malignant neoplasm: Duodenum
C17.1 Malignant neoplasm: Jejunum
C17.2 Malignant neoplasm: Ileum
C17.3 Malignant neoplasm: Meckel diverticulum
C17.8 Malignant neoplasm: Overlapping lesion of small intestine
C17.9 Malignant neoplasm: Small intestine, unspecified
C18 Malignant neoplasm of colon
C18.0 Malignant neoplasm: Caecum
C18.1 Malignant neoplasm: Appendix
C18.2 Malignant neoplasm: Ascending colon
C18.3 Malignant neoplasm: Hepatic flexure
C18.4 Malignant neoplasm: Transverse colon
C18.5 Malignant neoplasm: Splenic flexure
C18.6 Malignant neoplasm: Descending colon
C18.7 Malignant neoplasm: Sigmoid colon
C18.8 Malignant neoplasm: Overlapping lesion of colon

C18.9 Malignant neoplasm: Colon, unspecified
C19 Malignant neoplasm of rectosigmoid junction
C20 Malignant neoplasm of rectum
C21 Malignant neoplasm of anus and anal canal
C21.0 Malignant neoplasm: Anus, unspecified
C21.1 Malignant neoplasm: Anal canal
C21.2 Malignant neoplasm: Cloacogenic zone
C21.8 Malignant neoplasm: Overlapping lesion of rectum, anus and anal canal
C22 Malignant neoplasm of liver and intrahepatic bile ducts
C22.0 Malignant neoplasm: Liver cell carcinoma
C22.1 Malignant neoplasm: Intrahepatic bile duct carcinoma
C22.2 Malignant neoplasm: Hepatoblastoma
C22.3 Malignant neoplasm: Angiosarcoma of liver
C22.4 Malignant neoplasm: Other sarcomas of liver
C22.7 Malignant neoplasm: Other specified carcinomas of liver
C22.9 Malignant neoplasm: Liver, unspecified
C23 Malignant neoplasm of gallbladder
C24 Malignant neoplasm of other and unspecified parts of biliary tract
C24.0 Malignant neoplasm: Extrahepatic bile duct
C24.1 Malignant neoplasm: Ampulla of Vater
C24.8 Malignant neoplasm: Overlapping lesion of biliary tract
C24.9 Malignant neoplasm: Biliary tract, unspecified
C25 Malignant neoplasm of pancreas
C25.0 Malignant neoplasm: Head of pancreas
C25.1 Malignant neoplasm: Body of pancreas
C25.2 Malignant neoplasm: Tail of pancreas
C25.3 Malignant neoplasm: Pancreatic duct
C25.4 Malignant neoplasm: Endocrine pancreas
C25.7 Malignant neoplasm: Other parts of pancreas
C25.8 Malignant neoplasm: Overlapping lesion of pancreas
C25.9 Malignant neoplasm: Pancreas, unspecified
C26 Malignant neoplasm of other and ill-defined digestive organs
C26.0 Malignant neoplasm: Intestinal tract, part unspecified
C26.1 Malignant neoplasm: Spleen
C26.8 Malignant neoplasm: Overlapping lesion of digestive system
C26.9 Malignant neoplasm: Ill-defined sites within the digestive system
C30 Malignant neoplasm of nasal cavity and middle ear
C30.0 Malignant neoplasm: Nasal cavity
C30.1 Malignant neoplasm: Middle ear
C31 Malignant neoplasm of accessory sinuses
C31.0 Malignant neoplasm: Maxillary sinus
C31.1 Malignant neoplasm: Ethmoidal sinus
C31.2 Malignant neoplasm: Frontal sinus
C31.3 Malignant neoplasm: Sphenoidal sinus
C31.8 Malignant neoplasm: Overlapping lesion of accessory sinuses
C31.9 Malignant neoplasm: Accessory sinus, unspecified
C32 Malignant neoplasm of larynx
C32.0 Malignant neoplasm: Glottis
C32.1 Malignant neoplasm: Supraglottis
C32.2 Malignant neoplasm: Subglottis
C32.3 Malignant neoplasm: Laryngeal cartilage
C32.8 Malignant neoplasm: Overlapping lesion of larynx
C32.9 Malignant neoplasm: Larynx, unspecified
C33 Malignant neoplasm of trachea
C34 Malignant neoplasm of bronchus and lung
C34.0 Malignant neoplasm: Main bronchus
C34.1 Malignant neoplasm: Upper lobe, bronchus or lung
C34.2 Malignant neoplasm: Middle lobe, bronchus or lung
C34.3 Malignant neoplasm: Lower lobe, bronchus or lung
C34.8 Malignant neoplasm: Overlapping lesion of bronchus and lung
C34.9 Malignant neoplasm: Bronchus or lung, unspecified
C37 Malignant neoplasm of thymus
C38 Malignant neoplasm of heart, mediastinum and pleura

C38.0 Malignant neoplasm: Heart
C38.1 Malignant neoplasm: Anterior mediastinum
C38.2 Malignant neoplasm: Posterior mediastinum
C38.3 Malignant neoplasm: Mediastinum, part unspecified
C38.4 Malignant neoplasm: Pleura
C38.8 Malignant neoplasm: Overlapping lesion of heart, mediastinum and pleura
C39 Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs
C39.0 Malignant neoplasm: Upper respiratory tract, part unspecified
C39.8 Malignant neoplasm: Overlapping lesion of respiratory and intrathoracic organs
C39.9 Malignant neoplasm: Ill-defined sites within the respiratory system
C40 Malignant neoplasm of bone and articular cartilage of limbs
C40.0 Malignant neoplasm: Scapula and long bones of upper limb
C40.1 Malignant neoplasm: Short bones of upper limb
C40.2 Malignant neoplasm: Long bones of lower limb
C40.3 Malignant neoplasm: Short bones of lower limb
C40.8 Malignant neoplasm: Overlapping lesion of bone and articular cartilage of limbs
C40.9 Malignant neoplasm: Bone and articular cartilage of limb, unspecified
C41 Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C41.0 Malignant neoplasm: Bones of skull and face
C41.1 Malignant neoplasm: Mandible
C41.2 Malignant neoplasm: Vertebral column
C41.3 Malignant neoplasm: Ribs, sternum and clavicle
C41.4 Malignant neoplasm: Pelvic bones, sacrum and coccyx
C41.8 Malignant neoplasm: Overlapping lesion of bone and articular cartilage
C41.9 Malignant neoplasm: Bone and articular cartilage, unspecified
C43 Malignant melanoma of skin
C43.0 Malignant neoplasm: Malignant melanoma of lip
C43.1 Malignant neoplasm: Malignant melanoma of eyelid, including canthus
C43.2 Malignant neoplasm: Malignant melanoma of ear and external auricular canal
C43.3 Malignant neoplasm: Malignant melanoma of other and unspecified parts of face
C43.4 Malignant neoplasm: Malignant melanoma of scalp and neck
C43.5 Malignant neoplasm: Malignant melanoma of trunk
C43.6 Malignant neoplasm: Malignant melanoma of upper limb, including shoulder
C43.7 Malignant neoplasm: Malignant melanoma of lower limb, including hip
C43.8 Malignant neoplasm: Overlapping malignant melanoma of skin
C43.9 Malignant neoplasm: Malignant melanoma of skin, unspecified
C44 Other malignant neoplasms of skin
C44.0 Malignant neoplasm: Skin of lip
C44.1 Malignant neoplasm: Skin of eyelid, including canthus
C44.2 Malignant neoplasm: Skin of ear and external auricular canal
C44.3 Malignant neoplasm: Skin of other and unspecified parts of face
C44.4 Malignant neoplasm: Skin of scalp and neck
C44.5 Malignant neoplasm: Skin of trunk
C44.6 Malignant neoplasm: Skin of upper limb, including shoulder
C44.7 Malignant neoplasm: Skin of lower limb, including hip
C44.8 Malignant neoplasm: Overlapping lesion of skin
C44.9 Malignant neoplasm: Malignant neoplasm of skin, unspecified
C45 Mesothelioma
C45.0 Mesothelioma of pleura
C45.1 Mesothelioma of peritoneum
C45.2 Mesothelioma of pericardium
C45.7 Mesothelioma of other sites
C45.9 Mesothelioma, unspecified
C46 Kaposi sarcoma
C46.0 Kaposi sarcoma of skin
C46.1 Kaposi sarcoma of soft tissue
C46.2 Kaposi sarcoma of palate
C46.3 Kaposi sarcoma of lymph nodes
C46.7 Kaposi sarcoma of other sites
C46.8 Kaposi sarcoma of multiple organs
C46.9 Kaposi sarcoma, unspecified
C47 Malignant neoplasm of peripheral nerves and autonomic nervous system

C47.0 Malignant neoplasm: Peripheral nerves of head, face and neck
C47.1 Malignant neoplasm: Peripheral nerves of upper limb, including shoulder
C47.2 Malignant neoplasm: Peripheral nerves of lower limb, including hip
C47.3 Malignant neoplasm: Peripheral nerves of thorax
C47.4 Malignant neoplasm: Peripheral nerves of abdomen
C47.5 Malignant neoplasm: Peripheral nerves of pelvis
C47.6 Malignant neoplasm: Peripheral nerves of trunk, unspecified
C47.8 Malignant neoplasm: Overlapping lesion of peripheral nerves and autonomic nervous system
C47.9 Malignant neoplasm: Peripheral nerves and autonomic nervous system, unspecified
C48 Malignant neoplasm of retroperitoneum and peritoneum
C48.0 Malignant neoplasm: Retroperitoneum
C48.1 Malignant neoplasm: Specified parts of peritoneum
C48.2 Malignant neoplasm: Peritoneum, unspecified
C48.8 Malignant neoplasm: Overlapping lesion of retroperitoneum and peritoneum
C49 Malignant neoplasm of other connective and soft tissue
C49.0 Malignant neoplasm: Connective and soft tissue of head, face and neck
C49.1 Malignant neoplasm: Connective and soft tissue of upper limb, including shoulder
C49.2 Malignant neoplasm: Connective and soft tissue of lower limb, including hip
C49.3 Malignant neoplasm: Connective and soft tissue of thorax
C49.4 Malignant neoplasm: Connective and soft tissue of abdomen
C49.5 Malignant neoplasm: Connective and soft tissue of pelvis
C49.6 Malignant neoplasm: Connective and soft tissue of trunk, unspecified
C49.8 Malignant neoplasm: Overlapping lesion of connective and soft tissue
C49.9 Malignant neoplasm: Connective and soft tissue, unspecified
C50 Malignant neoplasm of breast
C50.0 Malignant neoplasm: Nipple and areola
C50.1 Malignant neoplasm: Central portion of breast
C50.2 Malignant neoplasm: Upper-inner quadrant of breast
C50.3 Malignant neoplasm: Lower-inner quadrant of breast
C50.4 Malignant neoplasm: Upper-outer quadrant of breast
C50.5 Malignant neoplasm: Lower-outer quadrant of breast
C50.6 Malignant neoplasm: Axillary tail of breast
C50.8 Malignant neoplasm: Overlapping lesion of breast
C50.9 Malignant neoplasm: Breast, unspecified
C51 Malignant neoplasm of vulva
C51.0 Malignant neoplasm: Labium majus
C51.1 Malignant neoplasm: Labium minus
C51.2 Malignant neoplasm: Clitoris
C51.8 Malignant neoplasm: Overlapping lesion of vulva
C51.9 Malignant neoplasm: Vulva, unspecified
C52 Malignant neoplasm of vagina
C53 Malignant neoplasm of cervix uteri
C53.0 Malignant neoplasm: Endocervix
C53.1 Malignant neoplasm: Exocervix
C53.8 Malignant neoplasm: Overlapping lesion of cervix uteri
C53.9 Malignant neoplasm: Cervix uteri, unspecified
C54 Malignant neoplasm of corpus uteri
C54.0 Malignant neoplasm: Isthmus uteri
C54.1 Malignant neoplasm: Endometrium
C54.2 Malignant neoplasm: Myometrium
C54.3 Malignant neoplasm: Fundus uteri
C54.8 Malignant neoplasm: Overlapping lesion of corpus uteri
C54.9 Malignant neoplasm: Corpus uteri, unspecified
C55 Malignant neoplasm of uterus, part unspecified
C56 Malignant neoplasm of ovary
C57 Malignant neoplasm of other and unspecified female genital organs
C57.0 Malignant neoplasm: Fallopian tube
C57.1 Malignant neoplasm: Broad ligament
C57.2 Malignant neoplasm: Round ligament
C57.3 Malignant neoplasm: Parametrium
C57.4 Malignant neoplasm: Uterine adnexa, unspecified
C57.7 Malignant neoplasm: Other specified female genital organs
C57.8 Malignant neoplasm: Overlapping lesion of female genital organs

C57.9 Malignant neoplasm: Female genital organ, unspecified
C58 Malignant neoplasm of placenta
C60 Malignant neoplasm of penis
C60.0 Malignant neoplasm: Prepuce
C60.1 Malignant neoplasm: Glans penis
C60.2 Malignant neoplasm: Body of penis
C60.8 Malignant neoplasm: Overlapping lesion of penis
C60.9 Malignant neoplasm: Penis, unspecified
C61 Malignant neoplasm of prostate
C62 Malignant neoplasm of testis
C62.0 Malignant neoplasm: Undescended testis
C62.1 Malignant neoplasm: Descended testis
C62.9 Malignant neoplasm: Testis, unspecified
C63 Malignant neoplasm of other and unspecified male genital organs
C63.0 Malignant neoplasm: Epididymis
C63.1 Malignant neoplasm: Spermatic cord
C63.2 Malignant neoplasm: Scrotum
C63.7 Malignant neoplasm: Other specified male genital organs
C63.8 Malignant neoplasm: Overlapping lesion of male genital organs
C63.9 Malignant neoplasm: Male genital organ, unspecified
C64 Malignant neoplasm of kidney, except renal pelvis
C65 Malignant neoplasm of renal pelvis
C66 Malignant neoplasm of ureter
C67 Malignant neoplasm of bladder
C67.0 Malignant neoplasm: Trigone of bladder
C67.1 Malignant neoplasm: Dome of bladder
C67.2 Malignant neoplasm: Lateral wall of bladder
C67.3 Malignant neoplasm: Anterior wall of bladder
C67.4 Malignant neoplasm: Posterior wall of bladder
C67.5 Malignant neoplasm: Bladder neck
C67.6 Malignant neoplasm: Ureteric orifice
C67.7 Malignant neoplasm: Urachus
C67.8 Malignant neoplasm: Overlapping lesion of bladder
C67.9 Malignant neoplasm: Bladder, unspecified
C68 Malignant neoplasm of other and unspecified urinary organs
C68.0 Malignant neoplasm: Urethra
C68.1 Malignant neoplasm: Paraurethral gland
C68.8 Malignant neoplasm: Overlapping lesion of urinary organs
C68.9 Malignant neoplasm: Urinary organ, unspecified
C69 Malignant neoplasm of eye and adnexa
C69.0 Malignant neoplasm: Conjunctiva
C69.1 Malignant neoplasm: Cornea
C69.2 Malignant neoplasm: Retina
C69.3 Malignant neoplasm: Choroid
C69.4 Malignant neoplasm: Ciliary body
C69.5 Malignant neoplasm: Lacrimal gland and duct
C69.6 Malignant neoplasm: Orbit
C69.8 Malignant neoplasm: Overlapping lesion of eye and adnexa
C69.9 Malignant neoplasm: Eye, unspecified
C70 Malignant neoplasm of meninges
C70.0 Malignant neoplasm: Cerebral meninges
C70.1 Malignant neoplasm: Spinal meninges
C70.9 Malignant neoplasm: Meninges, unspecified
C71 Malignant neoplasm of brain
C71.0 Malignant neoplasm: Cerebrum, except lobes and ventricles
C71.1 Malignant neoplasm: Frontal lobe
C71.2 Malignant neoplasm: Temporal lobe
C71.3 Malignant neoplasm: Parietal lobe
C71.4 Malignant neoplasm: Occipital lobe
C71.5 Malignant neoplasm: Cerebral ventricle
C71.6 Malignant neoplasm: Cerebellum
C71.7 Malignant neoplasm: Brain stem
C71.8 Malignant neoplasm: Overlapping lesion of brain

C71.9 Malignant neoplasm: Brain, unspecified
C72 Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system
C72.0 Malignant neoplasm: Spinal cord
C72.1 Malignant neoplasm: Cauda equina
C72.2 Malignant neoplasm: Olfactory nerve
C72.3 Malignant neoplasm: Optic nerve
C72.4 Malignant neoplasm: Acoustic nerve
C72.5 Malignant neoplasm: Other and unspecified cranial nerves
C72.8 Malignant neoplasm: Overlapping lesion of brain and other parts of central nervous system
C72.9 Malignant neoplasm: Central nervous system, unspecified
C73 Malignant neoplasm of thyroid gland
C74 Malignant neoplasm of adrenal gland
C74.0 Malignant neoplasm: Cortex of adrenal gland
C74.1 Malignant neoplasm: Medulla of adrenal gland
C74.9 Malignant neoplasm: Adrenal gland, unspecified
C75 Malignant neoplasm of other endocrine glands and related structures
C75.0 Malignant neoplasm: Parathyroid gland
C75.1 Malignant neoplasm: Pituitary gland
C75.2 Malignant neoplasm: Craniopharyngeal duct
C75.3 Malignant neoplasm: Pineal gland
C75.4 Malignant neoplasm: Carotid body
C75.5 Malignant neoplasm: Aortic body and other paraganglia
C75.8 Malignant neoplasm: Pluriglandular involvement, unspecified
C75.9 Malignant neoplasm: Endocrine gland, unspecified

IDA Therapy Molecule Name

Patients treated with immunosuppressive therapy

ATC code	Name
L04AA02	muromonab-CD3
L04AA03	antilymphocyte immunoglobulin (horse)
L04AA04	antithymocyte immunoglobulin (rabbit)
L04AA06	mycophenolic acid
L04AA10	sirolimus
L04AA13	leflunomide
L04AA15	alefacept
L04AA18	everolimus
L04AA19	gusperimus
L04AA21	efalizumab
L04AA22	abetimus
L04AA23	natalizumab
L04AA24	abatacept
L04AA25	eculizumab
L04AA26	belimumab
L04AA27	fingolimod
L04AA28	belatacept
L04AA29	tofacitinib
L04AA31	teriflunomide
L04AA32	apremilast
L04AA33	vedolizumab
L04AA34	alemtuzumab
L04AA35	begelomab
L04AA36	ocrelizumab
L04AA37	baricitinib

L04AA38	ozanimod
L04AA39	emapalumab
L04AA40	cladribine
L04AA41	imlifidase
L04AA42	siponimod
L04AA43	ravulizumab
L04AA44	upadacitinib
L04AA45	filgotinib
L04AA46	itacitinib
L04AA47	inebilizumab
L04AA48	belumosudil
L04AA49	peficitinib
L04AA50	ponesimod
L04AA51	anifrolumab
L04AA52	ofatumumab
L04AA53	teprotumumab
L04AA54	pegcetacoplan
L04AA55	sutimlimab
L04AA56	deucravacitinib
L04AB01	etanercept
L04AB02	infliximab
L04AB03	afelimomab
L04AB04	adalimumab
L04AB05	certolizumab pegol
L04AB06	golimumab
L04AB07	opinercept
L04AC01	daclizumab
L04AC02	basiliximab
L04AC03	anakinra
L04AC04	rilonacept
L04AC05	ustekinumab
L04AC07	tocilizumab
L04AC08	canakinumab
L04AC09	briakinumab
L04AC10	secukinumab
L04AC11	siltuximab
L04AC12	brodalumab
L04AC13	ixekizumab
L04AC14	sarilumab
L04AC15	sirukumab
L04AC16	guselkumab
L04AC17	tildrakizumab
L04AC18	risankizumab
L04AC19	satralizumab
L04AC20	netakimab
L04AC21	bimekizumab

L04AC22	spesolimab
L04AD01	ciclosporin
L04AD02	tacrolimus
L04AD03	voclosporin
L04AX01	azathioprine
L04AX02	thalidomide
L04AX03	methotrexate
L04AX04	lenalidomide
L04AX05	pirfenidone
L04AX06	pomalidomide
L04AX07	dimethyl fumarate
L04AX08	darvadstrocel
L04AX09	lenalidomide

EphMRA ATC Code List

Patients treated with corticosteroids

code	description
H02A1	INJ CORTICOSTEROIDS PLAIN
H02A2	ORAL CORTICOSTEROID PLAIN
H02A3	OTH SYS CORTICOSTERO PLN
H02B0	COMB CORTICOSTEROIDS
R03D2	CORTICOIDS, SYSTEMIC

Annex 2 – Information on Databases and Healthcare systems included

IQVIA™ Disease Analyzer Germany

IQVIA™ Disease Analyzer (IDA) Germany collects computerised information from specialised and general primary care practices throughout Germany since 1992. Around 3% of general practitioners (GP) practices are included, which covers all patients consulting a practice. Data from IDA Germany have been shown to be reasonably representative of German healthcare statistics for demographics and certain diseases and is considered one of the largest national medical databases worldwide. IDA Germany includes more than 2,500 practices and 3,100 physicians (13 speciality groups) representing over 15,000,000 patients.

This database used to be named IQVIA™ Germany and some use of this terminology may persist.

IQVIA™ Disease Analyzer France

IQVIA™ Disease Analyzer (IDA) France collects anonymised patient medical records since 1997 through a representative panel of GPs. The physician sample represents approximately 2% of physicians and is weighted by age and gender of the physician, doctor region and the SNIR of the physician (National Official Indicator of the GP volume of activity in terms of visits and consultations). Some 99% of the French population is insured, but there are differences regarding level of coverage. IDA France includes around 1,000 GPs and represents more than 4,000,000 of patients and considered representative for the French population.

This database used to be named IQVIA™ France and some use of this terminology may persist.