## Appendix

**Appendix table 1.** Characteristics of new active substances not submitted to Health Canada

| New active substances | First approval | Indication(s) | Top 25 manufacturer | Biologic | Oncology | Infectious Disease | Orphan | US prevalence (NIH GARD) | Pharm. subgroup (ATC3) | IQWiG Assess-ment | DINs marketed in subgroup | FDA approval | EMA approval | Countries with sales | PMPRB11 sales (CAD M) | US sales (CAD M) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Autologous Cultured Chondrocytes On A Porcine Collagen Membrane | 2016 | Repair of symptomatic, single or multiple full-thickness cartilage defects of the knee | | Y | | | | | M09A | | 8 | Y | W | | | |
| Betulae Cortex Dry Extract | 2016 | | | | | | | | D03A | | 0 | | W | | | |
| Bezlotoxumab | 2016 | Prevention of recurrence of Clostridium difficile infection | Y | Y | | Y | | | J06B | NQ | 36 | Y | Y | Au, Fr, Ge, It, Ja, No, Sp, Sw, UK, US | 1 to 10 | 10 to 100 |
| Etelcalcetide | 2016 | Treatment of secondary hyperparathyroidism in adult patients with chronic kidney disease (CKD) on haemodialysis therapy | Y | | | | | | H05B | NP | 29 | Y | Y | Be, Fr, Ge, It, Ja, Ne, No, Sp, Sw, UK, US | More than 100 | More than 100 |
| Eteplirsen | 2016 | Treatment of Duchenne muscular dystrophy | | Y | | | EMA, FDA | <50,000 | M09A | | 8 | Y | | US | | 10 to 100 |
| Fluciclovine F 18 | 2016 | Positron emission tomography (PET) imaging to detect recurrence of prostate cancer in adult men with a suspected recurrence | | | | | | | V09I | | 0 | Y | Y | | | |
| Gene Therapy Product | 2016 | Severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available | | Y | | | EMA | <50,000 | | | | | Y | | | |
| NalotimageneCarmaleucel | 2016 | | | Y | | | | | | | | | W | | | |
| Opicapone | 2016 | Adjunctive therapy to preparations of levodopa/ DOPA decarboxylase inhibitors (DDCI) in adult patients with Parkinson's disease | | | | | | | N04B | NP | 85 | Y | Y | Ge, It, Ja, Sp, UK, US | 10 to 100 | 10 to 100 |
| Pimavanserin | 2016 | Atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosi | | | | | | | N05A | | 481 | Y | | US | | More than 100 |
| Rucaparib | 2016 | a) Maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer; b) Monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy. | | | Y | | FDA | | L01X | NP | 74 | | Y | Fr, Ge, It, Sp, UK, US | 10 to 100 | 10 to 100 |
| Vaccine, Pandemic Influenza H5n1 | 2016 | Prophylaxis of influenza in an officially declared pandemic situation in children and adolescents from 12 months to less than 18 years of age | Y | Y | | Y | | | | | | | Y | | | |
| Angiotensin Ii | 2017 | Refractory hypotension in adults with septic or other distributive shock who remain hypotensive | | | | | | | | NP | | Y | Y | Ge, US | Less than 1 | 10 to 100 |



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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Benznidazole | 2017 | Treatment of Chagas disease | | | | Y | FDA | No data | P01C | | 2 | Y | | | | |
| Betrixaban | 2017 | Prophylaxis of venous thromboembolism | Y | | | | | | B01A | | 208 | W | | | | |
| Copanlisib | 2017 | Relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies | Y | | Y | | FDA | <50,000 | L01E | | 187 | Y | | US | | 10 to 100 |
| Delafloxacin | 2017 | a) Acute bacterial skin and skin structure infections; b) community-acquired pneumonia (CAP), when it is considered inappropriate to use other antibacterial agents | | | | Y | | | J01M | | 61 | Y | Y | UK, US | Less than 1 | 1 to 10 |
| Deutetrabenazine | 2017 | Chorea associated with Huntington's disease | | | | | FDA | <5,000 | N07X | | 19 | Y | | US | | More than 100 |
| Macimorelin | 2017 | Diagnosis of growth hormone deficiency (GHD) in adults. | Y | | | | FDA | No data | V04C | | 30 | Y | Y | US | | Less than 1 |
| Naldemedine | 2017 | Opioid-induced constipation | | | | | FDA | | A06A | NP | 87 | Y | Y | Ge, It, Ja, UK, US | 10 to 100 | 10 to 100 |
| Netarsudil | 2017 | Reduction of elevated intraocular pressure (IOP) in adult patients with primary open-angle glaucoma or ocular hypertension | | | | | | | S01E | | 71 | Y | Y | US | | More than 100 |
| Padeliporfin | 2017 | Adenocarcinoma of the prostate | | | Y | | | | L01X | NP | 74 | | Y | It | Less than 1 | |
| Tivozanib | 2017 | First line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC | | | Y | | | | L01E | NP | 187 | Y | Y | Ge, No, Sp, Sw, UK, US | 10 to 100 | 10 to 100 |
| Vaborbactam | 2017 | a) Complicated urinary tract infection, including pyelonephritis; b) Complicated intra-abdominal infection; c) Hospital-acquired pneumonia, including ventilator associated pneumonia | | | | Y | | | J01D | | 99 | Y | Y | Fr, It, Sp, Sw, UK, US | 1 to 10 | 10 to 100 |
| Valbenazine | 2017 | Tardive dyskinesia. | | | | | | | N07X | | 19 | Y | | US | | More than 100 |
| Vestronidase Alfa | 2017 | Non-neurological manifestations of Mucopolysaccharidosis VII | | Y | | | EMA, FDA | <1,000 | A16A | | 57 | Y | Y | US | | 1 to 10 |
| Avatrombopag | 2018 | a) Severe thrombocytopenia in adult patients with chronic liver disease; b) treatment of primary chronic immune thrombocytopenia | | | | | FDA | No data | B02B | NP | 104 | Y | Y | Be, Ge, It, Ne, No, Sp, Sw, UK, US | 1 to 10 | 10 to 100 |
| Duvelisib | 2018 | a) Relapsed or refractory chronic lymphocytic leukaemia after at least two prior therapies; b) Follicular lymphoma that is refractory to at least two prior systemic therapies. | | | Y | | FDA | | L01E | NP | 187 | Y | Y | US | | 10 to 100 |
| Elapegademase | 2018 | Adenosine deaminase severe combined immune deficiency in pediatric and adult patients. | | Y | | | FDA | <5,000 | L03A | | 31 | Y | | Ja | 1 to 10 | |
| Eravacycline | 2018 | Complicated intra-abdominal infections | | | | Y | | | J01A | | 15 | Y | Y | US | | 10 to 100 |
| Ibalizumab | 2018 | Heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen | | Y | | Y | FDA | No data | J05A | | 230 | Y | W | Fr, Ge, It, US | 1 to 10 | 10 to 100 |
| Ivosidenib | 2018 | Relapsed or refractory acute myeloid leukemia with a susceptible IDH1 mutation as detected by an FDA-approved test | | | Y | | FDA | <50,000 | L01X | | 74 | Y | W | US | | 10 to 100 |
| Lusutrombopag | 2018 | Severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures | | | | | | | B02B | NP | 104 | Y | Y | It, Ja, UK, US | 1 to 10 | 1 to 10 |



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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MoxetumomabPasudotox | 2018 | Hairy cell leukemia who received at least two prior systemic therapies | | Y | Y | | FDA | <5,000 | L01F | | 68 | Y | W | US | | 1 to 10 |
| Omadacycline | 2018 | a) Community-acquired bacterial pneumonia; b) Acute bacterial skin and skin structure infections | | | | Y | | | J01A | | 15 | Y | W | US | | 10 to 100 |
| Plazomicin | 2018 | Complicated Urinary Tract Infections including Pyelonephritis | | | | Y | | | J01G | | 20 | Y | W | US | | Less than 1 |
| Revefenacin | 2018 | Mmaintenance treatment of patients with chronic obstructive pulmonary disease | | | | | | | R03B | | 47 | Y | | US | | More than 100 |
| Sarecycline | 2018 | Inflammatory lesions of non-nodular moderate to severe acne vulgaris | | | | | | | J01A | | 15 | Y | | US | | More than 100 |
| Segesterone Acetate | 2018 | To prevent pregnancy | | | | | | | | | | Y | | US | | 10 to 100 |
| Tafenoquine | 2018 | Radical cure (prevention of relapse) of Plasmodium vivax malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute P. vivax infection. | Y | | | Y | FDA | <5,000 | P01B | | 20 | Y | | US | | Less than 1 |
| Tagraxofusp | 2018 | Blastic plasmacytoid dendritic cell neoplasm | | | Y | | EMA, FDA | <200,000 | L01X | | 74 | Y | Y | Ge | 1 to 10 | |
| Velmanase Alfa | 2018 | Non-neurological manifestations in patients with mild to moderate alpha-mannosidosis. | | | | | EMA | <5,000 | A16A | | 57 | | Y | Ge, It | 1 to 10 | |
| Air Polymer-Type A | 2019 | Ultrasound contrast agent indicated for sonohysterosalpingography to assess fallopian tube patency in women with known or suspected infertility. | | | | | | | | | | Y | | | | |
| BetibeglogeneAutotemcel | 2019 | | | Y | | | | | B06A | | 10 | | W | | | |
| Brexanolone | 2019 | Postpartum depression | | | | | | | N06A | | 477 | Y | | US | | 1 to 10 |
| Cefiderocol | 2019 | Infections due to aerobic Gram-negative organisms in adults with limited treatment options | | | | Y | | | J01D | | 99 | Y | Y | Fr, Ge, It, Sw, UK, US | 10 to 100 | 10 to 100 |
| Crizanlizumab | 2019 | Prevention of recurrent vaso occlusive crises in sickle cell disease | Y | Y | | | EMA, FDA | <200,000 | B06A | | 10 | Y | Y | Fr, Ge, US | 1 to 10 | More than 100 |
| Fluorodopa F 18 | 2019 | Radioactive diagnostic agent indicated for use in positron emission tomography (PET) to visualize dopaminergic nerve terminals in the striatum for the evaluation of adult patients with suspected Parkinsonian syndromes | | | | | | | V09I | | 0 | Y | | | | |
| Golodirsen | 2019 | Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping | | | | | FDA | <50,000 | M09A | | 8 | Y | | US | | 1 to 10 |
| Istradefylline | 2019 | Adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease | | | | | | | N04C | | 0 | Y | | Ja, US | 10 to 100 | 10 to 100 |
| LumateperoneTosylate | 2019 | a) Schizophrenia in adults; b) Depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate | | | | | | | N05A | | 481 | Y | | | | |
| Pexidartinib | 2019 | Symptomatic tenosynovial giant cell tumor | Y | | Y | | FDA | | L01E | | 187 | Y | | US | | 10 to 100 |
| Pretomanid | 2019 | In combination with bedaquiline and linezolid, in adults, for the treatment of pulmonary extensively drug resistant (XDR), or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis | | | | Y | EMA, FDA | | | | | Y | Y | US | | Less than 1 |



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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Relebactam | 2019 | a) Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP), in adults; b) Treatment of bacteraemia that occurs in association with, or is suspected to be associated with HAP or VAP, in adult;. c) Treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options | Y | | | Y | | | J01D | | 99 | Y | Y | Fr, Ge, Ja, Sw, UK, US | 1 to 10 | 10 to 100 |
| Voxelotor | 2019 | Haemolytic anaemia due to sickle cell disease | Y | | | | FDA | <200,000 | B06A | | 10 | Y | Y | US | | Less than 1 |
| Abametapir | 2020 | Head lice infestation | | | | Y | | | | | | Y | | | | |
| Ansuvimab | 2020 | Treatment of infection caused by Zaire ebolavirus in adult and pediatric patients, including neonates born to a mother who is RT-PCR positive for Zaire ebolavirus infection | | Y | | Y | FDA | <200,000 | J06B | | 36 | Y | | | | |
| Atoltivimab | 2020 | Infection caused by Zaire ebolavirus in adult and pediatric patients, including neonates born to a mother who is RT-PCR positive for Zaire ebolavirus infection | Y | Y | | Y | FDA | <200,000 | | | | Y | | | | |
| Avapritinib | 2020 | Unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation | | Y | Y | | EMA, FDA | <50,000 | L01E | | 187 | Y | Y | Ge, UK, US | 1 to 10 | 1 to 10 |
| BelantamabMafodotin | 2020 | Multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy. | Y | Y | Y | | EMA | <50,000 | L01X | NP | 74 | Y | Y | Fr, Ge, It, No, Sw, UK, US | 10 to 100 | More than 100 |
| Bempedoic Acid | 2020 | Primary hypercholesterolaemia (heterozygous familial and non familial) or mixed dyslipidaemia, as an adjunct to diet, in combination with a statin, or alone in statin intolerant. | Y | | | | | | C10A | NP | 339 | Y | Y | Ge, UK, US | 10 to 100 | 10 to 100 |
| Bulevirtide | 2020 | Chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease. | Y | Y | | Y | EMA | No data | J05A | | 230 | | Y | Fr, Ge | 10 to 100 | |
| Imlifidase | 2020 | Desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. | | Y | | | EMA | No data | L04A | | 294 | | Y | | | |
| Inebilizumab | 2020 | Adult patients with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin 4 immunoglobulin G (AQP4-IgG) seropositive | Y | Y | | | FDA | <5,000 | L04A | NP | 294 | Y | Y | Ja, US | 1 to 10 | 10 to 100 |
| Lonafarnib | 2020 | Hutchinson-Gilford progeria syndrome or a processing-deficient progeroid laminopathy associated with either a heterozygous LMNA mutation with progerin-like protein accumulation or a homozygous or compound heterozygous ZMPSTE24 mutation | | | | | EMA, FDA | <1,000 | A16A | | 57 | Y | Y | US | | 10 to 100 |



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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Naxitamab | 2020 | Relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a partial response, minor response, or stable disease to prior therapy. | | Y | Y | | FDA | <50,000 | L01F | | 68 | Y | | US | | 10 to 100 |
| Oliceridine | 2020 | Management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. | | | | | | | N02A | | 209 | Y | | US | | Less than 1 |
| Osilodrostat | 2020 | Endogenous Cushing's syndrome in adults | | | | | EMA, FDA | <5,000 | H02C | | 0 | Y | Y | Fr, Ge, It, Ja | 1 to 10 | |
| Remimazolam | 2020 | Procedural sedation | | | | | | | N05C | | 78 | Y | Y | Ja, US | 1 to 10 | Less than 1 |
| Rimegepant | 2020 | Acute treatment of migraine with or without aura in adults; Preventative treatment of episodic migraine in adults who have at least 4 migraine attacks per month. | Y | | | | | | N02C | | 117 | Y | Y | US | | More than 100 |
| Setmelanotide | 2020 | Obesity and the control of hunger associated with genetically confirmed Bardet Biedl syndrome (BBS), loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above | | | | | EMA, FDA | <1,000 | A08A | | 2 | Y | Y | | | |
| Tazemetostat | 2020 | Metastatic or locally advanced epithelioid sarcoma not eligible for complete resection | | | Y | | FDA | <1,000 | L01X | | 74 | Y | | Ja, US | Less than 1 | 1 to 10 |
| Teprotumumab | 2020 | Insulin-like growth factor-1 receptor inhibitor indicated for the treatment of Thyroid Eye Disease | Y | Y | | | FDA | No data | L04A | | 294 | Y | | US | | 10 to 100 |
| Vibegron | 2020 | Overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults | | | | | | | | | | Y | | Ja, US | More than 100 | 10 to 100 |
| Viltolarsen | 2020 | Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping | | | | | FDA | <50,000 | M09A | | 8 | Y | | Ja, US | 10 to 100 | 1 to 10 |

Abbreviations: IQWiG: *Institut für Qualität und WirtschaftlichkeitimGesundheitswesen* (Institute for Quality and Efficiency in Health Care); EMA: European Medicines Agency; FDA: Food and Drug Administration; DIN: Drug Identification Number; PMPRB11 countries: Australia, Belgium, France, Germany, Italy, Japan, Netherlands, Norway, Spain, Sweden, and the United Kingdom; Y, yes; NP: added benefit not proven; NQ: proof of non-quantifiable (at most considerable) added benefit; W: withdrawn.

Sources: *Meds Entry Watch*2016, 2017, 2018, 5th, and 6th editions[8-12], GlobalData, Drugs@FDA, European Medicines Agency, National Institutes of Health Genetic and Rare Disease Information Center (NIH GARD), Health Canada *Drug Product Database*,IQWiG, and IQVIA MIDAS®.

Notes: Top 25 manufacturers were identified using GlobalData Pharmaceutical's "Global: Companies by Market Cap" list [14].The biologic, oncology indication, infective disease indication, orphan indication, and multiple indications characteristics were non-exclusive. Biologic and oncology status were taken from the *Meds Entry Watch* report first listing the NAS. The US prevalence was assessed only for NAS with an FDA orphan designation. The prevalence was determined by conducting keyword searches of the indication(s) listed on the drug label on the NIH GARD website. A multiple indication status was assigned if more than one indication was listed on the EMA Human medicine European public assessment report (EPAR) or on the most recent FDA drug label. Pharmacological subgroups were defined by the 3rd level of the World Health Organization Anatomical Therapeutic Chemical classification system (ATC3) code of the drug, assessed using the EPAR or the ATC/DDD Index 2023 website. The number of DINS approved for sale in Canada was determined by counting DINs with the same ATC3 code



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approved for sale using a February 1, 2023 extract of the Health Canada DPD. IQWIG benefit assessments were extracted from the agency's annual *Zusatznutzen: Ja oderNein?* reports. FDA and EMA approval status and indications were assessed January 16-19, 2023.



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**Appendix table 2.** Distribution of new active substances with an orphan designation from the FDA or the EMA andnot submitted to Health Canada by drug characteristic and indication, international approval status, and 2021 sales levels in PMPRB11 countries and the United States

| | Orphan New Active Substances | |
|---|---|---|
| | **N** | **%** |
| **Orphan NAS not submitted to Health Canada** | **37** | **100** |
| Orphan designation received | | |
| Both the FDA and the EMA | 9 | 24% |
| FDA only | 23 | 62% |
| EMA only | 5 | 14% |
| US prevalence estimate | | |
| < 5,000 | 11 | 30% |
| 5,000 and more | 14 | 38% |
| Not assessed | 12 | 32% |
| Orphan NAS by characteristic and indication category | | |
| Top 25 manufacturer | 11 | 30% |
| Biologic | 16 | 43% |
| Oncology indication | 10 | 27% |
| Infectious disease indication | 7 | 19% |
| Multiple indications | 5 | 14% |
| Number of DINS approved for sale in Canada in the pharmacological subgroup | | |
| 6 or more DINs | 31 | 84% |
| 1 to 5 DINS | 2 | 5% |
| 0 DIN | 1 | 3% |
| Unknown pharmacological subgroup | 3 | 8% |
| Orphan NAS by IQWiG benefit assessment relative to existing therapies | | |
| Added benefit not proven | 6 | 16% |
| Not assessed | 31 | 84% |
| Orphan NAS by marketing status in US and PMPRB11 countries | | |
| Sold in both US and PMPRB11 countries | 10 | 27% |
| Sold in US only | 16 | 43% |
| Sold in PMPRB11 countries only | 5 | 14% |
| Recorded no sales | 6 | 16% |

Abbreviations: IQWiG: *Institut für Qualität und WirtschaftlichkeitimGesundheitswesen* (Institute for Quality and Efficiency in Health Care); EMA: European Medicines Agency; FDA: Food and Drug Administration; DIN: Drug Identification Number; PMPRB11 countries: Australia, Belgium, France, Germany, Italy, Japan, Netherlands, Norway, Spain, Sweden, and the United Kingdom.

Sources: *Meds Entry Watch*2016, 2017, 2018, 5th, and 6th editions[8-12], GlobalData, Drugs@FDA, European Medicines Agency, National Institutes of Health Genetic and Rare Disease Information Center (NIH GARD), Health Canada *Drug Product Database*, IQWiG, and IQVIA MIDAS®.

Notes: Top 25 manufacturers were identified using GlobalData Pharmaceutical's "Global: Companies by Market Cap" list [14].The biologic, oncology indication, infective disease indication, orphan indication, and multiple indications characteristics were non-exclusive. Biologic and oncology status were taken from the *Meds Entry Watch* report first listing the NAS. The US prevalence was assessed only for NAS with an FDA orphan designation. The US prevalence



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was determined by conducting keyword searches of the indication(s) listed on the drug label of a drug with an orphan indication on the NIH GARD website. A multiple indication status was assigned if more than one indication was listed on the EMA Human medicine European public assessment report (EPAR) or on the most recent FDA drug label. Pharmacological subgroups were defined by the 3rd level of the World Health Organization Anatomical Therapeutic Chemical classification system (ATC3) code of the drug, assessed using the EPAR or the ATC/DDD Index 2023 website. The number of DINS approved for sale in Canada was determined by counting DINs with the same ATC3 code approved for sale using a February 1, 2023 extract of the Health Canada DPD. IQWIG benefit assessments were extracted from the agency's annual *Zusatznutzen: Ja oderNein?* reports. FDA and EMA approval status and indications were assessed January 16-19, 2023.



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