***Supplementary Material***

***Safety of Dual Orexin Receptor Antagonist Daridorexant:***

***A Disproportionality Analysis of Publicly Available FAERS Data***

**Table S1:** ADRs Observed in Daridorexant and other DORAs related ICSRs regrouped by MedDRA High Level Group Terms

|  |  |  |
| --- | --- | --- |
| High Level Group Terms (HLGTs) | Daridorexant ICSRsa  n (%) | Other DORAICSRsa  n (%) |
| Sleep disorders and disturbances | 326 (38,6) | 2264 (25,2) |
| Therapeutic and nontherapeutic effects (excl toxicity) | 311 (36,8) | 3164 (35,2) |
| General system disorders NEC | 194 (23) | 1088 (12,1) |
| Neurological disorders NEC | 114 (13,5) | 1181 (13,1) |
| Medication errors and other product use errors and issues | 102 (12,1) | 891 (9,9) |
| Headaches | 69 (8,2) | 454 (5,1) |
| Product quality, supply, distribution, manufacturing and quality system issues | 69 (8,2) | 187 (2,1) |
| Disturbances in thinking and perception | 44 (5,2) | 410 (4,6) |
| Gastrointestinal signs and symptoms | 41 (4,9) | 346 (3,9) |
| Anxiety disorders and symptoms | 40 (4,7) | 413 (4,6) |
| Epidermal and dermal conditions | 34 (4) | 179 (2) |
| Sleep disturbances (incl subtypes) | 32 (3,8) | 369 (4,1) |
| Allergic conditions | 30 (3,6) | 45 (0,5) |
| Movement disorders (incl parkinsonism) | 26 (3,1) | 238 (2,6) |
| Depressed mood disorders and disturbances | 25 (3) | 132 (1,5) |
| Overdoses and underdoses NEC | 23 (2,7) | 273 (3) |
| Respiratory disorders NEC | 22 (2,6) | 175 (1,9) |
| Skin appendage conditions | 21 (2,5) | 90 (1) |
| Gastrointestinal motility and defaecation conditions | 21 (2,5) | 137 (1,5) |
| Cardiac disorders, signs and symptoms NEC | 16 (1,9) | 106 (1,2) |
| Suicidal and self-injurious behaviours NEC | 16 (1,9) | 166 (1,8) |
| Salivary gland conditions | 14 (1,7) | 68 (0,8) |
| Muscle disorders | 14 (1,7) | 150 (1,7) |
| Mood disorders and disturbances NEC | 11 (1,3) | 117 (1,3) |
| Cardiac and vascular investigations (excl enzyme tests) | 11 (1,3) | 95 (1,1) |
| Deliria (incl confusion) | 11 (1,3) | 191 (2,1) |
| Changes in physical activity | 10 (1,2) | 57 (0,6) |
| Lifestyle issues | 10 (1,2) | 32 (0,4) |
| Off label uses and intentional product misuses/use issues | 9 (1,1) | 105 (1,2) |
| Mental impairment disorders | 9 (1,1) | 189 (2,1) |
| Oral soft tissue conditions | 9 (1,1) | 31 (0,3) |
| Fatal outcomes | 8 (0,9) | 43 (0,5) |
| Urinary tract signs and symptoms | 8 (0,9) | 88 (1) |
| Inner ear and VIIIth cranial nerve disorders | 7 (0,8) | 48 (0,5) |
| Injuries NEC | 7 (0,8) | 162 (1,8) |
| Respiratory tract signs and symptoms | 7 (0,8) | 50 (0,6) |
| Musculoskeletal and connective tissue disorders NEC | 7 (0,8) | 90 (1) |
| Viral infectious disorders | 6 (0,7) | 26 (0,3) |
| Eye disorders NEC | 6 (0,7) | 27 (0,3) |
| Psychiatric and behavioural symptoms NEC | 6 (0,7) | 58 (0,6) |
| Angioedema and urticaria | 6 (0,7) | 22 (0,2) |
| Appetite and general nutritional disorders | 5 (0,6) | 52 (0,6) |
| Cardiac arrhythmias | 5 (0,6) | 71 (0,8) |
| Physical examination and organ system status topics | 5 (0,6) | 55 (0,6) |
| Infections - pathogen unspecified | 5 (0,6) | 74 (0,8) |
| Vision disorders | 4 (0,5) | 43 (0,5) |
| Vascular disorders NEC | 3 (0,4) | 18 (0,2) |
| Sexual dysfunctions, disturbances and gender identity disorders | 3 (0,4) | 9 (0,1) |
| Personality disorders and disturbances in behaviour | 3 (0,4) | 45 (0,5) |
| Upper respiratory tract disorders (excl infections) | 3 (0,4) | 28 (0,3) |
| Hepatic and hepatobiliary disorders | 2 (0,2) | 42 (0,5) |
| Tongue conditions | 2 (0,2) | 13 (0,1) |
| Cognitive and attention disorders and disturbances | 2 (0,2) | 7 (0,1) |
| Therapeutic procedures and supportive care NEC | 2 (0,2) | 19 (0,2) |
| Seizures (incl subtypes) | 2 (0,2) | 68 (0,8) |
| Bone disorders (excl congenital and fractures) | 1 (0,1) | 9 (0,1) |
| Bronchial disorders (excl neoplasms) | 1 (0,1) | 8 (0,1) |
| Cytogenetic investigations and genetic analyses | 1 (0,1) | 1 (0) |
| Central nervous system vascular disorders | 1 (0,1) | 37 (0,4) |
| Aural disorders NEC | 1 (0,1) | 1 (0) |
| Decreased and nonspecific blood pressure disorders and shock | 1 (0,1) | 16 (0,2) |
| Cranial nerve disorders (excl neoplasms) | 1 (0,1) | 7 (0,1) |
| Ocular infections, irritations and inflammations | 1 (0,1) | 12 (0,1) |
| Urolithiases | 1 (0,1) | 3 (0) |
| Toxicology and therapeutic drug monitoring | 1 (0,1) | 20 (0,2) |
| Skin vascular abnormalities | 1 (0,1) | 5 (0,1) |
| Renal disorders (excl nephropathies) | 1 (0,1) | 27 (0,3) |
| Psychiatric disorders NEC | 1 (0,1) | 56 (0,6) |
| Metabolic, nutritional and blood gas investigations | 1 (0,1) | 26 (0,3) |
| Ocular sensory symptoms NEC | 1 (0,1) | 7 (0,1) |
| Dental and gingival conditions | 1 (0,1) | 4 (0) |
| Nervous system, skull and spine therapeutic procedures | 1 (0,1) | 1 (0) |
| Vulvovaginal disorders (excl infections and inflammations) | 1 (0,1) | 2 (0) |
| Middle ear disorders (excl congenital) | 1 (0,1) | 1 (0) |
| Joint disorders | 1 (0,1) | 37 (0,4) |
| Hearing disorders | 1 (0,1) | 11 (0,1) |
| Gastrointestinal haemorrhages NEC | 1 (0,1) | 8 (0,1) |
| Prostatic disorders (excl infections and inflammations) | 1 (0,1) | 5 (0,1) |

a*ICSR: Individual Case Safety Report*

**Table S2:** ADRs Observed in Daridorexant and other DORAs related ICSRs by MedDRA High Level Group Terms and Preferred Terms

|  |  |  |  |
| --- | --- | --- | --- |
| High Level Group Terms (HLGTs) | Preferred Terms (PTs) | Daridorexant ICSRsa  N (%) | Other DORAICSRsa  N (%) |
| Sleep disorders and disturbances | Nightmare | 146 (17,3) | 729 (8,1) |
| Insomnia | 80 (9,5) | 449 (5) |
| Abnormal dreams | 64 (7,6) | 588 (6,5) |
| Somnambulism | 18 (2,1) | 127 (1,4) |
| Middle insomnia | 15 (1,8) | 159 (1,8) |
| Poor quality sleep | 10 (1,2) | 187 (2,1) |
| Sleep terror | 9 (1,1) | 52 (0,6) |
| Sleep-related eating disorder | 4 (0,5) | 16 (0,2) |
| Initial insomnia | 4 (0,5) | 69 (0,8) |
| Hypnagogic hallucination | 3 (0,4) | 8 (0,1) |
| Sleep talking | 2 (0,2) | 10 (0,1) |
| Parasomnia | 2 (0,2) | 5 (0,1) |
| Abnormal sleep-related event | 2 (0,2) | 32 (0,4) |
| Sleep disorder | 1 (0,1) | 170 (1,9) |
| Therapeutic and nontherapeutic effects (excl toxicity) | Drug ineffective | 233 (27,6) | 2699 (30) |
| Therapeutic product effect incomplete | 33 (3,9) | 167 (1,9) |
| Therapeutic product effect delayed | 18 (2,1) | 51 (0,6) |
| Therapeutic product effect variable | 8 (0,9) | 10 (0,1) |
| Therapeutic product effect decreased | 8 (0,9) | 73 (0,8) |
| Drug intolerance | 5 (0,6) | 14 (0,2) |
| Drug interaction | 4 (0,5) | 41 (0,5) |
| Therapeutic response unexpected | 4 (0,5) | 35 (0,4) |
| Drug effect less than expected | 1 (0,1) | 9 (0,1) |
| Treatment failure | 1 (0,1) | 6 (0,1) |
| Drug withdrawal syndrome | 1 (0,1) | 4 (0) |
| Therapeutic response delayed | 1 (0,1) | 14 (0,2) |
| General system disorders NEC | Feeling abnormal | 64 (7,6) | 395 (4,4) |
| Fatigue | 45 (5,3) | 209 (2,3) |
| Hangover | 20 (2,4) | 63 (0,7) |
| Illness | 17 (2) | 10 (0,1) |
| Malaise | 12 (1,4) | 116 (1,3) |
| Asthenia | 6 (0,7) | 52 (0,6) |
| Feeling jittery | 6 (0,7) | 51 (0,6) |
| Energy increased | 5 (0,6) | 8 (0,1) |
| Crying | 5 (0,6) | 19 (0,2) |
| Concomitant disease aggravated | 4 (0,5) | - |
| Chest pain | 4 (0,5) | 30 (0,3) |
| Pain | 4 (0,5) | 51 (0,6) |
| Sluggishness | 4 (0,5) | 13 (0,1) |
| Discomfort | 3 (0,4) | 11 (0,1) |
| Condition aggravated | 3 (0,4) | 16 (0,2) |
| Screaming | 3 (0,4) | 12 (0,1) |
| Swelling face | 3 (0,4) | 11 (0,1) |
| Chills | 2 (0,2) | 19 (0,2) |
| Chest discomfort | 2 (0,2) | 21 (0,2) |
| Feeling cold | 2 (0,2) | 7 (0,1) |
| Peripheral swelling | 2 (0,2) | 7 (0,1) |
| Gait disturbance | 2 (0,2) | 35 (0,4) |
| Gait inability | 2 (0,2) | 4 (0) |
| Performance status decreased | 1 (0,1) | - |
| Influenza like illness | 1 (0,1) | 7 (0,1) |
| Swelling | 1 (0,1) | 3 (0) |
| Localised oedema | 1 (0,1) | (0) |
| Face oedema | 1 (0,1) | 1 (0) |
| Feeling drunk | 1 (0,1) | 16 (0,2) |
| Neurological disorders NEC | Somnolence | 55 (6,5) | 600 (6,7) |
| Dizziness | 29 (3,4) | 213 (2,4) |
| Lethargy | 8 (0,9) | 25 (0,3) |
| Restless legs syndrome | 7 (0,8) | 34 (0,4) |
| Hypoaesthesia | 6 (0,7) | 35 (0,4) |
| Sedation | 5 (0,6) | 36 (0,4) |
| Paraesthesia | 4 (0,5) | 34 (0,4) |
| Speech disorder | 2 (0,2) | 27 (0,3) |
| Dysgeusia | 2 (0,2) | 24 (0,3) |
| Balance disorder | 1 (0,1) | 23 (0,3) |
| Loss of consciousness | 1 (0,1) | 48 (0,5) |
| Ageusia | 1 (0,1) | 2 (0) |
| Head discomfort | 1 (0,1) | 26 (0,3) |
| Myoclonus | 1 (0,1) | 5 (0,1) |
| Neuralgia | 1 (0,1) | - |
| Burning sensation | 1 (0,1) | 10 (0,1) |
| Aphasia | 1 (0,1) | 15 (0,2) |
| Medication errors and other product use errors and issues | Inappropriate schedule of product administration | 48 (5,7) | 82 (0,9) |
| Wrong technique in product usage process | 35 (4,1) | 210 (2,3) |
| Product prescribing error | 8 (0,9) | 15 (0,2) |
| Product use issue | 4 (0,5) | 108 (1,2) |
| Product prescribing issue | 4 (0,5) | 13 (0,1) |
| Product dispensing error | 3 (0,4) | 2 (0) |
| Contraindicated product administered | 2 (0,2) | 9 (0,1) |
| Intercepted product dispensing error | 1 (0,1) | 1 (0) |
| Intercepted product prescribing error | 1 (0,1) | 1 (0) |
| Product storage error | 1 (0,1) | 22 (0,2) |
| Incorrect dose administered | 1 (0,1) | 39 (0,4) |
| Headaches | Headache | 59 (7) | 419 (4,7) |
| Migraine | 8 (0,9) | 38 (0,4) |
| Migraine with aura | 2 (0,2) | 1 (0) |
| Product quality, supply, distribution, manufacturing and quality system issues | Product availability issue | 51 (6) | 18 (0,2) |
| Product packaging difficult to open | 7 (0,8) | 13 (0,1) |
| Product taste abnormal | 2 (0,2) | 2 (0) |
| Product physical issue | 2 (0,2) | 3 (0) |
| Product container seal issue | 2 (0,2) | - |
| Product container issue | 2 (0,2) | 2 (0) |
| Product shape issue | 1 (0,1) | 1 (0) |
| Product after taste | 1 (0,1) | - |
| Product packaging issue | 1 (0,1) | 10 (0,1) |
| Product quality issue | 1 (0,1) | 67 (0,7) |
| Product colour issue | 1 (0,1) | 6 (0,1) |
| Disturbances in thinking and perception | Hallucination | 30 (3,6) | 317 (3,5) |
| Tachyphrenia | 5 (0,6) | 14 (0,2) |
| Hallucination, visual | 3 (0,4) | 19 (0,2) |
| Hallucination, auditory | 2 (0,2) | 25 (0,3) |
| Autoscopy | 2 (0,2) | 6 (0,1) |
| Bradyphrenia | 1 (0,1) | 1 (0) |
| Thinking abnormal | 1 (0,1) | 31 (0,3) |
| Delusion | 1 (0,1) | 6 (0,1) |
| Gastrointestinal signs and symptoms | Nausea | 23 (2,7) | 197 (2,2) |
| Abdominal discomfort | 8 (0,9) | 43 (0,5) |
| Vomiting | 7 (0,8) | 65 (0,7) |
| Abdominal pain upper | 5 (0,6) | 24 (0,3) |
| Abdominal pain | 1 (0,1) | 20 (0,2) |
| Abdominal distension | 1 (0,1) | 7 (0,1) |
| Dyspepsia | 1 (0,1) | 18 (0,2) |
| Dysphagia | 1 (0,1) | 22 (0,2) |
| Anxiety disorders and symptoms | Agitation | 16 (1,9) | 98 (1,1) |
| Anxiety | 14 (1,7) | 203 (2,3) |
| Nervousness | 5 (0,6) | 43 (0,5) |
| Panic attack | 3 (0,4) | 29 (0,3) |
| Fear | 1 (0,1) | 40 (0,4) |
| Phobia of driving | 1 (0,1) | 1 (0) |
| Stress | 1 (0,1) | 16 (0,2) |
| Epidermal and dermal conditions | Pruritus | 15 (1,8) | 63 (0,7) |
| Rash | 15 (1,8) | 68 (0,8) |
| Erythema | 4 (0,5) | 14 (0,2) |
| Skin irritation | 1 (0,1) | - |
| Skin odour abnormal | 1 (0,1) | 1 (0) |
| Rash papular | 1 (0,1) | 1 (0) |
| Psoriasis | 1 (0,1) | 2 (0) |
| Dermatitis contact | 1 (0,1) | - |
| Rash erythematous | 1 (0,1) | 4 (0) |
| Sleep disturbances (incl subtypes) | Sleep paralysis | 21 (2,5) | 278 (3,1) |
| Hypersomnia | 10 (1,2) | 38 (0,4) |
| Narcolepsy | 1 (0,1) | 8 (0,1) |
| Allergic conditions | Hypersensitivity | 29 (3,4) | 11 (0,1) |
| Drug hypersensitivity | 1 (0,1) | 22 (0,2) |
| Movement disorders (incl parkinsonism) | Tremor | 15 (1,8) | 75 (0,8) |
| Dyskinesia | 5 (0,6) | 17 (0,2) |
| Psychomotor hyperactivity | 3 (0,4) | 27 (0,3) |
| Bradykinesia | 1 (0,1) | - |
| Paralysis | 1 (0,1) | 43 (0,5) |
| Resting tremor | 1 (0,1) | - |
| Freezing phenomenon | 1 (0,1) | - |
| Depressed mood disorders and disturbances | Depression | 22 (2,6) | 101 (1,1) |
| Depressed mood | 3 (0,4) | 21 (0,2) |
| Depression suicidal | 2 (0,2) | 1 (0) |
| Overdoses and underdoses NEC | Intentional overdose | 17 (2) | 56 (0,6) |
| Prescribed overdose | 3 (0,4) | 21 (0,2) |
| Overdose | 3 (0,4) | 133 (1,5) |
| Prescribed underdose | 1 (0,1) | 7 (0,1) |
| Respiratory disorders NEC | Dyspnoea | 20 (2,4) | 102 (1,1) |
| Respiratory tract congestion | 1 (0,1) | - |
| Cough | 1 (0,1) | 28 (0,3) |
| Gastrointestinal motility and defaecation conditions | Diarrhoea | 15 (1,8) | 98 (1,1) |
| Constipation | 4 (0,5) | 23 (0,3) |
| Gastrooesophageal reflux disease | 1 (0,1) | 13 (0,1) |
| Diarrhoea haemorrhagic | 1 (0,1) | - |
| Irritable bowel syndrome | 1 (0,1) | - |
| Skin appendage conditions | Night sweats | 11 (1,3) | 30 (0,3) |
| Hyperhidrosis | 8 (0,9) | 48 (0,5) |
| Alopecia | 2 (0,2) | 1 (0) |
| Cardiac disorders, signs and symptoms NEC | Palpitations | 15 (1,8) | 99 (1,1) |
| Cardiac discomfort | 1 (0,1) | - |
| Suicidal and self-injurious behaviours NEC | Suicidal ideation | 13 (1,5) | 77 (0,9) |
| Suicide attempt | 2 (0,2) | 40 (0,4) |
| Completed suicide | 1 (0,1) | 35 (0,4) |
| Muscle disorders | Muscle spasms | 5 (0,6) | 34 (0,4) |
| Muscular weakness | 3 (0,4) | 53 (0,6) |
| Muscle twitching | 3 (0,4) | 12 (0,1) |
| Myalgia | 3 (0,4) | 32 (0,4) |
| Muscle rigidity | 1 (0,1) | 5 (0,1) |
| Salivary gland conditions | Dry mouth | 14 (1,7) | 65 (0,7) |
| Cardiac and vascular investigations (excl enzyme tests) | Heart rate increased | 5 (0,6) | 34 (0,4) |
| Blood pressure increased | 4 (0,5) | 30 (0,3) |
| Heart rate irregular | 1 (0,1) | 4 (0) |
| Blood pressure decreased | 1 (0,1) | 15 (0,2) |
| Deliria (incl confusion) | Confusional state | 7 (0,8) | 79 (0,9) |
| Delirium | 2 (0,2) | 89 (1) |
| Disorientation | 2 (0,2) | 31 (0,3) |
| Mood disorders and disturbances NEC | Irritability | 4 (0,5) | 38 (0,4) |
| Mood swings | 2 (0,2) | 3 (0) |
| Mood altered | 2 (0,2) | 14 (0,2) |
| Frustration tolerance decreased | 1 (0,1) | 10 (0,1) |
| Emotional distress | 1 (0,1) | 6 (0,1) |
| Euphoric mood | 1 (0,1) | 10 (0,1) |
| Changes in physical activity | Restlessness | 10 (1,2) | 53 (0,6) |
| Lifestyle issues | Loss of personal independence in daily activities | 7 (0,8) | 7 (0,1) |
| Impaired driving ability | 2 (0,2) | 8 (0,1) |
| Impaired work ability | 2 (0,2) | 5 (0,1) |
| Mental impairment disorders | Disturbance in attention | 5 (0,6) | 24 (0,3) |
| Memory impairment | 3 (0,4) | 73 (0,8) |
| Amnesia | 1 (0,1) | 60 (0,7) |
| Off label uses and intentional product misuses/use issues | Intentional product misuse | 3 (0,4) | 42 (0,5) |
| Off label use | 3 (0,4) | 38 (0,4) |
| Intentional dose omission | 2 (0,2) | 4 (0) |
| Intentional product use issue | 1 (0,1) | 21 (0,2) |
| Oral soft tissue conditions | Lip swelling | 3 (0,4) | 8 (0,1) |
| Stomatitis | 2 (0,2) | 2 (0) |
| Lip exfoliation | 1 (0,1) | - |
| Cheilitis | 1 (0,1) | - |
| Hypoaesthesia oral | 1 (0,1) | 8 (0,1) |
| Oral mucosal eruption | 1 (0,1) | - |
| Paraesthesia oral | 1 (0,1) | 4 (0) |
| Fatal outcomes | Death | 8 (0,9) | 39 (0,4) |
| Urinary tract signs and symptoms | Nocturia | 4 (0,5) | 14 (0,2) |
| Pollakiuria | 3 (0,4) | 22 (0,2) |
| Urinary incontinence | 1 (0,1) | 6 (0,1) |
| Injuries NEC | Fall | 4 (0,5) | 101 (1,1) |
| Concussion | 1 (0,1) | 9 (0,1) |
| Scratch | 1 (0,1) | 6 (0,1) |
| Gun shot wound | 1 (0,1) | 1 (0) |
| Accident at home | 1 (0,1) | - |
| Inner ear and VIIIth cranial nerve disorders | Vertigo | 5 (0,6) | 14 (0,2) |
| Vertigo positional | 1 (0,1) | - |
| Tinnitus | 1 (0,1) | 31 (0,3) |
| Musculoskeletal and connective tissue disorders NEC | Pain in extremity | 4 (0,5) | 37 (0,4) |
| Musculoskeletal stiffness | 1 (0,1) | 13 (0,1) |
| Musculoskeletal discomfort | 1 (0,1) | 3 (0) |
| Mobility decreased | 1 (0,1) | 6 (0,1) |
| Respiratory tract signs and symptoms | Throat tightness | 3 (0,4) | 8 (0,1) |
| Oropharyngeal pain | 1 (0,1) | 6 (0,1) |
| Snoring | 1 (0,1) | 1 (0) |
| Yawning | 1 (0,1) | 2 (0) |
| Throat irritation | 1 (0,1) | 2 (0) |
| Angioedema and urticaria | Urticaria | 6 (0,7) | 19 (0,2) |
| Eye disorders NEC | Eye swelling | 2 (0,2) | 3 (0) |
| Dry eye | 1 (0,1) | 6 (0,1) |
| Eye pain | 1 (0,1) | 10 (0,1) |
| Periorbital swelling | 1 (0,1) | 1 (0) |
| Ocular discomfort | 1 (0,1) | 1 (0) |
| Psychiatric and behavioural symptoms NEC | Hypervigilance | 5 (0,6) | 6 (0,1) |
| Abnormal behaviour | 1 (0,1) | 44 (0,5) |
| Viral infectious disorders | COVID-19 | 2 (0,2) | 5 (0,1) |
| Influenza | 2 (0,2) | 11 (0,1) |
| Gastroenteritis viral | 1 (0,1) | - |
| COVID-19 pneumonia | 1 (0,1) | 1 (0) |
| Appetite and general nutritional disorders | Decreased appetite | 4 (0,5) | 21 (0,2) |
| Increased appetite | 1 (0,1) | 8 (0,1) |
| Cardiac arrhythmias | Tachycardia | 4 (0,5) | 13 (0,1) |
| Arrhythmia | 1 (0,1) | 12 (0,1) |
| Infections - pathogen unspecified | Pneumonia | 2 (0,2) | 25 (0,3) |
| Sinusitis | 1 (0,1) | 5 (0,1) |
| Pharyngitis | 1 (0,1) | 1 (0) |
| Oral infection | 1 (0,1) | - |
| Infected skin ulcer | 1 (0,1) | - |
| Physical examination and organ system status topics | Weight increased | 3 (0,4) | 37 (0,4) |
| Body temperature increased | 2 (0,2) | 1 (0) |
| Vision disorders | Vision blurred | 2 (0,2) | 16 (0,2) |
| Photopsia | 1 (0,1) | 6 (0,1) |
| Visual impairment | 1 (0,1) | 16 (0,2) |
| Diplopia | 1 (0,1) | 2 (0) |
| Personality disorders and disturbances in behaviour | Paranoia | 2 (0,2) | 10 (0,1) |
| Aggression | 1 (0,1) | 27 (0,3) |
| Sexual dysfunctions, disturbances and gender identity disorders | Disturbance in sexual arousal | 2 (0,2) | - |
| Hypersexuality | 1 (0,1) | 1 (0) |
| Upper respiratory tract disorders (excl infections) | Nasal congestion | 1 (0,1) | 3 (0) |
| Epistaxis | 1 (0,1) | 7 (0,1) |
| Pharyngeal swelling | 1 (0,1) | - |
| Vascular disorders NEC | Hot flush | 3 (0,4) | 8 (0,1) |
| Cognitive and attention disorders and disturbances | Mental fatigue | 1 (0,1) | 1 (0) |
| Daydreaming | 1 (0,1) | 4 (0) |
| Hepatic and hepatobiliary disorders | Liver disorder | 1 (0,1) | 8 (0,1) |
| Hepatic pain | 1 (0,1) | 1 (0) |
| Seizures (incl subtypes) | Seizure | 1 (0,1) | 52 (0,6) |
| Seizure like phenomena | 1 (0,1) | 3 (0) |
| Therapeutic procedures and supportive care NEC | Interventional procedure | 1 (0,1) | - |
| Therapy interrupted | 1 (0,1) | - |
| Tongue conditions | Swollen tongue | 2 (0,2) | 11 (0,1) |
| Aural disorders NEC | Ear discomfort | 1 (0,1) | 1 (0) |
| Bone disorders (excl congenital and fractures) | Spinal disorder | 1 (0,1) | 3 (0) |
| Bronchial disorders (excl neoplasms) | Asthma | 1 (0,1) | 3 (0) |
| Central nervous system vascular disorders | Transient ischaemic attack | 1 (0,1) | 5 (0,1) |
| Cranial nerve disorders (excl neoplasms) | Parosmia | 1 (0,1) | 1 (0) |
| Cytogenetic investigations and genetic analyses | Gene mutation identification test positive | 1 (0,1) | - |
| Decreased and nonspecific blood pressure disorders and shock | Hypotension | 1 (0,1) | 8 (0,1) |
| Dental and gingival conditions | Noninfective gingivitis | 1 (0,1) | - |
| Gastrointestinal haemorrhages NEC | Rectal haemorrhage | 1 (0,1) | 2 (0) |
| Hearing disorders | Deafness | 1 (0,1) | 2 (0) |
| Joint disorders | Rheumatoid arthritis | 1 (0,1) | - |
| Joint swelling | 1 (0,1) | 1 (0) |
| Joint stiffness | 1 (0,1) | 2 (0) |
| Metabolic, nutritional and blood gas investigations | Blood glucose increased | 1 (0,1) | 9 (0,1) |
| Middle ear disorders (excl congenital) | Middle ear effusion | 1 (0,1) | (0) |
| Nervous system, skull and spine therapeutic procedures | Spinal operation | 1 (0,1) | 1 (0) |
| Ocular infections, irritations and inflammations | Eye pruritus | 1 (0,1) | 1 (0) |
| Ocular sensory symptoms NEC | Asthenopia | 1 (0,1) | 3 (0) |
| Prostatic disorders (excl infections and inflammations) | Prostatic disorder | 1 (0,1) | 2 (0) |
| Psychiatric disorders NEC | Mental disorder | 1 (0,1) | 22 (0,2) |
| Renal disorders (excl nephropathies) | Renal disorder | 1 (0,1) | 3 (0) |
| Skin vascular abnormalities | Skin haemorrhage | 1 (0,1) | 1 (0) |
| Toxicology and therapeutic drug monitoring | Drug screen false positive | 1 (0,1) | 3 (0) |
| Urolithiases | Nephrolithiasis | 1 (0,1) | 3 (0) |
| Vulvovaginal disorders (excl infections and inflammations) | Vaginal disorder | 1 (0,1) | - |
| Vulvovaginal dryness | 1 (0,1) | 1 (0) |

a*ICSR: Individual Case Safety Report*

**Table S3:** Disproportionality analysis at Preferred Terms level for each High-Level Group Term observed in daridorexant-related ICSRs

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| High Level Group Term (HLGT) | Preferred Term (PT) | Daridorexant ICSRsa | Daridorexant VS RG1b  ROR [95%CI] | Daridorexant VS RG2c  ROR [95%CI] |
| Sleep disorders and disturbances | Hypnagogic hallucination | 3 | 267,22 [85,32 - 836,95] | 4 [1,06 - 15,1] |
| Nightmare | 146 | 113,74 [95,13 - 136] | 2,35 [1,93 - 2,85] |
| Sleep-related eating disorder | 4 | 113,13 [42,23 - 303,02] | 2,67 [0,89 - 7,99] |
| Parasomnia | 2 | 78,95 [19,66 - 317,15] | 4,26 [0,83 - 22] |
| Sleep terror | 9 | 61,64 [31,93 - 119,02] | 1,85 [0,91 - 3,77] |
| Somnambulism | 18 | 56,94 [35,67 - 90,9] | 1,51 [0,91 - 2,48] |
| Abnormal dreams | 64 | 52,79 [40,9 - 68,13] | 1,16 [0,89 - 1,52] |
| Abnormal sleep-related event | 2 | 33,14 [8,26 - 132,9] | 0,66 [0,16 - 2,77] |
| Sleep talking | 2 | 27,46 [6,85 - 110,11] | 2,13 [0,47 - 9,74] |
| Middle insomnia | 15 | 19,82 [11,89 - 33,03] | 0,98 [0,58 - 1,68] |
| Poor quality sleep | 10 | 11,51 [6,17 - 21,48] | 0,55 [0,29 - 1,04] |
| Initial insomnia | 4 | 9,91 [3,71 - 26,46] | 0,6 [0,22 - 1,64] |
| Insomnia | 80 | 7,41 [5,88 - 9,33] | 1,94 [1,51 - 2,49] |
| Sleep disorder | 1 | 0,36 [0,05 - 2,57] | 0,06 [0,01 - 0,43] |
| Sleep disturbances (incl subtypes) | Sleep paralysis | 21 | 389,34 [251,39 - 602,97] | 0,8 [0,51 - 1,25] |
| Narcolepsy | 1 | 12,11 [1,7 - 86,1] | 1,18 [0,15 - 9,34] |
| Hypersomnia | 10 | 8,29 [4,44 - 15,47] | 2,82 [1,4 - 5,68] |
| Disturbances in thinking and perception | Autoscopy | 2 | 111,01 [27,6 - 446,44] | 3,55 [0,72 - 17,62] |
| Tachyphrenia | 5 | 33,02 [13,7 - 79,61] | 3,56 [1,29 - 9,82] |
| Hallucination | 30 | 10,3 [7,15 - 14,83] | 1 [0,68 - 1,46] |
| Hallucination, visual | 3 | 3,79 [1,22 - 11,77] | 1,6 [0,47 - 5,39] |
| Bradyphrenia | 1 | 3,36 [0,47 - 23,89] | 10,65 [0,67 - 170,36] |
| Hallucination, auditory | 2 | 3,06 [0,76 - 12,26] | 0,79 [0,19 - 3,32] |
| Delusion | 1 | 1,62 [0,23 - 11,54] | 1,52 [0,19 - 12,37] |
| Thinking abnormal | 1 | 1,16 [0,16 - 8,23] | 0,34 [0,05 - 2,51] |
| Therapeutic and nontherapeutic effects (excl toxicity) | Therapeutic product effect delayed | 18 | 46,84 [29,34 - 74,75] | 3,74 [2,18 - 6,42] |
| Therapeutic product effect variable | 8 | 43,43 [21,63 - 87,2] | 8,58 [3,38 - 21,8] |
| Therapeutic response delayed | 1 | 8,28 [1,16 - 58,87] | 0,76 [0,1 - 5,78] |
| Therapeutic product effect incomplete | 33 | 7,95 [5,61 - 11,26] | 2,12 [1,45 - 3,1] |
| Drug ineffective | 233 | 5,59 [4,81 - 6,5] | 0,87 [0,74 - 1,02] |
| Drug effect less than expected | 1 | 4,57 [0,64 - 32,5] | 0,97 [0,12 - 7,5] |
| Therapeutic response unexpected | 4 | 1,8 [0,67 - 4,81] | 1,15 [0,41 - 3,24] |
| Therapeutic product effect decreased | 8 | 1,78 [0,89 - 3,57] | 1,15 [0,55 - 2,4] |
| Drug intolerance | 5 | 1,33 [0,55 - 3,21] | 3,56 [1,29 - 9,82] |
| Drug interaction | 4 | 0,7 [0,26 - 1,88] | 0,99 [0,35 - 2,76] |
| Treatment failure | 1 | 0,36 [0,05 - 2,54] | 1,77 [0,21 - 14,75] |
| Drug withdrawal syndrome | 1 | 0,23 [0,03 - 1,6] | 2,66 [0,3 - 23,83] |
| Changes in physical activity | Restlessness | 10 | 6,33 [3,4 - 11,82] | 2,02 [1,02 - 3,98] |
| Middle ear disorders (excl congenital) | Middle ear effusion | 1 | 10,84 [1,52 - 77,1] | - |
| Product quality, supply, distribution, manufacturing and quality system issues | Product packaging difficult to open | 7 | 104,91 [49,76 - 221,2] | 5,35 [2,15 - 13,3] |
| Product availability issue | 51 | 97,47 [73,39 - 129,45] | 32 [18,61 - 55,04] |
| Product after taste | 1 | 55,44 [7,78 - 395,19] | - |
| Product container seal issue | 2 | 41,78 [10,42 - 167,6] | - |
| Product shape issue | 1 | 24,03 [3,38 - 170,98] | 5,32 [0,48 - 58,76] |
| Product container issue | 2 | 6,21 [1,55 - 24,87] | 7,1 [1,19 - 42,58] |
| Product colour issue | 1 | 5,35 [0,75 - 38,02] | 1,77 [0,21 - 14,75] |
| Product taste abnormal | 2 | 3,54 [0,88 - 14,19] | 10,66 [1,5 - 75,76] |
| Product packaging issue | 1 | 2,7 [0,38 - 19,19] | 1,06 [0,14 - 8,32] |
| Product physical issue | 2 | 2,43 [0,61 - 9,74] | 7,1 [1,19 - 42,58] |
| Product quality issue | 1 | 0,15 [0,02 - 1,08] | 0,16 [0,02 - 1,12] |
| Salivary gland conditions | Dry mouth | 14 | 4,17 [2,46 - 7,07] | 2,31 [1,29 - 4,14] |
| Headaches | Migraine with aura | 2 | 16,56 [4,13 - 66,38] | 21,32 [1,93 - 235,34] |
| Headache | 59 | 2,27 [1,74 - 2,95] | 1,52 [1,15 - 2,01] |
| Migraine | 8 | 2,05 [1,02 - 4,12] | 2,25 [1,05 - 4,84] |
| Cognitive and attention disorders and disturbances | Mental fatigue | 1 | 20,68 [2,91 - 147,15] | 10,65 [0,67 - 170,36] |
| Daydreaming | 1 | 14,73 [2,07 - 104,75] | 2,66 [0,3 - 23,83] |
| Sexual dysfunctions, disturbances and gender identity disorders | Disturbance in sexual arousal | 2 | 50,12 [12,49 - 201,1] | - |
| Hypersexuality | 1 | 14,23 [2 - 101,22] | 10,65 [0,67 - 170,36] |
| Psychiatric and behavioural symptoms NEC | Hypervigilance | 5 | 124,4 [51,49 - 300,53] | 8,91 [2,71 - 29,25] |
| Abnormal behaviour | 1 | 0,53 [0,08 - 3,8] | 0,23 [0,03 - 1,67] |
| Anxiety disorders and symptoms | Phobia of driving | 1 | 145,1 [20,26 - 1039,18] | 10,65 [0,67 - 170,36] |
| Agitation | 16 | 5,06 [3,09 - 8,3] | 1,72 [1,01 - 2,92] |
| Nervousness | 5 | 2,02 [0,84 - 4,87] | 1,24 [0,49 - 3,13] |
| Panic attack | 3 | 1,88 [0,6 - 5,83] | 1,1 [0,33 - 3,62] |
| Anxiety | 14 | 1,1 [0,65 - 1,86] | 0,72 [0,42 - 1,24] |
| Fear | 1 | 0,76 [0,11 - 5,4] | 0,25 [0,03 - 1,84] |
| Stress | 1 | 0,33 [0,05 - 2,32] | 0,63 [0,08 - 4,7] |
| Depressed mood disorders and disturbances | Depression suicidal | 2 | 13,3 [3,32 - 53,31] | 21,32 [1,93 - 235,34] |
| Depression | 22 | 2,13 [1,39 - 3,25] | 2,31 [1,45 - 3,67] |
| Depressed mood | 3 | 1,36 [0,44 - 4,24] | 1,45 [0,43 - 4,86] |
| Suicidal and self-injurious behaviours NEC | Suicidal ideation | 13 | 3,3 [1,91 - 5,7] | 1,7 [0,94 - 3,06] |
| Suicide attempt | 2 | 0,84 [0,21 - 3,38] | 0,47 [0,11 - 1,95] |
| Completed suicide | 1 | 0,37 [0,05 - 2,63] | 0,29 [0,04 - 2,09] |
| Neurological disorders NEC | Restless legs syndrome | 7 | 8,81 [4,19 - 18,54] | 2,14 [0,95 - 4,82] |
| Somnolence | 55 | 6,88 [5,23 - 9,04] | 0,95 [0,71 - 1,26] |
| Sedation | 5 | 5,18 [2,15 - 12,47] | 1,37 [0,54 - 3,47] |
| Lethargy | 8 | 3,27 [1,63 - 6,57] | 3,43 [1,54 - 7,62] |
| Myoclonus | 1 | 2,36 [0,33 - 16,75] | 1,52 [0,19 - 12,37] |
| Head discomfort | 1 | 1,41 [0,2 - 10] | 0,41 [0,06 - 3,01] |
| Dizziness | 29 | 1,36 [0,94 - 1,97] | 1,45 [0,98 - 2,15] |
| Neuralgia | 1 | 0,99 [0,14 - 7,06] | - |
| Ageusia | 1 | 0,91 [0,13 - 6,5] | 5,32 [0,48 - 58,76] |
| Hypoaesthesia | 6 | 0,9 [0,4 - 2,02] | 1,83 [0,77 - 4,36] |
| Speech disorder | 2 | 0,87 [0,22 - 3,47] | 0,79 [0,19 - 3,32] |
| Aphasia | 1 | 0,75 [0,11 - 5,36] | 0,71 [0,09 - 5,37] |
| Dysgeusia | 2 | 0,58 [0,15 - 2,34] | 0,89 [0,21 - 3,76] |
| Paraesthesia | 4 | 0,56 [0,21 - 1,51] | 1,22 [0,43 - 3,43] |
| Burning sensation | 1 | 0,32 [0,04 - 2,27] | 1,06 [0,14 - 8,32] |
| Balance disorder | 1 | 0,26 [0,04 - 1,84] | 0,46 [0,06 - 3,42] |
| Loss of consciousness | 1 | 0,18 [0,03 - 1,28] | 0,22 [0,03 - 1,57] |
| Movement disorders (incl parkinsonism) | Resting tremor | 1 | 51,02 [7,16 - 363,62] | - |
| Freezing phenomenon | 1 | 7,91 [1,11 - 56,26] | - |
| Bradykinesia | 1 | 5,04 [0,71 - 35,81] | - |
| Psychomotor hyperactivity | 3 | 4,04 [1,3 - 12,55] | 1,18 [0,36 - 3,91] |
| Dyskinesia | 5 | 2,88 [1,2 - 6,94] | 3,14 [1,16 - 8,53] |
| Tremor | 15 | 2,07 [1,24 - 3,45] | 2,15 [1,23 - 3,76] |
| Paralysis | 1 | 1,6 [0,23 - 11,39] | 0,25 [0,03 - 1,79] |
| Inner ear and VIIIth cranial nerve disorders | Vertigo positional | 1 | 13,24 [1,86 - 94,14] | - |
| Vertigo | 5 | 1,86 [0,77 - 4,49] | 3,81 [1,37 - 10,62] |
| Tinnitus | 1 | 0,51 [0,07 - 3,61] | 0,32 [0,04 - 2,35] |
| Cardiac disorders, signs and symptoms NEC | Cardiac discomfort | 1 | 12,15 [1,71 - 86,44] | - |
| Palpitations | 15 | 3,01 [1,8 - 5,01] | 1,61 [0,93 - 2,78] |
| Overdoses and underdoses NEC | Intentional overdose | 17 | 7,73 [4,78 - 12,5] | 2,82 [1,64 - 4,83] |
| Prescribed overdose | 3 | 3,77 [1,21 - 11,72] | 1,52 [0,45 - 5,11] |
| Prescribed underdose | 1 | 1,25 [0,18 - 8,85] | 1,52 [0,19 - 12,37] |
| Overdose | 3 | 0,34 [0,11 - 1,05] | 0,23 [0,07 - 0,72] |
| Allergic conditions | Hypersensitivity | 29 | 3,78 [2,61 - 5,47] | 24,53 [12,7 - 47,37] |
| Drug hypersensitivity | 1 | 0,12 [0,02 - 0,82] | 0,44 [0,06 - 3,27] |
| Prostatic disorders (excl infections and inflammations) | Prostatic disorder | 1 | 3,85 [0,54 - 27,36] | 5,32 [0,48 - 58,76] |
| General system disorders NEC | Hangover | 20 | 127,92 [81,98 - 199,62] | 3,38 [2,04 - 5,61] |
| Energy increased | 5 | 18,7 [7,76 - 45,06] | 6,68 [2,18 - 20,47] |
| Concomitant disease aggravated | 4 | 15,43 [5,78 - 41,23] | - |
| Screaming | 3 | 10,74 [3,46 - 33,39] | 2,66 [0,75 - 9,46] |
| Sluggishness | 4 | 9,02 [3,38 - 24,09] | 3,05 [1 - 9,28] |
| Illness | 17 | 7,19 [4,44 - 11,62] | 18,43 [8,41 - 40,38] |
| Feeling jittery | 6 | 6,89 [3,08 - 15,37] | 1,25 [0,54 - 2,93] |
| Feeling abnormal | 64 | 6,19 [4,8 - 7,99] | 1,75 [1,33 - 2,29] |
| Performance status decreased | 1 | 5,04 [0,71 - 35,83] | - |
| Localised oedema | 1 | 4,89 [0,69 - 34,75] | - |
| Crying | 5 | 2,95 [1,22 - 7,1] | 2,67 [1 - 7,13] |
| Feeling drunk | 1 | 2,93 [0,41 - 20,83] | 0,59 [0,08 - 4,43] |
| Feeling cold | 2 | 1,63 [0,41 - 6,52] | 3,04 [0,63 - 14,67] |
| Fatigue | 45 | 1,41 [1,05 - 1,91] | 2,28 [1,64 - 3,17] |
| Face oedema | 1 | 1,36 [0,19 - 9,7] | 10,65 [0,67 - 170,36] |
| Discomfort | 3 | 1,16 [0,37 - 3,6] | 2,91 [0,81 - 10,44] |
| Swelling face | 3 | 1,06 [0,34 - 3,3] | 2,91 [0,81 - 10,44] |
| Gait inability | 2 | 0,81 [0,2 - 3,24] | 5,33 [0,97 - 29,13] |
| Malaise | 12 | 0,61 [0,34 - 1,07] | 1,07 [0,59 - 1,95] |
| Chest pain | 4 | 0,48 [0,18 - 1,28] | 1,29 [0,46 - 3,65] |
| Chest discomfort | 2 | 0,46 [0,12 - 1,86] | 0,92 [0,22 - 3,93] |
| Chills | 2 | 0,39 [0,1 - 1,57] | 1,12 [0,26 - 4,82] |
| Asthenia | 6 | 0,37 [0,17 - 0,83] | 1,16 [0,5 - 2,71] |
| Peripheral swelling | 2 | 0,32 [0,08 - 1,29] | 3,04 [0,63 - 14,67] |
| Condition aggravated | 3 | 0,27 [0,09 - 0,83] | 1,88 [0,55 - 6,43] |
| Influenza like illness | 1 | 0,26 [0,04 - 1,86] | 1,52 [0,19 - 12,37] |
| Gait disturbance | 2 | 0,23 [0,06 - 0,92] | 0,57 [0,14 - 2,39] |
| Swelling | 1 | 0,2 [0,03 - 1,46] | 3,55 [0,37 - 34,15] |
| Pain | 4 | 0,14 [0,05 - 0,38] | 0,82 [0,29 - 2,26] |
| Lifestyle issues | Impaired driving ability | 2 | 3,94 [0,98 - 15,77] | 2,66 [0,56 - 12,56] |
| Loss of personal independence in daily activities | 7 | 2,47 [1,17 - 5,19] | 10,71 [3,75 - 30,62] |
| Impaired work ability | 2 | 2,04 [0,51 - 8,16] | 4,26 [0,83 - 22] |
| Deliria (incl confusion) | Delirium | 2 | 1,63 [0,41 - 6,54] | 0,23 [0,06 - 0,95] |
| Disorientation | 2 | 1,13 [0,28 - 4,52] | 0,66 [0,16 - 2,77] |
| Confusional state | 7 | 1,01 [0,48 - 2,12] | 0,93 [0,43 - 2,02] |
| Medication errors and other product use errors and issues | Intercepted product prescribing error | 1 | 15,59 [2,19 - 110,92] | 10,65 [0,67 - 170,36] |
| Product prescribing issue | 4 | 9,53 [3,57 - 25,46] | 3,28 [1,07 - 10,09] |
| Intercepted product dispensing error | 1 | 8,41 [1,18 - 59,8] | 10,65 [0,67 - 170,36] |
| Inappropriate schedule of product administration | 48 | 5,47 [4,08 - 7,32] | 6,31 [4,39 - 9,05] |
| Product prescribing error | 8 | 4,36 [2,18 - 8,76] | 5,72 [2,42 - 13,52] |
| Wrong technique in product usage process | 35 | 3,7 [2,64 - 5,19] | 1,78 [1,24 - 2,56] |
| Product dispensing error | 3 | 1,96 [0,63 - 6,1] | 8 [1,79 - 35,81] |
| Contraindicated product administered | 2 | 1,72 [0,43 - 6,9] | 2,37 [0,51 - 10,97] |
| Product use issue | 4 | 0,55 [0,21 - 1,48] | 0,37 [0,14 - 1] |
| Product storage error | 1 | 0,32 [0,04 - 2,24] | 0,48 [0,06 - 3,59] |
| Incorrect dose administered | 1 | 0,13 [0,02 - 0,89] | 0,26 [0,04 - 1,88] |
| Nervous system, skull and spine therapeutic procedures | Spinal operation | 1 | 2,45 [0,34 - 17,43] | 10,65 [0,67 - 170,36] |
| Oral soft tissue conditions | Lip exfoliation | 1 | 17,74 [2,49 - 126,19] | - |
| Oral mucosal eruption | 1 | 15,95 [2,24 - 113,49] | - |
| Cheilitis | 1 | 4,2 [0,59 - 29,88] | - |
| Lip swelling | 3 | 2,1 [0,68 - 6,53] | 4 [1,06 - 15,1] |
| Paraesthesia oral | 1 | 1,66 [0,23 - 11,8] | 2,66 [0,3 - 23,83] |
| Hypoaesthesia oral | 1 | 1,51 [0,21 - 10,74] | 1,33 [0,17 - 10,64] |
| Stomatitis | 2 | 0,83 [0,21 - 3,31] | 10,66 [1,5 - 75,76] |
| Skin appendage conditions | Night sweats | 11 | 8,48 [4,68 - 15,38] | 3,94 [1,97 - 7,89] |
| Hyperhidrosis | 8 | 1,41 [0,7 - 2,82] | 1,78 [0,84 - 3,77] |
| Alopecia | 2 | 0,23 [0,06 - 0,92] | 10,66 [1,5 - 75,76] |
| Cytogenetic investigations and genetic analyses | Gene mutation identification test positive | 1 | 58,4 [8,19 - 416,38] | - |
| Ocular sensory symptoms NEC | Asthenopia | 1 | 4,44 [0,62 - 31,57] | 3,55 [0,37 - 34,15] |
| Eye disorders NEC | Periorbital swelling | 1 | 6,98 [0,98 - 49,62] | 10,65 [0,67 - 170,36] |
| Ocular discomfort | 1 | 2,74 [0,39 - 19,49] | 10,65 [0,67 - 170,36] |
| Eye swelling | 2 | 1,27 [0,32 - 5,11] | 7,1 [1,19 - 42,58] |
| Dry eye | 1 | 0,59 [0,08 - 4,2] | 1,77 [0,21 - 14,75] |
| Eye pain | 1 | 0,47 [0,07 - 3,34] | 1,06 [0,14 - 8,32] |
| Urinary tract signs and symptoms | Nocturia | 4 | 8,13 [3,04 - 21,72] | 3,05 [1 - 9,28] |
| Pollakiuria | 3 | 1,66 [0,53 - 5,16] | 1,45 [0,43 - 4,86] |
| Urinary incontinence | 1 | 0,78 [0,11 - 5,52] | 1,77 [0,21 - 14,75] |
| Mood disorders and disturbances NEC | Euphoric mood | 1 | 2,08 [0,29 - 14,79] | 1,06 [0,14 - 8,32] |
| Frustration tolerance decreased | 1 | 1,96 [0,28 - 13,94] | 1,06 [0,14 - 8,32] |
| Mood altered | 2 | 1,71 [0,43 - 6,86] | 1,52 [0,34 - 6,7] |
| Irritability | 4 | 1,49 [0,56 - 3,97] | 1,06 [0,38 - 2,98] |
| Mood swings | 2 | 1,36 [0,34 - 5,45] | 7,1 [1,19 - 42,58] |
| Emotional distress | 1 | 0,16 [0,02 - 1,16] | 1,77 [0,21 - 14,75] |
| Angioedema and urticaria | Urticaria | 6 | 0,88 [0,39 - 1,96] | 3,38 [1,34 - 8,47] |
| Personality disorders and disturbances in behaviour | Paranoia | 2 | 2,62 [0,65 - 10,48] | 2,13 [0,47 - 9,74] |
| Aggression | 1 | 0,45 [0,06 - 3,18] | 0,39 [0,05 - 2,9] |
| Mental impairment disorders | Disturbance in attention | 5 | 2,11 [0,87 - 5,07] | 2,22 [0,85 - 5,84] |
| Memory impairment | 3 | 0,5 [0,16 - 1,55] | 0,42 [0,13 - 1,35] |
| Amnesia | 1 | 0,34 [0,05 - 2,39] | 0,17 [0,02 - 1,21] |
| Tongue conditions | Swollen tongue | 2 | 1,43 [0,36 - 5,72] | 1,94 [0,43 - 8,75] |
| Muscle disorders | Muscle twitching | 3 | 2,98 [0,96 - 9,27] | 2,66 [0,75 - 9,46] |
| Muscle rigidity | 1 | 2,12 [0,3 - 15,05] | 2,13 [0,25 - 18,24] |
| Muscular weakness | 3 | 0,62 [0,2 - 1,92] | 0,59 [0,18 - 1,89] |
| Muscle spasms | 5 | 0,61 [0,25 - 1,47] | 1,57 [0,61 - 4,02] |
| Myalgia | 3 | 0,41 [0,13 - 1,27] | 1 [0,3 - 3,26] |
| Cardiac and vascular investigations (excl enzyme tests) | Heart rate increased | 5 | 1,18 [0,49 - 2,84] | 1,57 [0,61 - 4,02] |
| Heart rate irregular | 1 | 0,94 [0,13 - 6,69] | 2,66 [0,3 - 23,83] |
| Blood pressure increased | 4 | 0,6 [0,23 - 1,61] | 1,42 [0,5 - 4,04] |
| Blood pressure decreased | 1 | 0,35 [0,05 - 2,49] | 0,71 [0,09 - 5,37] |
| Gastrointestinal signs and symptoms | Abdominal discomfort | 8 | 1,1 [0,55 - 2,21] | 1,99 [0,93 - 4,24] |
| Nausea | 23 | 0,68 [0,45 - 1,03] | 1,24 [0,8 - 1,91] |
| Abdominal pain upper | 5 | 0,57 [0,24 - 1,38] | 2,22 [0,85 - 5,84] |
| Vomiting | 7 | 0,35 [0,17 - 0,75] | 1,08 [0,49 - 2,36] |
| Dysphagia | 1 | 0,24 [0,03 - 1,7] | 0,48 [0,06 - 3,59] |
| Dyspepsia | 1 | 0,24 [0,03 - 1,7] | 0,59 [0,08 - 4,43] |
| Abdominal distension | 1 | 0,23 [0,03 - 1,63] | 1,52 [0,19 - 12,37] |
| Abdominal pain | 1 | 0,1 [0,01 - 0,72] | 0,53 [0,07 - 3,96] |
| Aural disorders NEC | Ear discomfort | 1 | 2,31 [0,33 - 16,44] | 10,65 [0,67 - 170,36] |
| Gastrointestinal motility and defaecation conditions | Diarrhoea haemorrhagic | 1 | 2,54 [0,36 - 18,03] | - |
| Irritable bowel syndrome | 1 | 1,16 [0,16 - 8,24] | - |
| Diarrhoea | 15 | 0,57 [0,34 - 0,94] | 1,64 [0,95 - 2,84] |
| Constipation | 4 | 0,46 [0,17 - 1,22] | 1,85 [0,64 - 5,37] |
| Gastrooesophageal reflux disease | 1 | 0,28 [0,04 - 2,02] | 0,82 [0,11 - 6,26] |
| Epidermal and dermal conditions | Skin odour abnormal | 1 | 5,75 [0,81 - 40,88] | 10,65 [0,67 - 170,36] |
| Dermatitis contact | 1 | 2,16 [0,3 - 15,33] | - |
| Rash papular | 1 | 0,99 [0,14 - 7,06] | 10,65 [0,67 - 170,36] |
| Pruritus | 15 | 0,97 [0,58 - 1,62] | 2,52 [1,43 - 4,44] |
| Rash | 15 | 0,79 [0,47 - 1,32] | 2,34 [1,33 - 4,1] |
| Rash erythematous | 1 | 0,58 [0,08 - 4,1] | 2,66 [0,3 - 23,83] |
| Skin irritation | 1 | 0,48 [0,07 - 3,41] | - |
| Erythema | 4 | 0,44 [0,16 - 1,17] | 3,05 [1 - 9,28] |
| Psoriasis | 1 | 0,18 [0,02 - 1,25] | 5,32 [0,48 - 58,76] |
| Urolithiases | Nephrolithiasis | 1 | 0,53 [0,07 - 3,76] | 3,55 [0,37 - 34,15] |
| Respiratory disorders NEC | Respiratory tract congestion | 1 | 1,5 [0,21 - 10,68] | - |
| Dyspnoea | 20 | 0,82 [0,53 - 1,28] | 2,11 [1,3 - 3,43] |
| Cough | 1 | 0,09 [0,01 - 0,61] | 0,38 [0,05 - 2,79] |
| Skin vascular abnormalities | Skin haemorrhage | 1 | 2,01 [0,28 - 14,32] | 10,65 [0,67 - 170,36] |
| Respiratory tract signs and symptoms | Yawning | 1 | 8,43 [1,19 - 59,94] | 5,32 [0,48 - 58,76] |
| Snoring | 1 | 6,2 [0,87 - 44,08] | 10,65 [0,67 - 170,36] |
| Throat tightness | 3 | 2,55 [0,82 - 7,93] | 4 [1,06 - 15,1] |
| Throat irritation | 1 | 0,54 [0,08 - 3,8] | 5,32 [0,48 - 58,76] |
| Oropharyngeal pain | 1 | 0,25 [0,04 - 1,81] | 1,77 [0,21 - 14,75] |
| Cranial nerve disorders (excl neoplasms) | Parosmia | 1 | 3,1 [0,44 - 22,02] | 10,65 [0,67 - 170,36] |
| Toxicology and therapeutic drug monitoring | Drug screen false positive | 1 | 7,49 [1,05 - 53,26] | 3,55 [0,37 - 34,15] |
| Appetite and general nutritional disorders | Increased appetite | 1 | 1,42 [0,2 - 10,1] | 1,33 [0,17 - 10,64] |
| Decreased appetite | 4 | 0,39 [0,15 - 1,05] | 2,03 [0,7 - 5,93] |
| Vulvovaginal disorders (excl infections and inflammations) | Vaginal disorder | 1 | 22,57 [3,17 - 160,58] | - |
| Vulvovaginal dryness | 1 | 7,13 [1 - 50,72] | 10,65 [0,67 - 170,36] |
| Upper respiratory tract disorders (excl infections) | Pharyngeal swelling | 1 | 3,3 [0,46 - 23,44] | - |
| Nasal congestion | 1 | 0,42 [0,06 - 3,01] | 3,55 [0,37 - 34,15] |
| Epistaxis | 1 | 0,31 [0,04 - 2,19] | 1,52 [0,19 - 12,37] |
| Viral infectious disorders | COVID-19 pneumonia | 1 | 2,61 [0,37 - 18,57] | 10,65 [0,67 - 170,36] |
| Gastroenteritis viral | 1 | 1,36 [0,19 - 9,65] | - |
| Influenza | 2 | 0,45 [0,11 - 1,81] | 1,94 [0,43 - 8,75] |
| COVID-19 | 2 | 0,34 [0,08 - 1,34] | 2,66 [0,56 - 12,56] |
| Hearing disorders | Deafness | 1 | 0,93 [0,13 - 6,63] | 5,32 [0,48 - 58,76] |
| Vascular disorders NEC | Hot flush | 3 | 1 [0,32 - 3,11] | 4 [1,06 - 15,1] |
| Off label uses and intentional product misuses/use issues | Intentional dose omission | 2 | 3,45 [0,86 - 13,81] | 4,26 [0,83 - 22] |
| Intentional product misuse | 3 | 0,64 [0,2 - 1,97] | 0,76 [0,23 - 2,45] |
| Intentional product use issue | 1 | 0,32 [0,04 - 2,26] | 0,51 [0,07 - 3,77] |
| Off label use | 3 | 0,11 [0,03 - 0,33] | 0,78 [0,24 - 2,52] |
| Vision disorders | Photopsia | 1 | 3,57 [0,5 - 25,41] | 1,77 [0,21 - 14,75] |
| Diplopia | 1 | 0,94 [0,13 - 6,65] | 5,32 [0,48 - 58,76] |
| Vision blurred | 2 | 0,34 [0,09 - 1,38] | 1,33 [0,31 - 5,79] |
| Visual impairment | 1 | 0,19 [0,03 - 1,34] | 0,66 [0,09 - 5,02] |
| Cardiac arrhythmias | Tachycardia | 4 | 1,13 [0,42 - 3,01] | 3,28 [1,07 - 10,09] |
| Arrhythmia | 1 | 0,48 [0,07 - 3,44] | 0,82 [0,11 - 6,26] |
| Fatal outcomes | Death | 8 | 0,22 [0,11 - 0,44] | 2,04 [0,95 - 4,35] |
| Dental and gingival conditions | Noninfective gingivitis | 1 | 16,11 [2,26 - 114,58] | - |
| Injuries NEC | Accident at home | 1 | 45,52 [6,39 - 324,31] | - |
| Gun shot wound | 1 | 10,83 [1,52 - 77,01] | 10,65 [0,67 - 170,36] |
| Concussion | 1 | 3,05 [0,43 - 21,66] | 0,97 [0,12 - 7,5] |
| Scratch | 1 | 2,71 [0,38 - 19,27] | 1,77 [0,21 - 14,75] |
| Fall | 4 | 0,28 [0,1 - 0,74] | 0,41 [0,15 - 1,12] |
| Physical examination and organ system status topics | Body temperature increased | 2 | 2,2 [0,55 - 8,81] | 21,32 [1,93 - 235,34] |
| Weight increased | 3 | 0,32 [0,1 - 0,98] | 0,86 [0,27 - 2,8] |
| Musculoskeletal and connective tissue disorders NEC | Musculoskeletal discomfort | 1 | 1,35 [0,19 - 9,59] | 3,55 [0,37 - 34,15] |
| Mobility decreased | 1 | 0,33 [0,05 - 2,35] | 1,77 [0,21 - 14,75] |
| Pain in extremity | 4 | 0,3 [0,11 - 0,8] | 1,12 [0,4 - 3,15] |
| Musculoskeletal stiffness | 1 | 0,26 [0,04 - 1,88] | 0,82 [0,11 - 6,26] |
| Seizures (incl subtypes) | Seizure like phenomena | 1 | 16,51 [2,32 - 117,43] | 3,55 [0,37 - 34,15] |
| Seizure | 1 | 0,14 [0,02 - 0,98] | 0,2 [0,03 - 1,47] |
| Hepatic and hepatobiliary disorders | Hepatic pain | 1 | 5,36 [0,75 - 38,11] | 10,65 [0,67 - 170,36] |
| Liver disorder | 1 | 0,55 [0,08 - 3,92] | 1,33 [0,17 - 10,64] |
| Ocular infections, irritations and inflammations | Eye pruritus | 1 | 0,85 [0,12 - 6,06] | 10,65 [0,67 - 170,36] |
| Therapeutic procedures and supportive care NEC | Interventional procedure | 1 | 357,16 [49,32 - 2586,57] | - |
| Therapy interrupted | 1 | 0,64 [0,09 - 4,54] | - |
| Bronchial disorders (excl neoplasms) | Asthma | 1 | 0,24 [0,03 - 1,68] | 3,55 [0,37 - 34,15] |
| Bone disorders (excl congenital and fractures) | Spinal disorder | 1 | 2,37 [0,33 - 16,88] | 3,55 [0,37 - 34,15] |
| Gastrointestinal haemorrhages NEC | Rectal haemorrhage | 1 | 0,52 [0,07 - 3,71] | 5,32 [0,48 - 58,76] |
| Decreased and nonspecific blood pressure disorders and shock | Hypotension | 1 | 0,12 [0,02 - 0,88] | 1,33 [0,17 - 10,64] |
| Infections - pathogen unspecified | Infected skin ulcer | 1 | 11,81 [1,66 - 83,96] | - |
| Oral infection | 1 | 5,8 [0,82 - 41,24] | - |
| Pharyngitis | 1 | 1,82 [0,26 - 12,94] | 10,65 [0,67 - 170,36] |
| Sinusitis | 1 | 0,23 [0,03 - 1,61] | 2,13 [0,25 - 18,24] |
| Pneumonia | 2 | 0,14 [0,03 - 0,56] | 0,82 [0,19 - 3,45] |
| Psychiatric disorders NEC | Mental disorder | 1 | 0,53 [0,08 - 3,79] | 0,48 [0,06 - 3,59] |
| Central nervous system vascular disorders | Transient ischaemic attack | 1 | 0,65 [0,09 - 4,6] | 1,77 [0,21 - 14,75] |
| Metabolic, nutritional and blood gas investigations | Blood glucose increased | 1 | 0,12 [0,02 - 0,82] | 1,18 [0,15 - 9,34] |
| Renal disorders (excl nephropathies) | Renal disorder | 1 | 0,5 [0,07 - 3,54] | 3,55 [0,37 - 34,15] |
| Joint disorders | Joint stiffness | 1 | 0,87 [0,12 - 6,21] | 5,32 [0,48 - 58,76] |
| Rheumatoid arthritis | 1 | 0,21 [0,03 - 1,49] | - |
| Joint swelling | 1 | 0,2 [0,03 - 1,42] | 10,65 [0,67 - 170,36] |

*aICSR; Individual Case Safety Report*

*bRG1; Reference Group 1, report relative to all other drugs in the FAERS database*

*cRG2; Reference Group 2, report relative to other DORAs*