**Supplementary Table 1a. Conditions mentioned in the Contraindications and Warnings sections of the prescribing drug labeling for other analgesics (NSAIDs or weak opioids)**

|  |  |  |
| --- | --- | --- |
| **ICD code** | **Diagnosis** | |
| ***Conditions mentioned in the Contraindications section (absolute contraindications)*** | | |
| C15-C26 | Gastro-intestinal cancers | |
| D46 | Haematopoetic disorders | |
| D55.0 | Glucose-6-phosphate dehydrogenase deficiency | |
| D61 | Bone marrow disorders | |
| D65-D69 | Coagulation defects, purpura (bleeding disorders) | |
| E80.0 | Porphyria incl. acute hepatic porphyria | |
| E80.1 | Porphyria incl. acute hepatic porphyria | |
| E80.2 | Porphyria incl. acute hepatic porphyria | |
| G40-G41 | Epilepsy/Seizures | |
| G45 | Transient ischemic attack | |
| G46 | Stroke: Vascular syndromes of brain in cerebrovascular diseases | |
| G93.2 | Increased intracranial pressure/Raised intracranial pressure | |
| I20-I25 | Coronary artery disease (incl. myocardial infarction) | |
| I10-I15, I27 | Hypertension | |
| I46 | Heart attack | |
| I50 | Heart failure | |
| I60-I69 | Cerebrovascular disease incl. stroke, other intracranial haemorrhage | |
| I73 | Peripheral arterial disease | |
| J33 | Nasal polyps | |
| J43 | Emphysema | |
| J44 | Chronic obstructive pulmonary disease | |
| J45 | Asthma/Bronchial asthma | |
| J96 | Respiratory depression/ respiratory failure | |
| K25-K28 | Peptic ulcer | |
| K50-K52 | Inflammatory bowel disease incl. Chron disease and ulcerative colitis | |
| K57 | Diverticular disease of intestine | |
| K63.1, K92.2 | Gastro intestinal bleeding or perforation | |
| L50.0 | Allergic urticaria | |
| L51 | Erythema multiforme incl. Steven Johnson syndrome, toxic epidermal necrolysis | |
| N17-N19 | Kidney disase | |
| S00-S09 | Head injury | |
| T78.2 | Anaphylactic/anaphylactoid reactions | |
| T78.3 | Angioneurotic oedema/Angioedema | |
| T78.4 | Other allergic reactions | |
| T88.6 | Anaphylactic shock due to adverse effect of correct drug or medicament properly administered | |
| T88.7 | Allergic (hypersensitive) to the active ingredient or excepients/Hypersensitivity reactions | |
| ***Conditions mentioned in the Warnings section (relative contraindications)*** | |
| C74.1, D44.1 | Phaeochromocytoma |
| D12.6 | Sporadic adenomatous polyps (polyposis (hereditary) of colon) |
| D47 | Haematopoetic disorders |
| D50-D60 (excl. D55.0) | Anemia |
| D51 | Anemia |
| E03 | Hypothyroidism |
| E05 | Thyrotoxycosis |
| E10-E14 | Diabetes mellitus |
| E27.1 | Addison disease |
| E27.4 | Adrenocortical insufficiency |
| E73 | Lapp lactose intolerancy incl. congenial lactose intolerancy |
| E74.1 | Fructose intolerance |
| E74.3 | Galactose intolerance/Hereditary problems of galactose intolerance/Glucose- galactose malabsorption |
| E78 | Hypercholesterolemia/Hyperlipidaemia |
| E80.4 | Gilbert's syndrome |
| E86 | Extracellular volume depletion/Hypovolemia |
| E88.9 | Metabolic syndrom |
| F11-F19 | Drug dependence and abuse |
| F99 | Mental disorders/Psychiatric disorders |
| G20 | Parkinsonism |
| G80-G83 | Cerebral palsy and other paralytic syndromes |
| I95 | Hypotension |
| J30.1 | Hay fever |
| K20 | Oesophagitis |
| K29 | Gastritis/Inflammatory gastrointestinal disorder |
| K56 | Obstructive bowel disorders |
| K63.3 | Bowel ulcer/Intestinal ulceration |
| K63.5 | Sporadic adenomatous polyps (Polyp of colon) |
| K80, K81.1, K81.9, K82 | Gall bladder disease or gall stones |
| L26 | Exfoliative dermatitis |
| L27.0, L27.1 | Rash due to medication |
| L50.8 | Chronic urticaria |
| M05, M06 | Rheumatoid arthritis |
| M10 | Gout |
| M30-M36 | Connective tissue disorders incl. systemic lupus erythematosus and mixed connective tissue disorders |
| N04 | Nephrotic syndrome |
| N35 | Urethral stricture |
| N40 | Prostatic hypertrophy |
| R56 | Convulsive disorder |
| R57 | Shock |
| R60 | Fluid retention/Oedema/Pre-existing oedema |

**Supplementary Table 1b. Therapeutic drugs for treatment of conditions mentioned in the Contraindications and Warnings sections of the prescribing drug labeling for other analgesics (NSAIDs or weak opioids)**

|  |  |
| --- | --- |
| **Code** | **Therapeutic drug class** |
| ***Drugs indicated for conditions mentioned in the Contraindications section (absolute contraindications)*** | |
| A02B | Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD) |
| A03AB05 | Propantheline |
| A03BA03 | Hyoscyamine |
| A07E | Intestinal antiinflammatory drugs |
| B01A | Antithrombotic agents |
| B02BD | Blood coagulation factors |
| B02BX | Other systemic haemostatics |
| B03X | Other antianemic preparations |
| C01AA | Digitalis glycosides |
| C01D | Vasodialators used in cardiac diseases |
| C01EB17 | Ivabradine |
| C02 | Antihypertensives |
| C03 | Diuretics |
| C07A | Beta blocking agents |
| C08C | Selective calcium channel blockers with mainly vascular effects |
| C08D | Selective calcium channel blockers with direct cardiac effects |
| C09 | Agents acting on the renin-angiotensin system |
| C10 | Lipid modifying agents |
| H02AB | Glucocorticoids for systemic use |
| H02B | Corticosteroids for systemic use combinations |
| L01AA | Nitrogen mustard analogues |
| L01BA | Folic acid analogues |
| L01BB | Purine analogues |
| L01BC | Pyrimidine analogues |
| L01CA | Vinca alkaloids and analogues |
| L01CB | Podophyllotoxin derivatives |
| L01CD | Taxanes |
| L01DB | Anthracyclines and related substances |
| L01XA | Platinum compounds |
| L01XC | Monoclonal antibodies |
| L01XE | Protein kinase inhibitors |
| L01XX | Other antineoplastic agents |
| L03AA | Colony stimulating factors |
| L04A | Immunosuppressants |
| N03A | Antiepileptics |
| R01AC | Antiallergic agents, excl. corticosteroids |
| R01AD | Corticosteroids (nasal preparations) |
| R03A | Adrenergics, Inhalants |
| R03B | Other drugs for obstructive airway diseases, inhalants |
| R03DA | Xanthines |
| R03DC | Leukotriene receptor antagonists |
| R03DX | Other systemic drugs for obstructive airway diseases |
| R05CB | Mucolytics |
| ***Drugs indicated for conditions mentioned in the Warnings section (relative contraindications)*** | | |
| A09AA04 | Tilactase | |
| A10A | Insulins and analogues | |
| A10B | Blood glucose lowering drugs, excl. insulins | |
| B03A | Iron preparations | |
| B03B | Vitamin B12 and folic acid | |
| G04C | Drugs used in benign prostatic hypertrophy | |
| H02AA | Mineralocorticoids | |
| H03AA | Thyroid hormones | |
| H03B | Antithyroid preparations | |
| M04AA | Preparations inhibiting uric acid production | |
| M04AB | Preparations increasing uric acid excretion | |
| M04AX | Other antigout preparations | |
| N04A | Anticholinergic agents | |
| N04B | Dopamiergic agents | |
| N05A | Antipsychotics | |
| N07BC | Drugs used in opioid dependence | |
| P01BA01 | Chloroquine | |
| P01BA02 | Hydroxychloroquine | |
| R01AX | Other nasal preparations | |
| R01B | Nasal decongestants for systemic use | |
| R06A | Anti-Histamines for systemic use | |

**Supplementary Table 2. List of diagnoses associated with acute pain, acute pain episodes, acute pain exacerbations**

|  |  |
| --- | --- |
| **ICD code** | **Diagnosis** |
| G20-G26 | Extrapyramidal and movelent disorders |
| G20 | Parkinson disease |
| G21 | Secondary parkinsonism |
| G22 | Parkinsonism in diseases classified elsewhere |
| G23 | Other degenerative diseases of basal ganglia |
| G35-G37 | Demyelinating diseases of the central nervous system |
| G35 | Multiple sclerosis |
| G40-G47 | Episodic and paroxysmal disorders |
| G44 | Other headache syndromes |
| M15-M19 | Arthrosis |
| M15 | Polyarthrosis |
| M16 | Coxarthrosis [arthrosis of hip] |
| M17 | Gonarthrosis [arthrosis of knee] |
| M18 | Arthrosis of first carpometacarpal joint |
| M19 | Other arthrosis |
| M40-M43 | Deforming dorsopathies |
| M40 | Kyphosis and lordosis |
| M41 | Scoliosis |
| M42 | Spinal osteochondrosis |
| M43 | Other deforming dorsopathies |
| M45-M49 | Spondylopathies |
| M45 | Ankylosing spondylitis |
| M46 | Other inflammatory spondylopathies |
| M47 | Spondylosis |
| M48 | Other spondylopathies |
| M49 | Spondylopathies in diseases classified elsewhere |
| M50-M54 | Other dorsopathies |
| M50 | Cervical disc disorders |
| M51 | Other intervertebral disc disorders |
| M53 | Other dorsopathies, not elsewhere classified |
| M54 | Dorsalgia |
| M60-M63 | Disorders of muscles |
| M60 | Myositis |
| M61 | Calcification and ossification of muscle |
| M62 | Other disorders of muscle |
| M63 | Disorders of muscle in diseases classified elsewhere |
| M95-M99 | Other disorders of the musculoskeletal system and connective tissue |
| M95 | Other acquired deformities of musculoskeletal system and connective tissue |
| M96 | Postprocedural musculoskeletal disorders, not elsewhere classified |
| M99 | Biomechanical lesions, not elsewhere classified |
| R50-R69 | General symptoms and signs |
| R51 | Headache |
| R52 | Pain, not elsewhere classified |

**Supplementary Table 3. List of substances known to have potential hepatotoxic effect**

|  |  |  |
| --- | --- | --- |
| **Group** | **Substance** | **ATC-Code** |
| Antibiotics | Amoxicillin / clavulanate | J01CA04, J01CR02, A02BD06, A02BD07, A02BD10, A02BD03, A02BD05, A02BD01, A02BD04 |
| Isoniazid | J04AM03, J04AC01, J04AC51, J04AM02, J04AM05, J04AM06, J04AM01, J04AM04 |
| Trimethoprim / sulfamethoxazole | J01EE01 |
| Fluoroquinolones | J01MA, S01AE |
| Macrolides (Clarithromycin, Erythromycin) | J01F, J01FA; J01FA01, J01FA09 |
| Nitrofurantoin | J01XE01, J01XE51 |
| Minocycline | A01AB23, J01AA08 |
| Sulfamethoxazole | J01EC01, J01EE01 |
| Sulfonamide | J01E, A07AB, A10BC, C03BA, C03BB, C03BK, C03CA, C03CB, D06BA, G01AE, G01BE, J01EB, J01EC, J01ED, J01EE, S01AB, G01AE10, A10BD02, A10BD01, J01RA02 |
| Tetracycline | J01A, D06AA, J01AA, A02BD08, A01AB21, D06AA02, J01AA03, S01AA02, J01AA20, A02BD02, D06AA03, G01AA07, J01AA06, S01AA04, J01AA56, J01AA09, A01AB13, D06AA04, J01AA07, S01AA09, S02AA08, S03AA02, J01RA08 |
| Anti-epileptics | Phenytoin | N03AB05, N03AB04, N03AB54, N03AB02, N03AB52 |
| Carbamazepine | N03AF01 |
| Lamotrigine | N03AX09 |
| Valproate | N03AG01 |
| Non-steroidal anti-inflammatory drugs | Diclofenac | D11AX18, M01AB05, M02AA15, S01BC03, S01CC01, M01AB55 |
| Indomethazin | M01AB01, S01BC01, M02AA23 |
| Phenylbutazon | M01AA01, M02AA01, M01BA01 |
| Piroxicam | M01AC01, M02AA07, S01BC06 |
| Analgesics | Paracetamol | N02BE01, N02BE51, N02BE71 |
| Muscle relaxants | Dantrolene | M03CA, M03CA01 |
| Antidepressants | Imipramine | N06AA02, N06AA03, N06AA06 |
| Neuroleptics | Chlorpromazine | N05AA01 |
| Alcohol dependence treatment | Disulfiram | N07BB01, P03AA04, P03AA54 |
| Stimulants | Pemoline | N06BA05 |
| Cardiovascular disorders | Amiodarone | C01BD01 |
| Captopril | C09AA01, C09BA01 |
| Hydralazin, Dihydralazine | C02DB02, C02DB01 |
| Alpha-methyldopa | C02AB01 |
| Chronic intestinal disorders | Sulfasalazine | A07EC01 |
| H2-Antihistamines | Cimetidine | A02BA01, A02BA51 |
| Proton-pump-inhibitors | Pantoprazole | A02BC02, A02BD04 |
| Omeprazole | A02BC05, A02BD06, M01AE52, A02BC01, A02BD05, A02BD01 |
| Immune modulators | Interferon-β | L03AB02 |
| Interferon-α | L03AB01 |
| Anti-TNF agents | L04AB; L04AB01, L04AB02, L04AB03, L04AB04, L04AB05, L04AB06 |
| Azathioprine | L04AX01 |
| Urikostatic drugs | Allopurinol | M04AA01, M04AA51 |
| Uricosuric drugs | Probenecide | M04AB01 |
| Cytostatics | Methotrexate (oral) | L01BA01, L04AX03 |
| Dacarbazine | L01AX04 |
| Hyperthyroidism | Carbimazol | H03BB01 |
| Propylthiouracil | H03BA02 |
| Virostatic agent, reverse transcriptase inhibitors | Didanosine | J05AF02 |
| Inhaled anaesthetics | Enflurane | N01AB04 |
| Halothane | N01AB01 |
| Diuretics | Etacrynic acid | C03CC01 |
| Antimycotics | Ketoconazole | D01AC08, G01AF11, J02AB02 |
| Lipid lowering agents | Nicotinic acid | C04AC, C10AD, C10BA01, C04AC01, C10AD02, C10AD52 |
| Androgen-containing steroids | Testosterone | G04CB, G03FA05, G03BA02, G03EK01, G03EA01, G03BA03, G03EA02 |
| Androgen-containing steroids in combination with Estradiol or Estradiolvalerat | Testosteron + Estradiol | G03EA02; |
| Testosteron + Estradiolvalerat | G03EA02 |