# Appendix 1: complete EU(7)-PIM list

| **ATC-Code** (according to WHO ATC-code [30] (2011)) | **Potentially inappropriate drugs**<br><br>Lists or criteria which include the specific drug (following either category A or B)[a]:<br>1: Laroche (2007) [3]<br>2: McLeod (1997) [26]<br>3: Finnish (2013) [33]<br>4: PRISCUS (2010) [22]<br>5: Beers (2012) [18]<br>6: STOPP/START (2014) [19] | **Results of the Delphi survey**<br><br>(number of experts' answers at decisive Delphi round[b]; Likert-scale mean value [95% CI]; median) | **Main reason for PIM** | **Dose adjustment/special considerations of use** | **Alternative drugs and/or therapies** |
|---|---|---|---|---|---|
| **A** | **Alimentary tract and metabolism** | | | | |
| ***A02*** | ***Drugs for acid-related disorders*** | | | | |
| ***A02A*** | ***Antacids*** | | | | |
| A02AA04 | Magnesium hydroxide<br><br>In lists: 3 (A) | 20; 2.50 [2.01-2.99]; 2.00 | Risk of hypermagnesemia, which is higher in moderate to severe renal failure | Maximum dose: 5 ml/8h; reduce dose for moderate to severe renal failure. *E* | Used as laxative: osmotically active laxatives (macrogol, lactulose) *E*<br>Used as antacid, when indication is appropriate: PPI (<8 weeks, low dose) *E* |
| A02AB, A02AD | Aluminium-containing antacids<br><br>In lists: 3 (A); 6 (B) | 23; 2.09 [1.72-2.45]; 2.00 | Renal excretion of aluminium decreases in older individuals. Risk of CNS toxicity | Adjust dose in severe renal failure. *M*<br>Use for short periods (3-4 days). *E* | When indication is appropriate: PPI (<8 weeks, low dose) *E* |

# Appendix 1: complete EU(7)-PIM list

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| ***A02B*** | ***Drugs for peptic ulcer and gastro-oesophageal reflux disease*** | | | | |
| A02BA01 | Cimetidine<br><br>In lists: 1 (A); 2, 5 (B) | 23; 1.43 [1.18-1.69]; 1.00 | CNS adverse effects including confusion | 200 mg four times daily or 300 mg twice daily, due to a decrease in renal and hepatic function in adults aged ≥65 years old. *M* | When indication is appropriate: PPI (<8 weeks, low dose) *E* |
| A02BA02 | Ranitidine<br><br>In lists: 5 (B) | 23; 2.26 [1.84-2.68]; 2.00 | CNS adverse effects including confusion | CrCl <50 ml/min: 150 mg c/24h (oral); 50 mg c/18-24 h (iv) *E* | When indication is appropriate: PPI (<8 weeks, low dose) *E* |
| A02BA03 | Famotidine<br><br>In lists: 5 (B) | 23; 2.17 [1.84-2.51]; 2.00 | CNS adverse effects including confusion | CrCl <50 ml/min: administer 50% of dose or increase the dosing interval to every 36-48 h. *E* | When indication is appropriate: PPI (<8 weeks, low dose) *E* |
| A02BC | Proton pump inhibitors (PPI) (>8 weeks) e.g. omeprazole, pantoprazole<br><br>In lists: 6 (B) | 21; 2.00 [1.57-2.43]; 2.00 | Long-term high dose PPI therapy is associated with an increased risk of *C. difficile* infection and hip fracture. Inappropriate if used >8 weeks in maximal dose without clear indication | | When indication is appropriate: PPI (<8 weeks, low dose) *E* |
| ***A03*** | ***Drugs for functional gastrointestinal disorders*** | | | | |
| ***A03A*** | ***Drugs for functional bowel disorder*** | | | | |
| A03AA04 | Mebeverine[c]<br><br>In lists: does not appear as PIM | 20; 1.60 [1.16-2.04]; 1.00 | Side effects such as dizziness, insomnia, anorexia | Caution if marked renal insufficiency. *M* Use only for short periods. *E* | Non-pharmacological measures, e.g. diet. *E* |

# Appendix 1: complete EU(7)-PIM list

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| A03AA05 | Trimebutine<br><br>In lists: 1, 2, 6 (B) | 19; 1.47 [1.07-1.88]; 1.00 | Anticholinergic and antimuscarinic side effects like agitation, sedation or confusion; no proven efficacy | | Non-pharmacological measures, e.g. diet. *E* |
| A03AA08 | Dihexyverine<br><br>In lists: 1 (A); 2, 6 (B) | 14; 1.57 [1.03-2.11]; 1.00 | Anticholinergic and antimuscarinic side effects like agitation, sedation or confusion; no proven efficacy | | Phloroglucinol. *L*<br>Non-pharmacological measures, e.g. diet. *E, McL* |
| A03AB06 | Otilonium bromide<br><br>In lists: 2, 6 (B) | 18; 1.50 [1.07-1.93]; 1.00 | Anticholinergic and antimuscarinic side effects like agitation, sedation or confusion; no proven efficacy | | Non-pharmacological measures, e.g. diet. *E* |
| A03AB17 | Tiemonium (iodide)<br><br>In lists: 1 (A); 2, 6 (B) | 15; 1.60 [1.10-2.10]; 1.00 | Anticholinergic and antimuscarinic side effects like agitation, sedation or confusion; no proven efficacy | | Phloroglucinol. *L*<br>Non-pharmacological measures, e.g. diet. *E, McL* |
| A03AX04 | Pinaverium[c]<br><br>In lists: does not appear as PIM | 18; 1.50 [1.07-1.93]; 1.00 | Side effects such as dizziness or esophageal ulceration | | Non-pharmacological measures, e.g. diet. *E* |
| ***A03B*** | ***Belladonna and derivates, plain*** | | | | |
| A03BA03 | Hyoscyamine<br><br>In lists: 5 (A); 1, 2, 5, 6 (B) | 20; 1.05 [0.95-1.29]; 1.00 | Highly anticholinergic, substantial toxic effects in older adults and uncertain effectiveness / no proven efficacy | | Butylscopolamine 20mg/6-12h for a short time, especially in palliative care. *E*<br>Phloroglucinol *E*<br>Non-pharmacological measures, e.g. diet. *E, McL* |
| A03BA04 | Belladonna alkaloids<br><br>In lists: 1, 5 (A); 2, 5, 6 (B) | 22; 1.14 [0.98-1.29]; 1.00 | Highly anticholinergic, substantial toxic effects in older adults and uncertain effectiveness / no proven efficacy | | Butylscopolamine *E*<br>Phloroglucinol *E, L*<br>Non-pharmacological measures, e.g. diet. *E, McL* |

# Appendix 1: complete EU(7)-PIM list

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| ***A03C*** | ***Antispasmodics in combination with psycholeptics*** | | | | |
| A03CA02 | Clidinium-Chlordiazepoxide<br><br>In lists: 1, 3, 5 (A); 2, 6 (B) | 19; 1.21 [1.01-1.41]; 1.00 | Long half-life in older adults (often several days), producing prolonged sedation and increasing the risk of falls and fractures | Do not exceed chlordiazepoxide 10 mg, clidinium 5 mg/d; increase gradually and limit to the smallest effective dose. *M* | Phloroglucinol *E, L*<br>Non-pharmacological measures, e.g. diet. *E, McL* |
| ***A03D*** | ***Antispasmodics in combination with analgesics*** | | | | |
| A03DA02 | Pitofenone<br><br>In lists: 3 (A); 1, 2, 6 (B) | 18; 2.00 [1.55-2.45]; 2.00 | Anticholinergic side effects | | Non-pharmacological measures, e.g. diet. *E* |
| ***A03F*** | ***Propulsives*** | | | | |
| A03FA01 | Metoclopramide<br><br>In lists: 3, 5 (A); 6 (B) | 23; 2.43 [1.97-2.90]; 2.00 | Antidopaminergic and anticholinergic effects;<br>may worsen peripheral arterial blood flow and precipitate intermittent claudication | Short-term use and dose reduction; CrCl <40 ml/min: 50% of normal dose; maximum dose: 20 mg/d; may be used in palliative care. *E* | Domperidone (<30 mg/d) if no contraindications. *E* |
| A03FA03 | Domperidone (>30 mg/d)[c]<br><br>In lists: does not appear as PIM | 18; 2.11 [1.70-2.53]; 2.00 | Increased risk of serious ventricular arrhythmia or sudden cardiac death in older adults | Treatment should be initiated at the lowest possible dose and titrated cautiously. *E* | Domperidone (<30 mg/d) if no contraindications. *E* |
| A03FA05 | Alizapride<br><br>In lists: 1 (A) | 19; 1.53 [1.23-1.82]; 1.00 | No proven efficacy; muscarinic-blocking agents; side effects such as confusion and sedation | Adjustment may be recommended in cases of renal failure. *M* | |

# Appendix 1: complete EU(7)-PIM list

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| ***A04*** | ***Antiemetics and antinauseants*** | | | | |
| ***A04A*** | ***Antiemetics and antinauseants*** | | | | |
| A04AB02[g] | Dimenhydrinate<br><br>In lists: 1, 4 (A); 5, 6 (B) | 19; 1.68 [1.29-2.08]; 1.00 | Anticholinergic side effects | Caution for patients with enlarged prostate. *E* | Domperidone (<30 mg/d) if no contraindications. *E* |
| A04AD01 | Scopolamine<br><br>In lists: 1, 3 (A); 5 (B) | 22; 1.68 [1.36-2.00]; 2.00 | Anticholinergic side effects; no proven efficacy | 5 mg/4h; may be appropriate and useful in palliative care. *E* | Domperidone (<30 mg/d) if no contraindications. *E* |
| A04AD05 | Metopimazine<br><br>In lists: 1(A) | 19; 1.68 [1.26-2.11]; 1.00 | No proven efficacy; muscarinic blocking agent; side effects such as confusion and sedation | | Domperidone (<30 mg/d) if no contraindications. *E* |
| ***A06*** | ***Laxatives*** | | | | |
| ***A06A*** | ***Laxatives*** | | | | |
| A06AA01 | Viscous paraffin (=Liquid paraffin)<br><br>In lists: 4, 5 (A) | 21; 2.43 [1.88-2.98]; 2.00 | Pulmonary side effects if aspirated | | Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P* |
| A06AA02 | Docusate sodium (oral)<br><br>In lists: 1 (A) | 19; 1.95 [1.57-2.32]; 2.00 | Stool softener laxative. Adverse events include cramping, nausea, diarrhoea. May exacerbate bowel disfunction | | Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P* |
| A06AB02 | Bisacodyl (>3 days)<br><br>In lists: 1, 3 (A); 5 (B) | 21; 1.90 [1.59-2.22]; 2.00 | Stimulant laxative. Adverse events include abdominal pain, fluid and electrolyte imbalance and hypoalbuminemia. May exacerbate bowel disfunction | | Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P* |

# Appendix 1: complete EU(7)-PIM list

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| A06AB05 | Castor oil (=Ricinus communis, =Neoloid)<br><br>In lists: 1 (A), 5 (B) | 21; 2.24 [1.70-2.77]; 2.00 | Stimulant laxative. Adverse events include abdominal pain, fluid and electrolyte imbalance and hypoalbuminemia. May exacerbate bowel disfunction | | Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P* |
| A06AB06 | Senna glycosides<br><br>In lists: 3 (A) | 23; 2.35 [1.79-2.91]; 2.00 | Stimulant laxative. Adverse events include abdominal pain, fluid and electrolyte imbalance and hypoalbuminemia. May exacerbate bowel disfunction | | Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P* |
| A06AB07 | Cascara sagrada<br><br>In lists: 1 (A); 5 (B) | 19; 2.32 [1.71-2.92]; 2.00 | Stimulant laxative. Adverse events include abdominal pain, fluid and electrolyte imbalance and hypoalbuminemia. May exacerbate bowel disfunction | | Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P* |
| A06AB08 | Sodium picosulfate<br><br>In lists: 1, 3 (A) | 22; 2.32 [1.82-2.82]; 2.00 | Stimulant laxative. Adverse events include abdominal pain, fluid and electrolyte imbalance and hypoalbuminemia. May exacerbate bowel dysfunction | | Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P* |
| A06AB13[g] | Aloe<br><br>In lists: 1 (A) | 16; 2.13 [1.65-2.60]; 2.00 | Stimulant laxative. Adverse events include abdominal pain, fluid and electrolyte imbalance and hypoalbuminemia. May exacerbate bowel disfunction | | Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P* |
| A06AX05[h] | Prucalopride<br><br>In lists: does not appear as PIM | 11; 2.09 [1.46-2.73]; 2.00 | Adverse effects can include abdominal pain, diarrhoea, headache, dizziness | Reduce dose for older adults and in cases of severe renal failure (GFR<30 ml/min); starting dose for persons over 65 years old: 1 mg/d; maximum dose: 2 mg/d (1 mg/d if severe renal failure) *E, M* | Recommend proper dietary fibre and fluid intake; osmotically active laxatives: macrogol, lactulose. *E, P* |

# Appendix 1: complete EU(7)-PIM list

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| ***A07*** | ***Antidiarrhoeal, intestinal anti-inflammatory / anti-infective agents*** | | | | |
| ***A07D*** | ***Antipropulsives*** | | | | |
| A07DA01 (Diphenoxylate)<br>A03BA01 (Atropine) | Diphenoxylate-Atropine<br><br>In lists: 1 (A); 2, 5, 6 (B) | 22; 1.73 [1.29-2.16]; 1.00 | No proven efficacy; muscarinic blocking agent | | Non-pharmacological measures, e.g. diet. *E*<br>Phloroglucinol *L* |
| A07DA03 | Loperamide (>2 days)<br><br>In lists: does not appear as PIM | 21; 1.81 [1.47-2.15]; 2.00 | Risk of somnolence, constipation, nausea, abdominal pain and bloating. Rare adverse events include dizziness. May precipitate toxic megacolon in inflammatory bowel disease, may delay recovery in unrecognized gastroenteritis | Start with a dose of 4 mg followed by 2 mg in each deposition until normalisation of bowel; do not exceed 16 mg/d; use no longer than 2 days; may be useful in palliative care for persisting non-infectious diarrhoea. *E* | Non-pharmacological measures, e.g. diet; phloroglucinol. *E* |
| ***A07X*** | ***Other antidiarrheals*** | | | | |
| A07XA04 | Racecadotril<br><br>In lists: does not appear as PIM | 16; 2.31 [1.68-2.95]; 2.00 | No proven efficacy; selective inhibitor of enkephalinase enzyme responsible for the degradation of the enkephalins, endogenous opioids which act by decreasing the intestinal lumen secretion of water and electrolytes | Maximum dose 100 mg/8h; maximum duration 7 days. *E* | Non-pharmacological measures, e.g. diet. *E* |
| ***A10*** | ***Drug used in Diabetes*** | | | | |
| ***A10A*** | ***Insulins and analogues*** | | | | |

# Appendix 1: complete EU(7)-PIM list

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| no ATC, treatment concept PIM | Insulin, sliding scale<br><br>In lists: 5 (A) | 13; 2.00 [1.45-2.55]; 2.00 | No benefits demonstrated in using sliding-scale insulin. Might facilitate fluctuations in glycemic levels | Lower doses to avoid hypoglycemia. *E* | Basal insulin. *E* |
| ***A10B*** | ***Blood glucose lowering drugs, excl. insulins*** | | | | |
| A10BB01 | Glibenclamide<br><br>In lists: 1, 5 (A); 6 (B) | 23; 2.00 [1.55-2.45]; 2.00 | Risk of protracted hypoglycemia | Use conservative initial dose (1.25 mg/d for nonmicronized glibenclamide and 0.75 mg/d for micronized glibenclamide) and maintenance dose; not recommended if CrCl <50 ml/min. *M* | Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E* |
| A10BB02 | Chlorpropamide<br><br>In lists: 5 (A); 1, 6 (B) | 20; 1.40 [1.12-1.68]; 1.00 | Risk of protracted hypoglycemia | Use initial doses of 100 to 125 mg/d. *M*<br>In cases of mild renal failure (GFR >50 ml/min), decrease dose by 50%. *M, E*<br>In cases of moderate to severe renal failure (GFR <50 ml/min), avoid. *M* | Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E* |
| A10BB06 | Carbutamide<br><br>In lists: 1 (A), 6 (B) | 16; 2.06 [1.61-2.52]; 2.00 | Risk of protracted hypoglycemia | Adjust dose to renal function. *E* | Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E* |
| A10BB07 | Glipizide<br><br>In lists: 1 (A) | 22; 2.45 [2.01-2.90]; 2.00 | Risk of protracted hypoglycemia | Use conservative initial and maintenance doses. *M*<br>Starting dose: 2.5 mg/d *E, M*<br>Increase by 2.5-5 mg/d at 1 to 2 week intervals. *E* | Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E* |

# Appendix 1: complete EU(7)-PIM list

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| A10BB12 | Glimepiride<br><br>In lists: 3 (A); 6 (B) | 21; 2.05 [1.71-2.38]; 2.00 | Risk of protracted hypoglycemia | Adjust according to renal function. *E*<br>For patients with renal failure and for older adults, use initial dose of 1 mg/d followed by a conservative titration scheme. Titrate dose in increments of 1 to 2 mg no more than every 1 to 2 weeks based on individual glycemic response. *M* | Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E* |
| A10BF01 | Acarbose<br><br>In lists: does not appear as PIM | 23; 2.22 [1.68-2.75]; 2.00 | No proven efficacy | | Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E* |
| A10BG03 | Pioglitazone<br><br>In lists: 5, 6 (B) | 21; 1.71 [1.42-2.01]; 2.00 | Age-related risks include bladder cancer, fractures and heart failure. Use for more than one year has been associated with an increased risk of bladder cancer. May increase the incidence of fractures of the upper arms, hands and feet in female diabetics (compared to other oral antidiabetic agents). Can cause fluid retention in older adults, which may exacerbate or precipitate heart failure | | Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E* |
| A10BH01 | Sitagliptine<br><br>In lists: does not appear as PIM | 17; 1.94 [1.44-2.44]; 2.00 | Limited safety data is available for adults aged ≥75 years old. Subjects aged 65 to 80 years had higher plasma concentrations than younger subjects. Risk of hypoglycemia, dizziness, headache and peripheral oedema | Reduce dose to 50 mg/d in cases of renal failure (CrCl 30-50 ml/min); reduce dose to 25 mg/d in cases of severe renal insufficiency (CrCl <30 ml/min). *E, M* | Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E* |

# Appendix 1: complete EU(7)-PIM list

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| A10BH02 | Vildagliptine<br><br>In lists: does not appear as PIM | 15; 1.87 [1.21-2.52]; 2.00 | Limited safety data available in older subjects. In healthy older adults (≥70 years) the overall exposure of vildagliptin (100 mg once daily) was increased by 32%, with an 18% increase in peak plasma concentration as compared to young healthy subjects (18-40 years). Adverse events (general population) include risk of hypoglycemia, dizziness, headache and peripheral oedema | Reduce dose to 50 mg/d in cases of moderate or severe renal failure. *E, M* | Diet; metformin (<2 x 850 mg/d); insulin; gliclazide may be safer than the other short-acting sulphonilureas. *E* |
| **B** | **Blood and blood forming organs** | | | | |
| ***B01*** | ***Antithrombotic agents*** | | | | |
| ***B01A*** | ***Antithrombotic agents*** | | | | |
| B01AA07 | Acenocoumarol<br><br>In lists: 6 (B) | 17; 2.35 [1.84-2.87]; 2.00 | Risk of bleeding, especially in people with difficult control of INR value | | |
| B01AC05 | Ticlopidine<br><br>In lists: 1, 4, 5, 6 (A); 6 (B) | 20; 1.70 [1.36-2.04]; 2.00 | Risk of altered blood counts | Dose reductions may be required in cases of renal failure. *M* | Clopidogrel; aspirin (<325mg)[d]. *E, L* |
| B01AC07 | Dipyridamole<br><br>In lists: 1, 2, 3, 5 (A); 6 (B) | 22; 2.14 [1.70-2.58]; 2.00 | Less efficient than aspirin; risk of vasodilatation and orthostatic hypotension<br>Proven beneficial only for patients with artificial heart valves | | Clopidogrel; aspirin (<325mg)[d]. *E, L* |
| B01AC22 | Prasugrel<br><br>In lists: 4 (A); 6 (B) | 18; 2.00 [1.41-2.59]; 2.00 | Unfavourable risk/benefit profile, especially for adults aged 75 and older | | Clopidogrel; aspirin (<325mg)[d]. *E, L* |

# Appendix 1: complete EU(7)-PIM list

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| B01AE07 | Dabigatran[c]<br><br>In lists: 6 (B) | 22; 2.45 [2.01-2.90]; 2.00 | Limited information on use for older adults and on the risk of bleeding events in this population; no reversal agent is available in case of overdose | Reduce dose for adults aged >75 years old (150 mg/d) and CrCl 30-50 (110 mg twice per day); contraindicated if CrCl <30. *E* | |
| B01AF01[g, h] | Rivaroxaban[c]<br><br>In lists: 6 (B) | 19; 2.42 [2.02-2.82]; 2.00 | Limited information on use for older adults; risk of bleeding events; no reversal agent available in case of overdose; risk of bleeding may be higher in cases of severe renal failure | Reduce dose for adults aged >65 years and avoid use for persons with CrCl <30 ml/min. *E, M* | |
| B01AF02[i] | Apixaban[c]<br><br>In lists: 6 (B) | 16; 2.25 [1.75-2.75]; 2.00 | Limited information on use for older adults; risk of bleeding events; no reversal agent available in case of overdose | Reduce dose to 2.5 mg orally twice daily for patients with any 2 of the following *(M)* (1 of the following *(E)*): ≥80 years old, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.<br>Do not use if CrCl less than 15 mL/min or if undergoing dialysis; reduce dose to 2.5 mg twice per day in cases of severe renal failure (CrCl 15 mL/min to 29 mL/min); no dosage adjustment necessary in cases of mild (CrCl 51 to 80 mL/min) or moderate (CrCl 30 to 50 mL/min) renal failure. *M* | |
| ***B03*** | ***Antianemic preparations*** | | | | |
| ***B03A*** | ***Iron preparations*** | | | | |
| B03AA | Iron supplements / Ferrous sulfate (>325 mg/d)<br><br>In lists: 6 (B) | 23; 2.22 [1.68-2.75]; 2.00 | Doses >325 mg/d do not considerably increase the amount absorbed but greatly increase the incidence of constipation | | Intravenous iron *E* |

# Appendix 1: complete EU(7)-PIM list

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| **C** | **Cardiovascular system** | | | | |
| ***C01*** | ***Cardiac therapy*** | | | | |
| ***C01A*** | ***Cardiac glycosides*** | | | | |
| C01AA02 | Acetyldigoxin<br><br>In lists: 4 (A) | 14; 2.14 [1.47-2.82]; 2.00 | Elevated glycoside sensitivity in older adults (women >men); risk of intoxication | Calculate digitalizing doses based on lean body mass and maintenance doses using actual CrCl. *M* | For tachycardia/atrial fibrillation: beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P*<br>For congestive heart failure: diuretics (except spironolactone >25 mg/d), ACE-inhibitors. *E* |
| C01AA04 | Digitoxin<br><br>In lists: does not appear as PIM | 16; 2.19 [1.57-2.87]; 2.00 | Elevated glycoside sensitivity in older adults (women >men); risk of intoxication | Calculate digitalizing doses based on lean body mass and maintenance doses using actual CrCl. *M* | For tachycardia/atrial fibrillation: beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P*<br>For congestive heart failure: diuretics (except spironolactone >25 mg/d), ACE-inhibitors. *E* |
| C01AA05 | Digoxin<br><br>In lists: 4, 5 (A); 1, 6 (B) | 23; 2.35 [1.92-2.77]; 2.00 | Elevated glycoside sensitivity in older adults (women >men); risk of intoxication | Calculate digitalizing doses based on lean body mass and maintenance doses using actual CrCl. *M*<br>For older adults, use dose 0.0625-0.125mcg/d; in cases of renal failure (CrCl 10-50 ml/min), administer 25-75% of dose or every 36 hours; in cases of renal failure (CrCl <10 ml/min), administer 10-25% of dose or every 48 hours. *E* | For tachycardia/atrial fibrillation: beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P*<br>For congestive heart failure: diuretics (except spironolactone >25 mg/d), ACE-inhibitors. *E* |

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| C01AA08 | Metildigoxin<br><br>In lists: 4 (A) | 15; 2.20 [1.57-2.83]; 2.00 | Elevated glycoside sensitivity (women >men); risk of intoxication | Calculate digitalizing doses based on lean body mass and maintenance doses using actual CrCl. *M*<br>In old adults with heart failure and normal renal function, oral maintenance dose requirement of digoxin is 1.4 times higher than metildigoxin. *M* | For tachycardia/atrial fibrillation: beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P*<br>For congestive heart failure: diuretics (except spironolactone >25 mg/d), ACE-inhibitors. *E* |
| ***C01B*** | ***Antiarrhythmics, Class I and III*** | | | | |
| C01BA01 | Quinidine<br><br>In lists: 3, 4, 5 (A) | 23; 1.48 [1.22-1.73]; 1.00 | CNS side effects; increased mortality.<br>Data suggest that for most older adults rate control yields better balance of benefits and harms than rhythm control *B* | | Beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P* |
| C01BA02 | Procainamide<br><br>In lists: 5 (A) | 21; 1.76 [1.41-2.11]; 2.00 | High risk of drug interactions.<br>Data suggest that for most older adults rate control yields better balance of benefits and harms than rhythm control *B* | Adjust dose to the individual patient response. Lower doses or longer intervals between doses may be required. *M*<br>CrCl 10-50 ml/min administer every 6-12 h; CrCl <10 ml/min administer every 8-24 h. *E* | Beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P* |
| C01BA03 | Disopyramide<br><br>In lists: 1, 2, 5 (A) | 23; 1.43 [1.18-1.69]; 1.00 | Potent negative inotrope; anticholinergic side effects; may induce heart failure; may cause sudden cardiac death.<br>Data suggest that for most older adults rate control yields better balance of benefits and harms than rhythm control *B* | Start dose at the lower end of the dosing range and titrate upward to maximum dose as required for antiarrhythmic effects and based on CrCl. *M* | Beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P* |

# Appendix 1: complete EU(7)-PIM list

| | | | | | |
|---|---|---|---|---|---|
| C01BA51 | Quinidine in combination with verapamil<br><br>In lists: 4 (A) | 22; 1.36 [1.15-1.58]; 1.00 | CNS side effects and increased mortality.<br>Data suggest that for most older adults rate control yields better balance of benefits and harms than rhythm control *B* | | Beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P* |
| C01BC03 | Propafenone<br><br>In lists: 3, 5 (A) | 19; 1.89 [1.44-2.35]; 1.00 | High risk of drug interactions.<br>Data suggest that for most older adults rate control yields better balance of benefits and harms than rhythm control *B* | Start dose at the lower end of the dosing range and increase gradually. *M*<br>A single oral 600 mg loading dose may be effective for converting recent-onset atrial fibrillation to sinus rhythm in persons older than 60 years without signs or symptoms of heart failure. *M* | Beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P* |
| C01BC04 | Flecainide<br><br>In lists: 3, 4, 5 (A) | 22; 2.14 [1.66-2.62]; 2.00 | Higher rate of adverse effects, especially in older adults.<br>Data suggest that for most older adults rate control yields better balance of benefits and harms than rhythm control *B* | Adjust dose in cases of renal failure. *M* | Beta-blockers (except oxprenolol, pindolol, propranolol, sotalol, nadolol, labetalol). *E, P* |
| C01BD01 | Amiodarone<br><br>In lists: 3, 5 (A); 6 (B) | 23; 2.30 [1.81-2.80]; 2.00 | Associated with QT interval problems and risk of provoking torsades de pointes.<br>Data suggest that for most older adults rate control yields better balance of benefits and harms than rhythm control *B* | Start dose at the low end of the dosing range. *M*<br>Use lower maintenance dose, e.g. 200 mg/48h. *E* | |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| C01BD07 | Dronedarone<br><br>In lists: 3, 5 (A) | 21; 1.57 [1.23-1.91]; 2.00 | Frequent drug interactions; prolonged QT interval; not recommended in permanent atrial fibrillation; increased mortality due to cardiovascular causes.<br>Data suggest that for most older adults rate control yields better balance of benefits and harms than rhythm control *B* | | |
| ***C01E*** | ***Other cardiac preparations*** | | | | |
| C01EB15 | Trimetazidine<br><br>In lists: does not appear as PIM | 13; 1.62 [1.22-2.01]; 2.00 | Can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia); caution in cases of moderate renal failure and with older adults (>75 years old); efficacy for the treatment of tinnitus or dizziness not proven | 20 mg twice per day for patients with moderate renal insufficiency. *E* | |
| C01EB17 | Ivabradine<br><br>In lists: does not appear as PIM | 16; 2.13 [1.61-2.64]; 2.00 | Common adverse events (1-10% of patients) may include first-degree AV block, ventricular extrasystoles, dizziness and blurred vision | Lower initial dose for older adults; starting dose 2 x 2.5 mg/d in >75 years. *M, E*<br>Use with caution for patients with CrCl less than 15 mL/min. *M* | |
| ***C02*** | ***Antihypertensives*** | | | | |
| ***C02A*** | ***Antiadrenergic agents, centrally acting*** | | | | |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| C02AA02 | Reserpine<br><br>In lists: 1, 2, 4, 5 (A); 6 (B) | 20; 1.25 [1.04-1.46]; 1.00 | Risk of orthostatic hypotension, bradycardia, syncope, CNS side effects (sedation, depression, cognitive impairment) | Low initial dose, half of usual dose, taper in and out. *P*<br>Lower doses (0.05 mg/d) to normal doses (0.25 mg/d) are recommended. *M*<br>Avoid if CrCl <10 ml/min. *M, E* | Other antihypertensive drugs, e.g. ACE inhibitors, or other mediation groups depending on comorbidity (exclude PIM). *E* |
| C02AB01 | Methyldopa<br><br>In lists: 1, 4, 5 (A); 6 (B) | 21; 1.38 [1.11-1.65]; 1.00 | Risk of orthostatic hypotension, bradycardia, syncope, CNS side effects (sedation, depression, cognitive impairment) | Low initial dose, half of usual dose, taper in and out. *P*<br>Suggested initial daily dose is 250 mg of methyldopa with a maximal daily dose of 1000 mg. *M*<br>CrCl >50 ml/min administer every 8 h; CrCl 10-50 ml/min administer every 8-12 h; CrCl <10 ml/min administer every 12-24 h. *E* | Other antihypertensive drugs, e.g. ACE inhibitors, or other mediation groups depending on comorbidity (exclude PIM). *E* |
| C02AC01 | Clonidine<br><br>In lists: 1, 3, 4, 5 (A); 6 (B) | 22; 1.36 [1.04-1.69]; 1.00 | Risk of orthostatic hypotension, bradycardia, syncope, CNS side effects (sedation, depression, cognitive impairment) | Lower doses for initial treatment of hypertension; half of usual dose, taper in and out. *M, P* | Other antihypertensive drugs, e.g. ACE inhibitors, or other medication groups depending on comorbidity (exclude PIM). *E* |
| C02AC02 | Guanfacine<br><br>In lists: 1, 5 (A); 6 (B) | 19; 1.42 [1.13-1.71]; 1.00 | Risk of orthostatic hypotension, bradycardia, syncope, CNS side effects (sedation, depression, cognitive impairment) | Cautious dosing when using guanfacine hydrochloride immediate-release; start dosing at the low end of the range. *M* | Other antihypertensive drugs, e.g. ACE inhibitors, or other medication groups depending on comorbidity (exclude PIM). *E* |
| C02AC05 | Moxonidine<br><br>In lists: 1, 3 (A); 6 (B) | 22; 1.77 [1.34-2.20]; 1.50 | Risk of orthostatic hypotension, bradycardia, syncope, CNS side effects (sedation, depression, cognitive impairment) | Caution in cases of moderate renal insufficiency (CrCl 30-60 ml/min): maximum doses 0.4 mg/d; avoid if CrCl <30ml/min. *M, E* | Other antihypertensive drugs, e.g. ACE inhibitors, or other mediation groups depending on comorbidity (exclude PIM). *E* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| C02AC06 | Rilmenidine<br><br>In lists: 1 (A); 6 (B) | 17; 1.53 [1.16-1.90]; 1.00 | Risk of orthostatic hypotension, bradycardia, syncope, CNS side effects (sedation, depression, cognitive impairment) | Reduce dose in cases of renal failure (CrCl <15 ml/min), *M*, *E* | Other antihypertensive drugs, e.g. ACE inhibitors, or other medication groups depending on comorbidity (exclude PIM). *E* |
| ***C02C*** | ***Antiadrenergic agents, peripherally acting*** | | | | |
| C02CA01 | Prazosin<br><br>In lists: 1, 3, 4, 5 (A); 6 (B) | 20; 1.55 [1.27-1.83]; 1.50 | Higher risk of orthostatic hypotension, dry mouth, urinary incontinence/ impaired micturition, CNS side effects (e.g. vertigo, light-headedness, somnolence) and cerebrovascular and cardiovascular disease | Lower dose for initial treatment of hypertension. *M*<br>Start with half of usual dose, taper in and out. *P*<br>First dose given at bedtime: initial 1-2 mg/d. *E* | Other antihypertensive drugs, e.g. ACE inhibitors, or other medication groups depending on comorbidity (exclude PIM). *E* |
| C02CA04 | Doxazosin<br><br>In lists: 4, 5 (A); 6 (B) | 22; 1.95 [1.61-2.30]; 2.00 | Higher risk of orthostatic hypotension, dry mouth, urinary incontinence/ impaired micturition, CNS side effects (e.g. vertigo, light-headedness, somnolence) and cerebrovascular and cardiovascular disease | Start with half of usual dose, taper in and out. *P*<br>Start with 0.5mg/d (immediate release) or 4-8 mg/d (extended release). *E* | Other antihypertensive drugs, e.g. ACE inhibitors, or other medication groups depending on comorbidity (exclude PIM). *E* |
| C02CA06 | Urapidil<br><br>In lists: 1 (A); 6 (B) | 19; 1.68 [1.29-2.08]; 1.00 | Higher risk of orthostatic hypotension, dry mouth, urinary incontinence/ impaired micturition, CNS side effects (e.g. vertigo, light-headedness, somnolence) and cerebrovascular and cardiovascular disease | Reduce dose for older adults and patients with renal insufficiency. *M* | Other antihypertensive drugs, e.g. ACE inhibitors, or other medication groups depending on comorbidity (exclude PIM). *E* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| C02CC02 | Guanethidine<br><br>In lists: does not appear as PIM | 19; 1.58 [1.25-1.91]; 1.00 | Higher risk of orthostatic hypotension, dry mouth, urinary incontinence/ impaired micturition, CNS side effects (e.g. vertigo, light-headedness, somnolence) and cerebrovascular and cardiovascular disease | Start low–go slow;<br>Increase dose interval in cases of renal failure. *M* | Other antihypertensive drugs, e.g. ACE inhibitors, or other medication groups depending on comorbidity (exclude PIMs). *E* |
| ***C02D*** | ***Agents acting on Arteriolar Smooth muscle*** | | | | |
| C02DB02 | Hydralazine<br><br>In lists: 6 (B) | 21; 2.33 [1.73-2.93]; 2.00 | Risk of orthostatic hypotension | Start low–go slow;<br>Increase dose interval in cases of renal failure. *M*, *E* | |
| ***C03*** | ***Diuretics*** | | | | |
| ***C03D*** | ***Potassium-sparing agent*** | | | | |
| C03DA01 | Spironolactone (>25 mg/d)[c]<br><br>In lists: 5 (A); 6 (B) | 20; 2.50 [1.99-3.01]; 2.00 | Higher risk of hyperkalaemia and hyponatremia in older adults, especially if doses >25 mg/d, requiring periodic controls | Reduce dose in cases of moderate renal insufficiency. *E*, *M*<br>GFR ≥50 mL/min/1.73 m: initial dose 12.5-25 mg/d, increase up to 25 mg 1-2x/d;<br>GFR 30-49 mL/min/1.73 m: initial dose 12.5 mg/d, increase up to 12.5-25 mg/d; reduce dose if potassium levels increase or renal function worsens.<br>GFR <10 mL/min: avoid. *M* | Consider alternatives depending on the indication; exclude PIMs. |
| ***C04*** | ***Peripheral vasodilators*** | | | | |
| ***C04A*** | ***Peripheral vasodilators*** | | | | |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| C04AD03 | Pentoxifylline<br><br>In lists: 1, 2, 3, 4 (A); 6 (B) | 21; 1.95[1.42-2.48]; 2.00 | No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators | Reduce dose to 400 mg twice daily in cases of moderate renal failure and to 400 mg once daily in cases of severe renal failure; close monitoring for toxicities. Avoid use if CrCl <30 ml/min. *M* | |
| C04AE02 | Nicergoline<br><br>In lists: 1, 4 (A); 6 (B) | 19; 1.63 [1.12-2.15]; 1.00 | No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators | Reduce daily dose in cases of renal failure (serum creatinine >2 mg/dl). *M* | |
| C04AE04 | Dihydroergocristine<br><br>In lists: 1 (A), 6 (B) | 19; 1.42 [1.05-1.79]; 1.00 | No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators | | |
| C04AE54 | Raubasine-Dihydroergocristine<br><br>In lists: 1 (A); 6 (B) | 18; 1.33 [0.99-1.67]; 1.00 | No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators | | |
| C04AX01 | Cyclandelate (=Cyclospasmol)<br><br>In lists: 6 (B) | 18; 1.33 [1.04-1.63]; 1.00 | No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators | | |
| C04AX07 | Vincamine<br><br>In lists: 1 (A); 6 (B) | 17; 1.53 [1.12-1.94]; 1.00 | No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators | | |
| C04AX10 | Moxisylyte<br><br>In lists: 1 (A); 6 (B) | 17; 1.53 [1.12-1.94]; 1.00 | No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators | | |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| C04AX17 | Vinburnine<br><br>In lists: 1 (A); 6 (B) | 17; 1.53 [1.12-1.94]; 1.00 | No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators | | |
| C04AX20 | Buflomedil<br><br>In lists: 6 (B) | 16; 1.69 [1.08-2.29]; 1.00 | No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators | | |
| C04AX21 | Naftidrofuryl<br><br>In lists: 1, 4 (A); 6 (B) | 17; 1.59 [1.11-2.07]; 1.00 | No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators | | |
| ***C05*** | ***Vasoprotectives*** | | | | |
| ***C05C*** | ***Capillary stabilizing agents*** | | | | |
| C05CA05 | Hidrosmin<br><br>In lists: 6 (B) | 17; 1.82 [1.41-2.24]; 2.00 | No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators | | Compression stocking . *E* |
| C05CA07[g] | Escin (=Aescin)<br><br>In lists: 6 (B) | 18; 1.83 [1.37-2.29]; 2.00 | No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators | | Compression stocking . *E* |
| C05CA51 | Vincamine-Rutoside<br><br>In lists: 1 (A); 6 (B) | 16; 1.75 [1.34-2.16]; 2.00 | No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators | | Compression stocking . *E* |
| C05CA54 | Troxerutin-Vincamine<br><br>In lists: 1 (A); 6 (B) | 16; 1.81 [1.33-2.30]; 2.00 | No proven efficacy; unfavourable risk/benefit profile; orthostatic hypotension and fall risks are increased with most vasodilators | | Compression stocking . *E* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| ***C07*** | ***Beta-blocking agents*** | | | | |
| ***C07A*** | ***Beta-blocking agents*** | | | | |
| C07AA02 | Oxprenolol<br><br>In lists: 2, 6 (B) | 16; 2.25 [1.79-2.71]; 2.00 | Non-selective beta-adrenergic blocker; may exacerbate or cause respiratory depression; possible CNS adverse events | | Cardio-selective beta-blockers (e.g. metoprolol, bisoprolol, carvedilol, atenolol). *E* |
| C07AA03 | Pindolol<br><br>In lists: 3 (A); 2, 6 (B) | 20; 2.40 [1.91-2.89]; 2.00 | Non-selective beta-adrenergic blocker; may exacerbate or cause respiratory depression; possible CNS adverse events | | Cardio-selective beta-blockers (e.g. metoprolol, bisoprolol, carvedilol, atenolol). *E* |
| C07AA05 | Propranolol<br><br>In lists: 3 (A); 6 (B) | 21; 2.33 [1.94-2.72]; 2.00 | Non-selective beta-adrenergic blocker; may exacerbate or cause respiratory depression; possible CNS adverse events | 3 doses of 20 mg daily *E*<br>Start low–go slow for older adults and patients with renal failure. *M* | Depending on the indication: cardio-selective beta-blockers, ACE inhibitors, diuretics. *E* |
| C07AA07 | Sotalol<br><br>In lists: 4, 5 (A); 2, 6 (B) | 21; 1.86 [1.64-2.07]; 2.00 | Non-selective beta-adrenergic blocker; may exacerbate or cause respiratory depression; possible CNS adverse events | Start at half or one third of the typical dose and increase slowly. *P*<br>Reduce dose and dosing interval in cases of renal failure. *M* | Cardio-selective beta-blockers (e.g. metoprolol, bisoprolol, carvedilol, atenolol). *E* |
| C07AA12 | Nadolol<br><br>In lists: 2, 6 (B) | 16; 2.44 [1.89-2.99]; 2.00 | Non-selective beta-adrenergic blocker; may exacerbate or cause respiratory depression | If CrCl 31-50 ml/min: administer every 24-36 h; if CrCl 10-30 ml/min: administer every 24-48h; if CrCl <10 ml/min: administer every 40-60 h. *E, M* | Cardio-selective beta-blockers (e.g. metoprolol, bisoprolol, carvedilol, atenolol). *E* |
| C07AG01 | Labetalol<br><br>In lists: 2, 6 (B) | 20; 2.30 [1.87-2.73]; 2.00 | Non-selective beta-adrenergic blocker; may exacerbate or cause respiratory depression | Start dose 100 mg once or twice per day. E<br>Maintenance dose 100-200 mg once or twice per day. *M* | Cardio-selective beta-blockers (e.g. metoprolol, bisoprolol, carvedilol, atenolol). *E* |
| ***C08*** | ***Calcium channel blockers*** | | | | |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| ***C08C*** | ***Selective calcium channel blockers with mainly vascular effects*** | | | | |
| C08CA04 | Nicardipine<br><br>In lists: 1 (A); 2, 6 (B) | 19; 2.00 [1.38-2.62]; 1.00 | Risk of orthostatic hypotension, myocardial infarction or stroke | Lower initial dose. *M* | Other antihypertensive drugs (amlodipine, cardioselective beta-blockers, ACE inhibitors, diuretics). *E, L* |
| C08CA05 | Nifedipine (non-sustained-release)<br><br>In lists: 1, 4, 5 (A); 2, 6 (B) | 23; 1.74 [1.28-2.19]; 1.00 | Increased risk of hypotension; myocardial infarction; increased mortality | Lower initial dose, half of usual dose, taper in and out. *P* | Other antihypertensive drugs (amlodipine, cardioselective beta-blockers, ACE inhibitors, diuretics). *E, L* |
| C08CA05 | Nifedipine (sustained-release)<br><br>In lists: 1 (A); 2, 6 (B) | 21; 1.95 [1.51-2.40]; 2.00 | Increased risk of hypotension; myocardial infarction; increased mortality | Lower initial dose, half of usual dose, taper in and out. *P*<br>Initial dose: 30 mg/d; maitenance dose: 30-60 mg/d. *E* | Other antihypertensive drugs (amlodipine, cardioselective beta-blockers, ACE inhibitors, diuretics). *E, L* |
| ***C08D*** | ***Selective calcium channel blockers with direct cardiac effects*** | | | | |
| C08DA01 | Verapamil<br><br>In lists: 3, 5 (A); 2, 6 (B) | 23; 2.39 [1.98-2.80]; 2.00 | May worsen constipation; risk of bradycardia | Immediate release tablets: initial dose 40 mg three times daily; sustained release tablets: initial dose 120 mg daily; oral controlled onset extended release: initial dose 100 mg/d. *M* | Other antihypertensive drugs (amlodipine, cardioselective beta-blockers, ACE inhibitors, diuretics). *E* |
| C08DB01 | Diltiazem<br><br>In lists: 3, 5 (A); 2, 6 | 23; 2.57 [2.18-2.95]; 2.00 | May worsen constipation; risk of bradycardia | Reduce dose or increase dosing interval. *M*<br>60 mg three times daily. *E* | |

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|---|---|---|---|---|---|
| | (B) | | | | |
| ***C10*** | ***Lipid modifiying agents*** | | | | |
| ***C10A*** | ***Lipid modifiying agents, plain*** | | | | |
| C10AD02 | Niacin (=Nicotinic acid)<br><br>In lists: 2 (A) | 22; 1.77 [1.28-2.26]; 1.00 | Moderate risk of side effects; ineffective for the treatment of dementia | | |
| **G** | **Genito-urinary system and sex hormones** | | | | |
| ***G03*** | ***Sex hormones and modulator of the genital system*** | | | | |
| ***G03C*** | ***Oestrogens*** | | | | |
| G03C | Oestrogen (oral)<br><br>In lists: 5 (A); 6 (B) | 21; 1.52 [1.21-1.83]; 1.00 | Evidence for carcinogenic potential (breast and endometrial cancer) and lack of cardioprotective effect in older women | | Specific treatment for osteoporosis. *E*<br>Local administration (i.e. vaginal application) considered safe and efficient. *E, B* |
| ***G04*** | ***Urologicals*** | | | | |
| ***G04B*** | ***Other urologicals, incl. antispasmodics*** | | | | |
| G04BD02 | Flavoxat | 16; 1.75 [1.22-2.28]; 1.00 | May decrease urinary flow, leading to urinary retention | | Non-pharmacological treatment (pelvic floor exercises, physical |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| | In lists: 5, 6 (B) | | | | and behavioural therapy). *E* |
| G04BD04 | Oxybutynine (non-sustained-release)<br><br>In lists: 1, 3, 4, 5 (A); 5, 6 (B) | 23; 1.43 [1.78-1.69]; 1.00 | Anticholinergic side effects (e.g. constipation, dry mouth, CNS side effects); ECG changes (prolonged QT) | Start immediate-release oxybutynin chloride in frail older adults with 2.5 mg orally 2 or 3 times daily. *M* | Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapy). *E* |
| G04BD04 | Oxybutynine (sustained-release)<br><br>In lists: 1, 3, 4, 5 (A); 5, 6 (B) | 23; 1.57 [1.16-1.97]; 1.00 | Anticholinergic side effects (e.g. constipation, dry mouth, CNS side effects); ECG changes (prolonged QT) | | Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapy). *E* |
| G04BD07 | Tolterodine (non-sustained-release)<br><br>In lists: 1, 3, 4, 5 (A); 5, 6 (B) | 22; 1.59 [1.27-1.92]; 1.00 | Anticholinergic side effects (e.g. constipation, dry mouth, CNS side effects); ECG changes (prolonged QT) | 1 mg orally twice daily in cases of significantly impaired renal function. *M* | Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapy). *E* |
| G04BD07 | Tolterodine (sustained-release)<br><br>In lists: 1, 3, 5 (A); 5, 6 (B) | 22; 1.77 [1.32-2.23]; 1.00 | Anticholinergic side effects (e.g. constipation, dry mouth, CNS side effects); ECG changes (prolonged QT) | Use 2 mg orally once daily in cases of severe renal failure (CrCl 10-30 mL/min); avoid use if CrCl <10 mL/min. *M* | Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapy). *E* |
| G04BD08 | Solifenacin<br><br>In lists: 1, 3, 4, 5 (A); 5, 6 (B) | 21; 1.81 [1.34-2.28]; 1.00 | Anticholinergic side effects (e.g. constipation, dry mouth, CNS side effects); ECG changes (prolonged QT) | Dose reduction may be needed. *M* | Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapy). *E* |

# Appendix 1: complete EU(7)-PIM list

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| G04BD09 | Trospium<br><br>In lists: 5 (A); 5, 6 (B) | 18; 1.94 [1.42-2.47]; 2.00 | Anticholinergic side effects (e.g. constipation, dry mouth, CNS side effects) | CrCl <30 mL/min: 20 mg/d (immediate release); avoid the use of extended release trospium. *M*<br>In adults aged ≥75 years old, the dose frequency of trospium immediate release may be reduced to 20 mg/d. *M* | Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapy). *E* |
| G04BD10 | Darifenacin<br><br>In lists: 3, 5 (A); 5, 6 (B) | 14; 1.79 [2.27-2.30]; 2.00 | Higher incidence of antimuscarinic adverse events (e.g., dry mouth, constipation, dyspepsia, increased residual urine, dizziness) and urinary tract infection in persons aged 75 years and older compared with younger patients | | Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapy). *E* |
| G04BD11 | Fesoterodin<br><br>In lists: 3, 5 (A); 5, 6 (B) | 14; 1.71 [1.24-2.19]; 1.50 | Higher incidence of antimuscarinic adverse events (e.g., dry mouth, constipation, dyspepsia, increased residual urine, dizziness) and urinary tract infection in persons aged 75 years and older compared with younger patients | CrCl <30 mL/min: maximum dose 4 mg/d. *M* | Non-pharmacological treatment (pelvic floor exercises, physical and behavioural therapy). *E* |
| ***G04C*** | ***Drug used in benign prostatic hypertrophy*** | | | | |
| G04CA03 | Terazosin<br><br>In lists: 4, 5 (A); 6 (B) | 21; 1.52 [1.25-1.80]; 1.00 | Higher risk of orthostatic hypotension, dry mouth, urinary incontinence/ impaired micturition, CNS side effects (e.g. vertigo, light-headedness, somnolence) and cerebrovascular and cardiovascular disease | Low initial dose, half of usual dose, taper in and out. *P*<br>Initial dose: 1 mg at bedtime; up to 10 mg/d may be required. *E* | If used as antihypertensive, other antihypertensive agents: ACE inhibitors, beta-blockers, calcium antagonists, diuretics (exclude PIM). *E* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| **J** | **Antiinfectives for systematic use** | | | | |
| ***J01*** | ***Antibacterial for systemic use*** | | | | |
| ***J01M*** | ***Quinolone antibacterials*** | | | | |
| J01MA01 | Ofloxacin<br><br>In lists: does not appear as PIM | 22; 2.23 [1.70-2.76]; 2.00 | Its half-life may be prolonged with elevated serum concentrations in older adults; increased risk of torsade de pointes and tendinitis or tendon rupture | Reduce dose and increase dosing interval if renal failure. *M* | Other antibiotics in accordance with sensitivity and resistance testing. *E* |
| ***J01X*** | ***Other antibacterials*** | | | | |
| J01XE01 | Nitrofurantoin (>1 week)<br><br>In lists: 1, 4, 5 (A) | 21; 2.00 [1.59-2.41]; 2.00 | Unfavourable risk/benefit ratio, particularly with long-term use (pulmonary side effects, liver damage, etc.); contraindicated if severe renal failure due to decreased excretion and increased risk of toxicity | 50-100 mg/8h; use shorter than one week. *E* | Other antibiotics in accordance with sensitivity and resistance testing. *E* |
| **M** | **Musculo-skeletal system** | | | | |
| ***M01*** | ***Anti-inflammatory and anti-rheumatic products*** | | | | |
| ***M01A*** | ***Anti-inflammatory and anti-rheumatic products, non-steroid (NSAID)*** | | | | |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| M01AA01 | Phenylbutazone<br><br>In lists: 1, 2, 4 (A); 5, 6 (B) | 19; 1.21 [1.01-1.41]; 1.00 | Very high risk of GI bleeding, ulceration, or perforation, which may be fatal;<br>risk of blood dyscrasia | Use for the shortest period possible. *P*<br>The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |
| M01AB01 | Indometacin<br><br>In lists: 1, 3, 4, 5 (A); 2, 5, 6 (B) | 23; 1.39 [1.08-1.70]; 1.00 | Very high risk of GI bleeding, ulceration, or perforation, which may be fatal;<br>risk of CNS disturbances | Reduce dose reduction by 25%. *M*<br>Use for the shortest period possible. *P*<br>The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |
| M01AB05 | Diclofenac<br><br>In lists: 5 (A); 1, 2, 5, 6 (B) | 23; 2.00 [1.59-2.41]; 2.00 | Very high risk of GI bleeding, ulceration, or perforation, which may be fatal;<br>cardiovascular contraindications | 50 mg/d; start using low dose;<br>the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| M01AB11 | Acemetacin<br><br>In lists: 4 (A); 1, 2, 4, 5, 6 (B) | 16; 1.50 [1.22-1.78]; 1.50 | Very high risk of GI bleeding, ulceration, or perforation, which may be fatal | Use for the shortest period possible. *P*<br>The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |
| M01AB15 | Ketorolac<br><br>In lists: 5 (A); 1, 2, 5, 6 (B) | 21; 1.76 [1.44-2.08]; 2.00 | Very high risk of GI bleeding, ulceration, or perforation, which may be fatal | Contraindicated in cases of advanced renal failure; oral dose not indicated as initial dose; recommended continuation dose after intravenous or intramuscular dosing is 10 mg every 4-6 hours, maximum 40 mg/d and for 5 days. *M*<br>The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |
| M01AB16 | Aceclofenac<br><br>In lists: 1, 2, 5, 6 (B) | 20; 1.85 [1.50-2.20]; 2.00 | Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications | Start using low dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| M01AC01 | Piroxicam<br><br>In lists: 4, 5 (A); 1, 2, 5, 6 (B) | 22; 1.55 [1.28-1.81]; 1.50 | Very high risk of GI bleeding, ulceration, or perforation, which may be fatal | Doses >20 mg are associated with increased GI toxicity and ulceration, especially in older adults. *M*<br>Use for the shortest period possible. *P*<br>10 mg/d; start with lower dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |
| M01AC05 | Lornoxicam<br><br>In lists: 1, 2, 5, 6 (B) | 19; 1.74 [1.35-2.13]; 2.00 | Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications | Use for the shortest period possible. *P*<br>Start with lower dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |
| M01AC06 | Meloxicam<br><br>In lists: 4, 5 (A); 1, 2, 5, 6 (B) | 23; 1.65 [1.34-1.96]; 2.00 | Very high risk of GI bleeding, ulceration, or perforation, which may be fatal | 11 mg/d; start with lower dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| M01AE01 | Ibuprofen (>3 x 400 mg/d or for a period longer than one week)[c]<br><br>In lists: 5 (A); 5, 6 (B) | 21; 2.43 [1.98-2.87]; 2.00 | Risk of GI bleeding and increased risk of cardiovascular complications at higher doses (>1200 mg/d), especially in cases of previous cardiovascular disease | The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |
| M01AE02 | Naproxen (>2 x 250 mg/d or for a period longer than one week)[c]<br><br>In lists: 5 (A); 5, 6 (B) | 23; 2.04 [1.62-2.47]; 2.00 | Risk of GI bleeding | Reduce dose; start low–go slow in older adults; avoid if CrCl <30 mL/min. *M*<br>The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |
| M01AE03 | Ketoprofen<br><br>In lists: 4, 5 (A); 1, 2, 5, 6 (B) | 23; 1.87 [1.45-2.29]; 2.00 | Very high risk of GI bleeding, ulceration, or perforation, which may be fatal | Reduce dose if CrCl <20 mL/min; start with lower dose and use reduced maintenance dose in older adults. *M*<br>Use for the shortest period possible. *P*<br>The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| M01AE09 | Flurbiprofen<br><br>In lists: 1, 2, 5, 6 (B) | 19; 1.84 [1.41-2.28]; 2.00 | Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications | Start with lower dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |
| M01AE17 | Dexketoprofen<br><br>In lists: 1, 2, 5, 6 (B) | 23; 1.91 [1.50-2.32]; 2.00 | Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications | Start with lower dose, up to 50 mg/d in older adults; in postoperative pain: 50 mg/d in case of renal or hepatic failure, maximum dose 50 mg/8h; maximum length 48 hours; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |
| M01AG01 | Mefenamic acid<br><br>In lists: 5 (A); 1, 2, 5, 6 (B) | 18; 1.72 [1.35-2.10]; 2.00 | Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications | Start with lower dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| M01AH01 | Celecoxib<br><br>In lists: 1, 2, 5, 6 (B) | 21; 1.67 [1.28-2.06]; 1.00 | Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications | The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |
| M01AH05 | Etoricoxib<br><br>In lists: 4 (A); 1, 2, 5, 6 (B) | 22; 1.73 [1.34-2.12]; 1.50 | Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications | Shortest possible duration of therapy. *P*<br>Start with lower dose; the risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |
| M01AX01 | Nabumetone<br><br>In lists: 5 (A); 1, 2, 5, 6 (B) | 20; 1.70 [1.33-2.08]; 1.50 | Very high risk of GI bleeding, ulceration, or perforation, which may be fatal; cardiovascular contraindications | Adjust dose in cases of moderate or severe renal failure; maximum starting dose should not exceed 750 mg or 500 mg/d, to a maximum of 1500 mg and 1000 mg/d; older adults should receive single daily doses of 1000mg; dose reduction recommended, consider low starting dose. *M*<br>The risk of bleeding may be reduced if combined with proton-pump inhibitors (use <8 weeks, low dose). *E* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |
| ***M03*** | ***Muscle relaxants*** | | | | |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| ***M03B*** | ***Muscle relaxants, centrally acting agents*** | | | | |
| M03BA02 | Carisoprodol<br><br>In lists: 5 (A); 5 (B) | 13; 1.62 [1.15-2.08]; 1.00 | Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia | | |
| M03BA03 | Methocarbamol<br><br>In lists: 1, 2, 5 (A) | 13; 1.62 [1.15-2.08]; 1.00 | Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia | | Rehabilitation; botulinum toxin. *E* |
| M03BC01 | Orphenadrine<br><br>In lists: 3, 5 (A); 5 (B) | 16; 1.38 [1.11-1.64]; 1.00 | Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia | | Rehabilitation; botulinum toxin. *E* |
| M03BX01 | Baclofen<br><br>In lists: 1, 3, 4 (A) | 22; 2.14 [1.72-2.55]; 2.00 | Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia | Dose reductions may be required in cases of renal failure; start low–go slow in older adults. *M*<br>Start with 5 mg 2-3 times daily and increase gradually as needed; maximum dose: 10 mg 3 times daily. *E* | Rehabilitation; botulinum toxin. *E* |
| M03BX02 | Tizanidine<br><br>In lists: 3 (A), 5 (B) | 18; 1.94 [1.37-2.52]; 2.00 | Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia | Dose reductions may be required in cases of renal failure. *M* | Rehabilitation; botulinum toxin. *E* |
| M03BX07 | Tetrazepam<br><br>In lists: 1, 4 (A) | 15; 1.80 [1.37-2.23]; 2.00 | Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia | Cautious dosing in cases of renal failure. *M*<br>Conservative dosing for older adults. *M, E* | Rehabilitation; botulinum toxin. *E* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| M03BX08 | Cyclobenzaprine<br><br>In lists: 2, 5 (A); 5 (B) | 16; 1.69 [1.22-2.15]; 1.00 | Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia | Start low–go slow. *M* | |
| ***M04*** | ***Antigout preparations*** | | | | |
| ***M04A*** | ***Antigout preparations*** | | | | |
| M04AC01 | Colchicin<br><br>In lists: 6 (B) | 18; 2.11 [1.66-2.56]; 2.00 | Higher risk of toxicity in older adults, particularly in cases of existing renal, GI or cardiac disease | Reduce dose by 50% in older adults (>70 years old). *M*<br>Reduce dose in cases of renal failure. *E, M* | Ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E* |
| ***M05*** | ***Drugs for treatment of bone diseases*** | | | | |
| ***M05B*** | ***Drugs affecting bone structure and mineralization*** | | | | |
| M05BX03 | Strontium ranelate<br><br>In lists: does not appear as PIM | 18; 1.72 [1.35-2.10]; 2.00 | Higher risk of venous thromboembolism in persons who are temporarily or permanently immobilised. Evaluate the need for continued therapy for patients over 80 years old with increased risk of venous thromboembolism | Avoid in cases of severe renal failure (CrCl <30 mL/min). *M* | Bisphosphonates, Vitamin D. *E* |
| ***M09*** | ***Other drugs for disorders of the musculo-skeletal system*** | | | | |

# Appendix 1: complete EU(7)-PIM list

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| ***M09A*** | ***Other drugs for disorders of the musculo-skeletal system*** | | | | |
| M09AA | Quinine and derivatives<br><br>In lists: does not appear as PIM | 15; 2.13 [1.44-2.82]; 2.00 | Risk of cardiac and idiosyncratic adverse effects | Adjust dose in cases of renal failure. *M* | |
| **N** | **Nervous system** | | | | |
| ***N02*** | ***Analgesics*** | | | | |
| ***N02A*** | ***Opioids*** | | | | |
| N02AB02 | Pethidine (=Meperidine)<br><br>In lists: 4, 5 (A); 2, 6 (B) | 22; 1.50 [1.24-1.77]; 1.00 | Risk of falls, fractures, confusion, dependency and withdrawal syndrome | Start low–go slow. *M*, *P*<br>Use for the shortest period possible. *P*<br>50 mg every 4-6 hours. *E*<br>Use 75% of the normal dose at the usual intervals in cases of moderate renal failure (GFR 10-50 mL/min); use 50% of the normal dose at the usual intervals in cases of severe renal failure (GFR <10 mL/min). *M* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |
| N02AD01 | Pentazocine<br><br>In lists: 5 (A); 2, 6 (B) | 18; 1.28 [1.05-1.51]; 1.00 | Risk of delirium and agitation | For patients with GFR between 10 and 50 mL/min the dose should be reduced by 25% and for patients with GFR less than 10 mL/min, the dose should be decreased by 50%. *M* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| | | | | | *E, P* |
| N02AX02 | Tramadol (sustained-release)<br><br>In lists: 5, 6 (B) | 23; 1.83 [1.44-2.21]; 2.00 | More adverse effects in older adults; CNS side effects such as confusion, vertigo and nausea | Start low–go slow.<br>Not to be used in cases of severe renal failure. *E, M* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P* |
| N02AX02 | Tramadol (non-sustained-release)<br><br>In lists: 5, 6 (B) | 21; 2.33 [1.77-2.90]; 2.00 | More adverse effects in older adults; CNS side effects such as confusion, vertigo and nausea | Start low–go slow; in persons older than 75 years, daily doses over 300 mg are not recommended. *M*<br>Start with 12.5 mg/8h and progressive increases of 12.5 mg/8h; maximum 100mg/8h. *E*<br>Reduce dose and extend the dosing interval for patients with severe renal failure. *M* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| N07BC02 | Methadone<br><br>In lists: 6 (B) | 22; 1.82 [1.47-2.17]; 2.00 | Very long-acting especially in the elderly | Lowest possible dose. *E*<br>Start low–go slow.<br>Lower initial methadone dose with longer dosing intervals are recommended, along with a slower dose titration for patients with renal failure. *M* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |
| ***N02B*** | ***Other analgesics and antipyretics*** | | | | |
| N02BA01 | Acetylsalicylic acid (>325 mg)<br><br>In lists: 3, 5 (A); 2, 5, 6 (B) | 23; 1.83 [1.33-2.33]; 1.00 | May exacerbate existing GI ulcers or produce new GI ulcers; increased risk of bleeding due to prolongated clotting time, elevation of INR values or inhibition of platelet aggregation | | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E*, *P* |
| ***N02C*** | ***Antimigraine preparations*** | | | | |
| N02CA02 | Ergotamine<br><br>In lists: 4 (A) | 20; 1.55 [1.08-2.02]; 1.00 | Unfavourable risk/benefit profile | | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week); non-pharmacological treatment (silence, rest, darkness). *E* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| N02CC | Triptanes (e.g. Sumatriptan, Eletriptan, Naratriptan, Zolmitriptan)<br><br>In lists: does not appear as PIM | 23; 2.13 [1.78-2.48]; 2.00 | Safety and efficacy in older adults have not been established<br>Naratriptan and sumatriptan use for older adults has an increased risk of decreased hepatic function and reduced clearance due to renal dysfunction, higher risk for coronary artery disease, and increases in blood pressure *M* | Start low–go slow. *M*<br>Eletriptan Hydrobromide: initial dose of 20 mg, may be repeated after 2 hours; usual dose of 20-40 mg; maximum dose: 40 mg for older adults. *M*<br>Naratriptan: contraindicated in cases of severe renal failure (CrCl <15 mL/min). In cases of mild to moderate renal failure, a lower starting dose should be considered and the maximum dose is 2.5 mg/d. *M* | Paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week); non-pharmacological treatment (silence, rest, darkness). *E* |
| ***N03*** | ***Antiepileptics*** | | | | |
| ***N03A*** | ***Antiepileptics*** | | | | |
| N03AA02 | Phenobarbital<br><br>In lists: 4, 5 (A); 5 (B) | 22; 1.50 [1.24-1.77]; 1.00 | Risk of sedation, paradoxical excitation | Use lowest possible dose. *E, M*<br>Start at the lowest possible dose, taper down to half of the usual dose. *P*<br><br>Administer every 12-16 hours in cases of severe renal failure (GFR <10 ml/min). Avoid longer acting barbiturates for long term use in cases of renal failure. Decrease doses significantly for short-term therapy. *M* | Levetiracetam[d]; gabapentin[d]; lamotrigine[d]; valproic acid[d]. *E* |

# Appendix 1: complete EU(7)-PIM list

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| N03AB02 | Phenytoin<br><br>In lists: 3 (A); 5 (B) | 22; 2.18 [1.76-2.61]; 2.00 | Narrow therapeutic window; increased risk of toxicity in older adults (e.g. CNS and hematologic toxicity) | Lower doses or less frequent dosing may be necessary for older adults due to reduced clearance, hypoalbuminemia or renal disease. *M*<br>Start with 3 mg/kg/day, in divided doses, adjust the dosage according to serum hydantoin concentrations and patient response; use as a guide the plasma levels, increase the dose in increments of 50-100 mg/d every 5-7 days to achieve an effective dose; the usual maintenance dose is 300-500 mg/d or 4-7 mg / kg / d in 2 doses. *E* | Levetiracetam[d]; gabapentin[d]; lamotrigine[d]; valproic acid[d]. *E* |
| N03AE01 | Clonazepam<br><br>In lists: 3, 5 (A); 5 (B) | 23; 1.70 [1.45-1.94]; 2.00 | Risk of falls, paradoxical reactions | Start low–go slow;<br>0.5 mg/d. *E* | Levetiracetam[d]; gabapentin[d]; lamotrigine[d]; valproic acid[d]. *E* |
| N03AF01 | Carbamazepine<br><br>In lists: 5 (A); 5 (B) | 23; 2.17 [1.71-2.64]; 2.00 | Increased risk of SIADH-like syndrome; adverse events like carbamazepine-induced confusion and agitation, atrioventricular block and bradycardia | Adjust dose to the response and serum concentration. *E* | Levetiracetam[d]; gabapentin[d]; lamotrigine[d]; valproic acid[d]. *E* |

# Appendix 1: complete EU(7)-PIM list

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| N03AX11 | Topiramate<br><br>In lists: 5 (B) | 19; 2.53 [2.12-2.93]; 2.00 | Risk of cognitive-related dysfunction (e.g., confusion, psychomotor slowing) | Dosage adjustment may be indicated in older adults to the extent renal function is reduced. In cases of evident impaired renal function (CrCl <70 mL/min/1.73 m), use one-half the usual dose. *M*<br>Use initial dose of 25 mg/d and increase 25 mg/d weekly up to 100-200 mg/d. *E* | Levetiracetam[d]; gabapentin[d]; lamotrigine[d]; valproic acid[d]. *E* |
| ***N04*** | ***Antiparkinson drugs*** | | | | |
| ***N04A*** | ***Anticholinergic agents*** | | | | |
| N04AA01 | Trihexyphenidyl<br><br>In lists: 1, 5 (A); 2, 5, 6 (B) | 17; 1.53 [1.08-1.98]; 1.00 | Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia | Start low–go slow. *M* | Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E* |
| N04AA02 | Biperiden<br><br>In lists: 1, 3 (A); 2, 6 (B) | 20; 1.50 [1.78-1.82]; 1.00 | Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia | | Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E* |
| N04AA12 | Tropatepin<br><br>In lists: 1 (A); 2, 6 (B) | 15; 1.40 [1.05-1.75]; 1.00 | Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia | | Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E* |

# Appendix 1: complete EU(7)-PIM list

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| N04AC01 | Benzatropine<br><br>In lists: 2, 6 (B) | 14; 1.14 [0.93-1.35]; 1.00 | Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia | Start low–go slow. *M* | Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E* |
| ***N04B*** | ***Dopaminergic agents*** | | | | |
| N04BB01 | Amantadine<br><br>In lists: does not appear as PIM | 20; 1.70 [1.39-2.00]; 2.00 | Risk of anticholinergic and CNS side effects including orthostatic hypotension, falls, sedation, weakness, confusion, amnesia | Start with 100 mg/d in 2 divided daily doses. *E* | Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E* |
| N04BC01 | Bromocriptine<br><br>In lists: 3 (A); 6 (B) | 22; 1.86 [1.38-2.34]; 1.50 | Risk of CNS side effects | | Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E* |
| N04BC02 | Pergolide<br><br>In lists: 6 (B) | 16; 1.88 [1.45-2.30]; 2.00 | Adverse events include dyskinesia, dizziness, hallucinations, dystonia, confusion, somnolence, insomnia, anxiety, nausea | | Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E* |
| N04BC03 | Dihydroergocryptine<br><br>In lists: 1, 4 (A); 6 (B) | 13; 2.15 [1.42-2.89]; 2.00 | Unfavourable risk/benefit profile | | Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E* |

# Appendix 1: complete EU(7)-PIM list

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| N04BC04 | Ropinirole[c]<br><br>In lists: 6 (B) | 17; 2.47 [1.92-3.02]; 2.00 | Risk of orthostatic hypotension, hallucinations, confusion, somnolence, nausea | Start with three intakes of 0.25 mg per day, increase gradually by 0.25 mg per intake each week for four weeks, up to 3 mg/d. Afterwards the dose may be increased weekly by 1.5 mg/d up to 24 mg/d. *E* | Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E* |
| N04BC05 | Pramipexole[c]<br><br>In lists: 6 (A) | 19; 2.32 [1.86-2.77]; 2.00 | Side effects include orthostatic hypotension, GI tract symptoms, hallucinations, confusion, insomnia, peripheral oedema | Reduce dose in cases of moderate to severe renal failure. *M*<br>Start with three intakes of 0.125 per day, increase gradually by 0.125 mg per intake every five to seven days, up to 1.5 to 4.5 mg. *E* | Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E* |
| N04BC06 | Cabergoline[c]<br><br>In lists: 3 (A); 6 (B) | 18; 1.78 [1.25-2.31]; 1.50 | CNS side effects | | Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E* |
| N04BC08 | Piribedil<br><br>In lists: 1 (A); 6 (B) | 11; 1.73 [1.29-2.16]; 2.00 | Risk of orthostatic hypotension and falls | | Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E* |
| N04BC09 | Rotigotine<br><br>In lists: 6 (B) | 15; 2.33 [1.68-2.98]; 2.00 | Side effects include orthostatic hypotension, headache, nausea, fatigue, sleep disorder, sudden onset of sleep, somnolence | One patch per day, usually started at 2 mg/24h and titrated weekly by increasing the patch size in increments of 2 mg/24h, up to 6 mg/24h; do not stop the treatment abruptly: sudden withdrawal may produce a syndrome resembling neuroleptic malignant syndrome or akinetic crisis. *E* | Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E* |

# Appendix 1: complete EU(7)-PIM list

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| N04BD01 | Selegiline<br><br>In lists: 3 (A) | 21; 2.29 [1.78-2.79]; 2.00 | Increased risk of orthostatic hypotension and dizziness | Do not use at doses >10 mg/d; 6mg/24h patch recommended; increase dose cautiously, paying attention to changes in orthostatic blood pressure. *E* | Levodopa; carbidopa-levodopa; benserazide levodopa; irreversible inhibitor of monoamine oxidase as rasagiline. *E* |
| ***N05*** | ***Psycholeptics*** | | | | |
| ***N05A*** | ***Antipsychotics*** | | | | |
| N05AA01 | Chlorpromazine<br><br>In lists: 1, 5 (A); 2, 5, 6 (B) | 21; 1.38 [1.11-1.65]; 1.00 | Muscarinic-blocking drug; risk of orthostatic hypotension and falls; may lower seizure thresholds in patients with seizures or epilepsy | Start low–go slow; use one-third to one-half the normal adult dose for debilitated older adults; use maintenance doses of 300 mg or less; doses greater than 1 gram do not usually offer any benefit, but may be responsible for an increased incidence of adverse effects. *M* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |
| N05AA02 | Levomepromazine<br><br>In lists: 1, 3, 4 (A); 5, 6 (B) | 22; 1.36 [1.15-1.58]; 1.00 | Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia | Administer cautiously in cases of renal failure; start with doses of 5 to 10 mg in geriatric patients. *M* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |
| N05AA04<br>N05BA05 | Clorazepate-Acepromazine<br><br>In lists: 1 (A); 6 (B) | 14; 1.57 [1.08-2.06]; 1.00 | Protracted activity; risk of adverse effects such as drowsiness and falls | | Non-pharmacological treatment; antidepressant with anxiolytic profile (SSRI[e]). *E* |
| N05AA06 | Cyamemazine<br><br>In lists: 1 (A); 5, 6 (B) | 12; 1.58 [1.08-2.09]; 1.00 | Muscarinic-blocking drug | | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |

# Appendix 1: complete EU(7)-PIM list

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| N05AB02 | Fluphenazine<br><br>In lists: 1, 4, 5 (A); 5, 6 (B) | 21; 1.43 [1.09-1.77]; 1.00 | Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia | Start with oral dose of 1-2.5 mg/day. *M* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |
| N05AB03 | Perphenazine<br><br>In lists: 1, 3, 4, 5 (A); 5, 6 (B) | 20; 1.40 [1.05-1.75]; 1.00 | Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia | Start low–go slow; use one-third to one-half the usual adult dose. *M* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |
| N05AB04 | Prochlorperazine<br><br>In lists: 3, 5 (A); 5, 6 (B) | 17; 1.47 [1.10-1.84]; 1.00 | Risk of anticholinergic side effects, sedation, falls, QTc-prolongation | Reduce dose; start low–go slow. *E, M* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |
| N05AB06 | Trifluoperazine<br><br>In lists: 5 (A); 5, 6 (B) | 15; 1.80 [1.37-2.23]; 2.00 | Risk of hypotension and neuromuscular reactions | Start low go slow. *M* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |
| N05AC01 | Propericiazine (=Periciazine)<br><br>In lists: 1, 3 (A); 5, 6 (B) | 14; 1.79 [1.32-2.25]; 2.00 | Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia | | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |

# Appendix 1: complete EU(7)-PIM list

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| N05AC02 | Thioridazine<br><br>In lists: 4, 5 (A); 5, 6 (B) | 19; 1.37 [1.08-1.65]; 1.00 | Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia | Reduce dose. *M* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |
| N05AC04 | Pipotiazine<br><br>In lists: 1 (A); 5, 6 (B) | 14; 1.50 [1.06-1.94]; 1.00 | Muscarinic-blocking drug | Reduce dose; start with doses of less than 25 mg. *M* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |
| N05AD01 | Haloperidol (>2 mg single dose; >5mg/d)<br><br>In lists: 4, 5 (A); 5, 6 (B) | 22; 1.59 [1.33-1.85]; 2.00 | Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia | Use oral doses of 0.75-1.5 mg; use for the shortest period possible. *E* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |
| N05AD08 | Droperidol<br><br>In lists: 5, 6 (B) | 15; 1.73 [1.20-2.27]; 1.00 | Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia | Reduce dose in cases of renal failure and in older adults. *M* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |
| N05AE03 | Sertindole<br><br>In lists: 3 (A); 5, 6 (B) | 16; 1.63 [1.20-2.05]; 1.00 | Risk of hypotension, falls, QTc-prolongation | 10 mg/d. *E* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |

# Appendix 1: complete EU(7)-PIM list

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| N05AE04 | Ziprasidone<br><br>In lists: 5, 6 (B) | 16; 2.13 [1.51-2.74]; 2.00 | Risk of QTc-prolongation, torsades de pointes, sedation, insomnia and orthostatic hypotension. Not approved for the treatment of dementia-related psychosis. Risk of increased mortality, increased with higher doses, when used for behavioural problems in dementia may be similar to the risk for risperidone | Starting dose 20 mg/d. *E* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |
| N05AF01 | Flupentixole<br><br>In lists: 3 (A); 5, 6 (B) | 17; 1.71 [1.27-2.14]; 2.00 | Adverse effects like tiredness, dizziness, QTc-prolongation | Dose adjustment may be required. *M* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |
| N05AF03 | Chlorprothixen<br><br>In lists: 3 (A); 5, 6 (B) | 15; 1.87 [1.24-2.49]; 2.00 | Lower seizure threshold | Start low–go slow. *M* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |
| N05AF05 | Zuclopenthixol<br><br>In lists: 3 (A); 5, 6 (B) | 12; 1.50 [1.07-1.93]; 1.00 | Risk of hypotension, falls, extrapyramidal effects, QT-prolongation | Use low oral doses of 2.5-5 mg/d. *M* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |

# Appendix 1: complete EU(7)-PIM list

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| N05AG02 | Pimozide<br><br>In lists: 5, 6 (B) | 14; 1.57 [1.27-1.87]; 2.00 | Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality and risk of cerebrovascular accident in persons with dementia. More rarely: neuroleptic malignant syndrome and QT-prolongation | Recommended initial dose of 1 mg/d. *E*, *M* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |
| N05AH02 | Clozapine<br><br>In lists: 3, 4, 5 (A); 5, 6 (B) | 22; 1.55 [1.28-1.81]; 1.50 | Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia; increased risk of agranulocytosis and myocarditis | Start with 12.5 mg/d. *E*<br>Start low–go slow; reduce dose in cases of significant renal failure. *M* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |
| N05AH03 | Olanzapine (>10 mg/d)<br><br>In lists: 4, 5 (A); 5, 6 (B) | 22; 1.64 [1.29-1.99]; 1.50 | Anticholinergic and extrapyramidal side effects (tardive dyskinesia); parkinsonism; hypotonia; sedation; risk of falling; increased mortality in persons with dementia | | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |

# Appendix 1: complete EU(7)-PIM list

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| N05AN01 | Lithium<br><br>In lists: 3 (A); 5, 6 (B) | 22; 2.27 [1.80-2.75]; 2.00 | Narrow therapeutic window; cumulation in renal failure | 300-600 mg/d. *E*<br>Start low–go slow; it may be necessary to decrease dosage by as much as 50% in older adults to compensate for reduced clearance; dose reduction in cases of renal failure: GFR 10-50 ml/min, 50-75% of the usual dose; GFR <10 ml/min, 25-50% of the usual dose given at the normal dosage interval. *M, E* | Non-pharmacological treatment; SSRI[e], mirtazapine[d], trazodone. *E* |
| N05AX08 | Risperidone (>6 weeks)<br><br>In lists: 5 (A); 5, 6 (B) | 20; 2.45 [1.96-2.94]; 2.00 | Problematic risk-benefit profile for the treatment of behavioural symptoms of dementia; increased mortality, with higher dose, in patients with dementia | Use the lowest dose required (0.5-1.5 mg/d) for the shortest time period necessary. *E* For geriatric patients or in cases of severe renal failure (CrCl <30 mL/min), start with 0.5 mg twice daily; increase doses by 0.5 mg twice daily; increases above 1.5 mg twice daily should be done at intervals of at least 1 week; slower titration may be necessary. For geriatric patients, if once-daily dosing desired, initiate and titrate on a twice-daily regimen for 2 to 3 days to achieve target dose and switch to once-daily dosing thereafter. *M* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |
| N05AX12 | Aripiprazole<br><br>In lists: 5 (A); 5, 6 (B) | 16; 2.60 [1.46-2.66]; 2.00 | Risk of increased mortality when used for behavioural problems in dementia | Use the lowest dose required (7-12mg/d) for the shortest time period necessary. *E* | Non-pharmacological treatment; risperidone (<6 weeks), olanzapine (<10 mg/d), haloperidol (<2 mg single dose; <5mg/d); quetiapine[d]. *E* |
| ***N05B*** | ***Anxiolytics*** | | | | |

# Appendix 1: complete EU(7)-PIM list

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| N05BA01 | Diazepam<br><br>In lists: 1, 4, 5 (A); 2, 5, 6 (B) | 23; 1.61 [1.32-1.89]; 2.00 | Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P, M U*se initial oral dose of 2-2.5 mg once a day to twice a day. *M* | Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P*<br>If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C. |
| N05BA02 | Chlordiazepoxide<br><br>In lists: 1, 4, 5 (A); 5, 6 (B) | 19; 1.37 [1.08-1.66]; 1.00 | Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*<br>Reduce dose; for older adults use daily oral dose of 5 mg two to four times a day; in cases of severe renal failure (CrCl <10 ml/min), decrease dose by 50%. *M* | Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P*<br>If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C. |
| N05BA03 | Medazepam<br><br>In lists: 4 (A); 2, 5, 6 (B) | 14; 1.50 [1.12-1.88]; 1.00 | Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*<br>Reduce dose for older adults and for patients with renal failure. *M* | Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P*<br>If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C. |

# Appendix 1: complete EU(7)-PIM list

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| N05BA04 | Oxazepam (>60 mg/d)<br><br>In lists: 1, 4, 5 (A); 5, 6 (B) | 22; 1.50 [1.20-1.80]; 1.00 | Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*<br>Use doses of 10-20 mg/d; maximum dose: 30 mg/d. *E* | Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P*<br>If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C. |
| N05BA05 | Dipotassium clorazepate<br><br>In lists: 1, 4 (A); 2, 5, 6 (B) | 15; 1.40 [0.99-1.81]; 1.00 | Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* | Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P*<br>If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C. |
| N05BA06 | Lorazepam (>1 mg/d)<br><br>In lists: 1, 4, 5 (A); 5, 6 (B) | 21; 1.67 [1.23-2.11]; 1.00 | Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression | Reduce dose; use doses of 0.25-1 mg/d. *E* | Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P*<br>If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C. |

# Appendix 1: complete EU(7)-PIM list

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| N05BA08 | Bromazepam<br><br>In lists: 1, 4 (A); 5, 6 (B) | 19; 1.63 [1.30-1.96]; 2.00 | Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* | Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P*<br>If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C. |
| N05BA09 | Clobazam<br><br>In lists: 1, 3, 4 (A), 5, 6 (B) | 17; 1.41 [1.09-1.73]; 1.00 | Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *E, P*<br>Reduce dose; start with 5 mg/d orally and titrate no faster than every 7 days to 10-20 mg/d in 2 divided doses, depending on weight. If well tolerated, further titrate if necessary starting on day 21 to a maximum of 20-40 mg/d, depending on weight; older adults may receive half of the usual adult dose. *M* | Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P*<br>If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C. |

# Appendix 1: complete EU(7)-PIM list

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| N05BA11 | Prazepam<br><br>In lists: 1, 4 (A); 2, 5 (B) | 16; 1.31 [0.99-1.63]; 1.00 | Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*<br>Reduce dose; for older adults or debilitated patients, start with 10-15 mg/d orally (in divided doses). *M* | Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P*<br>If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C. |
| N05BA12 | Alprazolam<br><br>In lists: 1, 3, 4, 5 (A); 5, 6 (B) | 22; 1.91 [1.40-2.42]; 2.00 | Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*<br>Starting dose 0.25mg/12h. *E*<br>Immediate release tablets (including orally disintegrating tablets): start with 0.25 mg administered two to three times a day, and titrate as tolerated; extended-release tablets: start with 0.5 mg once daily, gradually increase as needed and tolerated. *M* | Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P*<br>If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C. |
| N05BA13 | Halazepam<br><br>In lists: 6 (B) | 9; 2.00 [1.33-2.67]; 2.00 | Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression | Reduce dose; start with 20 mg once or twice daily for patients 70 years or older; adjust dose according to response. *M, E* | Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P*<br>If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C. |

# Appendix 1: complete EU(7)-PIM list

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| N05BA16 | Nordazepam<br><br>In lists: 1 (A); 2, 5, 6 (B) | 12; 1.75 [1.20-2.30]; 1.50 | Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression | Reduce dose. *M* | Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P*<br>If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C. |
| N05BA18 | (Ethyl-) Loflazepate<br><br>In lists: 1 (A); 5, 6 (B) | 12; 1.75 [1.20-2.30]; 1.50 | Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression | Reduce dose. *M* | Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P*<br>If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C. |
| N05BA21 | Clotiazepam (>5 mg/d)<br><br>In lists: 1 (A); 5, 6 (B) | 16; 1.56 [1.17-1.95]; 1.00 | Risk of falling with hip fracture; prolonged reaction times; psychiatric reactions (can also be paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression | Reduce dose. *M* | Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P*<br>If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C. |

# Appendix 1: complete EU(7)-PIM list

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| N05BC01 | Meprobamate<br><br>In lists: 1, 5 (A) | 18; 1.33 [1.09-1.57]; 1.00 | Risk of drowsiness, confusion | Reduce dose; start low–go slow; increase dosage interval in cases of renal failure; administer every 6 hours in cases of mild renal failure (GFR>50 ml/min), every 9 to 12 hours in cases of moderate renal failure (10 to 50 ml/min) and every 12 to 18 hours in cases of severe renal failure. *M* | Non-pharmacological treatment; low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); antidepressants with anxiolytic profile (SSRI[e]). *E, P*<br>If used as hypnotics / sedatives: see alternatives proposed for drugs coded with N05C. |
| ***N05C*** | ***Hypnotics and sedatives*** | | | | |
| N05CC01 | Chloralhydrate<br><br>In lists: 4, 5 (A); 5 (B) | 17; 1.53 [1.21-1.85]; 1.00 | Risk of dizziness and electrocardiographic changes. Higher risk in cases of renal failure | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*<br>For the management of insomnia in geriatric patients, use initial oral dose of 250 mg/d. *M* | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E*, *P* |
| N05CD01 | Flurazepam<br><br>In lists: 4, 5 (A); 5, 6 (B) | 20; 1.25 [1.04-1.46]; 1.00 | Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*<br>Start with 15 mg/d. *M* | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E*, *P* |

# Appendix 1: complete EU(7)-PIM list

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| N05CD02 | Nitrazepam<br><br>In lists: 1, 3, 4 (A); 2, 5, 6 (B) | 20; 1.40 [1.12-1.68]; 1.00 | Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*<br>Use 2.5-5 mg/d at bedtime. *E, M* | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P* |
| N05CD03 | Flunitrazepam<br><br>In lists: 1, 4 (A); 5, 6 (B) | 22; 1.32 [1.03-1.60]; 1.00 | Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. P Reduce dose, e.g. 0.5 mg/d; start low–go slow. *E, M* For induction of anaesthesia in older, poor-risk adults, titrate dose carefully; administer in small intravenous increments of 0.3 to 0.5 mg, at 30-second intervals. *M* | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P* |
| N05CD04 | Estazolam<br><br>In lists: 1, 5 (A); 5, 6 (B) | 12; 1.42 [0.99-1.84]; 1.00 | Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression | For older adults who are debilitated or have a low weight, consider initial dose of 0.5 mg at bedtime. *M* | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P* |

# Appendix 1: complete EU(7)-PIM list

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| N05CD05 | Triazolam<br><br>In lists: 1, 2, 3, 4, 5 (A); 5, 6 (B) | 18; 1.67 [1.18-2.15]; 1.00 | Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*<br>Reduce dose: 0.125-0.25 mg/d at bedtime Start low–go slow. *E, M* | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P* |
| N05CD06 | Lormetazepam (>0.5 mg/d)<br><br>In lists: 1, 4 (A); 5, 6 (B) | 17; 1.47 [1.15-1.79]; 1.00 | Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P* |
| N05CD07 | Temazepam<br><br>In lists: 1, 4, 5 (A); 5, 6 (B) | 17; 1.88 [1.34-2.42]; 2.00 | Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*<br>Start with 7.5 mg/d and watch individual response. *M* | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P* |
| N05CD08 | Midazolam<br><br>In lists: 3 (A); 5, 6 (B) | 22; 2.45 [1.93-2.98]; 2.50 | Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression | Reduce dose to 50% of the dose used in healthy younger adults; start with 0.5-1 mg/d. *E*<br>In cases of severe renal failure (CrCl <10 ml/min), the dose should be decreased by 50%. *M* | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E, P* |

# Appendix 1: complete EU(7)-PIM list

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| N05CD09 | Brotizolam (>0.125 mg/d)<br><br>In lists: 4 (A); 5, 6 (B) | 15; 1.73 [1.29-2.18]; 2.00 | Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression | Reduce dose; start low–go slow. *E*<br>Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E*, *P* |
| N05CD10 | Quazepam<br><br>In lists: 5 (A); 2, 5, 6 (B) | 11; 1.82 [1.31-2.32]; 2.00 | Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression | Reduce dose; start low–go slow. *E* | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E*, *P* |
| N05CD11 | Loprazolam (>0.5 mg/d)[c]<br><br>In lists: 1 (A); 5, 6 (B) | 16; 1.63 [1.24-2.01]; 1.50 | Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression | Reduce dose; start low–go slow.<br>Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*; *E* | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E*, *P* |
| N05CF01 | Zopiclone (>3.75 mg/d)<br><br>In lists: 1, 4, 5, 6 (A); 5 (B) | 22; 2.27 [1.82-2.73]; 2.00 | Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E*, *P* |

# Appendix 1: complete EU(7)-PIM list

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| N05CF02 | Zolpidem (>5 mg/d)<br><br>In lists: 1, 4, 5, 6 (A); 5 (B) | 22; 2.09 [1.66-2.52]; 2.00 | Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E*, *P* |
| N05CF03 | Zaleplone (>5 mg/d)<br><br>In lists: 3, 4, 5, 6 (A); 5 (B) | 17; 1.94 [1.56-2.33]; 2.00 | Risk of falls and hip fracture, prolonged reaction time, psychiatric reactions (which can be paradoxical, e.g. agitation, irritability, hallucinations, psychosis), cognitive impairment and depression | Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E*, *P* |
| N05CM02 | Clomethiazole<br><br>In lists: 5 (B) | 13; 2.23 [1.53-2.94]; 2.00 | Risk of respiratory depression | Reduce dose. *E*, *M*<br>Use sedative dose 500-1000 mg at bedtime. *M* | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E*, *P* |
| N05CM06 | Propiomazine<br><br>In lists: 5, 6 (B) | 10; 1.20 [0.90-1.50]; 1.00 | Risk of antimuscarinic effects, sedation and hypotension, dry mouth and extrapyramidal reactions | | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E*, *P* |

# Appendix 1: complete EU(7)-PIM list

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| No ATC | Aceprometazine<br><br>In lists: 1 (A); 6 (B) | 14; 1.64 [1.21-2.07]; 1.50 | Muscarinic-blocking drug, risk of cognitve impairment | | Non-pharmacological treatment; mirtazapine[d]; passiflora, low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d); trazodone. *E*, *P* |
| ***N06*** | ***Psychoanaleptics*** | | | | |
| ***N06A*** | ***Antidepressants*** | | | | |
| N06AA01 | Desipramine<br><br>In lists: 2, 5, 6 (B) | 14; 1.50 [1.12-1.88]; 1.00 | Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling | Use doses of 25-100 mg/d; maximum dose: 150 mg/d. *M* | Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E* |
| N06AA02 | Imipramine<br><br>In lists: 1, 4, 5 (A); 2, 5, 6 (B) | 20; 1.50 [1.14-1.86]; 1.00 | Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling | Start at half the usual daily dose, increase slowly; reduce dose. *P*<br>Use doses of 25-50 mg/d at bedtime; maximum dose: 100 mg/d. *E* | Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E* |

# Appendix 1: complete EU(7)-PIM list

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| N06AA04 | Clomipramine<br><br>In lists: 1, 3, 4, 5 (A); 1, 2, 5, 6 (B) | 21; 1.48 [1.14-1.82]; 1.00 | Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling | Start with half the usual daily dose, increase slowly; reduce dose. *E, M, P*<br>Starting dose 10-20 mg/d, max. 250 mg/day. *E* | Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E* |
| N06AA06 | Trimipramine<br><br>In lists: 1, 3, 4, 5 (A); 2, 5, 6 (B) | 16; 1.44 [1.10-1.77]; 1.00 | Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling | Start at half the usual daily dose, increase slowly; reduce dose. *M, P*<br>Start with 50 mg/d and do not exceed 100 mg/d. *M* | Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E* |
| N06AA09 | Amitriptyline<br><br>In lists: 1, 3, 4, 5 (A); 2, 5, 6 (B) | 22; 1.68 [1.26-2.10]; 1.00 | Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling | Start at half the usual daily dose, increase slowly; reduce dose; start with 10 mg 3 times per day and 20 mg at bedtime. *M, E, P*<br>Its use for treating neuropathic pain may be considered appropriate, with benefits overweighing the risks. *E* | Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E* |

# Appendix 1: complete EU(7)-PIM list

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| N06AA10 | Nortriptyline<br><br>In lists: 3 (A); 2, 5, 6 (B) | 21; 2.10 [2.52-2.67]; 2.00 | Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling | Use 30-50 mg/d in divided doses. *E, M*<br>Its use for treating neuropathic pain may be considered appropriate, with benefits overweighing the risks. *E* | Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E* |
| N06AA12 | Doxepin<br><br>In lists: 1, 3, 4, 5 (A); 2, 5, 6 (B) | 20; 1.40 [1.05-1.75]; 1.00 | Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling | Start at half the usual daily dose, increase slowly. *P*<br>0.5 mg/d. *E*<br>3 mg/d, maximum dose: 6 mg/d. *M* | Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E* |
| N06AA16 | Dosulepin<br><br>In lists: 1 (A); 2, 5, 6 (B) | 17; 1.29 [1.05-1.54]; 1.00 | Muscarinic-blocking agents with cardiotoxicity when overdosed | Start with 50-75 mg/d. *E, M*<br>Reduce dose in cases of renal failure. *M* | Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E* |
| N06AA17 | Amoxapine<br><br>In lists: 1 (A); 2, 5, 6 (B) | 14; 1.50 [1.12-1.88]; 1.00 | Muscarinic-blocking agents with cardiotoxicity when overdosed | Start with 25 mg given two to three times per day; by the end of the first week, increase to 50 mg given two to three times per day. 2-3x/d. *M* | Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| N06AA21 | Maprotiline<br><br>In lists: 1, 4 (A); 2, 5, 6 (B) | 21; 1.43 [1.09-1.77]; 1.00 | Peripheral anticholinergic side effects (e.g. constipation, dry mouth, orthostatic hypotension, cardiac arrhythmia); central anticholinergic side effects (drowsiness, inner unrest, confusion, other types of delirium); cognitive deficit; increased risk of falling | Start at half the usual daily dose, increase slowly; reduce dose. *P, E*<br>Start with 25 mg/d, increase by 25 mg increments up to 50-75 mg/d. *M* | Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E* |
| N06AB03 | Fluoxetine<br><br>In lists: 3, 4 (A); 2, 5, 6 (B) | 22; 2.27 [1.80-2.75]; 2.00 | CNS side effects (nausea, insomnia, dizziness, confusion); hyponatremia | Reduce dose; start with 20 mg/d; maximum dose also 20 mg/d; avoid administration at bedtime. *E, M* | Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E* |
| N06AB05 | Paroxetine<br><br>In lists: 2, 5, 6 (B) | 21; 2.29 [1.99-2.58]; 2.00 | Higher risk of all-cause mortality, higher risk of seizures, falls and fractures. Anticholinergic adverse effects | For older adults or for patients with renal failure, start immediate-release tablets with 10 mg/d (12.5 mg/d if controlled-release tablets), increased by 10 mg/d (12.5 mg/d if controlled-release tablets), up to 40 mg/d (50 mg/d if controlled-release tablets). *E, M* | Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E* |
| N06AB08 | Fluvoxamine<br><br>In lists: 2, 5, 6 (B) | 20; 2.05 [1.69-2.41]; 2.00 | Higher risk of all-cause mortality, self-harm, falls, fractures and hyponatraemia | Reduce dose for older adults and patients with renal failure; start with 50-100 mg/d; titrate slowly. *E, M* | Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E* |
| N06AF04 | Tranylcypromine<br><br>In lists: 4 (A) | 15; 1.73 [1.06-2.41]; 1.00 | Irreversible MAO inhibitor. Risk of hypertensive crises, cerebral hemorrhage and malignant hyperthermia | Reduce dose: 30 mg/d; maximum dose: 60 mg/d. *E* | Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E* |
| N06AX12 | Bupropion<br><br>In lists: 5 (B) | 20; 2.30 [1.77-2.83]; 2.00 | May lower seizure threshold | Reduce dose and dosing frequency for older adults and patients with renal failure. *M* | Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| N06AX16 | Venlafaxine<br><br>In lists: does not appear as PIM | 21; 2.43 [2.06-2.80]; 2.00 | Higher risk of all-cause mortality, attempted suicide, stroke, seizures, upper gastrointestinal bleeding, falls and fracture | Start with 25-50 mg, two times per day and increase by 25 mg/dose; for extended-release formulation start with 37.5 mg once daily and increase by 37.5 mg every 4-7 days as tolerated. *E*<br>Reduce the total daily dose by 25-50% in cases of mild to moderate renal failure. *M* | Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E* |
| N06AX18 | Reboxetine<br><br>In lists: does not appear as PIM | 15; 1.87 [1.46-2.28]; 2.00 | Side effects (dry mouth, constipation, headache, drowsiness, dizziness, excessive sweating and insomnia). Higher risk of conduction disturbances, tachycardia, occasional atrial and ventricular ectopy | Reduce dose in cases of renal failure; start with 2 mg two times per day in cases of renal failure; for older adults, reduce dose to 4-6 mg/d. *M* | Non-pharmacological treatment, SSRI (except PIM: fluoxetine, paroxetine, fluvoxamine)[e], mirtazapine[d], trazodone. *E* |
| ***N06B*** | ***Psychostimulants, agents used for ADHD and nootropics*** | | | | |
| N06BA04 | Methylphenidat<br><br>In lists: 2 (A); 5 (B) | 19; 1.63 [1.14-2.12]; 1.00 | May cause or worsen insomnia; concern due to CNS-altering effects; concern due to appetite-supressing effects | | Non-pharmacological treatment; consider pharmacotherapy of Alzheimer-type dementia: acetylcholinesterase, memantine[d]. *E* |
| N06BX03 | Piracetam<br><br>In lists: 1, 4 (A) | 19; 2.05 [1.40-2.70]; 2.00 | No efficacy proven; unfavorable risk/benefit profile | Reduce dose for older adults and for patients with renal failure. *M* | Non-pharmacological treatment; consider pharmacotherapy of Alzheimer-type dementia: acetylcholinesterase, memantine[d] *E* |
| ***N06D*** | ***Anti-dementia drugs*** | | | | |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| N06DX02 | Ginkgo biloba<br><br>In lists: 1 (A) | 20; 2.05 [1.42-2.68]; 1.50 | No efficacy proven; increased risk of orthostatic hypotension and fall | | Non-pharmacological treatment; consider pharmacotherapy of Alzheimer-type dementia: acetylcholinesterase, memantine[d]. *E* |
| C04AE01 | Ergoloid mesylate (dihydroergotoxine)<br><br>In lists: 1, 4 (A); 6 (B) | 21; 1.48 [1.03-1.92]; 1.00 | No efficacy proven; unfavourable risk/benefit profile; increased risk of orthostatic hypotension and fall | 1 mg three times daily. *M* | Non-pharmacological treatment; consider pharmacotherapy of Alzheimer-type dementia: acetylcholinesterase, memantine[d]. *E* |
| ***N07*** | ***Other nervous system drugs*** | | | | |
| ***N07A*** | ***Parasympathomimetics*** | | | | |
| N07AB02 | Bethanechol<br><br>In lists: does not appear as PIM | 14; 1.71 [1.24-2.19]; 1.50 | Anticholinergic bladder relaxants may cause obstruction in persons with benign prostatic hyperplasia | | |
| **R** | **Respiratory system** | | | | |
| ***R01*** | ***Nasal preparations*** | | | | |
| ***R01B*** | ***Nasal decongestants for systemic use*** | | | | |
| R01BA01 | Norephedrine (=Phenylpropanolamine)<br><br>In lists: 3 (A) | 21; 2.05 [1.56-2.54]; 2.00 | Higher risk of elevation of blood pressure secondary to sympathomimetic activity | | |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| R01BA02 | Pseudoephedrine<br><br>In lists: 5 (B) | 21; 2.00 [1.52-2.48]; 2.00 | Higher risk of elevation of blood pressure secondary to sympathomimetic activity | Adjust dose in cases of renal failure; 15-30 mg three times per day for the treatment of urinary incontinence in older adults. *M* | |
| ***R03*** | ***Drugs for obstructive airway diseases*** | | | | |
| ***R03C*** | ***Adrenergics for systemic use*** | | | | |
| R03CC03 | Terbutaline (oral)<br><br>In lists: does not appear as PIM | 20; 1.75 [1.25-2.25]; 1.00 | Higher risk of adverse effects as compared to the inhaled form | Use 50% of the usual dose for patients with moderate renal failure (GFR 10-50 ml/min); avoid in cases of severe renal failure (GFR <10 ml/min). *M* | Inhaled form. *E* |
| ***R03D*** | ***Other systemic drugs for airway diseases*** | | | | |
| R03DA04 | Theophylline<br><br>In lists: 3 (A); 5, 6 (B) | 22; 2.27 [1.76-2.79]; 2.00 | Higher risk of CNS stimulant effects | Start with a 25% reduction compared to the doses for younger adults. *E*<br>Start with a maximum dose of 400 mg/d; monitor serum levels and reduce doses if needed; for healthy older adults (>60 years), theophylline clearance is decreased by an average of 30%. *M* | |
| ***R05*** | ***Cough and cold preparation*** | | | | |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| ***R05D*** | ***Cough suppressants, excl. combinations with expectorants*** | | | | |
| R05DA01 | Ethylmorphine<br><br>In lists: 3 (A) | 21; 1.90 [1.43-2.38]; 2.00 | No clear evidence in the treatment of acute cough | | |
| R05DA04 | Codeine (>2 weeks)<br><br>In lists: 6 (B) | 21; 2.00 [1.68-2.32]; 2.00 | Higher risk of adverse events (hypotension, sweating, constipation, vomiting, dizziness, sedation, respiratory depression). Avoid use for longer than 2 weeks for persons with chronic constipation without concurrent use of laxatives and for persons with renal failure | Start treatment cautiously for older adults (especially in cases of renal failure); start low–go slow; reduce dose to 75% of the usual dose if GFR 10-50 ml/min and to 50% if GFR <10 ml/min. *M* | If used for pain management consider alternative drugs proposed for analgesics: paracetamol; ibuprofen (≤3 x 400 mg/d or for a period shorter than one week); naproxen (≤2 x 250 mg/d or for a period shorter than one week). *E*<br>Opioids with lower risk of delirium (e.g., tilidine/naloxone, morphine[d], oxycodone, buprenorphine, hydromorphone). *E, P* |
| R05DA09 | Dextrometorphan<br><br>In lists: 3 (A) | 20; 2.10 [1.55-2.65]; 2.00 | No clear evidence in the treatment of acute cough | | |
| ***R06*** | ***Antihistamines for systemic use*** | | | | |
| ***R06A*** | ***Antihistamines for systemic use*** | | | | |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| R06AA02 | Diphenhydramine<br><br>In lists: 1, 4, 5 (A); 5, 6 (B) | 21; 1.48 [1.20-1.75]; 1.00 | Anticholinergic side effects, sedation, dizziness; electrocardiographic changes | Reduce dose for older adults; start low–go slow. *M*<br>Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P*<br>Increase the dosing interval to every 6 hours in cases of mild renal failure (GFR >50 ml/min), every 6-12 hours in cases of moderate renal failure (GFR 10-50 ml/min), and every 12-18 hours in cases of severe renal failure (GFR <10 ml/min). *M* | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*<br>If used for insomnia: non-pharmacological treatment, passiflora, mirtazapine[d], trazodone. *E*<br>Consider low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d) (suggested aternatives to hypnotic/sedative drugs) |
| R06AA04 | Clemastine<br><br>In lists: 4 (A); 5, 6 (B) | 22; 1.77 [1.37-2.18]; 2.00 | Anticholinergic side effects (e.g. constipation, dry mouth); impaired cognitive performance; electrocardiographic changes (prolonged QT) | Reduce dose. *M* | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |
| R06AA08 | Carbinoxamine<br><br>In lists: 1 (A); 5, 6 (B) | 14; 1.64 [1.16-2.13]; 1.00 | Muscarinic-blocking drug; higher risk of sedation, drowsiness | Start low–go slow. *M* | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| R06AA09 | Doxylamine<br><br>In lists: 1, 4, 5 (A); 5, 6 (B) | 16; 1.38 [1.05-1.70]; 1.00 | Anticholinergic side effects, dizziness; electrocardiographic changes | Reduce dose. *M*<br>Use the lowest possible dose, up to half of the usual dose, taper in and out, shortest possible duration of treatment. *P* | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*<br>If used for insomnia: non-pharmacological treatment, passiflora, mirtazapine[d], trazodone. *E*<br>Consider low doses of short-acting benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d) (suggested aternatives to hypnotic/sedative drugs) |
| R06AB01 | Brompheniramine<br><br>In lists: 1 (A); 5, 6 (B) | 15; 1.60 [1.14-2.06]; 1.00 | Muscarinic-blocking drug; higher risk of sedation, drowsiness | | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |
| R06AB02 | Dexchlorpheniramine<br><br>In lists: 1, 4, 5 (A); 5, 6 (B) | 17; 1.47 [1.10-1.84]; 1.00 | Anticholinergic side effects (e.g. confusion, sedation) | 5 mg/d. *E* | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |
| R06AB03 | Dimetindene<br><br>In lists: 4 (A); 6 (B) | 16; 1.56 [1.13-2.00]; 1.00 | Anticholinergic side effects (e.g. constipation, dry mouth); impaired cognitive performance; electrocardiographic changes (prolonged QT) | | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| R06AB04 | Chlorpheniramine (=Chlorphenamine)<br><br>In lists: 1, 4 (A); 5, 6 (B) | 17; 1.41 [1.05-1.78]; 1.00 | Anticholinergic side effects (e.g. constipation, dry mouth); impaired cognitive performance; electrocardiographic changes (prolonged QT) | | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |
| R06AB05 | Pheniramine<br><br>In lists: 1 (A); 6 (B) | 15; 1.40 [1.12-1.68]; 1.00 | No proven efficacy; muscarinic-blocking agents; higher risk of confusion, sedation | | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |
| R06AB52 | Dexchlorpheniramine-Betamethason<br><br>In lists: 1, 5 (A); 5, 6 (B) | 16; 1.31 [0.99-1.63]; 1.00 | Muscarinic-blocking drug; higher risk of sedation, drowsiness | | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |
| R06AC04 | Tripelennamine<br><br>In lists: 6 (B) | 16; 1.75 [1.22-2.28]; 1.00 | Anticholinergic side effects (e.g. confusion, sedation) | | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |
| R06AD01 | Alimemazine<br><br>In lists: 1 (A); 6 (B) | 13; 1.31 [1.02-1.60]; 1.00 | Muscarinic-blocking drug; higher risk of sedation, drowsiness | Reduce dose; start low–go slow. *M* | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| R06AD02 | Promethazine<br><br>In lists: 1, 5 (A); 5, 6 (B) | 18; 1.44 [1.14-1.75]; 1.00 | Anticholinergic side effects (e.g. confusion, sedation) | Reduce dose; start low–go slow. *M*<br>Reduce starting dose to 6.25-12.5 mg for iv injection. *M* | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*<br>If used for insomnia: non-pharmacological treatment, passiflora, mirtazapine[d], trazodone. *E*<br>Consider low doses of short to intermediate benzodiazepines such as lormetazepam (≤0.5 mg/d), brotizolam (≤0.125 mg/d); zolpidem (≤5 mg/d), zopiclon (≤3.75 mg/d), zaleplon (≤5 mg/d) (suggested aternatives to hypnotic/sedative drugs) |
| R06AD07 | Mequitazine<br><br>In lists: 1 (A); 6 (B) | 12; 1.33 [0.92-1.75]; 1.00 | Anticholinergic side effects (e.g. confusion, sedation) | | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |
| R06AD08 | Oxomemazine<br><br>In lists: 1 (A); 6 (B) | 11; 1.36 [0.91-1.82]; 1.00 | No proven efficacy; muscarinic-blocking agents; higher risk of confusion, sedation | | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |
| R06AE01 | Buclizine<br><br>In lists: 1 (A); 6 (B) | 12; 1.33 [0.92-1.75]; 1.00 | No proven efficacy; muscarinic-blocking agents; higher risk of confusion, sedation | | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |
| R06AE03 | Cyclizine<br><br>In lists: 3 (A); 6 (B) | 17; 1.53 [1.21-1.85]; 1.00 | No proven efficacy; muscarinic-blocking agents; higher risk of confusion, sedation | | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |

# Appendix 1: complete EU(7)-PIM list

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|---|---|---|---|---|---|
| R06AE05 | Meclozine<br><br>In lists: 1, 3 (A); 6 (B) | 16; 1.44 [1.05-1.83]; 1.00 | No proven efficacy; muscarinic-blocking agents; higher risk of confusion, sedation | | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |
| R06AX02 | Cyproheptadine<br><br>In lists: 1, 5 (A); 5, 6 (B) | 18; 1.28 [0.99-1.56]; 1.00 | Anticholinergic side effects (e.g. confusion, sedation) | | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |
| R06AX07 | Triprolidine<br><br>In lists: 1, 4, 5 (A); 5, 6 (B) | 14; 1.43 [0.99-1.87]; 1.00 | Anticholinergic side effects (e.g. constipation, dry mouth); impaired cognitive performance; electrocardiographic changes (prolonged QT) | | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |
| R06AX12 | Terfenadine<br><br>In lists: does not appear as PIM | 17; 1.88 [1.52-2.24]; 2.00 | Adverse effects include prolonged QT interval, tachyarrhythmia, weakness, anxiety, agitation | Administer one tablet daily if CrCl <40 ml/min. *M* | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |
| R06AX22 | Ebastine<br><br>In lists: does not appear as PIM | 19; 2.26 [1.84-2.68]; 2.00 | Adverse events include impaired psychomotor performance with 50 mg or greater, somnolence, tachycardia, fatigue | Avoid / reduce dose if severe renal failure. *M* | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |
| R06AX23 | Pimethixene<br><br>In lists: 1 (A); 6 (B) | 11; 1.36 [0.91-1.82]; 1.00 | No proven efficacy; muscarinic-blocking agents; higher risk of confusion, sedation | | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E* |
| N05BB01 | Hydroxyzine<br><br>In lists: 1, 3, 4, 5 (A); 5 (B) | 20; 1.40 [1.12-1.68]; 1.00 | Anticholinergic side effects (e.g. constipation, dry mouth); impaired cognitive performance, confusion, sedation; electrocardiographic changes (prolonged QT) | Reduce dose to at least 50% less than dose used for healthy younger adults. *E, M* | Non-sedating, non-anticholinergic antihistamines[f] like loratadine, cetirizine, but not terfenadine (which is PIM). *E*<br>Alternative therapies depending on indication. *E* |

# Appendix 1: complete EU(7)-PIM list

[a]Category A (A): precisely this active substance is named as a PIM. Category B (B): i) this active substance is characterized as a PIM only in the case of certain clinical conditions or comorbidities or ii) this active substance is not specifically named but considered as a PIM drug class (e.g. anticholinergics or long-acting benzodiazepines). [b]Decisive Delphi round: Delphi round in which consensus was reached (1st Delphi round: 26 experts participated; 2nd Delphi round: 24 experts participated; these numbers comprise two groups of 2 and 3 experts, respectively, doing joint assessments). [c]Drug reevaluated during the last brief survey. [d]Caution, this drug was judged to be questionable PIM. [e]The following drugs belonging to this medication group were judged to be questionable PIM: citalopram, sertraline, escitalopram. [f]In the group of non-sedating antihistamines, only loratadine was evaluated and judged to be questionable PIM; other drugs such as cetirizine were not evaluated. [g]ATC according to WIDO (2013) [46]; [h]ATC according to WHO ATC-code website 2013; [i]ATC according to WHO ATC-code website 2014.
*E*: Experts; *M*: Micromedex® [32]; *P*: PRISCUS list [22]; *L*: Laroche et al (2007) [3]; *McL*: McLeod et al (1997) [26]; *B*: Beers list (2012) [18]. ACE: Angiotensin-Converting-Enzyme; ADHD: Attention Deficit Hyperactivity Disorder; CNS: Central Nervous System; ECG: Electrocardiographic; GI: Gastrointestinal; PIM: Potentially Inappropriate Medication; PPI: Proton-Pump Inhibitors; SIADH: Syndrome of Inappropriate Antidiuretic Hormone secretion. Dosing abbreviations: CrCl: Creatinine Clearance; d: day; GFR: Glomerular Filtration Rate; iv: intravenous; mcg: micrograms; mg: milligram; min: minute; mL: millilitre; q: every.
Note: if nothing is stated under "Dose adjustment / special considerations of use", this means that no suggestion was made either by the experts or in Micromedex®.

The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. European Journal of Clinical Pharmacology.
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