

SUPPORTING INFORMATION ANNEXES

Safer prescription of drugs: Impact of the PREFASEG System to Aid Clinical Decision-making in

Primary Care in Catalonia

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Annex Table 1. Description of the types of PREFASEG alerts

MRP alert	Description
Interactions	
Contraindications for health problems	Detection of patients with absolute contraindications defined in the ICS Clinical Practice Guidelines and the CatSalut Harmonisation Guidelines for the following pathologies: Diabetes mellitus II, heart failure, chronic kidney disease, hypercholesterolemia, and depression.
Contraindications for clinical variables	Detection of patients with contraindications due to renal insufficiency: <ul style="list-style-type: none"> • Severe renal insufficiency: glomerular filtration of 15 or 30 mL/min/1.73 m² • End-stage renal failure: glomerular filtration <15 mL/min/1.73 m² Detection of patients with contraindications due to abnormal potassium levels: <ul style="list-style-type: none"> • Hypokalaemia <3.5 mmol/L • Hyperkalaemia >5.5 mmol/L.
Contraindications with a specific AEMPS alert	Detection of patients with contraindications due to the use of an active ingredient that has a relevant safety alert from the Spanish Agency for Medicines and Health Products (AEMPS). The active ingredients included are: Aliskiren, citalopram, escitalopram, cilostazol, trimetazidine, raloxifene and bazedoxifene, COXIBS, diclofenac, aceclofenac, ivabradine, agomelatine, canagliflozin, and the “Triple Whammy” (i.e., NSAIDs + diuretics + RAS inhibitors).
Teratogenic pharmaceuticals	Detection of female patients with contraindications based on the use of active ingredients in pregnancy (diagnoses registered in the ECW). Teratogenic drugs are considered those who fall into categories D and X of the old FDA Reproductive Risk Classification. It should be noted that in June 2015, the FDA decided to remove this classification.
Drugs advised against for use in geriatrics	Detection of patients >75 years of age who are taking any inappropriate medication that exhibits a more unfavourable risk-benefit profile due to their age.
Duplicate therapies	Detection of patients who are classed as receiving a non-beneficial prescription of two or more drugs with the same active ingredient (alone or in combination) and/or with the same pharmacological action. Duplicities considered relevant and duplicities considered dose adjustments (i.e., combinations sought at the therapeutic level) are clearly differentiated.
Anticholinergic drug combinations	Detection of patients receiving a prescription of any urinary antispasmodic together with another drug that exhibits significant anticholinergic effects (e.g., antihistamines, tricyclic antidepressants, etc.).
History of suspected	Detection of patients for whom a history of unconfirmed

hypersensitivity	hypersensitivity has been recorded.
Adverse drug events (ADEs)	Detection of patients for whom an ADE has been registered.

ANNEX Table 2. Groups of pharmacological duplications included in PREFASEG in 2018

TYPE OF DRUG OR SYSTEM UPON WHICH THE DRUG ACTS	TYPE OF DUPLICATION
CARDIOVASCULAR SYSTEM	<ol style="list-style-type: none"> 1. Antithrombotic agents: acetylsalicylic acid (Aspirin) 2. Antiplatelet agents: clopidogrel 3. Oral anticoagulants 4. Digitalis 5. Antiarrhythmics
ANTIHYPERTENSIVES	<ol style="list-style-type: none"> 6. Diuretics: thiazides 7. Loop diuretics 8. Potassium sparing diuretics 9. β-Blockers 10. Non-dihydropyridine calcium antagonists 11. Dihydropyridine calcium antagonists 12. High blood pressure medications: renin-angiotensin system inhibitors (ACEIs, AIIRAs) 13. α-Adrenergic antagonists
ANTIULCER AGENTS	<ol style="list-style-type: none"> 14. Gastric protectors 15. Antacids
MUSCULOSKELETAL SYSTEM	<ol style="list-style-type: none"> 16. Anti-inflammatories 17. Anti-gout agents: allopurinol 18. Anti-gout agents: uricosuric 19. Anti-gout agents: colchicines 20. Analgesics: metamizole 21. Analgesics: paracetamol 22. Minor opiates 23. Triptans
ANTIBIOTICS	<ol style="list-style-type: none"> 24. Penicillins 25. Tetracyclines 26. Macrolides 27. Quinolones
HYPOLIPIDEMIC AGENTS	<ol style="list-style-type: none"> 28. Statins 29. Other lipid-modifying agents 30. Fibrates
ANXIOLYTICS AND HYPNOTICS	<ol style="list-style-type: none"> 31. Long-acting benzodiazepines 32. Intermediate-acting benzodiazepines 33. Short-acting benzodiazepines 34. Z-Drugs and others
ANTIEPILEPTICS	<ol style="list-style-type: none"> 35. Barbiturates 36. Other antiepileptics
ANTIDEPRESSANTS	<ol style="list-style-type: none"> 37. Tricyclic antidepressants 38. SSRI antidepressants 39. Other antidepressants (I) 40. Other antidepressants (II) 41. Bupropion and naltrexone

ORAL ANTIDIABETICS	<ul style="list-style-type: none"> 42. Biguanides 43. Secretagogues (sulfonylureas and glinides) 44. Glitazones 45. Incretins (glyptins and GLP-1 analogues) 46. Type 2 sodium-glucose cotransporter inhibitors (SGLT-2) 47. Long-acting insulin (injected form)
GENITOURINARY SYSTEM	<ul style="list-style-type: none"> 48. Urinary antispasmodics 49. Prostate drugs: testosterone inhibitors
SYSTEMIC HORMONAL PREPARATIONS	<ul style="list-style-type: none"> 50. Systemic corticosteroids 51. Aromatase inhibitors 52. Osteoporosis treatments 53. Oestrogens and progestogens
RESPIRATORY SYSTEM	<ul style="list-style-type: none"> 54. Long-acting β2-agonists 55. Anticholinergics 56. Inhaled glucocorticoids
OTHERS	<ul style="list-style-type: none"> 57. Calcium supplements 58. Potassium supplements 59. Iron supplements 60. Magnesium supplements 61. Vitamin D

ANNEX Table 3. Definitions of the AEMPS safety alerts included in PREFASEG in 2018

DRUG	ATC	YEAR OF ALERT PUBLICATION	ALERT CRITERIA
Citalopram	N06AB04	2011	High doses: - Above 40 mg/day. - Above 20 mg/day in patients >65 years of age. - Above 20 mg/day in patients suffering from liver dysfunction. Administered in combination with other drugs that also prolong the QT interval of the electrocardiogram.
Escitalopram	N06AB10	2011	High doses (>10 mg/day in patients >65 years of age). Administered in combination with other drugs that also prolong the QT interval of the electrocardiogram.
Aliskiren	Aliskiren alone (C09XA02) Aliskiren + hydrochlorothiazide (C09XA52) Aliskiren + amlodipine (C09XA53) Aliskiren + hydrochlorothiazide + amlodipine (C09XA54)	2014	In patients with a diagnosis of diabetes mellitus II or undergoing treatment with antidiabetic drugs (ATC A10). Jointly administered with ACE inhibitors (ATC: C09AA, C09BA, C09BB) and/or ARA-IIIs (ATC: C09CA, C09DA, C09DB, C09DX).
Cilostazol	B01AC23	2013	In patients suffering from a health problem where its use is contraindicated, i.e., cerebral haemorrhage, severe ventricular arrhythmias, or heart failure. Or, in concomitant treatment with: - 2 Antiplatelet agents - Antiplatelet + oral anticoagulant
Trimetazidine	C01EB15	2012	In patients with a diagnosis of extrapyramidal and movement disorders.

Raloxifene or bazedoxifene	Raloxifene (G03XC01) Bazedoxifene (G03XC02)		In patients suffering from any health problem where it is contraindicated, e.g., venous thromboembolism, uterine sac, endometrial cancer, or liver failure of any degree.
COXIBS	Celecoxib (M01AH01) Etoricoxib (M01AH05)		In patients suffering from any health problem where it is contraindicated, e.g., ischemic heart disease, peripheral arterial disease, cerebrovascular disease, heart failure, or inflammatory bowel disease.
Diclofenac or Aceclofenac	Diclofenac alone (M01AB05) or combined (M01AB55) Aceclofenac (M01AB16)	2013, 2014	In patients suffering from any health problem where its use is contraindicated, e.g., ischemic heart disease, peripheral arterial disease, cerebrovascular disease, or heart failure.
Agomelatine	N06AX22	2014	In patients ≥75 years of age.
Ivabradine	N06AX22	2014	Co-administration with verapamil (C08DA01, C08DA51, C09BB10) or (C08DB01).
“Triple Whammy” (NSAIDs + RAS inhibitors + diuretics)	NSAIDs alone and in combination	2014	In patients ≥75 years of age or undergoing treatment for diabetes (ATC A10).
Canagliflozin	A10BK02 Metformin + canagliflozin (A10BD16)	2016, 2017	In patients suffering from a health problem in which it is necessary to be more careful due to an increased risk of amputation.

ANNEX Table 4. List of drugs not recommended for use in geriatrics in 2018

A03A: AGENTS AGAINST FUNCTIONAL ALTERATIONS OF THE STOMACH		M03B: CENTRAL ACTION MUSCLE RELAXANTS	
A03AB06	Otilonium bromide	M03BA03	Methocarbamol
A03F: PROKINETIC AGENTS		M03BX02	Tizanidine
A03FA01	Metoclopramide	M03BX07	Tetrazepam
A10B: HYPOGLYCEMANTS (EXCEPT INSULINS)		M03BX08	Cyclobenzaprine
A10BB01	Glibenclamide	N02A: OPIOIDS	
A10BB02	Clorpropamide	N02AB02	Pethidine
B01A: ANTITHROMBOTICS		N02AD01	Pentazocine
B01AC05	Ticlopidine	N02C: ANTIMIGRANE AGENTS	
B01AC07	Dipyridamole	N02CA01	Dihydroergotamine
B01AC22	Prasugrel	N02CA51	Combinations with Dihydroergotamine
B01AC24	Ticagrelor	N02CA52	Combinations with ergotamine
B01AC23	Cilostazol	N04A: ANTIPARKINSONIAN AGENTS	
C02A: CENTRAL ACTION ANTIADRENERGICS		N04AA01	Trihexyphenidyl
C02AB01	Methyldopa	N05B: ANSIOLYTICS and N05C: HYPNOTICS AND SEDANTS	
C02AC01	Clonidine	SHORT- AND INTERMEDIATE-ACTING BENZODIAZEPINES	
C02AC05	Moxonidine	N05BA08	Bromazepam (INTERMEDIATE)
C02C: PERIPHERAL ACTION ANTIADRENERGICS		N05BA12	Alprazolam
C02CA01	Prazosin	N05BA14	Pinazepam (INTERMEDIATE)
C02CA04	Doxazosin	N05BA21	Clotiazepam
G04CA03	Terazosin	N05BA91	Benzazepam
C04A: PERIPHERAL VASODILATORS		N05CD05	Triazolam
C04AD03	Pentoxifylline	N05CD08	Midazolam
C04AE02	Nicergoline	N05CD09	Brotizolam
C04AX21	Naftidrofuryl	N05CD11	Loprazolam
C07A: BETA-BLOCKING AGENTS		LONG-ACTING BENZODIAZEPINES	

C07AA07	Sotalol	N03AE01	Clonazepam (N03A)
G04B: OTHER UROLOGICAL PRODUCTS, INCLUDING ANTI-SPASMODIC PRODUCTS		N05BA02	Clordiazepoxid
G04BD04	Oxybutynin	N05BA05	Clorazepat dipotassium salt
L02A: HORMONES AND RELATED AGENTS		N05BA09	Clobazam
L02AB01	Megestrol	N05BA10	Ketazolam
M01A: NSAIDs: NON-STEROIDAL ANTI-INFLAMMATORY AND ANTI-RHEUMATIC		N05BA13	Halazepam
M01AA01	Phenylbutazone	N05BA51	Combinations with diazepam
M01AB01	Indomethacin	N05BA55	Combinations with clorazepat dipotassium salt
M01AB15	Ketorolac (H)	N05CD01	Flurazepam
M01AB16	Aceclofenac	N05CD03	Flunitrazepam
M01AB05	Diclofenac	N05CD10	Quazepam
M01AB55	Combinations with diclofenac	NON-BENZODIAZEPINE HYPNOTICS	
M01AC01	Piroxicam	N05CF02	Zolpidem
M01AC02	Tenoxicam	N05CF01	Zopiclone
M01AC05	Lornoxicam	R06A: ANTIHISTAMINES FOR SYSTEMIC USE	
M01AC06	Meloxicam	H1 ANTIHISTAMINES 1ST GENERATION	
M01AE03	Ketoprofen	R06AB06	Dexbrompheniramine
M01AE09	Flurbiprofen	R06AB56	Combinations with dexbrompheniramine
M01AE14	Dexibuprofen	R06AB01	Brompheniramine
M01AE17	Dexketoprofen	R06AB51	Combinations with brompheniramine
M01AG01	Mefenamic acid	R06AX07	Tripolidine
M01AH01	Celecoxib	R06AA02	Dimenhydrinate
M01AH05	Etoricoxib	R06AA09	Doxylamine
M01AX01	Nabumetone	R06AA52	Combinations with diphenhydramine
N06A: ANTIDEPRESSANTS		R06AB02	Dexchlorpheniramine
TRICYCLIC ANTIDEPRESSANTS		R06AC01	Mepyramine
N06AA12	Doxepine >6mg/d	R06AD01	Alimemazine
N06AA02	Imipramine	R06AD02	Promethazine

N06AA04	Clomipramine	R06AD03	Tiethylperazine
N06AA06	Trimipramine	R06AD07	Mequitazine
N06AA21	Maprotiline	R06AE05	Meclozine
SSRIs		R06AE92	Combinations with clocizine
N06AB03	Fluoxetine	R06AX02	Cyproheptadine
N06B: PSYCHOSTIMULANTS AND NOOTROPICS		R06AX17	Ketotifen
N06BX03	Piracetam	R06AX19	Azelastine
R03D: OTHER SYSTEMIC AGENTS AGAINST OBSTRUCTION OF THE RESPIRATORY TRACT		H02BX92	Clemastine
R03DA04	Theophylline	N05BB01	Hydroxyzine