



REVIEW

Review of Use of Drugs for Conditions Not Included in Product Characteristics[☆]

A. García-Sabina^{a,*}, R. Rabuñal Rey^b, R. Martínez-Pacheco^c

^a Servicio de Farmacia, Hospital Lucus Augusti, Lugo, Spain

^b Servicio de Medicina Interna, Hospital Lucus Augusti, Lugo, Spain

^c Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Santiago de Compostela, La Coruña, Spain

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PALABRAS CLAVE

Off-label;
Uso compasivo;
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Ficha técnica;
Indicaciones no aprobadas;

Abstract Off-label use of medication is common in hospital clinical practice and should be applied together with follow-up of a healthcare treatment protocol and in compliance with a procedure which ensures that the patient is informed and that he or she provides informed consent.

A review of the literature on controlling 310 disorders showed that off-label use was indicated for 69 of them (22.3%) with the minimum required scientific evidence.

It would be useful for the Pharmacy and Therapeutics Committee to have a list of the disorders that can be controlled using off-label drugs, providing a reference to those disorders which must follow a healthcare treatment protocol.

A list of the mentioned characteristics is also useful for the hospital pharmacist for validating prescriptions, as it would provide a reference for assessing prescriptions which at first sight could seem questionable.

Finally, this list would be very useful if a search index of all the drugs by disorder was to be included in the Pharmacotherapeutic Guide. It would complement the usual indices which include active ingredients and specialities.

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Revisión sobre el uso de medicamentos en condiciones no incluidas en su ficha técnica

Resumen El uso de medicamentos en indicaciones no aprobadas en sus fichas técnicas (indicaciones *off-label*) es común en la práctica clínica hospitalaria y su aplicación debería ir unida al seguimiento de un protocolo terapéutico asistencial y al cumplimiento de un procedimiento que garantice la información y el consentimiento informado del paciente.

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* Corresponding author.

E-mail address: antonio.garcia.sabina@sergas.es (A. García-Sabina).

Fuera de ficha técnica (FFT);
Medicamentos en situaciones especiales

La revisión bibliográfica sobre manejo de 310 enfermedades puso de manifiesto que en 69 de ellas (22,3%) está descrito el uso de medicamentos en indicaciones *off-label* con un mínimo exigible de aval científico.

Disponer de esta lista de enfermedades en cuyo manejo se usan medicamentos *off-label* puede resultar de utilidad a la Comisión de Farmacia y Terapéutica al ofrecerle una referencia de aquellas enfermedades en las que sería prioritario monitorizar la existencia de protocolos terapéuticos asistenciales.

Una lista de las mencionadas características también es útil al farmacéutico de hospital en su función de validar prescripciones médicas, pues le ofrece una referencia para evaluar prescripciones que a primera vista pueden ser cuestionables.

Finalmente, tal lista es muy útil si se pretende añadir a la guía farmacoterapéutica del hospital un índice de búsqueda de medicamentos usados por enfermedades, que complemente los índices habituales de principios activos y especialidades.

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Introduction

Spanish Royal Decree 1015/2009,¹ which regulates the availability of medications in special situations, involves the following three components:

- *Compassionate use of medications in research*: The use of a medication before it is authorised for commercial use in Spain in patients with chronic or severely debilitating diseases or life-threatening conditions that cannot be satisfactorily treated using authorised medications. The medication must be in the process of authorisation for commercialisation, or at least be subject to clinical trials.
- *Use of medications under conditions other than those authorised*: The use of a medication under conditions other than those authorised in its summary of product characteristics (which is referred to in the scientific literature as "off-label" use).
- *Access to medications that are not authorised in Spain*: The use of medications that are authorised in other countries, but not in Spain, when these do not fall within the definition of compassionate use of medication in research, as previously described.

With regard to access to medications in conditions different from those indicated in the summary of product characteristics, article 13.1 of the Royal Decree states that:

The use of authorised medications for uses other than those established in the summary of product characteristics will be exceptions to the rule, and this will be limited to those cases in which authorised therapeutic alternatives are not available to any given patient, while respecting any restrictions that may have been established with regard to the prescription and/or dispensing of the medication and the health care protocol at the hospital. The prescribing physician must explain the need for using the medication in the clinical history, and must inform the patient as to the possible benefits and potential risks of treatment, and obtain informed consent as per Law 41/2002, of November 14.

Under these conditions, the use of a medication under circumstances other than those indicated in the summary of product characteristics has been established in common medical practice. Health care protocols also establish the possible alternatives for treatment and the order in which they may be used, and thus the attending physician must follow a protocol or series of restrictions for the prescription of these types of medications. Strict compliance is also needed with the law of patient autonomy with regard to obtaining informed consent.²⁻⁴

We should consider that the approved indications in the summary of product characteristics established by the European Medicines Agency (EMA) or the Spanish Agency for Medicines and Healthcare Products (AEMPS, for its initials in Spanish) do not necessarily coincide with those approved by other health agencies such as the Food and Drug Administration (FDA).

The off-label use of a medication can range from being the first option to being the last line of treatment. The conditions for the use of each medication must be well defined, since, if a drug is a more effective and/or safer therapeutic alternative than other, it may be the treatment of choice for the disease in question, regardless of the presence of its use for said condition on the summary of product characteristics.

Information is very scarce regarding the off-label use of medications. Some studies report that certain drugs are frequently used off-label. In the USA, the use of medications not approved by the FDA has been estimated at 21% of all prescriptions, although this percentage can be higher for certain drugs, such as gabapentin (83%), amitriptyline (81%), oral dexamethasone (79%), isosorbide mononitrate (75%), rituximab (75%), risperidone (66%) and digoxin (66%). According to the scientific literature, the same restrictions or level of evidence are not required for the off-label use of all medications, and although the off-label use of isosorbide mononitrate and digoxin is sufficiently accredited, the same cannot be said for gabapentin, risperidone, or amitriptyline.^{5,6}

On the other hand, the off-label use of drugs can create conflicts for the different expectations held by certain interested parties: health administrators, physicians, the pharmaceutical industry, and patients. In this manner,

Table 1 Drugs Used in Dermatology Under Indications Are Not Included in Their Summary of Product Characteristics.

Disease	Drug	Observations
Alopecia areata	Topical clobetasol propionate 0.05%	Its use has been described with occlusive dressings through a daily application 6 days per week over 6 months, and can also be used as a foam application. It must be used with caution due to the risk of adverse side effects. ¹⁵
Hirsutism	Spirolactone Finasteride	Spirolactone: acts as a competitive aldosterone inhibitor by joining to its receptors, and also has an anti-androgenic effect, probably due to peripheral antagonism of androgens. Although insufficient evidence exists to demonstrate effectiveness in reducing the severity of hirsutism, some guidelines recommend using it twice per day at 25–100 mg Finasteride: has been approved in other indications related to cutaneous hyperandrogenism, such as androgenic alopecia ^{16,17}
Lichen planus	Oral acitretin Cyclosporine Tacrolimus	Used in cases of corticosteroid resistance The possibility of increased risk of carcinogenesis is being studied in association with tacrolimus ^{18,19}
Discoid lupus erythematosus (DLE)	Methotrexate Oral acitretin Thalidomide	Used as second or third line treatment options ²⁰
Pemphigus vulgaris/bullous dermatosis	Mycophenolate mofetil Non-specific immunoglobulin IV Rituximab	Mycophenolate: in cases of resistant pemphigus vulgaris or in situations in which neither azathioprine nor cyclophosphamide can be used Immunoglobulins: in bullous dermatosis with complications in using corticosteroids or no response to immunosuppressive agents, 0.4 g/kg/day can be administered for 5 days, repeating this cycle every 21 days, reducing the number of cycles in the absence of lesions Rituximab: used in cases of resistance to other treatments, at 375 mg/m ² once a week for 4 weeks. Some authors recommend a dosage of immunoglobulins at 0.4 g/kg the day before (as prophylaxis to infections). In the case of relapse, a single dose of rituximab according to the evolution of the condition ²¹
Itching associated with allergic cutaneous reactions	Doxepin	In patients who do not respond to conventional antihistamines. One of the recommended regimes indicates a dosage of 10 mg three times per day ²²
Psoriasis	Mycophenolate mofetil	This treatment has been described to reduce the extent and severity of psoriasis ²³
Chronic urticaria	Doxepin	Used in low doses (between 10 and 30 mg/day) ^{24,25}

health administrators may question the need for paying for unapproved drugs in the treatment of a disease, physicians may desire the freedom to prescribe whatever drugs they deem fit, the pharmaceutical industry may seek to expand the market with new drugs and new uses for established drugs, and finally, patients desire safe, effective, and accessible medications.⁷

When evaluating the off-label inclusion of a drug in treatment protocols, several different important aspects must be taken into account^{8,9}:

- If the drug in question is new, the scientific evidence that endorses its off-label use may not be based on high-quality trials, and only limited information may be available regarding the safety of using the drug.
- If the drug in question has been commercialised for some time, its off-label use may involve widely ranging circumstances, varying from cases in which, due to a reduced price of the drug, the clinical costs for obtaining a new indication are not offset by the benefits acquired from a hypothetical authorisation of the new use, to those cases of a presumed *lack of interest* in obtaining authorisation for a new indication, such as in the use of bevacizumab in the treatment of age-related macular degeneration.^{10–12}

Table 2 Drugs Used in the Gastrointestinal System Under Indications Not Included in Their Summary of Product Characteristics.

Disease	Drug	Observations
Primary biliary cirrhosis	Colchicine Oral budesonide	Colchicine is indicated in patients with incomplete response to ursodeoxycholic acid Budesonide: its use has been described along with ursodeoxycholic acid ²⁶
Ulcerative colitis	Adalimumab	In patients intolerant to or with no response to infliximab ²⁷
Hepatic encephalopathy	Oral metronidazole	As a adjuvant treatment ²⁸
Crohn's disease	Mercaptopurine	See Markowitz et al. ²⁹
Gastroesophageal reflux disease	Sucralfate	See Tytgat et al. ³⁰
Hepatic veno-occlusive disease	Defibrotide	Not commercialised in Spain ^{31,32}
Cystic fibrosis	Azithromycin Ursodeoxycholic acid	Azithromycin: used for the long-term treatment of respiratory pathologies. Indications are for treatment of 500 mg 3 times a week or 1200 mg once a week for 6 months Ursodeoxycholic acid: may delay the evolution to cirrhosis ^{33,34}
Upper gastrointestinal bleeding (UGIB)	Esomeprazole Pantoprazole	Esomeprazole is indicated in the prevention of recurrent bleeding following a therapeutic endoscopy performed for acute bleeding due to peptic ulcers Proton pump inhibitors have been indicated: initial dose of 80 mg i.v., followed by an i.v. perfusion for 72 h at 8 mg/h, followed by oral proton pump inhibitors for 8 weeks ^{35,36}
Autoimmune hepatitis	Cyclosporine Tacrolimus Mycophenolate mofetil Oral budesonide	Cyclosporine, tacrolimus: in cases resistant to treatment with azathioprine and corticosteroids Mycophenolate mofetil: in patients intolerant to treatment with azathioprine and corticosteroids Budesonide: in mild cases of the disease or if maintenance therapy with azathioprine is insufficient ^{37,38}
Spontaneous bacterial peritonitis	Albumin	Associated with cefotaxime ³⁹
Chronic intestinal pseudo-obstruction	Erythromycin IV Neostigmine Octreotide	The use of IV erythromycin in intestinal pseudo-obstruction is based on its activity as a motilin antagonist and gastric prokinetic agent. Dosage is 1 mg/kg every 8 h ⁴⁰⁻⁴²
Irritable bowel syndrome (IBS)	Tricyclic antidepressants	Some studies support the use of tricyclic antidepressants in doses lower than those used to treat depression in order to improve visceral hypersensitivity (abdominal discomfort or pain at thresholds lower than those of healthy subjects) that occurs in patients with IBS. Other studies have produced inconsistent results ⁴³

- In the case of the off-label use of drugs with established severe adverse reactions, patient safety requires special attention.
- The off-label use of high-cost medications requires reasonable expectations with regard to clinical results.
- In all cases, the off-label use of medications requires some minimum level of scientific evidence that endorses said use.

Methods

With the objective of evaluating the off-label use of medications, we reviewed recent editions of two different Spanish manuals, the *Cliniguía*¹³ (clinical guidelines) and *Normas de actuación en urgencias*¹⁴ (emergency medicine guidelines).

They offer basic information regarding the management of different diseases in adults and are extensively used among physicians both in the primary care setting and specialised medicine. We also carried out a Medline literature search regarding the treatment of several different diseases, focusing on data compiled in clinical guidelines and recently published systematic reviews, and in their absence, publications that have been widely cited in medical literature.

We considered those drugs whose use is recommended for the treatment of certain diseases in the cited sources and is not included in the summary of product characteristics detailed in the EMEA or AEMPS.

For the inclusion of a drug in this context, we evaluated the available evidence for its off-label use, according to the following criteria:

Table 3 Drugs Used in Endocrinology/Metabolism/Nephrology Under Indications Are Not Included in Their Summary of Product Characteristics.

Disease	Drug	Observations
Bulimia nervosa	Naltrexone	Its use is based on the endogenous opiate system's involvement in addiction to binge, which provokes bulimia ⁴⁴
Primary glomerulonephritis	Mycophenolate mofetil	Only in association with corticosteroids ⁴⁵
Hypercalcaemia	Regular insulin Parenteral salbutamol	Salbutamol: the beta-adrenergic stimulus of salbutamol favours the uptake of potassium by the cell. In hypercalcaemia, appropriate dosage is 0.5 mg dissolved in 100 ml of glycosyl at 5% by IV perfusion for 20 min Regular insulin: administered along with glucose stimulates the uptake of potassium by muscle, liver, and adipose cells, with action starting within 30 min and lasting 2 h. In hypercalcaemia, prescriptions range from 0.5–1 g/kg of glucose and 0.1–0.2 UI/kg of insulin (glycaemia must be monitored). For example, 10UI doses of insulin are used in an i.v. bolus followed by 50 ml of glucose at 50%; or perfusions of 12 UI insulin in 500 ml of glycosyl at 5% for 30 min ⁴⁶
Hypervolemic and euvoletic hyponatraemia in heart failure or cirrhosis	Tolvaptan	Indication approved by the FDA ⁴⁷
Sclerosing encapsulating peritonitis	Tamoxifen	Usually prescribed at 20 mg/day, but doses have been administered between 10 mg/day and 20 mg twice per day ^{48,49}
Precocious puberty	Buserelin Nafarelin	Buserelin and nafarelin have been approved for this indication by the FDA Other gonadotropin-releasing hormone antagonists such as leuprorelin and triptorelin have been approved for this indication in Spain ^{50,51}
Cachexia/anorexia syndrome	Thalidomide	In cachexia/anorexia syndrome associated with advanced neoplasia, the use of thalidomide has been indicated at doses of 100–200 mg/day for 2 weeks ⁵²
Cushing's syndrome	Ketoconazole Mitotane Etomidate	The use of ketoconazole is based on the inhibition of cholesterol, sex steroid, and cortisol synthesis due to its activity on the enzymes 11 β -hydroxylase and C17-20-lyase. Ketoconazole is used in Cushing's syndrome at 400–1200 mg, divided into several administrations Mitotane diminishes cortisol production by blocking the cholesterol and 11 β -hydroxylase pathway Etomidate can be used to treat severely ill patients with ectopic ACTH production that cannot take oral treatment and require immediate correction of hypercortisolaemia. Administered by IV perfusion at 2.5 mg/h ^{53,54}

- We did not include those drugs that the consulted medical texts mentioned as having a doubtful efficacy in the disorder in question.
- We did not include those drugs for which the consulted sources indicated the scarcity or deficiency of scientific literature endorsing their use for the disease in question.
- We did include drugs that have been recommended in all or most of the consulted sources.
- We did not consider off-label indications those diseases in which a proprietary drug did not include that particular indication but another drug exists (whether commercialised in Spain or not) with the same active ingredient for which the EMEA had approved said indication (for example, the indication for the treatment of sickle cell anaemia has not been approved for the brand name Hydrea[®], but this indication has been approved by the EMEA for another proprietary drug that also contains hydroxyurea, Siklos[®]).
- We also did not consider off-label use those cases in which the drug is employed using the conditions of administration and dosage established in the summary of product characteristics for certain approved indications which constitute a symptom or a sub-pathology of the primary disease (for example, the use of propranolol in porphyria

Table 4 Drugs Used in Obstetrics and Gynaecology Under Indications Not Included in Their Summary of Product Characteristics.

Disease	Drug	Observations
Symptoms of preterm labour	Nifedipine Indomethacin	Indomethacin is used in patients refractory to β -mimetic treatment with updated ultrasound indicating normal volume of amniotic fluid and amenorrhoea of less than 32 weeks. Foetal echocardiogram is required. In this treatment, neonatal complications must be taken into consideration, such as transitory kidney dysfunction and premature closing of the ductus arteriosus ⁵⁵⁻⁵⁷
Ectopic pregnancy	Intramuscular methotrexate	Administered by intramuscular injection of 50–75 mg/m ² ⁵⁸
Polycystic ovary syndrome	Metformin	Metformin improves muscular sensitivity to insulin. Metformin can also reduce the levels of circulating androgens and improve ovulation and menstrual cyclicity ⁵⁹
Uterine leiomyoma	Raloxifene	Several different prescriptions have been described in the scientific literature, such as its use over 3 months prior to surgery in pre-menopausal women at doses of 60 mg/day (some have mentioned doses as high as 180 mg/day) ^{60,61}
Premenstrual syndrome/Premenstrual dysphoric disorder	Calcium Citalopram Fluoxetine Paroxetine Sertraline Goserelin Leuprorelin Spironolactone Alprazolam Buspirone	For emotional and physical symptoms: calcium, goserelin, leuprorelin, and spironolactone For emotional symptoms: citalopram, fluoxetine, paroxetine, sertraline, alprazolam, and buspirone ⁶²

Table 5 Drugs Used in Neurology Under Indications Not Included in Their Summary of Product Characteristics.

Disease	Drug	Observations
Neuropathic pain	Carbamazepine Oxcarbazepine Nortriptyline Venlafaxine Baclofen Oral ketamine	Carbamazepine, oxcarbazepine, venlafaxine: in painful diabetic neuropathy Nortriptyline: in painful diabetic neuropathy and post-herpetic neuralgia Baclofen: in trigeminal neuralgia Oral ketamine: for untreatable neuropathic pain ⁶³⁻⁶⁵
Fatigue associated with multiple sclerosis	Modafinil Amantadine	Modafinil: 100–200 mg per day in a single dose (maximum of 400 mg/day) Amantadine: usually taken at 100 mg twice per day (maximum of 600 mg per day) ^{66,67}
Intractable hiccups	Chlorpromazine	Indication approved by the FDA ⁶⁸
Lambert-Eaton syndrome	Non-specific immunoglobulin IV	First line of treatment is 3–4 diaminopyridine ^{69,70}
Myasthenia gravis	Cyclophosphamide Cyclosporine Non-specific immunoglobulin IV	Used as second line of treatment if the patient does not respond to corticosteroids ^{71,72}

Table 5 (Continued)

Disease	Drug	Observations
Prophylaxis against seizures in subarachnoid haemorrhage from a ruptured aneurysm	Sodium valproate	See Suarez et al. ⁷³
Prophylaxis against migraine	Amitriptyline Sodium valproate Nifedipine Verapamil	Used when other options such as β -blockers have not been effective ⁷⁴
Tourette syndrome	Pimozide Oral clonidine	Pimozide has been proposed at doses of 0.5–18 mg/day Clonidine: has been proposed at doses of 3–5 $\mu\text{g}/\text{kg}/\text{day}$ ^{75,76} In resistant cases ⁷⁷
Lennox-Gastaut syndrome	Non-specific immunoglobulin IV	
Essential tremor	Primidone Gabapentin Topiramate Alprazolam	Primidone: considered a second line anti-tremor treatment due to its potential adverse side effects Gabapentin: the primary issue is the low response rate (an improvement is observed in approximately one third of patients). It is considered a second line anti-tremor medication, if beta-blockers are not tolerated or if contraindications exist Topiramate: involves a large and complicated dosage with poor tolerance, making this a third line anti-tremor medication Alprazolam: used as adjuvant treatment in association with other anti-tremor medications ⁷⁸

Table 6 Drugs Used in Ophthalmology and ENT Under Indications Are Not Included in Their Summary of Product Characteristics.

Disease	Drug	Observations
Conjunctivitis (viral, bacterial, and irritability)	Diclofenac drops	See Arcos González and Castro Delgado ⁷⁹ and Galvez et al. ⁸⁰
Neovascular (wet) age-related macular degeneration (AMD)	Intravitreal bevacizumab	The cumulative experience and results from several scientific studies have shown that bevacizumab can provide similar benefits to ranibizumab (which is approved for intraocular use under the indications for AMD). When considering this alternative, we must not overlook the substantially lower annual cost of treatment with bevacizumab as compared to ranibizumab In AMD, bevacizumab is administered intravitreal at 1.25 mg every 4 weeks ^{10–12}
Uveitis	Methotrexate Infliximab	Methotrexate is used as a second or third line treatment option The use of infliximab has been described for controlling ocular inflammation in children with non-infectious chronic uveitis associated with resistant juvenile idiopathic arthritis; also for uveitis and uveoretinitis associated with Behçet's disease ^{81–83}
Recurrent aphthous stomatitis	Colchicine Dapsone Pentoxifylline Sucralfate Thalidomide	See Mimura et al., ⁸⁴ Altengurg et al., ⁸⁵ Pizarro et al., ⁸⁶ Rattan et al., ⁸⁷ and Bonnetblanc et al. ⁸⁸

Table 6 (Continued)

Disease	Drug	Observations
Sudden hearing loss	Piracetam Nimodipine Pentoxifylline Methylprednisolone IV	An example of the treatment protocol for sudden hearing loss mentions the use of IV methylprednisolone at 40–80 mg/day for 5 days, along with B1B6B12 complex by intramuscular injection, IV piracetam at 3 g every 8 h, and IV perfusion of nimodipine at 15–30 µg/kg/h, passing on later to oral treatment for 15 days of methylprednisolone at 40 mg/day (progressively reducing dosage), B-complex pills, 800 mg of piracetam every 8 h and 30 mg of nimodipine every 8 h ^{89,90}
Vertigo	Parenteral haloperidol	Its use has been indicated in the acute phase (until symptoms disappear), and treatment must be suspended when the vertigo ceases ⁹¹

Table 7 Drugs Used in Rheumatology Under Indications Not Included in Their Summary of Product Characteristics.

Disease	Drug	Observations
Hereditary angioedema	Stanozolol	Indicated by the FDA as a prophylaxis treatment for reducing the frequency and severity of angioedema crises ⁹²
Juvenile idiopathic arthritis	Leflunomide Sulfasalazine	Leflunomide is indicated as an alternative to methotrexate Sulfasalazine is contraindicated as a systemic medication, since the secondary side effects are more common and severe than in other categories ⁹³
Dermatomyositis/polymyositis	Methotrexate Cyclosporine Non-specific immunoglobulin IV	Used in cases resistant to first line treatments ⁹⁴
Adult Still's disease	Methotrexate Anakinra Infliximab	Methotrexate is used in cases resistant to corticosteroids Anakinra is used in cases resistant to corticosteroids/methotrexate Infliximab is used in association with methotrexate and corticosteroids in cases of resistance to corticosteroids/methotrexate ^{95–97}
Fibromyalgia	Amitriptyline Duloxetine Fluoxetine Paroxetine Pregabalin	See Häuser et al. ⁹⁸
Wegener's granulomatosis	Methotrexate Cotrimoxazole Rituximab	Cotrimoxazole is used to prevent relapse and acts through an unknown mechanism, although it is probably associated with anti-inflammatory or anti-oxidant activity, rather than due to its antibiotic activity ⁹⁹ Rituximab has produced promising results in some studies, but further research is needed to confirm these findings ¹⁰⁰
Systemic lupus erythematosus (SLE)	Rituximab Mycophenolate mofetil	Rituximab is used in severe resistant cases of SLE and lupus nephritis ¹⁰¹ Mycophenolate mofetil is used in lupus nephritis ¹⁰²

Table 7 (Continued)

Disease	Drug	Observations
Heterotopic ossification	Celecoxib Indomethacin	Celecoxib: used as prophylaxis against heterotopic ossification due to surgical hip replacement Indomethacin: used as prophylaxis treatment against heterotopic ossification due to spinal injury or surgical hip replacement ^{103,104}
Behçet's syndrome	Colchicine Infliximab Interferon alpha-2b Sulfasalazine Thalidomide	Colchicine: used to treat oral ulcers and cutaneous and joint manifestations Infliximab: used to treat uveitis and uveoretinitis Interferon alpha-2b: used to treat joint manifestations Sulfasalazine: used to treat intestinal manifestations Thalidomide: used to treat oral ulcers and gastrointestinal manifestations ^{105,106}

for the control of crises of tachycardia and hypertension, or drugs such as clozapine and quetiapine in Huntington's chorea for the treatment of associated psychosis).

- We did consider off-label use that, in the treatment of these sub-pathologies, the drug is administered at a dosage or form of administration different from that recommended in the summary of product characteristics (for example, omeprazole at high doses in continuous intravenous perfusion for upper gastrointestinal bleeding).
- We also considered off-label use that a drug is approved for any given indication by the FDA, but not by the EMEA or the AEMPS.
- For those drugs that had not been commercialised in Spain, we only considered off-label use to have occurred in those diseases that were not authorised as an indication in the summary of product characteristics from the country of origin.

Results

We reviewed manuals and protocols published on the management of 310 different diseases/treatment circumstances corresponding to the following medical specialties: neurology/psychiatry: 52 (16.8%), endocrinology/metabolism/nephrology: 47 (15.2%), digestive tract: 33 (10.6%), rheumatology/traumatology: 30 (9.7%), cardiovascular: 26 (8.4%), dermatology: 23 (7.4%), haematology: 23 (7.4%), gynaecology: 20 (6.4%), emergency medicine/ICU: 18 (5.8%), and other (surgery, ophthalmology, ENT, pneumology, urology): 38 (12.3%).

In 69 of these diseases (22.3%), the off-label use of the drug was described.

The results detailed in our review are summarised in Tables 1–9. The column *observations* summarises the data that are especially relevant with regard to the off-label use

Table 8 Drugs Used in Emergency Medicine Under Indications Not Included in Their Summary of Product Characteristics.

Disease	Drug	Observations
Anaphylaxis in patients treated with beta-blockers	Glucagon	The cardiac inotropic effects of glucagon are the basis of its use in the treatment of anaphylaxis in patients taking β -blockers, in which the response to adrenalin may be diminished, thus requiring a greater dose. In these patients, IV glucagon has been used at 5–10 mg in a single bolus followed by a perfusion at an initial rate of 4 mg/h, which is then progressively reduced ¹³
<i>Amanita phalloides</i> toxicity	Penicillin G sodium	Benzylpenicillin has been effectively used in dogs 5–24 h following poisoning by <i>A. phalloides</i> . The mechanism of action of penicillin against <i>A. phalloides</i> toxicity is unknown, and although it has been suggested that penicillin may inhibit the uptake of amatoxins by hepatocytes, this is still a point of controversy. Penicillin is administered at 300 000–1 000 000 UI/kg/day on continuous perfusion for treating <i>A. phalloides</i> toxicity. Treatment must be continued for several days, until all symptoms have disappeared. ¹⁰⁷
Organophosphate toxicity	Atropine	Indication approved by the FDA. Administered along with pralidoxime ^{108,109}
Hypertensive emergencies	Captopril Nifedipine	See Moya Mir et al. ¹⁴

Table 9 Drugs Used in Haematology and Other Diseases Under Indications Not Included in Their Summary of Product Characteristics.

Disease	Drug	Observations
Aplastic anaemia	Cyclosporine	Used along with anti-thymocyte immunoglobulin (from rabbits and horses) and corticosteroids ¹¹⁰
Autoimmune haemolytic anaemia	Non-specific immunoglobulin IV Cyclophosphamide Cyclosporine Mycophenolate mofetil Rituximab	Autoimmune haemolytic anaemia (AIHA) includes 2 types: warm agglutinin AIHA (WA-AIHA), which is mediated by IgG autoantibodies and usually responds to corticosteroids and immunosuppressants, and cold agglutinin AIHA (CA-AIHA), which is mediated by IgM autoantibodies, although the efficacy of this treatment is not well established Association of IV Ig and corticosteroids is frequently used as the first line of treatment for WA-AIHA Rituximab is the only drug that may have activity against CA-AIHA ¹¹¹ See Table 2 ^{32,33}
Cystic fibrosis	Azithromycin Ursodeoxycholic acid	
Acute pericarditis	Acetylsalicylic acid (aspirin) NSAID (ibuprofen, indomethacin) Colchicine Corticosteroids	Acetylsalicylic acid is used at high doses (500–1000 mg every 6 h), and when pain and fever cease the prescription can be gradually reduced (for example, 500 mg every 8 h for one week, then 250 mg every 8–12 h for 2 weeks) If the patient does not respond or if contraindications exist for acetylsalicylic acid, ibuprofen (1200–1800 mg/day) or indomethacin (75–150 mg/day) may be used Corticosteroids may be necessary at moderate doses (for example prednisone at 0.2–0.5 mg/kg/day) Colchicine (0.5–1.2 mg/day) is useful for preventing relapse ^{112,113}
Idiopathic thrombocytopenic purpura (ITP)	Anti-D immunoglobulin Rituximab	Anti-D immunoglobulin: used to increase platelet count in adult patients that are Rho (D)-positive and with no history of splenectomy. This indication is approved by other non-Spanish medicines agencies for the same medication that has been commercialised in Spain ¹¹⁴ Rituximab: normally administered in doses of 375 mg/m ² 1 day per week for 4 weeks ¹⁰⁰
Thrombotic thrombocytopenic purpura (TTP)	Rituximab Vincristine Cyclosporine Defibrotide	Rituximab: normally prescribed at 375 mg/m ² one day per week for 4 weeks Vincristine: for cases of TTP resistant to other treatments Cyclosporine: used to prevent relapse of TTP in cases resistant to other treatments Defibrotide: not commercialised in Spain ^{115,116}
Unclogging venous catheters Kawasaki disease	Urokinase Acetylsalicylic acid (ASA)	Applied through an injection into the catheter ¹¹⁷ This indication is not included in the summary of product characteristics for ASA, but the concomitant use of immunoglobulin is mentioned in that for immunoglobulin IV ASA is indicated in Kawasaki disease at initial doses during the acute phase of 80–100 mg/kg/day (divided into 4 doses) for 14 days or up until 48–72 h after the patient's fever has ceased, and afterwards, at 3–5 mg/kg/day for 6–8 weeks or until platelet levels have normalised ^{118–120}

of each drug. In addition to the bibliographic references, we mention the most relevant aspects of each use, i.e., the mechanism of action of the drug for the off-label indication, the line of treatment of the drug within the treatment plan, the approval of using the drug for a given pathology by the FDA (if the indication was not approved by the EMEA or the AEMPS), dosage (if the off-label indication is different from the approved uses), and any other aspect considered to be unusual in the off-label use of each drug.

Discussion

The off-label use of a drug can be based on any of the following circumstances:

- The assumption that a given drug will have a certain activity that is known to be present in other drugs of the same class (for example, the summary of product characteristics for busserelin and nafarelin do not mention indications for use in precocious puberty, which is an indication that has been approved for leuprorelin and triptorelin; the same goes for oral metronidazole as a adjuvant treatment in hepatic encephalopathy, which is an approved indication in other oral antibiotics that act on the intestines, such as paromomycin, neomycin, and rifaximin).
- An extension of the indications for a given drug to others that are 'related' to the already approved uses in the summary of product characteristics (for example, the off-label use of methotrexate in different auto-immune diseases, or the use of captopril or nifedipine in hypertensive emergencies, or adalimumab, which is approved for use in Crohn's disease and has an off-label use for ulcerative colitis).
- The use of a drug's mechanism of action in order to obtain a beneficial effect in an off-label indication (for example, using insulin to treat hypercalcaemia is based on the stimulation of potassium uptake in muscle, liver, and adipose cells; the use of ketoconazole in Cushing's syndrome is based on the inhibition of cholesterol, sex steroid, and cortisol synthesis due to its activity on the enzymes 11 β -hydroxylase and C17-20-lyase; the use of intravenous erythromycin in intestinal pseudo-obstruction is based on its action as a motilin antagonist and gastric prokinetic agent; the activity of metformin to improve peripheral uptake of insulin is the basis for its off-label use in polycystic ovary syndrome).
- In certain cases, the mechanism of action in the off-label indication is completely unknown (for example, the use of penicillin G to treat *Amanita phalloides* toxicity).

In the hospital environment, medications are frequently used off-label, and these situations should be compiled into health care protocols. The physician should comply with these protocols, and the Pharmacy and Therapeutics Committee should play an important role in their control.

A list of all diseases or treatment situations in which the scientific literature recommends the off-label use of drugs would also help the Pharmacy and Therapeutics Committee to provide reference information on the diseases for which drugs are frequently prescribed outside of the realm of their approved indications, and/or regarding those that should

be used with special caution under a specific health care protocol.

Additionally, having a reference list for drugs used off-label could help hospital pharmacists who must validate medical prescriptions in understanding and justifying certain prescriptions that at first glance might seem unreasonable (for example, prescribing ketoconazole in doses as high as 1200 mg/day to treat Cushing's syndrome and not a fungal infection; insulin can be used to treat hypercalcaemia even though the patient may not be diabetic; an intravenous dose of erythromycin as low as 1 mg/kg/8 h would indicate that the patient is being treated for intestinal pseudo-obstruction; a prescription of 500 mg of azithromycin three times per week or 1200 mg once per week over 6 months would indicate that the patient has cystic fibrosis; the use of tamoxifen in a male patient would indicate that the patient does not have breast cancer, but rather a complication of peritoneal dialysis, such as sclerosing encapsulating peritonitis).

Furthermore, a list of off-label indications for medications would provide a significant help in incorporating a search index by disease, including a list of drugs used for each disease, in a hospital Pharmacotherapy Guide or any other database. This would provide incomplete information if only those indications approved by each medication's summary of product characteristics were to be included.¹²¹

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Real Decreto Real Decreto 1015/2009 por el que se regula la disponibilidad de medicamentos en situaciones especiales. BOE, n.º 174 de lunes 20 de julio de 2009.
2. Delgado O, Puigventos F, Clopés A. Posicionamiento del farmacéutico de hospital ante la utilización de medicamentos en condiciones diferentes a las autorizadas. *Farm Hosp*. 2009;33:237-9.
3. Avendaño Solá C. Uso compasivo de medicamentos: un cambio necesario en España. *Med Clin (Barc)*. 2009;133:425-6.
4. Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica. BOE, n.º 274 de 15 de noviembre de 2002.
5. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med*. 2006;166:1021-6.
6. Kocs D, Fendrick M. Effect of off-label. Use of oncology drugs on pharmaceutical costs: the rituximab experience. *Am J Manage Care*. 2003;393-400.
7. Stafford RS. Regulating off-label drug use: rethinking the role of the FDA. *N Engl J Med*. 2008;358:1427-9.
8. Largent EA, Miller FG, Pearson SD. Going off-label without venturing off-course. Evidence and ethical off-label prescribing. *Arch Intern Med*. 2009;169:1745-7.
9. Walton SM, Schumock GT, Lee KV, Alexander GC, Meltzer D, Stafford RS. Prioritizing future research on off-label prescribing: results of a quantitative evaluation. *Pharmacotherapy*. 2008;28:1443-52.
10. Flores-Moreno S, Bautista-Paloma J. Tratamiento de la degeneración macular asociada a la edad: una asignatura pendiente. *Arch Soc Esp Oftalmol*. 2008;83:405-6.

11. Ruiz-Moreno, JM, coordinador. Guías de práctica clínica de la SERV: Tratamiento de la degeneración macular asociada a la edad (DMEA) exudativa. Arch Soc Esp Oftalmol 2009;84:333-44.
12. Monzón Moreno A. Bevacizumab en el tratamiento de la deenergación macular neovascular asociada a la edad. Farm Hosp. 2006;30:385-90.
13. Cliniguía. Actualización de diagnóstico y terapéutica 2009. 4th ed. Madrid: Eviscience Publicaciones; 2009.
14. Moya Mir M. Normas de actuación en Urgencias. 3rd ed. Madrid: Medica Panamericana; 2004.
15. Tosti A, Iorizzo M, Botta GL, Milani M. Efficacy and safety of a new clobetasol propionate 0.05% foam in alopecia areata: a randomized, double-blind placebo-controlled trial. J Eur Acad Dermatol Venereol. 2006;20:1243-7.
16. Moghetti P, Tosi F, Tosti A, Negri C, Misciali C, Perrone F, et al. Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. J Clin Endocrinol Metab. 2000;85:89-94.
17. Enzo Devoto C, Aravena L. Actualización de la terapia del hirsutismo. Rev Chil Obstet Ginecol. 2006;71:425-31.
18. Katta R. Lichen planus. AFP. 2000;61:3319.
19. Crispian Scully C, Carrozzo M. Oral mucosal disease: lichen planus. Br J Oral Maxillofacial Surg. 2008;46:15-21.
20. Panjwani S. Early diagnosis and treatment of discoid lupus erythematosus. JABFM. 2009;22:206-13.
21. Suarez-Fernandez R, Espana-Alonso A, Herrero-Gonzalez JE, Mascaro-Galy JM. Manejo practico de las enfermedades ampollas autoinmunes mas frecuentes. Actas Dermosifiliogr. 2008;99:441-55.
22. Smith PF, Corelli RL. Doxepin in the management of pruritus associated with allergic cutaneous reactions. Ann Pharmacother. 1997;31:633-5.
23. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol. 2009;61:451-85.
24. Greene SL, Reed CE, Schroeter AL. Double blind crossover study comparing doxepin with diphenhydramine for the treatment of chronic urticaria. J Am Acad Dermatol. 1985;12:669-75.
25. Harto A, Sendagorta E, Ledo A. Doxepin in the treatment of chronic urticaria. Dermatologica. 1985;170:90-3.
26. Kaplan MM, Gershwin ME. Primary biliary cirrhosis. N Engl J Med. 2005;353:1261-73.
27. Afif W, Leighton JA, Hanauer SB, Loftus Jr EV, Faubion WA, Pardi DS, et al. Open-label study of adalimumab in patients with ulcerative colitis including those with prior loss of response or intolerance to infliximab. Inflamm Bowel Dis. 2009;15:1302-7.
28. Morgan MH, Read AE, Speller DC. Treatment of hepatic encephalopathy with metronidazole. Gut. 1982;23:1-7.
29. Markowitz J, Rosa J, Grancher K, Aiges H, Daum F. Long-term 6-mercaptopurine treatment in adolescents with Crohn's disease. Gastroenterology. 1990;99:1347-51.
30. Tytgat GNJ, Koelz HR, Voesmaer GDC, The sucralfate investigational working team. Sucralfate maintenance therapy in reflux esophagitis. Am J Gastroenterol. 1995;90:1233-7.
31. Richardson PG, Elias AD, Krishnan A, Wheeler C, Nath R, Hoppensteadt D, et al. Treatment of severe veno-occlusive disease with defibrotide: compassionate use results in response without significant toxicity in a high-risk population. Blood. 1998;92:737-44.
32. Kumar S, DeLeve LD, Kamath PS, Tefferi A. Hepatic veno-occlusive disease (sinusoidal obstruction syndrome) after hematopoietic stem cell transplantation. Mayo Clin Proc. 2003;78:589-98.
33. McCormack J, Bell S, Senini S, Walmsley K, Patel K, Wainwright C, et al. Daily versus weekly azithromycin in cystic fibrosis patients. Eur Respir J. 2007;30:487-95.
34. Pérez-Aguilar F, Ferrer-Calvete J, Nicolás D, Berenguer J, Ponce J. Digestive alterations in cystic fibrosis. Retrospective study of a series of 46 adult patients. Gastroenterol Hepatol. 1999;22:72-8.
35. Laboratorios AstraZeneca Farmacéutica Spain, S.A. Ficha técnica de Nexium® iny (esomeprazol) [updated 2009 Sept]. Available from: <http://www.aemps.es/>.
36. Huggins RM, Scates AC, Latour JK. Intravenous proton-pump inhibitors versus H2-antagonists for treatment of GI bleeding. Ann Pharmacother. 2003;37:433-7.
37. Czaja AJ. Difficult treatment decisions in autoimmune hepatitis. World J Gastroenterol. 2010;16:934-47.
38. Morillas RM, Bargallo A. Hepatitis autoimmune. Semin Fund Esp Reumatol. 2008;9:166-73.
39. Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. Hepatology. 2009;49:2087-107.
40. Muñoz MT, Solís-Herruzo JA. Pseudo-obstrucción intestinal crónica. Revista Española de Enfermedades digestivas. 2007;99:100-11.
41. Ponc R, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. N Engl J Med. 1999;341:137-41.
42. De Giorgio R, Barbara G, Stanghellini V, Tonini M, Vasina V, Cola B, et al. Review article: the pharmacological treatment of acute colonic pseudo-obstruction. Aliment Pharmacol Ther. 2001;15:1717-27.
43. Grupo de trabajo de la guía de práctica clínica sobre el síndrome del intestino irritable. Manejo del paciente con síndrome del intestino irritable. Barcelona: Asociación Española de Gastroenterología, Sociedad Española de Familia y Comunitaria y Centro Cochrane Iberoamericano; 2005.
44. Borrego Hernando O. Tratamiento de los trastornos de la conducta alimentaria: anorexia y bulimia. Inf Ter Sist Nac Salud. 2000;24:44-50.
45. Koukoulaki M, Goumenos DS. The accumulated experience with the use of mycophenolate mofetil in primary glomerulonephritis. Expert Opin Investig Drugs. 2010;19:673-87.
46. Iglesias Lepine ML, Gutiérrez Cebollada J, López Casanovas MJ, Pedro-Botet Montoya J. Eficacia del salbutamol en el tratamiento de la hiperpotasemia aguda grave. Emergencias. 1999;11:54-7.
47. Lab Lab Otsuka America Pharmaceutical Inc (USA). Información técnica FDA para Samsca® (tolváltán) [updated 2009 Jun]. Available from: <http://www.otsuka-us.com/>.
48. Kawaguchi Y, Saito A, Kawanishi H, Nakayama M, Miyazaki M, Nakamoto H, et al. Recommendations on the management of encapsulating peritoneal sclerosis in Japan, 2005: diagnosis, predictive markers, treatment, and preventive measures. Perit Dial Int. 2005; Suppl 4:S83-95.
49. Del Peso G, Bajo MA, Gil F, Aguilera A, Ros S, Costero O, et al. Clinical experience with tamoxifen in peritoneal fibrosing syndromes. Adv Perit Dial. 2003;19:32-5.
50. Drop SL, Odink RJ, Rouwé C, Otten BJ, Van Maarschalkerweerd MW, Gons M, et al. The effect of treatment with an LH-RH agonist (Buserelin) on gonadal activity growth and bone maturation in children with central precocious puberty. Eur J Pediatr. 1987;146:272-8.
51. Lab Pfizer, Inc., New York (NY, USA). Información técnica de Synarel® (nafarelina) [updated 2005 Jul]. Available from: <https://www.pfizermedicalinformation.com/>.
52. Bruera E, Neumann CM, Pituskin E, Calder K, Ball G, Hanson J. Thalidomide in patients with cachexia due to terminal cancer: preliminary report. Ann Oncol. 1999;10:857-9.

53. Dang CN, Trainer P. Pharmacological management of Cushing's Syndrome: an update. *Arq Bras Endocrinol Metab.* 2007;51:1339-48.
54. Albiger NME, Scaroni CM, Mantero F. Cyclic Cushing's Syndrome: an overview. *Arq Bras Endocrinol Metab.* 2007;51:1253-60.
55. Papatsonis DN, Van Geijn HP, Adèr HJ, Lange FM, Bleker OP, Dekker GA. Nifedipine and ritodrine in the management of preterm labor: a randomized multicenter trial. *Obstet Gynecol.* 1997;90:230-4.
56. Thorp JM, Berkman ND. The Cochrane Library. *Manage Preterm Labor.* 2000;2:1-54.
57. Bukowski R, Saade GR. New developments in the management of preterm labor. *Semin Perinatol.* 2001;25:272-94.
58. Verma U, Goharkhay N. Conservative management of cervical ectopic pregnancy. *Fertil Steril.* 2009;91:671-4.
59. Nestler JE. Metformin for the treatment of the polycystic ovary syndrome. *N Engl J Med.* 2008;358:47-54.
60. Baytur YB, Ozbilgin K, Cilaker S, Lacin S, Kurtul O, Oruc S, et al. A comparative study of the effect of raloxifene and gosereline on uterine leiomyoma volume changes and estrogen receptor, progesterone receptor, bcl-2 and p53 expression immunohistochemically in premenopausal women. *Eur J Obstet Gynecol Reprod Biol.* 2007;135:94-103.
61. Palomba S, Sammartino A, Di Carlo C, Affinito P, Zullo F, Nappi C. Effects of raloxifene treatment on uterine leiomyomas in postmenopausal women. *Fertil Steril.* 2001;76:38-43.
62. Jarvis CI, Lynch AM, Morin AK. Management strategies for premenstrual syndrome/premenstrual dysphoric disorder. *Ann Pharmacother.* 2008;42:967-78.
63. Guevara-López U, Covarrubias-Gómez A, García-Ramos G. Parámetros de práctica para el manejo del dolor neuropático. *Rev Invest Clin.* 2006;58:126-38.
64. Pérez Molina I, Ayuga Loro F. Dolor neuropático. Toledo: SESCAM. Área de Farmacia; 2000.
65. Carrazana E, Mikoshiva I. Rationale and evidence for the use of oxcarbazepine in neuropathic pain. *J Pain Symptom Manage.* 2003;25:S31.
66. García Merino JA, Blasco Quílez MR. Tratamiento farmacológico de la esclerosis múltiple. *Inf Ter Sist Nac Salud.* 2007;31:111-7.
67. Lapiere Y, Hum S. Treating fatigue. *Int MS J.* 2007;14:64-71.
68. Lab Smithkline Beecham Pharmaceuticals (Philadelphia, PA, USA). Información técnica de Thorazine® (clorpromazina); texto actualizado; 2002.
69. Skeie GO, Apostolski S, Evoli A, Gilhus NE, Illa I, Harms L, et al. Guidelines for treatment of autoimmune neuromuscular transmission disorders. *Eur J Neurol.* 2010;17:893-902.
70. Bain PG, Motomura M, Newsom-Davis J, Misbah SA, Chapel HM, Lee ML, et al. Effects of intravenous immunoglobulin on muscle weakness and calcium-channel autoantibodies in the Lambert-Eaton myasthenic syndrome. *Neurology.* 1996;47:678-83.
71. Suárez GA. Miastenia gravis: diagnóstico y tratamiento. *Rev Neurol.* 1999;29:162-5.
72. Gajdos P, Chevret S, Toyka KV. Inmunoglobulina intravenosa para la miastenia gravis (Revisión Cochrane traducida). In: *La Biblioteca Cochrane Plus*, 2008. n.º 4. Oxford: Update Software Ltd. Available from: <http://www.updatesoftware.com>.
73. Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. 2006:354-96.
74. Echarri E, Bernardo M, Pol E. Neurología y Psiquiatría. In: *Curso de Formación Continuada de la SEFH. Módulo III.* Madrid: Arán Ediciones; 2007.
75. Robertson MM. Tourette syndrome, associated conditions and the complexities of treatment. *Brain.* 2000;123:425-62.
76. Stern JS, Burza S, Robertson MM. Gilles de la Tourette's syndrome and its impact in the UK. *Postgrad Med J.* 2005;81:12-9.
77. van Rijckevorsel K. Treatment of Lennox-Gastaut syndrome: overview and recent findings. *Neuropsychiatr Dis Treat.* 2008;4.
78. Gironell A. Estrategias terapéuticas en el temblor esencial. *Med Clin (Barc).* 2007;129:632-7.
79. Arcos González P, Castro Delgado R, directores. Manual de procedimientos de evaluación y respuesta sanitaria a emergencias y desastres. Fundación para la Cooperación y Salud Internacional Carlos III. Madrid: Litografía Arte; 2008. p. 123.
80. Galvez Tello JF, Chacón de Antonio J, García Muñoz C. Protocolo diagnóstico y tratamiento empírico de las conjuntivitis. *Medicine.* 2006;9:3502-5.
81. Bom S, Zamiri P, Lightman S. Use of methotrexate in the management of sight-threatening uveitis. *Ocul Immunol Inflamm.* 2001;9:35-40.
82. Tugal-Tutkun I, Mudun A, Urgancioglu M, Kamali S, Kasapoglu E, Inanc M, et al. Efficacy of infliximab in the treatment of uveitis that is resistant to treatment with the combination of azathioprine, cyclosporine, and corticosteroids in Behçet's disease: an open-label trial. *Arthritis Rheum.* 2005;52:2478-84.
83. Tynjälä P, Lindahl P, Honkanen V, Lahdenne P, Kotaniemi K. Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. *Ann Rheum Dis.* 2007;66:548-50.
84. Mimura MA, Hirota SK, Sugaya NN, Sanches Jr JA, Migliari DA. Systemic treatment in severe cases of recurrent aphthous stomatitis: an open trial. *Clinics.* 2009;64:193-8.
85. Altenburg A, Abdel-Naser MB, Seeber H, Abdallah M, Zouboulis CC. Practical aspects of management of recurrent aphthous stomatitis. *J Eur Acad Dermatol Venereol.* 2007;21:1019-26.
86. Pizarro A, Herranz P, Navarro A, Casado M. Recurrent aphthous stomatitis: treatment with pentoxifylline. *Acta Derm Venereol.* 1996;76:79-80.
87. Rattan J, Schneider M, Arber N, Gorsky M, Dayan D. Sucralfate suspension as a treatment of recurrent aphthous stomatitis. *J Intern Med.* 1994;236:341-3.
88. Bonnetblanc JM, Royer C, Bedane C. Thalidomide and recurrent aphthous stomatitis: a follow up study. *Dermatology.* 1996;193:321-3.
89. Salas M, Ventura Díaz J. Hipoacusia brusca: aproximación diagnóstica y terapéutica. *SEMERGEN.* 2000;26:395-8.
90. Pino Rivero V. Comparación de dos protocolos diferentes en el tratamiento de la hipoacusia brusca. *Acta Otorrinolaringol Esp.* 2005;55:63-7.
91. Ramirez Camacho R. Tratamiento de los trastornos del equilibrio. *Inf Ter Sist Nac Salud.* 2002;26:44-7.
92. Sheffer AL, Fearon DT, Austen KF. Hereditary angioedema: a decade of management with stanazolol. *J Allergy Clin Immunol.* 1987;80:855-80.
93. Pérez Gómez A, Sánchez Atrio AI, Albarrán Hernández F, Cuende Quintana E. Artritis idiopática juvenil. *Medicine.* 2009;10:1933-41.
94. Koler RA, Montemarano A. Dermatomyositis. *Am Fam Physician.* 2001;64:1565-72.
95. Kontzias A, Efthimiou P. Adult-onset Still's disease pathogenesis, clinical manifestations and therapeutic advances. *Drugs.* 2008;68:319-37.
96. Fautrel B, Borget C, Rozenberg S, Meyer O, Le Loët X, Masson C, et al. Corticosteroid sparing effect of low dose methotrexate treatment in adult Still's disease. *J Rheumatol.* 1999;26:373-8.

97. Vasques Godinho FM, Parreira Santos MJ, Canas da Silva J. Refractory adult onset Still's disease successfully treated with anakinra. *Ann Rheum Dis*. 2005;64:647-68.
98. Häuser W, Eich W, Herrmann M, Nutzinger DO, Schiltenwolf M, Henningsen P. Fibromyalgia syndrome: classification, diagnosis, and treatment. *Dtsch Arztebl Int*. 2009;106:383-91.
99. Stegeman CA, Tervaert JW, De Jong PE, Kallenberg CG. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. *N Engl J Med*. 1996;335:16-20.
100. Sailler L. Rituximab off label use for difficult-to-treat autoimmune diseases: reappraisal of benefits and risks. *Clinic Rev Allerg Immunol*. 2008;34:103-10.
101. Ramos-Casals M, Soto MJ, Cuadrado MJ, Khamashta MA. Rituximab in systemic lupus erythematosus: a systematic review of off-label use in 188 cases. *Lupus*. 2009;18:767-76.
102. Dooley MA, Ginzler EM. Newer therapeutic approaches for systemic lupus erythematosus: immunosuppressive agents. *Rheum Dis Clin N Am*. 2006;32:91-102.
103. Vanden Bossche L, Vanderstraeten G. Heterotopic ossification: a review. *J Rehabil Med*. 2005;37:129-36.
104. Romanò CL, Duci D, Romanò D, Mazza M, Meani E. Celecoxib versus indomethacin in the prevention of heterotopic ossification after total hip arthroplasty. *J Arthroplasty*. 2004;19:14-8.
105. Seyahi E, Fresko I, Melikoglu M, Yazici H. The management of Behçet's syndrome. *Acta Reumatol Port*. 2006;31:125-31.
106. Villader Palacin A, Robert Olalla J, Sanuy Jiménez B, Rufi Rigau G, Folch Civit J, Chalte González A. Tratamiento de la enfermedad de Behçet. *An Med Interna (Madrid)*. 2002;19:594-8.
107. Berger KJ, Guss DA. Micotoxins revisited: part I. *J Emerg Med*. 2005;28:53-62.
108. Lab Hospira Inc (Lake Forest, IL, USA). Información de Atropine-Sulfate® for injection [updated text 2004]. Available from: .
109. Kavalci C, Durukan P, Ozer M, Cevik Y, Kavalci G. Organophosphate poisoning due to a wheat bagel. *Intern Med*. 2009;48:85-8.
110. Bacigalupo A, Passweg J. Diagnosis and treatment of acquired aplastic anemia. *Hematol Oncol Clin N Am*. 2009;23:159-70.
111. Valent P, Lechner K. Diagnosis and treatment of autoimmune haemolytic anaemias in adults: a clinical review. *Wien Klin Wochenschr*. 2008;120 5-6:136-51.
112. Imazio M, Brucato A, Trincherò R, Spodick D, Adler Y. Individualized therapy for pericarditis. *Expert Rev Cardiovasc Ther*. 2009;7:965-75.
113. Sagristà Sauleda J, Permanyer Miralda G, Soler Soler J. Orientación diagnóstica y manejo de los síndromes pericárdicos agudos. *Rev Esp Cardiol*. 2005;58:830-41.
114. Lab CSL Behring AG (Berna -Suiza-). Ficha técnica de Rhophylac® [accessed 2011 Mar]. Available from: <http://www.rhophylac.com/>.
115. De la Rubia J, Contreras E, Del Río-Garma J. Púrpura trombótica trombocitopénica. *Med Clin (Barc)*. 2010 [In press].
116. Corti P, Uderzo C, Tagliabue A, Della Volpe A, Annaloro C, Tagliaferri E, et al. Defibrotide as a promising treatment for thrombotic thrombocytopenic purpura in patients undergoing bone marrow transplantation. *Bone Marrow Transplant*. 2002;29:542-3.
117. Trissel LA. Handbook on injectable drugs. 10th ed. Bethesda: American Society of Health-System Pharmacists; 1998.
118. Kim DS. Kawasaki disease. *Yonsei Med J*. 2006;47:759-72.
119. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics*. 2004;114:1708-33.
120. Lab Baxter, S.L. Ficha técnica de Gammagard S/D® [updated 2009 May]. Available from: <http://www.aemps.es/>.
121. García-Sabina A. Emecum. Ayuda en la toma de decisiones farmacoterapéuticas. AWWE, 2009. Available from: www.emecum.com.