



Towards better patient care: drugs to avoid in 2021

ABSTRACT

● To make it easier to choose high-quality care, and to prevent disproportionate harm to patients, *Prescrire* has published its annual update of drugs to avoid.

● *Prescrire's* assessment of a drug's harm-benefit balance in a given situation reflects a rigorous procedure based on: a systematic and reproducible literature search; patient-relevant outcomes; prioritisation of the supporting data according to strength of evidence; comparison with standard treatment (if one exists); weighing the adverse effects, including the uncertainties and the gaps in knowledge surrounding them.

● This annual review of drugs to avoid covers all the drugs examined by *Prescrire* between 2010 and 2020 that are authorised in the European Union or in France. We identified 112 drugs (93 of which are marketed in France) that are more harmful than beneficial in all their approved indications (with rare exceptions explained in a footnote).

● In most cases, when drug therapy appears to be the best course of action, other drugs with a better harm-benefit balance are available.

● Even for patients with a serious condition, who have exhausted all other treatment options, there is no justification for exposing them to drugs with major risks but no proven efficacy. It is sometimes acceptable to test these drugs in clinical trials, but patients must be informed of the uncertainties over their harm-benefit balance as well as the trial's

objectives. For patients who choose not to take part in a clinical trial, appropriate support and symptomatic care should be implemented when there are no effective treatments for improving the prognosis or quality of life.

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This is *Prescrire's* ninth consecutive annual review of drugs to avoid, which includes documented cases of drugs that are more dangerous than beneficial (1,2). The aim is to make it easier to choose safe, effective treatments, primarily to avoid exposing patients to unacceptable harms. The drugs listed (sometimes a particular form or dose strength) should be avoided in all the clinical situations for which they are authorised in France or in the European Union (with rare exceptions explained in a footnote).

A reliable, rigorous and independent methodology

What data sources and methodology do we use to assess a drug's harm-benefit balance?

Our review of drugs to avoid lists drugs and indications analysed in detail in our French edition over the 11-year period from 2010 through 2020 inclusive. Some drugs and indications were examined for the first time, while others were re-evaluated as new data on efficacy or adverse effects have become available.

One of the main objectives of our publications is to provide health professionals (and thereby their patients) with the clear, independent, reliable and

up-to-date information they need, free from conflicts of interest and commercial pressures.

Prescrire is structured in such a way as to guarantee the quality of the information provided to our subscribers. The Editorial Staff comprise a broad range of health professionals working in various sectors and free from conflicts of interest. We also call on an extensive network of external reviewers (specialists in the relevant area, methodologists and various practitioners), and each article undergoes multiple quality controls and cross-checking at each step of the editorial process (see *About Prescrire > How we work* at english.prescrire.org). Our editorial process is a collective one, as symbolised by the “©*Prescrire*” byline.

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Comparison with standard treatments. The harm-benefit balance of a given drug has to be continually re-evaluated as new data on efficacy or adverse effects become available. Similarly, treatment options evolve as new drugs arrive on the market.

Some drugs offer a therapeutic advantage, while others are more dangerous than beneficial and should not be used (3).

Prescrire's assessments of drugs and indications are all based on a systematic and reproducible literature search. The resulting data are then analysed collectively by our Editorial Staff, using an established procedure:

- efficacy data are prioritised so that most weight is given to studies providing robust supporting evidence, i.e. double-blind, randomised controlled trials;
- the drug is compared with the standard treatment (not necessarily a drug) when one exists, after careful determination of the best comparator;
- the results taken into account are those based on the clinical endpoints most relevant to the patients concerned. This means that wherever possible we ignore surrogate endpoints such as laboratory markers that have not been shown to correlate with a favourable clinical outcome (4,5).

Careful analysis of adverse effects. Adverse effects can be more difficult to analyse, as they are often less thoroughly documented than efficacy. This discrepancy must be taken into account.

The adverse effect profile of each drug is assessed by examining data from clinical trials and animal pharmacotoxicology studies, and any pharmacological affiliation.

When a new drug is approved, many uncertainties remain. Some rare but serious adverse effects may have been overlooked during clinical trials and may only emerge after several years of routine use by a large number of patients. Some adverse effects may also have been underestimated because the patients enrolled in clinical trials are highly selected (3).

Empirical data and personal experience: risk of major bias. Empirical assessment of a drug's harm-benefit balance, based on individual experience, can help to guide further research, but it is subject to major bias that strongly reduces the level of evidence of the findings (3,4). For example, it can be difficult to attribute a specific outcome to a particular drug, as other factors must be taken into account, including the natural history of the disease, the placebo effect, the effect of another treatment the patient may not have mentioned, or a change in diet or lifestyle. Similarly, a doctor who sees an improvement in certain patients cannot know how many other patients' conditions worsened when they received the same treatment (3).

The best way to minimise subjective bias caused by non-comparative evaluation of a few patients is to prioritise the results of clinical trials, particularly double-blind, randomised trials versus standard care (3,4).

Serious conditions with no effective treatment: patients should be informed of the consequences of interventions. When faced with a serious condition for which there is no effective treatment, some patients opt to forgo treatment while others are willing to try any drug that might bring them even temporary relief, despite a risk of serious adverse effects.

When the short-term prognosis is poor, some health professionals may propose “last-chance” treatments without fully informing the patient of the harms, either intentionally or unintentionally.

But patients in this situation must not be treated as guinea pigs. “Trials” of drugs belong in the sphere of formal, properly-conducted clinical research, not health care. It is of course useful to enrol patients in clinical trials, provided they are informed of the harms and the uncertain nature of the possible benefits. The trial results should be published (whether positive, negative or inconclusive) in order to advance medical knowledge.

However, patients must always be made aware that they have the option of refusing to participate in clinical trials or to receive “last-chance” treatments with an uncertain harm-benefit balance. They must also be reassured that, if they do refuse, they will not be abandoned but will continue to receive the best available care. Even though supportive care and symptomatic treatment are not intended to cure or slow progression of the underlying disease, they are useful elements of patient care.

Marketing authorisation should offer certain guarantees. While a great deal of uncertainty surrounds the harm-benefit balance of drugs that are under evaluation in clinical trials, drugs used for routine care must have a favourable harm-benefit balance. Marketing authorisation should only be granted on the basis of proven efficacy relative to standard care wherever possible, along with an acceptable adverse effect profile: in general, little, if any, additional information on efficacy is collected once marketing authorisation has been granted (3).

Main changes in the 2021 update

Prescrire updates its review of drugs to avoid every year. As a result, some drugs are added to the list, while others are removed, either because the pharmaceutical company or a health authority decided to withdraw the drug from the market, or pending the outcome of our reassessment of the drug's harm-benefit balance, which may change in light of new data. Here we outline the main differences between the 2020 and 2021 lists of drugs to avoid.

Three drugs removed from the list of drugs to avoid. In 2019, we added **ulipristal 5 mg** (Esmya^o) to the list of drugs to avoid, because this antagonist and partial agonist of progesterone receptors, used for uterine fibroids, can cause serious liver injury, sometimes requiring liver transplantation (*Prescrire Int* n° 198; *Rev Prescrire* n° 418) (a). Esmya^o's marketing authorisation was suspended in the European Union in March 2020 due to these serious hepatic effects, and in September 2020, the European Pharmacovigilance Risk Assessment Committee (PRAC) recommended withdrawal of its marketing authorisation.

The intestinal "anti-infective" agent **nifuroxazide** was also removed from our list of drugs to avoid, because it is supposedly no longer marketed in France. This drug has no proven efficacy against diarrhoea, but it provokes serious, albeit rare, immune-mediated and haematological adverse effects.

We also removed the antiangiogenic tyrosine kinase inhibitor **nintedanib** from the list while we assess its harm-benefit balance in two new indications added in 2020: chronic fibrosing interstitial lung diseases with a progressive phenotype, and systemic sclerosis-associated interstitial lung disease. *Nintedanib*'s harm-benefit balance remains unfavourable in the other situations for which it is authorised: idiopathic pulmonary fibrosis (*Prescrire Int* n° 173) and certain forms of non-small cell lung cancer (*Rev Prescrire* n° 389).

Gliflozins back on the list of drugs to avoid in diabetes. Glucose-lowering drugs belonging to the gliflozin class have been authorised for type 2 diabetes in the European Union since the mid-2010s. Increasing evidence of their unfavourable harm-benefit balance has accrued over time (*Prescrire Int* n° 160). Those currently marketed in

Europe are **canagliflozin** (alone or combined with *metformin*), **dapagliflozin** (alone or combined with *metformin* or *saxagliptin*), **empagliflozin** (alone or combined with *metformin* or *linagliptin*), and **ertugliflozin** (alone or combined with *metformin* or *sitagliptin*). Gliflozins were included in our 2019 list of drugs to avoid. They were removed in 2020 while we evaluated the harm-benefit balance of *dapagliflozin* in type 1 diabetes. *Dapagliflozin* has no more place in the treatment of type 1 diabetes than in type 2 diabetes. Following this re-evaluation, the gliflozin class of glucose-lowering drugs was reinstated on *Prescrire*'s list of drugs to avoid.

New drugs to avoid: finasteride 1 mg, piracetam, esketamine, etc. Two drugs were added to our 2021 list of drugs to avoid because their adverse effects are disproportionate when weighed against their weak efficacy or the benign condition for which they are authorised. They are **finasteride 1 mg**, authorised for use in men with male-pattern baldness, and the "vasodilator" **piracetam**, authorised for various clinical situations including vertigo and cognitive impairment.

Three other drugs have some efficacy, but their adverse effects are disproportionate or other, less dangerous options exist: **esketamine** nasal spray in "treatment-resistant" depression; **pimecrolimus** in atopic eczema; and **romosozumab** in severe postmenopausal osteoporosis.

Meloxicam joins the other nonsteroidal anti-inflammatory drugs (NSAIDs) on our list that belong to the oxicam class: *piroxicam* and *tenoxicam*. Its omission from last year's review was simply an oversight.

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a- In postcoital contraception, ulipristal (still marketed under the brand name EllaOne^o) is taken as a single 30 mg dose. Although it has not been shown to cause hepatitis when used in this way, levonorgestrel is a more cautious choice, especially since interactions between ulipristal and hormonal contraceptives can reduce the efficacy of ulipristal or the contraceptive (Prescrire Int n° 198 and n° 212).

112 authorised drugs that are more dangerous than beneficial

As of late 2020, based on the drugs examined by *Prescrire* between 2010 and 2020 that are authorised in France or in the European Union, 112 drugs were identified as more dangerous than beneficial in all their authorised indications. 93 of these drugs are marketed in France.

They are listed, based first on the therapeutic area in which they are used, and then in alphabetical order according to their international nonproprietary names (INNs).

These 112 drugs comprise:

- Active substances with adverse effects that, given the clinical situations in which they are used, are disproportionate to the benefits they provide;
- Older drugs that have been superseded by newer drugs with a better harm-benefit balance;
- Recent drugs that have a less favourable harm-benefit balance than existing options;
- Drugs that have no proven efficacy beyond that of a placebo, but that carry a risk of particularly severe adverse effects.

The main reasons why these drugs are considered to have an unfavourable harm-benefit balance are

explained on a case-by-case basis. When available, better options are briefly mentioned, as are situations (serious or non-serious) in which there is no suitable treatment.

The differences between this year's and last year's lists are detailed in "Main changes in the 2021 update", on page 51-3.



Cardiology

- **Aliskiren**, a blood pressure-lowering renin inhibitor, has not been shown to prevent cardiovascular events. On the contrary, a trial in diabetic patients showed that *aliskiren* was associated with an increase in cardiovascular events and renal failure (*Prescrire Int* n° 106, 129, 166, 184). It is better to choose one of the many established blood pressure-lowering drugs, such as a thiazide diuretic or an angiotensin converting enzyme (ACE) inhibitor.
- **Bezafibrate**, **ciprofibrate** and **fenofibrate** are cholesterol-lowering drugs with no proven efficacy in the prevention of cardiovascular events, yet they all have numerous adverse effects, including cutaneous, haematological and renal disorders (*Prescrire Int* n° 85, 117, 174). When the use of a fibrate is justified, *gemfibrozil* is the only one that has been shown to prevent the cardiovascular complications of hypercholesterolaemia, provided renal function and serum creatine phosphokinase levels are closely monitored.
- **Dronedarone**, an antiarrhythmic chemically related to *amiodarone*, is less effective than *amiodarone* at preventing atrial fibrillation recurrence, yet it has at least as many severe adverse effects, in particular hepatic, pulmonary and cardiac disorders (*Prescrire Int* n° 108, 120, 122; *Rev Prescrire* n° 339). *Amiodarone* is a better option.
- **Ivabradine**, a cardiac I_f current inhibitor, can cause visual disturbances, cardiovascular disorders (including myocardial infarction), potentially severe bradycardia and other cardiac arrhythmias. It has no advantages over other available options in either angina or heart failure (*Prescrire Int* n° 88, 110, 111, 118, 155, 165; *Rev Prescrire* n° 403, 413). Established treatments shown to be effective in angina include beta-blockers or, as an alternative, calcium channel blockers such as *amlodipine* and *verapamil*. There are also better options for heart failure: one is to refrain from adding another drug to an optimised treatment regimen; another is to use a beta-blocker with a proven impact on mortality.
- **Nicorandil**, a vasodilator with solely symptomatic efficacy in preventing effort angina, can cause severe mucocutaneous ulceration (*Prescrire Int* n° 81, 95, 110, 132, 163, 175; *Rev Prescrire* n° 419). A nitrate is a better option for prevention of angina attacks.
- **Olmесartan**, an angiotensin II receptor blocker (ARB or "sartan") marketed alone or in combination with *hydrochlorothiazide* or *amlodipine*, is no more effective than other ARBs against the complications of hypertension. However, it can cause sprue-like enteropathy leading to chronic diarrhoea (poten-

tially severe) and weight loss, and possibly an increased risk of cardiovascular mortality (*Prescrire Int* n° 148, 171). Among the many other ARBs available, it is better to choose *losartan* or *valsartan*, which do not appear to have these adverse effects.

- **Ranolazine**, an antianginal agent with a poorly understood mechanism, provokes adverse effects that are disproportionate to its minimal efficacy in reducing the frequency of angina attacks, including: gastrointestinal disorders, neuropsychiatric disorders, palpitations, bradycardia, hypotension, QT prolongation and peripheral oedema (*Prescrire Int* n° 102; *Rev Prescrire* n° 350; *Interactions Médicamenteuses Prescrire*).
- **Trimetazidine**, a drug with uncertain properties, is used in angina despite its modest effect on symptoms (shown mainly in stress tests), yet it can cause parkinsonism, hallucinations and thrombocytopenia (*Prescrire Int* n° 84, 100, 106; *Rev Prescrire* n° 404). It is better to choose better-known treatments for angina: certain beta-blockers, or, as an alternative, calcium channel blockers such as *amlodipine* and *verapamil*.
- **Vernakalant**, an injectable antiarrhythmic used in atrial fibrillation, has not been shown to reduce mortality or the incidence of thromboembolic or cardiovascular events. Its adverse effects include various arrhythmias (*Prescrire Int* n° 127). *Amiodarone* is a more prudent choice for pharmacological cardioversion.



Dermatology - Allergy

- **Finasteride 1 mg**, a 5-alpha reductase inhibitor, has very modest efficacy against male-pattern baldness in men, slightly increasing hair density on the crown of the head (by about 10%), but only while treatment continues. Notable adverse effects include sexual dysfunction (erectile dysfunction, ejaculatory disorders, decreased libido), depression, suicidal ideation and breast cancer (*Prescrire Int* n° 175, 196; *Rev Prescrire* n° 335). When a pharmacological approach is chosen, topical *minoxidil* is less dangerous although certain precautions must be taken (a).
- **Mequitazine**, a sedating antihistamine with antimuscarinic activity, authorised for allergies, has only modest efficacy. However, it carries a higher risk of cardiac arrhythmias through QT prolongation than other antihistamines, in particular in patients whose cytochrome P450 isoenzyme CYP2D6 metabolises the drug slowly (a characteristic not generally known to the patient or the doctor), or when co-administered with drugs that inhibit CYP2D6 (*Rev Prescrire* n° 337). A "non-sedating" antihistamine without antimuscarinic activity, such as *cetirizine* or *loratadine*, is a better option in this situation.

a- *Prescrire* plans to reassess the harm-benefit balance of *finasteride* 5 mg in benign prostatic hyperplasia.

• **Topical pimecrolimus** and **tacrolimus**, two immunosuppressants used in atopic eczema, can cause skin cancer and lymphoma, yet their efficacy is barely different from that of high-potency topical corticosteroids (*Prescrire Int* n° 101, 110, 131; *Rev Prescrire* n° 367, 428, 446) (b). Judicious use of a topical corticosteroid to treat flare-ups is a better option in this situation. Hardly any comparative evaluation data are available on *pimecrolimus* or *tacrolimus* in patients in whom a topical corticosteroid has failed.

• **Injectable promethazine**, an antihistamine used to treat severe urticaria, can cause thrombosis, skin necrosis and gangrene following extravasation or accidental injection into an artery (*Prescrire Int* n° 109). Injectable *dexchlorpheniramine*, which does not appear to carry these risks, is a better option.



Diabetes - Nutrition

Diabetes. A variety of glucose-lowering drugs have an unfavourable harm-benefit balance. They reduce blood glucose slightly, but have no proven efficacy against the complications of diabetes (cardiovascular events, renal failure, neurological disorders) and have many adverse effects. The first-choice glucose-lowering drug for type 2 diabetes is *metformin*. If *metformin* is insufficiently effective, other options to consider are: a sulfonylurea such as *glibenclamide*, an insulin, a combination of *metformin* + *liraglutide* or *metformin* + *semaglutide*, or, in some cases, slightly raising the HbA1c target.

• **Gliptins** (sodium-glucose cotransporter 2 (SGLT2) inhibitors), i.e. **canagliflozin** (alone or combined with *metformin*), **dapagliflozin** (alone or combined with *metformin* or *saxagliptin*), **empagliflozin** (alone or combined with *metformin* or *linagliptin*), and **ertugliflozin** (alone or combined with *metformin* or *sitagliptin*), have a burdensome adverse effect profile, including urogenital infections, serious skin infections involving the perineum, ketoacidosis, and possibly an increased risk of toe amputation (*Prescrire Int* n° 147, 157, 169, 175, 196, 206, 211, 213; *Rev Prescrire* n° 400).

Dapagliflozin is also authorised for use in type 1 diabetes, in which it has an unfavourable harm-benefit balance (*Prescrire Int* n° 220). When control of blood glucose levels is inadequate despite optimal insulin therapy, it is preferable to use other options or revise the targets, rather than expose patients to the serious adverse effects of *dapagliflozin*.

• **Gliptins** (dipeptidyl peptidase-4 (DPP-4) inhibitors), i.e. **alogliptin**, **linagliptin**, **saxagliptin**, **sitagliptin** and **vildagliptin**, marketed alone or in combination, have an unfavourable adverse effect profile that includes serious hypersensitivity reactions (anaphylaxis and cutaneous reactions such as Stevens-Johnson syndrome), infections (of the urinary tract and upper respiratory tract in particular), pancreatitis, bullous pemphigoid, and intestinal obstruction (*Prescrire Int* n° 121, 135, 138, 152, 158, 167, 186, 216; *Rev Prescrire* n° 365, 379).

• **Pioglitazone** has a long list of adverse effects, including heart failure, bladder cancer and bone fractures (*Prescrire Int* n° 129, 160).

Weight loss. As of late 2020, no drugs are capable of inducing lasting weight loss without harm. It is better to focus on dietary changes and physical activity, with psychological support if necessary.

• The weight loss product **bupropion + naltrexone** combines a drug chemically related to some amphetamine-like drugs (*bupropion*) with an opioid receptor antagonist (also see *bupropion* in the Smoking cessation section) (*Prescrire Int* n° 164).

• **Orlistat** has only a modest and transient effect on weight loss: patients lost about 3.5 kg compared with placebo over 12-24 months, with no evidence of long-term efficacy. Gastrointestinal disorders are very common, while other adverse effects include liver damage, hyperoxaluria, and bone fractures in adolescents. *Orlistat* alters the gastrointestinal absorption of many nutrients (fat-soluble vitamins A, D, E and K), leading to a risk of deficiency, and also reduces the efficacy of some drugs (thyroid hormones, some antiepileptics). The severe diarrhoea caused by *orlistat* can reduce the efficacy of oral contraceptives (*Prescrire Int* n° 57, 71, 107, 110; *Interactions Médicamenteuses Prescrire*).



Gastroenterology

• **Obeticholic acid**, a bile acid derivative authorised for primary biliary cholangitis, does not improve patients' health status, either used alone or in combination with *ursodeoxycholic acid*. It often worsens the main symptoms of the disease (pruritus and fatigue) and appears to provoke severe and sometimes fatal hepatic adverse effects. Even after other treatments have failed, *obeticholic acid* is a drug to avoid (*Prescrire Int* n° 197).

• The **medicinal clays attapulgite, diosmectite, hydrotalcite, beidellitic montmorillonite and kaolin**, used alone or in multi-ingredient products to treat various intestinal disorders, including diarrhoea, heartburn and gastroesophageal reflux disease, should be avoided because they are naturally contaminated with lead. Lead has neurological, haematological, renal, cardiovascular and reproductive toxicity, and the severity of most of these toxic effects increases with the dose to which patients are exposed (*Prescrire Int* n° 203; *Rev Prescrire* n° 429, 430). In diarrhoea, clays alter stool appearance without reducing fluid loss or the consequent risk of dehydration. In uncomplicated gastroesophageal reflux disease, when pharmacological treatment seems the best course of action, other drugs have a positive harm-benefit balance, such as a short course of treatment with a clay-free antacid, used

b- Oral or injectable tacrolimus is a standard immunosuppressant for transplant recipients, and in this situation, its harm-benefit balance is clearly favourable.

at moderate doses, for example *sodium bicarbonate* + *sodium alginate*.

- **Cimetidine** is a histamine H₂-antagonist authorised for various gastroesophageal disorders. When used concomitantly with many other drugs, *cimetidine* can cause these drugs to accumulate in the body, thereby enhancing their dose-dependent adverse effects, due to its inhibitory effect on numerous cytochrome P450 isoenzymes. Its harm-benefit balance is unfavourable compared with other H₂-receptor antagonists that do not expose patients to these drug interactions (*Interactions Médicamentuses Prescrire*).

- The neuroleptics **domperidone**, **droperidol** and **metopimazine** can provoke arrhythmias and sudden death. These adverse effects are unacceptable given the symptoms they are used to treat (nausea and vomiting, and gastroesophageal reflux in the case of *domperidone*) and their weak efficacy (*Prescrire Int* n° 129, 144, 175, 176, 179, 193; *Rev Prescrire* n° 403, 404). Other drugs have a favourable harm-benefit balance in gastroesophageal reflux disease, such as clay-free antacids or, when symptoms are severe or persistent, *omeprazole* for a few weeks at most. In the rare situations in which treatment with an antiemetic neuroleptic appears justified, *metoclopramide* is a less risky option. It also provokes serious cardiac events, but has proven efficacy against nausea and vomiting. It should be used at the lowest possible dose, taking drug interactions into account, and closely monitoring the patient.

- **Prucalopride**, a drug chemically related to neuroleptics, is authorised for chronic constipation but shows only modest efficacy, and only in about one in six patients. Its adverse effect profile is poorly documented, and includes in particular cardiovascular disorders (palpitations, ischaemic cardiovascular events, possible QT prolongation), depression and suicidal ideation, and teratogenicity (*Prescrire Int* n° 116, 137, 175). There is no justification for exposing patients with simple constipation to such risks. If dietary measures are ineffective, bulk-forming laxatives, osmotic laxatives or, very occasionally, other laxatives (lubricants, stimulants, or rectal preparations), used carefully and patiently, are safer than *prucalopride*.

- **Glyceril trinitrate** 0.4% ointment, a nitrate authorised for anal fissure, has no proven efficacy beyond that of a placebo in healing chronic anal fissures or alleviating the pain they cause. Headache is a very common adverse effect, and can be severe (*Prescrire Int* n° 94). Treatment of the pain associated with anal fissure is based on an oral analgesic such as *paracetamol* and sometimes topical *lidocaine*.



Gynaecology - Endocrinology

Menopause. Two drugs authorised for postmenopausal hormone replacement therapy have an unfavourable harm-benefit balance and should therefore be avoided. When hormone therapy is chosen despite its adverse effects, the most reason-

able option is an oestrogen-progestogen combination, used at the lowest possible dose and for the shortest possible duration.

- The fixed-dose combination **conjugated equine oestrogens** + **bazedoxifene** contains oestrogen and an oestrogen receptor agonist-antagonist, but the risks of thrombosis and hormone-dependent cancers have not been adequately evaluated (*Prescrire Int* n° 184).

- **Tibolone**, a synthetic steroid hormone, has androgenic, oestrogenic and progestogenic properties and carries a risk of cardiovascular disorders, breast cancer and endometrial cancer (*Prescrire Int* n° 83, 111, 137; *Rev Prescrire* n° 427).



Infectious diseases

- **Moxifloxacin**, a fluoroquinolone antibiotic that is no more effective than other antibiotics of this class, can cause toxic epidermal necrolysis and fulminant hepatitis, and has also been linked to an increased risk of cardiac disorders (*Prescrire Int* n° 62, 103; *Rev Prescrire* n° 371). Another fluoroquinolone such as *ciprofloxacin* or *ofloxacin* is a better option.



Neurology

Alzheimer's disease. The drugs available in late 2020 for Alzheimer's disease have only minimal and transient efficacy. They are also difficult to use because of their disproportionate adverse effects and many interactions with other drugs. None of the available drugs has been shown to slow progression toward dependence, yet all carry a risk of life-threatening adverse effects and severe drug interactions (*Prescrire Int* n° 128, 150; *Rev Prescrire* n° 363). The priorities in the management of Alzheimer's disease are to reorganise the patient's daily life, keep him or her active, and provide support and help for caregivers and family members.

- The cholinesterase inhibitors **donepezil**, **galantamine** and **rivastigmine** can provoke gastrointestinal disorders (including severe vomiting), neuropsychiatric disorders, cardiac disorders (bradycardia, collapse and syncope), and cardiac conduction disorders. *Donepezil* can also cause compulsive sexual behaviour (*Prescrire Int* n° 162, 166, 192, 204; *Rev Prescrire* n° 337, 340, 344, 349, 398, 416).

- **Memantine**, an NMDA glutamate receptor antagonist, can cause neuropsychiatric disorders (hallucinations, confusion, dizziness and headache) that can lead to violent behaviour, as well as seizures and heart failure (*Prescrire Int* n° 204; *Rev Prescrire* n° 359, 398).

Multiple sclerosis. The standard "disease-modifying" treatment for multiple sclerosis is *interferon beta*, despite its limitations and many adverse effects. The harm-benefit balance of the other disease-modifying treatments is no better and sometimes clearly unfavourable. This applies in particular to three immunosuppressants that have disproportionate adverse effects and should be avoided.

- **Alemtuzumab**, an antilymphocyte monoclonal antibody with uncertain efficacy and no demonstrated advantages over *interferon beta*, has many serious and sometimes fatal adverse effects, in particular: infusion-related reactions (including atrial fibrillation and hypotension), infections, frequent autoimmune disorders (including autoimmune thyroid disorders, immune thrombocytopenic purpura, cytopenia, nephropathy and hepatitis), myocardial infarction, pulmonary haemorrhage, stroke, and cervicocephalic arterial dissection (*Prescrire Int* n° 158, 218; *Rev Prescrire* n° 384, 428).
- **Natalizumab**, another monoclonal antibody, can lead to fatal opportunistic infections, including progressive multifocal leukoencephalopathy, potentially serious hypersensitivity reactions, and liver damage (*Prescrire Int* n° 122, 158, 182; 183; *Rev Prescrire* n° 330).
- **Teriflunomide** has serious and potentially fatal adverse effects, including liver damage, leukopenia and infections. There is also a risk of peripheral neuropathy (*Prescrire Int* n° 158).

Miscellaneous. A number of drugs used in particular in migraine, cognitive impairment, vertigo, intermittent claudication and Parkinson's disease should also be avoided.

- **Flunarizine** and **oxetorone**, two neuroleptics used to prevent migraine attacks, have at best only modest efficacy (*flunarizine* prevents about one attack every two months), but can cause extrapyramidal disorders, cardiac disorders and weight gain (*Rev Prescrire* n° 321, 359). *Oxetorone* also causes chronic diarrhoea (*Prescrire Int* n° 193). Other options, such as *propranolol*, are preferable.
- **Ginkgo biloba**, used in cognitive impairment in elderly patients, has no proven efficacy beyond that of a placebo, but can cause haemorrhage, gastrointestinal disorders, skin disorders, seizures, hypersensitivity reactions and possibly arrhythmias (*Prescrire Int* n° 205, 224; *Rev Prescrire* n° 365). *G. biloba* is also used in some countries for venous insufficiency, as part of a fixed-dose combination with *heptaminol* and *troxerutin*, but its efficacy in this indication is no better (*Rev Prescrire* n° 413). There are no drugs with a favourable harm-benefit balance in these situations.
- **Naftidrofuryl**, a "vasodilator" authorised for intermittent claudication associated with peripheral artery disease, increases walking distance by a few dozen metres but can cause headache, oesophagitis, mouth ulceration, skin disorders, kidney stones and potentially severe hepatic disorders (*Prescrire Int* n° 192; *Rev Prescrire* n° 427). A walking exercise programme is an effective and less risky treatment.
- **Piracetam**, a "psychostimulant", is authorised for use in various clinical situations, including vertigo, cognitive or neurosensory impairment in elderly patients, dyslexia in children, and myoclonus of cortical origin. *Piracetam's* efficacy in these situations has not been established, but it can provoke haemorrhage, nervousness, agitation and weight gain (*Rev Prescrire* n° 294, 342, 443). No drugs are known

to have a favourable harm-benefit balance in vertigo, cognitive or neurosensory impairment, or dyslexia. The antiepileptics *valproic acid* and *clonazepam* are options for cortical myoclonus.

- **Tolcapone**, an antiparkinsonian COMT inhibitor, can cause life-threatening liver damage (*Prescrire Int* n° 82; *Rev Prescrire* n° 330). When other treatment options have been exhausted, *entacapone* is a better option.



Oncology – Transplantation – Haematology

- **Defibrotide**, an antithrombotic authorised for severe hepatic veno-occlusive disease following haemopoietic stem cell transplantation, was no more effective in reducing mortality or inducing complete disease remission than symptomatic treatment in a non-blinded trial, yet provokes sometimes fatal haemorrhages (*Prescrire Int* n° 164). A more prudent option would be to focus on preventive measures and symptomatic treatments.

Antineoplastics. Various antineoplastic drugs have a clearly unfavourable harm-benefit balance. They are often authorised for situations in which other treatments seem ineffective. When exposure to highly toxic drugs is not justified by proven benefits, focusing on appropriate symptomatic care and on preserving the patient's quality of life is a prudent choice.

- **Mifamurtide** is authorised in combination with other chemotherapy for osteosarcoma, but has not been shown to prolong survival and can provoke serious hypersensitivity reactions, pleural and pericardial effusions, neurological adverse effects and hearing loss (*Prescrire Int* n° 115; *Rev Prescrire* n° 341). It is more prudent to propose chemotherapy without *mifamurtide*.
- **Panobinostat** has not been shown to prolong survival in refractory or relapsed multiple myeloma. It provokes many, often serious, adverse effects that affect many vital functions, hastening the death of many patients (*Prescrire Int* n° 176).
- **Trabectedin** showed no tangible efficacy in comparative trials in ovarian cancer or soft-tissue sarcomas, but has very frequent and severe gastrointestinal, haematological, hepatic and muscular adverse effects (*Prescrire Int* n° 102, 115; *Rev Prescrire* n° 360, 426). It is unreasonable to add *trabectedin* to platinum-based chemotherapy for ovarian cancer. When chemotherapy is ineffective in patients with soft-tissue sarcomas, it is best to focus on symptomatic treatments, to limit the clinical consequences of the disease.
- **Vandetanib** has not been shown to prolong survival in patients with metastatic or inoperable medullary thyroid cancer. Too many patients were lost to follow-up in placebo-controlled trials to even show an increase in progression-free survival. Serious adverse effects (diarrhoea, pneumonia, hypertension) occur in about one-third of patients.

There is also a risk of interstitial lung disease, torsade de pointes and sudden death (*Prescrire Int* n° 131; *Rev Prescrire* n° 408).

- **Vinflunine** has uncertain efficacy in advanced or metastatic bladder cancer. A clinical trial provided weak evidence that *vinflunine* prolongs median survival by two months at best compared with symptomatic treatment. There is a high risk of haematological adverse effects (including aplastic anaemia), and a risk of serious infections and cardiovascular disorders (torsade de pointes, myocardial infarction, ischaemic heart disease), sometimes resulting in death (*Prescrire Int* n° 112; *Rev Prescrire* n° 360).



Ophthalmology

- **Ciclosporin eye drops**, authorised for the treatment of dry eye disease with severe keratitis, frequently provoke eye pain and irritation, have immunosuppressive effects and may cause ocular or periocular cancer, yet have no proven efficacy (*Prescrire Int* n° 181). It is better to use artificial tears for example for symptomatic relief, several types of which are available (c).

- **Idebenone** was no more effective than placebo in a trial in Leber's hereditary optic neuropathy, and carries a risk of adverse effects including hepatic disorders (*Prescrire Int* n° 179). As of late 2020, there are no treatments with a favourable harm-benefit balance for this rare disease.



Psychiatry - Addiction

Drugs for depression. Several drugs authorised for depression carry a greater risk of severe adverse effects than other antidepressants, without offering greater efficacy. Antidepressants have only modest efficacy and often take some time to work. It is better to choose one of the longer-established antidepressants with an adequately documented adverse effect profile.

- **Agomelatine** has no proven efficacy beyond that of a placebo, but can cause hepatitis and pancreatitis, suicide and aggressive outbursts, rhabdomyolysis, and serious skin disorders including Stevens-Johnson syndrome (*Prescrire Int* n° 104, 136; *Rev Prescrire* n° 397, 419, 432).

- **Citalopram** and **escitalopram** are so-called selective serotonin reuptake inhibitor (SSRI) antidepressants that expose patients to a higher incidence of QT prolongation and torsade de pointes than other SSRIs, as well as worse outcomes in the event of overdose (*Prescrire Int* n° 170, 174; *Rev Prescrire* n° 369).

- **Duloxetine**, **milnacipran** and **venlafaxine** are serotonin and noradrenaline (norepinephrine) reuptake inhibitors that, as well as provoking the adverse effects of SSRI antidepressants, carry a risk of cardiac disorders due to their noradrenergic activity, including hypertension, tachycardia, arrhythmias,

and QT prolongation. In addition, *venlafaxine* overdose is associated with a high risk of cardiac arrest (*Prescrire Int* n° 131, 170, 206; *Rev Prescrire* n° 338; *Interactions Médicamenteuses Prescrire*). *Duloxetine* can also cause hepatitis and severe cutaneous adverse reactions such as Stevens-Johnson syndrome (*Prescrire Int* n° 85, 100, 111, 142; *Rev Prescrire* n° 384).

- **Esketamine** nasal spray is authorised for use in "treatment-resistant" depression, but its efficacy is highly uncertain. Its neuropsychiatric adverse effects are common and include dissociative symptoms. Addiction and misuse are likely (*Prescrire Int* n° 222). In this difficult clinical situation, it is more prudent to consider other less dangerous options, even if their efficacy is uncertain: psychotherapy; increasing the dose of the initial antidepressant; switching to an antidepressant from a different pharmacological class; adding a so-called atypical neuroleptic; or electroconvulsive (electroshock) therapy. The treatment will mainly be chosen on the basis of its adverse effect profile.

- **Tianeptine**, a drug with no proven efficacy beyond that of a placebo, can cause hepatitis, life-threatening skin reactions (including bullous rash) and addiction (*Prescrire Int* n° 127, 132; *Rev Prescrire* n° 349).

Other psychotropic drugs. Some other psychotropic drugs have unacceptable adverse effects:

- **Dapoxetine**, a so-called selective serotonin reuptake inhibitor (SSRI) antidepressant, is used for sexual dissatisfaction related to premature ejaculation. Its adverse effects are disproportionate to its very modest efficacy and include aggressive outbursts, serotonin syndrome, and syncope (*Prescrire Int* n° 105; *Rev Prescrire* n° 355). A psychological and behavioural approach, or application of the anaesthetic combination *lidocaine* + *prilocaine* on the glans penis are better options in this situation (*Prescrire Int* n° 197).

- **Etifoxine**, a drug poorly evaluated in anxiety, can cause hepatitis and severe hypersensitivity reactions, including DRESS syndrome, Stevens-Johnson syndrome and toxic epidermal necrolysis (*Prescrire Int* n° 136; *Rev Prescrire* n° 376). When an anxiolytic drug is justified, a benzodiazepine, used for the shortest possible duration, is a better choice.



Pulmonology - ENT

Cough suppressants. A number of drugs used to relieve cough, a sometimes bothersome but minor ailment, have disproportionate adverse effects. When drug therapy for cough seems justified, the opioid *dextromethorphan* is an option, despite its limitations (*Rev Prescrire* n° 358, 391).

c- Oral or injectable *ciclosporin* is a standard immunosuppressant for transplant recipients, and in this situation, its harm-benefit balance is clearly favourable.

- **Ambroxol** and **bromhexine**, mucolytics authorised for cough and sore throat, have no proven efficacy beyond that of a placebo, yet they carry a risk of anaphylactic reactions and sometimes fatal cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (*Prescrire Int* n° 159, 184, 192).
- **Oxomemazine** is a sedating antihistamine of the phenothiazine class with antimuscarinic activity and neuroleptic properties. Its adverse effects are disproportionate for a drug used to relieve cough symptoms (*Rev Prescrire* n° 334, 386; *Interactions Médicamenteuses Prescrire*).
- **Pentoxifyverine**, a centrally-acting cough suppressant, can cause cardiac disorders including QT prolongation, and serious allergic reactions (*Prescrire Int* n° 208).
- **Pholcodine**, an opioid authorised as an antitussive, can cause sensitisation to neuromuscular blocking agents used in general anaesthesia (*Prescrire Int* n° 184; *Rev Prescrire* n° 349, 441). This serious adverse effect is not known to occur with other opioids.

Sore throat. When a drug appears necessary to relieve sore throat, in conjunction with non-drug measures such as sipping water or sucking on hard candy, the best option is *paracetamol*, taken at the appropriate dosage.

- **Alpha-amylase**, an enzyme with no proven efficacy against sore throat beyond that of a placebo, can cause sometimes severe cutaneous or allergic disorders, including urticaria, pruritus, angioedema, maculopapular rash and erythema (*Rev Prescrire* n° 426).
- **Tixocortol mouth spray** (sometimes combined with *chlorhexidine*), a corticosteroid authorised for sore throat, can cause allergic reactions such as facial mucocutaneous oedema, glossitis or angioedema (*Rev Prescrire* n° 320) (d).

Miscellaneous. A variety of other drugs used in pulmonary or ENT disorders are best avoided.

- Decongestants for oral or nasal use (**ephedrine**, **naphazoline**, **oxymetazoline**, **phenylephrine**, **pseudoephedrine** and **tuaminoheptane**) are sympathomimetic vasoconstrictors. They can cause serious and even life-threatening cardiovascular disorders (hypertensive crisis, stroke, and arrhythmias, including atrial fibrillation), as well as ischaemic colitis. These adverse effects are unacceptable for drugs indicated for minor, rapidly self-resolving symptoms such as those associated with the common cold (*Prescrire Int* n° 136, 172, 178, 183, 208; *Rev Prescrire* n° 312, 342, 345, 348, 361, 424).
- **Mannitol inhalation powder**, authorised as a mucolytic for patients with cystic fibrosis despite the lack of convincing evidence of efficacy, can cause bronchospasm and haemoptysis (*Prescrire Int* n° 148). It is best to choose other mucolytics such as *dornase alfa*, in the absence of a better alternative.

- **Roflumilast**, a phosphodiesterase type-4 inhibitor with anti-inflammatory effects, has not been shown to reduce mortality or improve the quality of life of patients with severe chronic obstructive pulmonary disease (COPD), but can provoke gastrointestinal adverse effects, weight loss, mental disorders (including depression and suicide), and possibly cancer (*Prescrire Int* n° 134, 176). Despite its limitations, the treatment of these patients is based above all on inhaled bronchodilators, sometimes with an inhaled corticosteroid, and possibly oxygen therapy.



Rheumatology - Pain

Certain nonsteroidal anti-inflammatory drugs. Although nonsteroidal anti-inflammatory drugs (NSAIDs) share a similar adverse effect profile, some expose patients to less risk than others. When *paracetamol* proves inadequate, *ibuprofen* and *naproxen*, used at the lowest effective dose and for the shortest possible duration, are the least risky options.

- **Oral aceclofenac** and **oral diclofenac** cause more cardiovascular adverse effects (including myocardial infarction and heart failure) and more cardiovascular deaths than other equally effective NSAIDs (*Prescrire Int* n° 167, 210; *Rev Prescrire* n° 362, 374).
- **Cox-2 inhibitors** (coxibs), **celecoxib**, **etoricoxib** and **parecoxib**, have been linked to an excess of cardiovascular events (including myocardial infarction and thrombosis) and skin reactions compared with other equally effective NSAIDs (*Prescrire Int* n° 167; *Rev Prescrire* n° 344, 361, 374, 409).
- **Ketoprofen gel** causes more photosensitivity reactions (eczema, bullous rash) than other equally effective topical NSAIDs (*Prescrire Int* n° 109, 137, 193).
- **Meloxicam**, **piroxicam** and **tenoxicam**, when used systemically, expose patients to an increased risk of gastrointestinal disorders and cutaneous disorders (including Stevens-Johnson syndrome and toxic epidermal necrolysis), but are no more effective than other NSAIDs (*Prescrire Int* n° 212; *Rev Prescrire* n° 321).

“Muscle relaxants”. Various drugs used as muscle relaxants have no proven efficacy beyond that of a placebo, but expose patients to the risk of sometimes severe adverse effects. An effective analgesic is a better option, with *paracetamol* as the first choice, taken at the appropriate dosage, or *ibuprofen* or *naproxen* as alternatives.

- Oral **mephenesin** provokes drowsiness, nausea, vomiting, hypersensitivity reactions (including rash and anaphylactic shock), abuse and addiction; *mephenesin* ointment provokes severe skin dis-

d- *Tixocortol* is also authorised as a nasal suspension, notably for allergic rhinitis, a situation in which the harm-benefit balance of a corticosteroid is not unfavourable.

orders, including erythema multiforme and acute generalised exanthematous pustulosis (*Prescrire Int* n° 125, 138; *Rev Prescrire* n° 414, 430).

- **Methocarbamol** has many adverse effects, notably gastrointestinal and cutaneous disorders (including angioedema) (*Rev Prescrire* n° 282, 338).

- **Thiocolchicoside**, which is related to *colchicine*, causes diarrhoea, stomach pain, photodermatitis and possibly convulsions, as well as being genotoxic and teratogenic (*Prescrire Int* n° 168; *Rev Prescrire* n° 282, 313, 321, 367, 400, 412).

Osteoarthritis. Drugs authorised for their supposed effect on the process that results in osteoarthritis should be avoided because they have significant adverse effects but no proven efficacy beyond that of a placebo. As of late 2020, there are no drugs known to have efficacy against joint degeneration and a favourable harm-benefit balance.

- **Diacerein** causes gastrointestinal disorders (including gastrointestinal bleeding and melanosis coli), angioedema and hepatitis (*Prescrire Int* n° 159; *Rev Prescrire* n° 282, 321).

- **Glucosamine** causes allergic reactions (angioedema, acute interstitial nephritis) and hepatitis (*Prescrire Int* n° 84, 137; *Rev Prescrire* n° 380).

Osteoporosis. Two drugs used in osteoporosis have an unfavourable harm-benefit balance.

When non-drug measures plus calcium and vitamin D supplementation are insufficiently effective, *alendronic acid*, or *raloxifene* as an alternative, have a better harm-benefit balance in reducing the incidence of clinical fractures, despite their considerable limitations. There is no known satisfactory drug treatment for “bone loss”.

- **Denosumab 60 mg** has very modest efficacy in the prevention of osteoporotic fractures and no efficacy for “bone loss” during prostate cancer (e). It carries a disproportionate risk of adverse effects, including back, muscle and bone pain, multiple fractures after discontinuation of the drug, osteonecrosis, immune dysfunction, and serious infections (including endocarditis) due to the immunosuppressive effects of this monoclonal antibody (*Prescrire Int* n° 117, 130, 168, 198).

- **Romozumab** is authorised for severe osteoporosis in postmenopausal women, on the basis of a trial in several thousand women that showed a slightly lower risk of clinical fractures than with *alendronic acid*. This gain must be weighed against a possible increase in the risk of cardiovascular events, with higher mortality among patients aged 75 years and older (*Prescrire Int* n° 223).

Miscellaneous. A number of other drugs used for specific types of pain or in rheumatology are best avoided.

- **Capsaicin**, a red chilli pepper extract authorised in patch form for neuropathic pain, is barely more effective than placebo, but can provoke irritation, severe pain and burns (*Prescrire Int* n° 108, 180; *Rev Prescrire* n° 425). *Capsaicin* remains an unreasonable

choice even when systemic pain medications or local ones such as *lidocaine* medicated plasters fail to provide adequate relief.

- Colchimax° (**colchicine + opium powder + tiemonium**) has an unfavourable harm-benefit balance, notably in gout attacks and acute pericarditis, because the action of *opium powder* and *tiemonium* can mask the onset of diarrhoea, which is an early sign of potentially fatal *colchicine* overdose (*Prescrire Int* n° 147, 211). A nonsteroidal anti-inflammatory drug or a corticosteroid as an alternative are better options for gout attacks.

- Topical **prednisolone + dipropylene glycol salicylate** exposes patients to the adverse effects of corticosteroids and to the risk of *salicylate* hypersensitivity reactions (*Rev Prescrire* n° 338). Other drugs such as oral *paracetamol* (at the appropriate dosage) and topical *ibuprofen* have a favourable harm-benefit balance in patients with painful sprains or tendinopathy, in conjunction with non-drug measures (rest, ice, splints, etc.).

- **Quinine**, authorised for cramps, can have life-threatening adverse effects including anaphylactic reactions, haematological effects (including thrombocytopenia, haemolytic anaemia, agranulocytosis, and pancytopenia) and cardiac arrhythmias. These adverse effects are disproportionate in view of its poor efficacy (*Prescrire Int* n° 188; *Rev Prescrire* n° 337, 344). There are no drugs with a favourable harm-benefit balance for patients with cramps. Regular stretching can be beneficial (*Rev Prescrire* n° 362) (f).



Smoking cessation

- **Bupropion**, an amphetamine-like drug authorised for smoking cessation, is no more effective than *nicotine* but can cause neuropsychiatric disorders (including aggressiveness, depression and suicidal ideation), potentially severe allergic reactions (including angioedema and Stevens-Johnson syndrome), addiction, and congenital heart defects in children exposed to the drug in utero (*Prescrire Int* n° 131; *Rev Prescrire* n° 377). When a drug is needed to help with smoking cessation, *nicotine* is a better choice.

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e- A 120-mg strength *denosumab* product is authorised for use in patients with bone metastases from solid tumours. In this situation, *denosumab* is just one of several options, but its harms do not clearly outweigh its benefits (*Prescrire Int* n° 130).

f- *Quinine* is sometimes useful in malaria (*Prescrire Int* n° 145).



Urology

• **Oral pentosan polysulfate**, a heparin derivative authorised for bladder pain syndrome (interstitial cystitis), has uncertain efficacy in relieving the symptoms of this condition and serious adverse effects, including pigmentary maculopathy with visual disturbance, and immune-mediated thrombocytopenia with a consequent risk of arterial thrombosis (*Prescrire Int* n° 204; *Rev Prescrire* n° 443) (g). In the absence of a better alternative, it is more prudent to offer these patients analgesic medication and non-drug measures with a low risk of adverse effects, such as applying heat or cold to the bladder or perineum, and avoiding foods or activities that exacerbate symptoms.

Putting patients first

Our analyses show that the harm-benefit balance of the drugs listed here is unfavourable in all their authorised indications (unless otherwise mentioned in a footnote). Yet some have been marketed for many years and are commonly used. From the patient's viewpoint, what possible justification is there for exposing them to drugs that have more adverse effects than other members of the same pharmacological class or other similarly effective drugs? And how can one justify exposing patients to drugs with severe adverse effects but no proven efficacy beyond that of a placebo, or no benefit on patient-relevant clinical outcomes?

Healthcare professionals need to actively remove these drugs, which pharmaceutical companies persist in marketing, from their list of useful treatments. But regulators and health authorities must also take concrete steps to protect patients and promote the use of treatments that have an acceptable harm-benefit balance.

The drugs listed above are more dangerous than beneficial. There is no valid reason for them to retain their marketing authorisations.

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g- Pentosan polysulfate is also authorised in France for topical use as a local adjunctive treatment for minor trauma. It has no proven efficacy in this situation beyond that of a placebo, and little is known about its systemic adverse effect profile.