THE PRESCRIRE AWARDS FOR 2020

The three annual Prescrire Awards, for Drugs, Packaging and Information, are granted in total independence by the Prescrire Editorial staff. The rules governing all three awards are available online (in French) at english.prescrire.org > Topics > Annual Prescrire Awards > The Prescrire Drug Awards for 2020.

2020 Prescrire Drug Awards

Every month, in the New Products section of our French edition, *Prescrire*'s Editorial Staff single out, among the plethora of new products, those worth adding to one's list of useful treatment options or worth using instead of other products, while also pointing out which medicines are best avoided. This is achieved by systematically analysing the evaluation data available on new drugs, existing drugs authorised for different clinical situations, and new forms or new dose strengths of existing drugs. Occasionally, a previously analysed drug is re-examined "with more follow-up", when more recent data justify reassessing its harm-benefit balance.

Prescrire's multidisciplinary team has been analysing drugs for 40 years, free from influence from the health industry or institutions. We ensure our independence by the fact that *Prescrire* is funded exclusively by its subscribers, carrying no paid advertising in either the French or the English edition, and receiving no grants or subsidies of any kind.

The 2020 Prescrire Drug Awards are based on the analyses published in the "New Products" section of our French edition in 2020. These awards recognise products that represent a therapeutic advance, in that they offer better efficacy than existing treatments, provoke less frequent or less severe adverse effects (provided they also have similar efficacy), or enable a drug with a favourable harm-benefit balance to be used more safely or easily.

A Pilule d'Or for 2020!

One new product examined in 2020 represents a major therapeutic advance worthy of a Pilule d'Or (Golden Pill Award), six years after it was last awarded. Two products earned a place on the 2020 Honours List. None made the "Noteworthy" list.

Ebola vaccine rVSV-Zebov in an outbreak of Ebola virus disease: markedly reduces the incidence of this often fatal infection

Ebola virus disease is a serious infection. Most outbreaks have occurred in Africa, killing 30% to 90% of infected patients, depending on the outbreak. Death occurs in a context of generalised haemorrhage and multiorgan failure. Prevention is based mainly on strict hygiene and protective measures for anyone likely to have been in contact with infected patients, including healthcare professionals. Treatment is mainly symptomatic.

Ebola vaccine rVSV-Zebov is a live attenuated vaccine based on vesicular stomatitis virus (VSV), engineered (rVSV) to express a protein from Zaire Ebola virus (Zebov).

The evaluation data show that, during an outbreak of Zaire Ebola virus disease, vaccination protects at least two-thirds of persons who have potentially been in contact with infected patients, and that its protective effect starts from day 10 after vaccination. Its harms are acceptable, given the severity of this disease, and include adverse effects common to all vaccines, as well as joint and skin disorders. Ervebo° was awarded the Pilule d'Or on the basis of these data.

A number of risks and unknowns must be taken into account, however. For example, although vesicular stomatitis virus is not generally pathogenic in humans, it has been found in certain body fluids of vaccinees, which raises the possibility that they could transmit this virus to other people. *Ebola vaccine rVSV-Zebov* is a live vaccine that has not been evaluated in immunocompromised individuals, and the consequences of infection with the vaccine virus in this situation are unknown. In addition, a threefold risk of miscarriage was reported in women who became pregnant during the 2 months after vaccination. Compliance with the vaccine's storage conditions (between -80°C and -60°C) is challenging and complicates its use in many countries. The duration of the vaccine's protective effect is unknown. Finally, vaccination does not eliminate the need for strict protective and hygiene measures around patients infected with Ebola virus.

Fexinidazole in sleeping sickness due to Trypanosoma brucei gambiense: effective, and more convenient than standard treatments

Human African trypanosomiasis (or sleeping sickness) is caused by a parasite of the genus *Trypanosoma*, usually *T. brucei gambiense*. This disease is endemic in many countries in sub-Saharan Africa. It typically affects people living in rural or periurban areas.

If left untreated, the disease is usually fatal within 2 to 3 years on average from the start of infection with *T. brucei gambiense*. The disease progresses through two stages: the early haemolymphatic stage, characterised by recurrent fever, joint pain, muscle pain and fatigue, followed by the avanced meningoencephalitic stage, during which the parasites infect the central nervous system, causing neuropsychiatric disorders that almost always progress to coma and death.

Cure rates with *pentamidine* or *nifurtimox + eflornithine* combination therapy (NECT), depending on the

disease stage, exceed 95%. But these treatments require daily injections or infusions for 7 days, administered in a healthcare facility, which limits access to these treatments in regions with limited health infrastructure, some of which are also affected by armed conflict.

Fexinidazole is an antiparasitic drug for oral use. After 10 days of treatment, its cure rate exceeds 90% at both stages of the disease. Its adverse effects are acceptable when weighed against this level of efficacy: nausea, vomiting, neuropsychiatric disorders, and QT prolongation. Fexinidazole Winthrop° earned a place on the Honours List in the 2020 Prescrire Drug Awards because of *fexinidazole*'s positive harm-benefit balance and because the availability of an oral treatment for this disease represents a clear practical advance for patients.

However, NECT remains the first-choice treatment for patients with the most advanced forms of the disease and who have access to this treatment, as it is probably slightly more effective in this situation.

Tafamidis in transthyretin amyloid cardiomyopathy: reduction in mortality

Transthyretin amyloidosis is a rare, fatal disease that generally presents between 30 and 50 years of age. Patients have a life expectancy of about ten years after diagnosis. This disorder is caused by instability of the protein transthyretin and leads to amyloid deposits in a range of organs. The clinical signs vary depending on the organs affected, but include cardiac disorders (heart failure, thrombosis and conduction disturbances).

Tafamidis is a drug that binds to and appears to stabilise transthyretin. In a placebo-controlled trial in 441 patients with symptomatic transthyretin amyloid cardiomyopathy, mortality after 30 months of treatment was lower in the *tafamidis* group: 30% versus 43% in the placebo group. One limitation of these results is that they remain to be confirmed in at least one other trial, conducted by a different team.

The benefits of *tafamidis* must be weighed against its harms: infections and gastrointestinal, ocular and probably hepatic disorders. Uncertainty remains over the optimum daily dose. Nevertheless, the magnitude of the effect observed led *Prescrire* to place Vyndaqel° on the Honours List of the 2020 Prescrire Drug Awards.

2020 Pilule d'Or/Golden Pill

The Pilule d'Or (Golden Pill) is granted to drugs that represent a major therapeutic advance in a field in which no treatment was previously available.

- **ERVEBO° (*Ebola vaccine rVSV-Zebov*)**
  MSD
  For active immunisation of individuals 18 years of age or older to protect against Ebola virus disease caused by Zaire Ebola virus (Prescrire Int n° 223).

2020 Honours List

Drugs included on the Honours List constitute a clear advance for some patients compared with existing therapeutic options, albeit with limitations. Those on this year's list, in alphabetical order, are:

- **FEXINIDAZOLE WINTHROP° (*fexinidazole*)**
  Sanofi Aventis
  For human African trypanosomiasis (sleeping sickness) due to *Trypanosoma brucei gambiense* (Prescrire Int n° 221).
- **VYNDAQEL° (*tafamidis*)**
  Pfizer
  For adults with transthyretin amyloid cardiomyopathy (Prescrire Int n° 222).

2020 Prescrire Packaging Awards

When *Prescrire* evaluates a drug's harm-benefit balance, the quality of the drug's packaging is one of the factors examined. Does the packaging ensure the safety of patients, their family and their carers, enabling the drug to be accurately and easily used? Conversely, are any aspects of the packaging dangerous, or does it lack anything necessary for the safe use of the drug?

Our packaging examinations take many factors into account: the clinical situation in which the drug will be used; the patients liable to receive it, especially pregnant women, children or elderly patients; whether family members, carers or a nurse will prepare and administer it; and whether it will be used in an emergency, hospital or community setting, obtained on prescription, on the advice of a community pharmacist, or bought by the patient from an internet retailer.

Every aspect of the packaging is assessed for quality and user safety. We examine in particular: whether international nonproprietary names (INNs) are clearly legible and whether different dose strengths of the same drug are easily distinguishable; the clarity of any information presented graphically, such as diagrams, dosing schedules, symbols or pictograms; the devices for preparing, measuring and administering doses; the risk that children will be able to ingest the drug unnoticed by their carers; and the quality and clarity of the information provided in the patient leaflet on how to use the product, its adverse effects, and the situations and patient groups in which the drug poses a particular risk.

The 2020 Prescrire Packaging Awards pertain to the packaging of drugs evaluated in our French edition in 2020.

2020 PACKAGING AWARDS

Maviret° tablets (***glecaprevir*** + ***pibrentasvir***) AbbVie (Rev Prescrire n° 439)
For the quality of its primary packaging, consisting of blister packs, each containing the daily dose of 3 tablets, and each blister pocket labelled with the INNs of both antiviral agents and their strengths. Also for its secondary packaging, which includes 4 boxes, each containing one week of treatment (7 blister packs with 3 tablets each), and a reminder of the dosing instructions on the lid of each box, stating "*take all 3 tablets in 1 blister once daily with food*" alongside a photo of the 3 tablets. This reminder helps patients take their treatment properly, enhancing the quality of packaging that also features boxes and blister packs that clearly identify the drugs they contain and their strength.

Tiapridal° oral solution (***tiapride***) Sanofi Aventis (Rev Prescrire n° 442)
For the improvements made to its packaging: addition of a child-proof cap and an oral dosing syringe graduated in milligrams of the drug, and labelled with its INN and the concentration of the solution. Previously, Tiapridal° had a dropper inserted into the neck of the vial that carried a risk of error when counting the number of drops, especially for high doses. A syringe graduated in milligrams of *tiapride* eliminates the need to convert the number of milligrams prescribed into the number of millilitres of product to be administered, which can lead to errors.

RED CARDS

Cytotoxic drugs packaged in bulk bottles

Imeth° 10 mg tablets (***methotrexate***) Nordic Pharma and **Méthotrexate Bellon°** tablets (***methotrexate***) Sanofi Aventis (**a**) (Prescrire Int n° 216); **Rubraca°** tablets (***rucaparib***) Clovis Oncology (Rev Prescrire n° 443); and **Talzenna°** hard capsules (***talazoparib***) Pfizer (Rev Prescrire n° 440)
When tablets or capsules supplied in bulk bottles are placed in a pill organiser, they are no longer identifiable, unlike dry oral forms packaged in perforated unit-dose blisters.

Methotrexate, *rucaparib* and *talazoparib* are cytotoxic drugs. With bulk bottles, there is a risk of accidentally spilling the contents and therefore a risk that someone other than the patient, especially a child, might ingest the drug. Even a child-proof cap does not prevent this potentially fatal risk.

Switch from blister packs to bulk bottles: a decline in quality

Lamictal° 5 mg dispersible or chewable tablets (***lamotrigine***) GlaxoSmithKline (Rev Prescrire n° 445)
For switching from non-unit-dose blister packs to a bulk bottle. The child-proof cap is insufficient to eliminate all the harms associated with bulk bottles, such as accidental spillage of tablets and the risk that someone other than the patient, especially a child, might take them by mistake. A better option would have been to upgrade to perforated unit-dose blister packs, to ensure that tablets remain easily identifiable, and to add a child-resistant film.

Packaging that increases the risk of dosing errors

Haldol° oral solution (***haloperidol***) Janssen (Rev Prescrire n° 441)
For persisting in marketing this drug in a dropper bottle unsuited to measuring doses greater than 2 mg (20 drops) due to the risk of miscounting the number of drops required (up to 100 drops in some cases). Up until early 2020, a *haloperidol* oral solution was marketed in a 100-ml bottle with an oral dosing syringe graduated in milligrams, well-suited to measuring doses greater than 2 mg. The disappearance from the market of the product supplied with a syringe, leaving only the one supplied in a dropper bottle, is a decline in quality, placing patients at greater risk than they were before.

a- *The pharmaceutical company has informed us that Méthotrexate Bellon° is no longer marketed in France since late December 2020.*

Istendo° solution for endotracheopulmonary instillation (***acetylcysteine***) Delbert (Rev Prescrire n° 442)
For supplying this drug in 5-ml ampoules when the recommended doses are from 1 ml to 2 ml, for not providing a device with which to measure the volume to be administered, and for the scant explanation in the patient leaflet on how to prepare the dose to be administered.

Preminor° hard capsules (***ramipril*** + ***amlodipine***) Leurquin Mediolanum (Rev Prescrire n° 442) and **Triplixam°** tablets (***perindopril*** + ***indapamide*** + ***amlodipine***) Servier (Rev Prescrire n° 444)
For the strong resemblance between the boxes and primary packaging (bottle labels, blister pack films) of the various dose strengths of these fixed-dose combinations, and the consequent risk of wrong-dose errors.

Furthermore, Triplixam° is supplied in a bulk bottle with no child-proof cap, a container of very poor quality. The flow restrictor moderately reduces the risk of accidental spillage and the consequent risk that someone other than the patient, especially a child, might ingest the drug. However, the tablets are no longer identifiable when removed from the bulk bottle and placed in a pill organiser.

Prexate° solution for injection in a pre-filled syringe (***methotrexate***) Alfasigma (Rev Prescrire n° 438)
For failing to add a reminder on the box that the drug is for weekly administration, exposing patients to the risk of potentially fatal dosing frequency errors. In late 2019, the European Commission ratified measures recommended by the Pharmacovigilance Risk Assessment Committee (PRAC) aimed at preventing errors involving *methotrexate*, which included adding a reminder that injectable *methotrexate* products used for immunosuppression are administered once weekly.

Insufficient efforts to prevent ingestion by children

Buprénorphine/Naloxone Arrow° Arrow Génériques and **Buprénorphine/Naloxone Mylan°** Mylan sublingual tablets (***buprenorphine*** + ***naloxone***) (Rev Prescrire n° 435)
For packaging these sublingual tablets in blister packs without a child-resistant film, in contrast to the originator Suboxone°, thereby exposing children to the risk of accidental ingestion of *buprenorphine* and *naloxone*, both of which have serious adverse effects. It is regrettable that the packaging of the generic versions of this fixed-dose combination is less safe than that of the originator.

Bonasol° oral solution (***alendronic acid***) X.O; the ***chlorhexidine*** 0.12% mouthwashes **Chlorhexidine Arrow°** Arrow Génériques, **Chlorhexidine Biogaran°** Biogaran, **Chlorhexidine Mylan°** Mylan, **Paroex°** Centre Spécialités Pharmaceutiques, and **Prexidine°** X.O; the ***chlorhexidine*** 0.20% mouthwash **Eludrilperio°** Pierre Fabre Médicament; **Fluisédal°** syrup (***promethazine*** + ***meglumine benzoate*** + ***polysorbate 20***) Elerté; and **Tussisédal°** syrup (***promethazine*** + ***noscapine***) Elerté (Rev Prescrire n° 438)

For the absence of a child-proof cap on the bottles of these 9 products. Children are insufficiently protected by an ordinary cap, which gives them easy access to the contents of these bottles and puts them at risk of exposure to the adverse effects of the drugs they contain.

Boxes and bottles of Bonasol° lack a prominent reminder that it is for weekly administration, increasing the risk of dosing errors.

Fluisédal° and Tussisédal° have several dangerous packaging flaws: insufficient prominence is given to INNs and dose strengths on the boxes and bottles, the dosing device provided (a measuring spoon) is inaccurate, and the box lacks a pictogram indicating the risks posed during pregnancy, due in particular to the presence of *promethazine*.

Patient leaflets that understate the product's harms

Prontadol° tablets (***paracetamol*** + ***caffeine***) Ipsen (Rev Prescrire n° 442)
For failing to adequately inform users of the hepatic harms associated with *paracetamol* overdose. Despite the statement on the box "*overdose = danger*", the patient leaflet does not explain the nature of the danger or describe the signs suggestive of *paracetamol* poisoning.

Flector° non-gastro-resistant tablets (***diclofenac***) Genévrier (Rev Prescrire n° 438) and **Nurofenplast°** medicated plasters (***ibuprofen***) Reckitt Benckiser (Rev Prescrire n° 435)
For providing insufficient information in the patient leaflet about the dangers of exposure to nonsteroidal anti-inflammatory drugs (NSAIDs) during pregnancy. The patient leaflet for Flector° does not rule out its use during the first 5 months of pregnancy, since the warning in the pregnancy pictogram only states: *"Not to be used by pregnant women from the 6th month of pregnancy"*.

The patient leaflet for Nurofenplast° does not warn patients about the risks of using these medicated plasters during the first 6 months of pregnancy, despite the pictogram on the box rightly prohibiting its use throughout pregnancy.

NSAIDs should be avoided throughout pregnancy, because there is no evidence that a contraindication starting at the sixth month of pregnancy is sufficient to eliminate the risk of harming the unborn child. Taking an NSAID during the first days of pregnancy can provoke spontaneous abortion.

Furthermore, insufficient prominence is given to the INNs of these 2 NSAIDs on the packaging of these products, making it difficult for patients to identify their composition, and increasing the risk that they might be used by women who are or could become pregnant.

2020 Information Awards

The 2020 Prescrire Information Awards are based on the quality of the information and documentation provided to *Prescrire* by the pharmaceutical companies whose products we examined in 2020 in the New Products section of our French edition. They reflect the degree of transparency or secrecy companies have shown in response to *Prescrire*'s requests for information and documentation.

Why does Prescrire ask companies for information? The information held by pharmaceutical companies concerning their drugs, from the developmental phase through post-marketing surveillance to market withdrawal, is important for patient care and patient safety. Among other benefits, sharing this information helps ensure that drugs are used appropriately and helps protect patients from certain harms. It is an integral part of a pharmaceutical company's responsibilities.

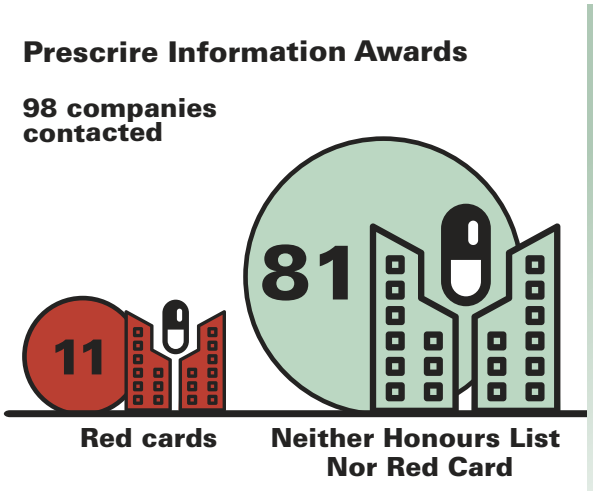
The main types of data *Prescrire* requests from pharmaceutical companies are: data on the drug's efficacy and adverse effects (assessment reports, pharmacovigilance data, updated clinical study reports); information about the conditions governing access to the drug, reimbursement of the cost by the national health insurance system, and the planned date of its market introduction (or market withdrawal) in France; and packaging materials, and so on. All of these data are compared with those obtained through the systematic literature search we defined.

Transparency varies widely. We requested information from 98 pharmaceutical companies in 2020. Some of them chose to be open, which they demonstrated by providing detailed, relevant information in response to *Prescrire*'s requests. These companies earned a place on the 2020 Information Awards Honours List. Companies that provided *Prescrire* with particularly useful, detailed, explanatory information without delay, sometimes without being asked, were rated as "Outstanding".

Other drug companies failed to respond to some or all of our requests for information, or provided only limited data. Some of them delayed their response and provided no usable information. Some omitted the most relevant or sensitive data and chose to provide just a smattering of carefully chosen data, of little or no use for our analysis. Red Cards are given to highlight persistent and multiple deficiencies in the provision of information.

Providing information useful for health care is often a low priority. Pharmaceutical companies often lack the willingness rather than the resources to be transparent. When reviewing *fexinidazole* (Fexinidazole Winthrop®) in sleeping sickness caused by *Trypanosoma brucei gambiense* (see "2020 Prescrire Drug Awards" pp. 77-78), we requested information from the international non-profit organisation responsible for developing this drug, the Drugs for Neglected Diseases initiative (DNDi). DNDi provided a range of information and documentation that helped explain the issues, including data from the drug's evaluation and development. In contrast, many pharmaceutical companies clearly attach little importance to providing non-promotional information. This was also apparent from the growing number of companies that outsourced this task to public relations agencies, not a choice one would immediately associate with transparency and high-quality information.

Secrecy still prevailed in 2020. The public health crisis caused by the covid-19 pandemic made 2020 an extraordinary year, but it does not explain the failure of certain pharmaceutical companies to communicate with *Prescrire*. As in previous years, few pharmaceutical companies embraced transparency in 2020, agreeing to share the data in their possession. Most companies often preferred to be secretive, keeping relevant and detailed documentation to themselves, even though it is useful to healthcare professionals and, through them, to patients.



6 Companies on the Honours List

Outstanding:
- Arrow Génériques

Followed by:
- Accord Healthcare
- Alnylam
- Bouchara Recordati
- EG Labo
- Medipha Santé

11 Red Cards

- AkceaTherapeutics
- Amgen
- Bayer Healthcare
- Gedeon Richter
- Genévrier
- Janssen Cilag
- Menarini
- MSD
- Sanofi Aventis
- Teva Santé
- X.O