THE PRESCRIRE AWARDS FOR 2019

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

2019 Prescrire Drug Awards

Each month, the *Prescrire* Editorial Staff publish systematic analyses of the data available on the evaluation of: new drugs, existing drugs authorised for different clinical situations, and new forms or new dose strengths of existing drugs. Occasionally, when the latest data on a drug we have already analysed justify reassessing its harm-benefit balance, we repeat our analysis "with more follow-up". The goal is to help readers distinguish, among the plethora of new products, those worth adding to their list of useful therapies or worth using instead of other products, and also to point out which medicines are best avoided.

Our analyses are based on rigorous procedures, described in detail at English.prescrire.org. The *Prescrire* Editorial Staff conduct these analyses free from influence by the health industry or institutions. We ensure our independence by being wholly funded by *Prescrire*'s subscribers, carrying no paid advertising in either the French or the English edition, and receiving no grants or subsidies of any kind.

The 2019 *Prescrire* Drug Awards are based on the analyses published in our French edition in 2019. 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.

Six Prescrire Drug Awards for 2019, but no Pilule d'Or

For the fifth year running, none of the drugs examined in 2019 represented a major therapeutic advance worthy of a Pilule d'Or (Golden Pill Award). Nevertheless, six received a *Prescrire* Drug Award.

Emicizumab for haemophilia A with "factor VIII inhibitors": prevents bleeding episodes

Haemophilia A is a bleeding disorder due to a deficiency in clotting factor VIII. The standard treatment for preventing or treating bleeding episodes in patients with haemophilia A is to administer the factor VIII they lack. One major adverse effect of this treatment is the development of "factor VIII inhibitors", which are antibodies produced by the patient's immune system against the administered *factor VIII* that render it ineffective. One option in this situation is to administer a "bypassing" agent, so called because it bypasses the factor VIII-dependent step of the coagulation cascade.

Emicizumab is a monoclonal antibody that acts at the same step of the coagulation cascade as factor VIII but is not neutralised by "factor VIII inhibitors". *Emicizumab* is effective in preventing bleeding episodes in patients with these inhibitors, even in those who have frequent bleeds while using bypassing agents. *Emicizumab* is administered by subcutaneous injection once a week (or once every 4 weeks), whereas preventive therapy with bypassing agents requires several intravenous infusions a week. Hemlibra° earned a place on the 2019 Honours List for these advantages.

These advantages must be weighed against the lack of evaluation in certain clinical situations, the risk of thrombotic events, the foreseeable allergic reactions, and many uncertainties over its adverse effects.

CAR T-cell therapies for haematological malignancies when other treatment options have been exhausted: probably prolong survival, but further evaluation required

In chimeric antigen receptor (CAR) T-cell therapy, the patient receives their own T cells that have been genetically modified to express a receptor at their surface designed to cause the T cells to bind to cancer cells so they can destroy them.

The 2019 Honours List features two CAR T-cell therapies: *tisagenlecleucel* (Kymriah°), authorised for the treatment of B-cell acute lymphoblastic leukaemia in children and young adults with no further treatment options, and *axicabtagene ciloleucel* (Yescarta°) for patients with certain types of large B-cell lymphoma and no further treatment options. The prognosis in both these clinical situations is poor, and patients often survive for no more than a few months. CAR T-cell therapy appears to prolong their survival: at least half of the patients in trials were still alive 1 to 2 years after receiving this treatment. It is difficult to quantify this advance because the trials were small and non-comparative. Further clinical evaluation of these therapies is required.

CAR T-cell therapies provoke a great many adverse effects that are often serious or even fatal, including cytokine release syndrome, neurological disorders, infections and haematological disorders.

Because CAR T cells are prepared specifically for one patient, special procedures are required to ensure they are given to the right person.

Ruxolitinib and trastuzumab emtansine: revealed to be advances by further evaluation

Two drugs were recognised as Noteworthy in 2019, several years after their market introduction. In both cases, it was not possible to determine their harm-benefit balance from their initial, inadequate clinical evaluation, but more recent data showed them to represent a therapeutic advance.

Further evaluation of the Janus kinase (JAK) inhibitor *ruxolitinib* (Jakavi°) in patients with symptomatic myelofibrosis showed that it reduces spleen volume in about half of patients, for as long as treatment continues. The spleen can be very large in this situation, impairing the patient's quality of life. *Ruxolitinib* has not been shown to affect other symptoms, but probably extends survival. These benefits must be weighed against its harms, in particular infections, worsening of the haematological disorders associated with myelofibrosis, and neurological disorders. Patients commonly discontinue treatment due to its adverse effects.

Two randomised trials have shown that, compared with other antineoplastic drugs, *trastuzumab emtansine* (Kadcyla°), an anti-HER2 monoclonal antibody conjugated to a cytotoxic drug, increases survival by 4 to 7 months in women with inoperable breast cancer overexpressing the protein HER2 who have already received a taxane and *trastuzumab*. This modest survival gain is tempered by its serious adverse effects, including heart failure, thrombocytopenia, haemorrhages and liver injury. Deaths have been caused by confusion between *trastuzumab emtansine* and *trastuzumab*.

Pembrolizumab as first-line therapy for certain types of lung cancer: alone or with other antineoplastic drugs, depending on PD-L1 expression

In four randomised clinical trials of first-line therapy for patients with metastatic non-small cell lung cancer, the immunostimulatory anti-PD-1 monoclonal antibody *pembrolizumab* (Keytruda°) extended median survival by several months. When most of the tumour cells express the PD-L1 protein, *pembrolizumab* is used alone. When fewer than half of the tumour cells express PD-L1, the benefit of *pembrolizumab* has mainly been demonstrated when added to platinum-based chemotherapy. Keytruda° was deemed Noteworthy in 2019 on the basis of these data.

Pembrolizumab's adverse effects are mainly of immunological origin and can affect multiple organs. They include pneumonitis, myocarditis, colitis, stomatitis, gastritis, pancreatitis, hepatitis and nephritis.

2019 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.

2019	NOT AWARDED

2019 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:

- **HEMLIBRA° (*emicizumab*)**
  Roche
  Prophylaxis of bleeding episodes in patients with haemophilia A and "factor VIII inhibitors" (Prescrire Int n° 210)
- **KYMRIAH° (*tisagenlecleucel*)**
  Novartis
  B-cell acute lymphoblastic leukaemia in children and young adults when other treatment options have been exhausted (Prescrire Int n° 208)
- **YESCARTA° (*axicabtagene ciloleucel*)**
  Kite Pharma (a Gilead company)
  Certain types of large B-cell lymphomas when other treatment options have been exhausted (Prescrire Int n° 208)

Noteworthy in 2019

Drugs deemed "Noteworthy" provide a modest improvement in patient care. This year's Noteworthy drugs are, in alphabetical order:

- **JAKAVI° (*ruxolitinib*)**
  Novartis
  Symptomatic myelofibrosis (Prescrire Int n° 137 and Prescrire Int n° 205, with more follow-up)
- **KADCYLA° (*trastuzumab emtansine*)**
  Roche
  HER2-positive inoperable breast cancer in women who previously received *trastuzumab* and a taxane (Prescrire Int n° 155 and Prescrire Int n° 207, with more follow-up)
- **KEYTRUDA° (*pembrolizumab*)**
  MSD
  Metastatic non-small cell lung cancer, as first-line treatment (Prescrire Int n° 210 and Prescrire Int n° 212)

2019 Prescrire Packaging Awards

When *Prescrire* evaluates a drug's harm-benefit balance, the quality of its packaging is one of the factors examined. We answer several questions during our packaging examinations. Does the packaging ensure that the drug is easily and accurately used, does it ensure the safety of patients and their family and carers? 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 account of many factors: 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 2019 Packaging Awards pertain to the packaging of drugs evaluated in our French edition in 2019.

2019 PACKAGING AWARD

Isentress° granules for oral suspension (***raltegravir***) MSD (Rev Prescrire n° 431)

For the clear, informative "*instructions for use*" booklet inside the box of the paediatric form of this antiretroviral drug, now authorised for use in neonates. This booklet, provided in addition to the patient leaflet, contains a wealth of useful information to help prevent errors and the dangers posed by the extemporaneous preparation of this drug, including a precise description of the items required for its preparation (all of which are supplied in the box), and each preparation step. Various procedures are illustrated, such as how to read the graduations on the syringe correctly, how to administer the preparation, and how to clean all the equipment after use.

The lower excipient content of reconstituted powders is an advantage over ready-to-use oral preparations, because some excipients, such as propylene glycol, ethanol and castor oil, can have serious adverse effects in children. But their reconstitution is often complex and rarely adequately explained in the patient leaflet. This booklet is an example of what ought to be the rule, due to the effort invested in providing unambiguous, easy-to-follow instructions.

RED CARDS

Packaging for children: savings at the expense of safety

Firazyr° solution for subcutaneous injection (***icatibant***) Shire (Rev Prescrire n° 423)

For not marketing a paediatric version of this drug, initially authorised for adults with a rare genetic disorder, when it was subsequently authorised for use in children from the age of 2 years. Adults receive the same dose at each injection, justifying the fact that the syringe supplied has no graduations. The syringe has not been adapted for use in children, even though paediatric doses are based on body weight. The solution chosen by the pharmaceutical company and drug regulatory agencies is to give parents a separate box, containing a graduated syringe and a device to connect the two syringes to transfer the contents of the non-graduated syringe into the graduated one. This unnecessarily complicated solution is likely to cause errors.

Inovelon° oral suspension (***rufinamide***) Eisai (Rev Prescrire n° 429)

For not adapting the dosing device supplied in the box when the product's indications were extended to include infants. Infants require lower doses of this antiepileptic than adults and children from 4 years of age. The syringe capacity (20 ml) remains unchanged but is far higher than necessary for measuring infant doses (e.g. 1.25 ml for an infant weighing 10 kg), making overdoses likely.

Phosphoneuros° oral solution (***phosphorus***) Bouchara Recordati (Rev Prescrire n° 428)

For insufficient improvements to packaging that has caused fatal overdoses of this medicine used in neonatology. The smallest volume that can be measured with the dosing device is 5 drops, precluding accurate measurement of the lower doses required for children weighing less than 5 kg. The patient leaflet makes no mention of this lower limit and offers no advice on how to prepare smaller doses. It also lacks a table to enable users to convert the number of milligrams of *phosphorus* prescribed to the number of drops to measure out. There are no detailed explanations or illustrations of how to prepare and administer the drug.

Rotarix° oral suspension (***rotavirus vaccine***) GlaxoSmith-Kline (Rev Prescrire n° 432)

For the strong resemblance of the administration device provided in France with this oral vaccine to a syringe for injection, which has resulted in wrong-route errors, whereas Rotarix° is authorised in the European Union in a different container that does not resemble a syringe.

Siklos° 100 mg and 1000 mg scored tablets (***hydroxycarbamide***) Addmedica (Rev Prescrire n° 431)

For not improving the labelling so that the two dose strengths of this cytotoxic drug are easier to distinguish, to mitigate the risk of confusing one for the other. Overdoses have occurred in children as a result of dispensing and administration errors, provoking serious haematological disorders. Furthermore, it is dangerous to supply cytotoxic drugs as loose tablets in a bulk bottle. The person preparing the tablets is at higher risk of exposure to the drug and, in the hospital setting, the tablets must be repackaged and relabelled, creating an additional step at which wrong-strength errors can occur.

RED CARDS

Insufficient efforts to prevent ingestion by children

Alfa-Amylase Biogaran Conseil° (**a**) Biogaran and **Maxilase Maux de Gorge°** (**a**) Sanofi Aventis syrups (***alpha-amylase***) (Rev Prescrire n° 426); **Clarix Toux Sèche Adultes°** (**a**), **Clarix Toux Sèche Enfants°** Cooper, and **Vicks Sirop Pectoral°** (**a**) Procter & Gamble Pharmaceuticals syrups (***pentoxyverine***) (Prescrire Int n° 208); **Dolko°** (**b**) oral solution (***paracetamol***) Thérabel Lucien Pharma (Rev Prescrire n° 434); **Nausicalm°** syrup (***dimenhydrinate***) Nogues (Rev Prescrire n° 423) (**c**); **Phénergan°** (**d**) syrup (***promethazine***) DB Pharma (Rev Prescrire n° 424); **Phosphoneuros°** oral solution (***phosphorus***) Bouchara Recordati (Rev Prescrire n° 428); **Potassium Liberty Pharma°** (**e**) syrup (***potassium***) H2 Pharma (Rev Prescrire n° 426).

For the absence of a child-proof cap on the bottles of these 10 products, especially when child-proof caps are present on so many other medicines in bottles. The caps on these 10 medicines do not sufficiently protect children. They give children easy access to the contents of the bottle, placing them at risk of the adverse effects of the substances they contain.

Umbrella brands that give insufficient prominence to INNs and dose strengths

Actifed LP Rhinite Allergique° (**d**) tablets (***cetirizine + pseudoephedrine***), **Actifed Rhume°** tablets (***paracetamol + pseudoephedrine + triprolidine***), **Actifed Rhume Jour et Nuit°** tablets (***paracetamol + pseudoephedrine*** or ***paracetamol + diphenhydramine***) Johnson & Johnson Santé Beauté; **Dolirhume°** tablets (***paracetamol + pseudoephedrine***), **Dolirhumepro°** tablets (***paracetamol + pseudoephedrine*** or ***paracetamol + doxylamine***) Sanofi Aventis; **Humex Rhume°** tablets and hard capsules (***paracetamol + pseudoephedrine*** or ***paracetamol + chlorphenamine***) Urgo Healthcare; **Nurofen Rhume°**, **Rhinureflex°** tablets (***ibuprofen + pseudoephedrine***) Reckitt Benckiser Healthcare; **Rhinadvil Rhume°** tablets, **Rhinadvilcaps Rhume°** soft capsules (***ibuprofen + pseudoephedrine***) Pfizer Santé Familiale; **Rhumagrip°** tablets (***paracetamol + pseudoephedrine***) Cooper (Rev Prescrire n° 424).

For packaging that gives too little prominence to the international nonproprietary names (INNs) and dose strengths of the drugs these products contain. It makes it difficult to identify the presence of the sympathomimetic vasoconstrictor *pseudoephedrine*, which can provoke cardiovascular events and ischaemic colitis. It also makes it difficult to identify the presence and quantity of *paracetamol*, an overdose of which can damage the liver. All but Rhumagrip° belong to umbrella brands, the principle of which is to sell a variety of medicines, containing different active substances, under the same brand name.

The French Health Products Agency (ANSM) has recommended ending the use of umbrella brands, due to the risk of confusion between products of the same brand and the dangers they pose to patients.

Psychotropic oral suspension with a confusing, inaccurate dosing device

Deroxat° oral suspension (***paroxetine***) GlaxoSmithKline (Rev Prescrire n° 423).

For the confusing measuring cup provided with this antidepressant, graduated in both milligrams and millilitres, which has already caused dosing errors. Even without this flaw, a measuring cup is not an accurate dosing device.

Patient leaflets that understate the harms

Ellaone° tablet (***ulipristal***) HRA Pharma (Prescrire Int n° 212).

For the insufficient information in the patient leaflet on the risk that using hormonal contraception within 5 days of taking *ulipristal* will reduce the efficacy of *ulipristal*. It has been known since 2015 that administration of hormonal contraception during this 5-day period increases the likelihood of ovulation, which could result in an unintended pregnancy.

Entalgine° cutaneous gel (***diclofenac***) Cooper (Rev Prescrire n° 434); **Flurbiprofène Sandoz Conseil°** (**d**) Sandoz, **Strefen°**, **Strefen Sans Sucre°** lozenges (***flurbiprofen***) Reckitt Benckiser Healthcare (Prescrire Int n° 202); **Rhinadvil Rhume°** tablets (***ibuprofen + pseudoephedrine***) Pfizer Santé Familiale (Rev Prescrire n° 424); **Ipraféine°** tablets (***ibuprofen + caffeine***) Sanofi Aventis (Rev Prescrire n° 426).

For the insufficient information in the patient leaflets on the potential harms of taking nonsteroidal anti-inflammatory drugs (NSAIDs) during pregnancy. These patient leaflets do not mention the increased risk of spontaneous abortion or concerns over the risk of malformations when NSAIDs are taken during the first trimester of pregnancy, or the risk of potentially irreversible renal damage or pulmonary arterial hypertension in the unborn child when taken in the second trimester. They only state that the product is contraindicated from the sixth or seventh month of pregnancy.

NSAIDs should be avoided throughout pregnancy, because there is no evidence that contraindicating their use from the sixth month of pregnancy is sufficient to avoid harming the unborn child.

a- *In addition, the packaging of these multidose oral liquids lacks a dosing device.*
b- *In addition, the INN paracetamol and its dose strength are difficult to see.*
c- *Addition of a child-proof cap was authorised in 2018. It was still absent however from a batch purchased from a wholesale distributor on 2 January 2020, due to expire in November 2021.*
d- *The pharmaceutical companies concerned no longer market these products in France. We left them on this list in case any pharmacies still have them in stock.*
e- *In response to our request, H2 Pharma informed us that plans are underway to add a child-proof cap to the bottle. This company markets another multidose potassium syrup (Potassium H2 Pharma°) that acquired a child-proof cap in 2019, as well as a dosing device, in the form of a measuring cup with 5 ml and 15 ml graduations.*

2019 Information Awards

Pharmaceutical companies hold a wealth of useful information on the drugs they market, from the moment work begins on bringing a drug to the market until its withdrawal. They have a responsibility to share this information, in part to help better determine the drugs' harm-benefit balance and to help protect patients from certain harms.

Prescrire systematically asks pharmaceutical companies for clinical data and packaging information for ex-ample, in order to collate and compare them with data obtained through the systematic literature search conducted by the Editorial Staff (including drug regulatory agencies' assessment reports, administrative and regulatory information, and packaging).

The Information Awards are based on the quality of the information provided to *Prescrire* by the companies whose products we examined in 2019 in the New Products section of our French edition. They reveal the importance each company attaches to informing health professionals about their drugs, and the reluctance displayed by some.

It is perfectly possible for companies to share information about their drugs... We requested information from 112 pharmaceutical companies in 2019. Six of them chose to be open, and demonstrated this by providing detailed, relevant information in response to *Prescrire*'s requests. These companies earned a place on the Honours List. One of these six companies provided us with particularly useful and detailed information without delay, and was therefore rated as "Outstanding".

... but many companies are unwilling. Other drug companies failed to respond to some or all of *Prescrire*'s requests, or provided only limited data. Some of them delayed their response and provided no usable information. Some omitted the most important or sensitive data. Red Cards are given to highlight persistent deficiencies in the provision of information. This was the case for 14 of the 112 pharmaceutical companies we approached in 2019.

Evaluation data announced, but not shared with Prescrire. Among the remaining 92 pharmaceutical companies we approached, AstraZeneca and Lilly each announced via press release and through other channels that they had new favourable evaluation data on one of their drugs: *osimertinib* (Tagrisso°) in certain types of metastatic or inoperable lung cancer, and *abemaciclib* (Verzenios°) in certain types of breast cancer. But they did not share the detailed quantitative data with *Prescrire* and our subscribers.

Secrecy is still well entrenched in 2019. As in previous years, we found that few pharmaceutical companies we dealt with in 2019 were committed to providing health professionals with practical information about their drugs by sharing the data in their possession with *Prescrire*. They often preferred to eschew transparency and keep important detailed documentation to themselves. This throws into sharp relief the responsible attitude of the few pharmaceutical companies willing to help improve medication quality and safety. Surely patients and healthcare professionals have the right to be informed of all the data obtained on a given drug, in order to decide, with full knowledge of the facts, whether to use it or not?

6 Companies on the Honours List

Outstanding:

– EG Labo

Followed by:

– Arrow Génériques
– Bioprojet Pharma
– Bouchara Recordati
– GlaxoSmithKline
– Vectans Pharma

14 Red Cards

– Alk Abelló
– Bayer Healthcare
– Biogaran
– Genévrier
– GMP Orphan
– Janssen Cilag
– Kyowa Kirin Pharma
– Menarini
– MSD
– Otsuka Pharmaceutical
– Sandoz
– Takeda
– Teva Santé
– Vifor

How we rate the quality of the information provided by pharmaceutical companies:

Detailed information including unpublished data and packaging items.

Information limited to published administrative data or packaging items.

Minimal information, mainly administrative and packaging items.

No information.