

The Prescrire Awards 2015



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 at english.prescrire.org.



2015 Prescrire Drug Awards

New products or new indications evaluated during the previous year in the New Products section of our French edition are eligible for the *Prescrire* Drug Awards.

Each month, the *Prescrire* Editorial Staff presents systematic comparative assessment of available data on drugs newly approved in France and the EU, and on new therapeutic indications granted for existing drugs. The goal is to help the reader distinguish, among the plethora of lavishly promoted new products, those medications worth adding to their drug list or worth using instead of existing products, as well as drugs to be avoided.

This evaluation is based on rigorous procedures that include a thorough literature search, input from a group of reviewers specific to each review, and various quality controls to verify that the text is consistent with the data in the references (see our website for further information: english.prescrire.org).

Total independence. This work is carried out by the *Prescrire* Editorial Staff in total independence, free from any industry or institutional influence. *Prescrire* is financed exclusively by its subscribers. Neither the French nor the English edition carries any paid advertising, nor do we receive grants or subsidies of any kind (see our annual financial report in each June issue of *Prescrire International*).

At the end of each year, the *Prescrire* Drug Awards are based on the reviews published that year in the French edition, and take into account any new data made available since the initial articles were published.

Pilule d'Or / Golden Pill

The Pilule d'Or (Golden Pill) has been granted since 1981 to drugs that constitute a major therapeutic advance in a field in which no treatment was previously available



2015	NOT AWARDED
2014 (n° 376)	ORPHACOL° (<i>cholic acid</i>)
2007 (n° 292)	CARBAGLU° (<i>carglumic acid</i>)
2006 (n° 280)	ORFADIN° (<i>nitisinone</i>)
1998 (n° 192)	CRIXIVAN° (<i>indinavir</i>)
1996 (n° 169)	DIGIDOT° (<i>digoxin-specific antibody</i>) (1)
1992 (n° 125)	SURFEXO° (<i>pulmonary surfactant</i>) (1)
1989 (n° 92)	EPREX° (<i>epoetin alfa</i>) • MECTIZAN° (<i>ivermectin</i>)
1988 (n° 81)	LARIAM° (<i>mefloquine</i>) • RETROVIR° (<i>zidovudine</i>)
1987 (n° 71)	LUTRELEF° (<i>gonadorelin</i>) • DECAPEPTYL° (<i>triptorelin</i>)
1986 (n° 61)	ZOVIRAX° IV and tablets (<i>aciclovir</i>)
1983 (n° 31)	LOPRIL° (<i>captopril</i>)
1981 (n° 10)	VACCIN HEVAC B° (<i>hepatitis B vaccine</i>)

No Golden Pill was awarded in 1982, 1984, 1985, 1990, 1991, 1993, 1994, 1995, 1997, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2008, 2009, 2010, 2011, 2012 and 2013.

1- No longer marketed in France.

These awards honour drugs that constitute a therapeutic advance, in that they offer better efficacy, fewer or less severe adverse effects (for similar efficacy), or safer or easier administration.

No Golden Pill awarded in 2015.

Three of the products featured in the New Products section of our French edition in 2015 earned a *Prescrire* Drug Award this year. One was included on the Honours List, two were deemed "Noteworthy", but none constituted a sufficient therapeutic advance to warrant a Golden Pill Award. None of these three products contain a novel active ingredient. However, in the clinical situation for which they were granted marketing authorisation, they constitute an advance over the products already available.

Propranolol oral solution and severe haemangioma: a chance discovery, followed by development of a paediatric form. Some infants have a severe haemangioma that could cause complications (due to its size and location), ulceration, bleeding or disfigurement. *Propranolol* oral solution has become the drug of choice in this situation. It is more effective than placebo and its adverse effects are more acceptable overall than that of long-term oral corticosteroid therapy. Treatment initiation and dose increases should take place in hospital, with careful monitoring of the child. *Propranolol* oral solution has been granted marketing authorisation in the European Union solely for paediatric use. Its packaging is conducive to safe use and safe dose preparation.

Permethrin in scabies, ketoconazole in Cushing's syndrome: welcome marketing authorisations. *Permethrin* 5% cream is at last readily obtainable in France to treat classic scabies, since being granted full marketing authorisation, and being made available in the community and reimbursable by the national health insurance system. Its main value is for the treatment of young children, because *ivermectin* is not approved for use in children weighing less than 15 kg.

After about 30 years of off-label use in the rare but serious endogenous Cushing's syndrome, oral *ketoconazole* has finally been granted marketing authorisation for this indication. In

Honours list

Drugs are included on the Honours List because they represent a clear advance for some patients compared with existing therapeutic options, albeit with limitations.

2015	• HEMANGIOL® (propranolol oral solution) Pierre Fabre Dermatology - Severe infantile haemangioma (<i>Prescrire</i> Int n° 162)
2014 (n° 376)	• Glivec® (<i>imatinib</i>) (acute lymphoblastic leukaemia in children) • Malacet® (intravenous <i>artesunate</i>) (severe malaria) • Sovaldi® (<i>sofosbuvir</i>) (hepatitis C)
2010 (n° 328)	• Glivec® (<i>imatinib</i>) (unresectable or metastatic gastrointestinal stromal tumours, with more follow-up)
2007 (n° 292)	• Glivec® (<i>imatinib</i>) (chronic myeloid leukaemia with more follow-up) • Herceptin® (<i>trastuzumab</i>)
2006 (n° 280)	• Egaten® (<i>triclabendazole</i>)
2005 (n° 269)	• Varivax® (<i>varicella-zoster vaccine</i>)
2004 (n° 258)	• Diacomit® (<i>stiripentol</i>) • Fuzeon® (<i>enfuvirtide</i>) • Morphine Aguettant® syrup (oral <i>morphine</i>) (1)
2003 (n° 247)	• Carbaglu® (<i>carglumic acid</i>) • IVheBex® (<i>hepatitis B immunoglobulin</i>) • Meningitec® (<i>conjugate meningococcal C vaccine</i>)
2002 (n° 236)	• Replagal® (<i>agalsidase alfa</i>) (2) • Ceprotin® (1) - Protexel® (<i>human protein C</i>) • Stromectol® (<i>ivermectin</i>) (scabies)
2001 (n° 225)	• Esterasine® (<i>C1 esterase inhibitor</i>) (1) • Trolovol® (<i>penicillamine</i>) (chelator)
2000 (n° 214)	• Remicade® (<i>infliximab</i>)

Drugs were included on the Honours List every year between 1981 and 2007. No drugs were included in 2008, 2009, 2011, 2012 or 2013. The full list of drugs included on the Honours List from 1981 to 2013 can be found in *Prescrire International* n° 67 page 168.

1- No longer marketed in France; 2- New data published after the inclusion of this drug on the Honours List led us to revise our rating, see *Prescrire* Int n° 67 page 168.

Noteworthy

Drugs deemed "Noteworthy" provide a modest improvement in patient care.

2015	• TOPISCAB® (permethrin 5% cream) Codexial Dermatologie – Scabies from 2 months of age (<i>Rev Prescrire</i> n° 384)
	• KÉTOCONAZOLE HRA® (ketoconazole) HRA Pharma – Endogenous Cushing's syndrome (<i>Rev Prescrire</i> n° 386)

this situation, data from non-comparative case series in a total of 800 patients suggest that oral *ketoconazole* is effective in more than half of patients. However, its use requires precautions on account of its hepatotoxicity and strong potential for drug interactions.

Few therapeutic advances. While many new marketing authorisations were granted in 2015, few constituted a real therapeutic advance. Knowing how to sift through the multitude of available drugs to identify those with the best harm-benefit balance in a given situation, and knowing to avoid drugs that are more dangerous than useful is also an area where important advances can be made for the benefit

of patients (see Towards better patient care: drugs to avoid in 2016 on english *prescrire.org* and in April issue).

Regulators and policy makers should impose stricter requirements on new drugs, by demanding evidence that they actually constitute a therapeutic advance. This would prevent inundation of the market with products that offer no advantages in patient care and that, in some cases, are more dangerous than useful. It would also help contain the excesses this situation generates: extravagant marketing aimed at health professionals and patients, incentives to prescribe and purchase drugs, and spiralling health expenditure.

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2015 Prescrire Packaging Awards

The Packaging Awards focus on the quality of the packaging of drugs evaluated in 2015 in our French edition.

No Packaging Award in 2015

Prescrire's systematic reviews in the New Products section include evaluation of the drugs' packaging. Is it clear from the labelling which active substance or substances the product contains? How are doses prepared and administered? Does the

information in the patient leaflet help users avoid errors and dangers?

When analysing a drug's packaging, including the patient leaflet, and how convenient it is to use, we take into account every aspect of the context in which it will be used: the clinical situation; the patients concerned, in particular children, pregnant women and elderly patients; and the setting in which it will be obtained, prepared and administered (in hospital, with the intervention of a nurse, or in the community, either prescribed by a doctor,

advised by a community pharmacist, or bought by the patient from a pharmacy or an Internet retailer).

Every aspect of the packaging is examined to determine its quality and safety (clarity, accuracy, suitability to the situation). Is the drug supplied in a multidose container or is each dose packaged individually? What measures have been taken to protect children from poisoning? We examine: the information on the labelling that is useful for patient care, including the legibility of international nonproprietary

Red cards



Dangerous shortcomings in the information provided in the labelling or patient leaflet

- **Doli État Grippal**° powder for oral solution in sachets (**paracetamol + pheniramine + vitamin C**) Sanofi Aventis (*Rev Prescrire* n° 375)
"Doli" is printed in large, bold characters on the box, as it is on the boxes of all the products of the Doli° umbrella brand. This can lead to confusion between the products, some of which contain different active ingredients, such as the dangerous vasoconstrictor *pseudoephedrine*. The INNs *paracetamol* and *pheniramine* are much less obvious than "Doli".

- **Antalcalm**° medicated plasters (**diclofenac**) Pierre Fabre Médicament (*Rev Prescrire* n° 383) • **Asproflash**° tablets (**acetylsalicylic acid**) Bayer Healthcare (Consumer Care division) (*Rev Prescrire* n° 381)
- **Opalgyné**° vaginal solution (**benzydamine**) Innotech International (*Rev Prescrire* n° 375)

The patient leaflets of these products contain insufficient information about the harms of nonsteroidal anti-inflammatory drugs (NSAIDs) during pregnancy. They fail to warn patients about concerns that NSAIDs may provoke spontaneous abortion and malformations when taken during the first trimester of pregnancy, or about the sometimes irreversible renal damage or pulmonary arterial hypertension reported in children following exposure to an NSAID during the second trimester. These leaflets only state that the product concerned is contraindicated from the sixth or seventh month of pregnancy. It would be better to avoid NSAIDs throughout pregnancy until their use before the sixth month of pregnancy has been proven harmless.

- **Colpotrophine**° vaginal cream and capsules (**promestriene**) Teva Santé (*Rev Prescrire* n° 383) • **Gydrelle**° vaginal cream (**estriol**) Iprad Pharma (*Rev Prescrire* n° 383) • **Physiogine**° vaginal cream and pessaries (**estriol**) H.A.C. Pharma (*Rev Prescrire* n° 383) • **Trophicrème**° vaginal cream (**estriol**) Sanofi Aventis (*Rev Prescrire* n° 383)

The patient leaflets of these products contain insufficient information about the long-term harms of vaginal oestrogens, which are identical in nature to those of oral oestrogen therapy: arterial and venous thrombosis, as well as breast and endometrial cancer.

Packaging liable to cause dangerous dose preparation errors

- **Vaccin BCG SSI**° powder and solvent for suspension for injection (**BCG**) Sanofi Pasteur MSD (*Rev Prescrire* n° 385)

The vial contains 10 to 20 doses of the vaccine and the graduation scale on the syringe supplied in the box corresponds to 10 to 20 times the recommended dose. These flaws are liable to cause overdoses and adverse effects. This product already received a *Prescrire* Red Card in 2007. Its packaging has not been improved and serious errors continue to occur.

- **Venlafaxine Abbott**° sustained-release tablets (**venlafaxine**) Mylan Medical (*Rev Prescrire* n° 379)

This antidepressant (with an unfavourable harm-benefit balance) is taken once a day, yet the dosing schedule on the box shows 3 boxes, labelled "morning", "midday" and "evening". The confusion this is likely to cause could result in overdoses and more, or more severe, adverse effects.

- **Diacomit**° hard capsules and powder for oral suspension in sachets (**stiripentol**) Biocodex (*Rev Prescrire* n° 384) • **Votubia**° dispersible tablets (**everolimus**) Novartis Pharma (*Rev Prescrire* n° 378)

Neither the pharmaceutical forms nor the packaging of these products is suitable for preparation of the recommended paediatric doses, which could lead to confusion, wrong-dose errors and adverse effects.

- **Cometriq**° 20 mg and 80 mg hard capsules (**cabozantinib**) Swedish Orphan Biovitrum (*Prescrire Int* n° 167)

The complexity of the packaging of this cancer drug is liable to cause confusion and dose preparation errors: the doses prescribed are 140 mg, 100 mg or 60 mg, while the dose strengths available are 20 mg or a mixture of 20 mg and 80 mg capsules. The labelling on the boxes does not help clarify the situation.

Packaging that poses a risk of poisoning to children

- **Atarax**° syrup (**hydroxyzine**) UCB Pharma (*Rev Prescrire* n° 385)

- **Diacomit**° hard capsules (**stiripentol**) Biocodex (*Rev Prescrire* n° 384)

- **Normison**° tablets (**temazepam**) Primus (*Rev Prescrire* n° 377) • **Simbrinza**° eye drops (**brimonidine + brinzolamide**) Alcon (*Rev Prescrire* n° 381)

None of the bottles used for these products has a child-proof cap. Children could therefore ingest their contents, with potentially serious consequences.

names (INNs) and the dose strength; information presented graphically, such as dosing schedules and pictograms; any devices provided for preparing or administering the required dose; the quality and clarity of the information provided in the patient leaflet on how to prepare the doses to be administered, on adverse effects, and on the situations and patient groups in which the drug poses a risk.

The Packaging Awards are based on the assessments conducted by *Prescrire's* Packaging Working Group, in total independence, free from any influence from packaging manufacturers.

No Award in 2015, but various dangers to report. None of the packaging examined in 2015 satisfied all the requirements concerning safety and therapeutic advance to earn a *Prescrire* Packaging Award. However, the dangers identified are illustrated in this year's edition by the 20 or so products that received a Red or Yellow

Yellow cards



- **Monosept° eye drops in single-dose containers (*cethexonium bromide*)** Horus Pharma (*Rev Prescrire* n° 376)

The INN is not displayed on the single-dose containers.

- **Zovirax° 200 mg/5 ml oral suspension (*aciclovir*)** GlaxoSmithKline (*Rev Prescrire* n° 386)

The new dosing device (a double-ended measuring spoon, one end for measuring 2.5 ml and the other 5 ml) is unsuitable and could cause wrong-dose errors, given that the recommended dose is 5 ml or 10 ml.

- **Ribavox° tablets (*ribavirin*)** Bioprojet Pharma (*Rev Prescrire* n° 386)

The boxes and bottles are covered with fanciful graphics (a tablet depicted as a rocket, clouds and the sun) that increase the resemblance between the three dose strengths and could lead to confusion when dispensing them or preparing doses.

Card: some lack a child-proof cap, others provide no means of preparing doses for children, some patient leaflets fail to warn users of known dangers.

A non-exhaustive list of packaging flaws. Increasing numbers of drugs are placed on the market in packaging that could lead to difficulty or poorly evaluated dangers, for example:

cancer drugs such as cytotoxic agents, in bulk bottles; insulins marketed at different concentrations; and the continued growth of umbrella brands.

The *Prescrire* Packaging Awards and the annual drug packaging review (to be published in a coming issue) reflect the true state of affairs as regards the safe use of drugs. The overall picture is disturbing.

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2015 Prescrire Information Awards



The Information Awards focus on the information provided to *Prescrire* by the companies whose products we examined in the New Products section of our French edition in 2015.

Honours List (in alphabetic order)

- **Outstanding :**
EG Labo,
Lucane Pharma
- **Followed by :**
Arrow Génériques,
Codexial Dermatologie,
GlaxoSmithKline

Pharmaceutical companies hold a wealth of information on the drugs they market or withdraw from the market. They have a responsibility to share this information, in part to help ensure that their drugs are used appropriately and to protect patients from certain risks.

As part of its systematic literature search, *Prescrire* requests clinical data, packaging, and administrative and regulatory information from drug companies, then compares them with information obtained from other sources. *Prescrire's* Information Awards reflect how each company assumes this responsibility to share information.

tation containing unpublished data, which for example could include details about adverse effects.

Some companies choose to be transparent. These companies are placed on the Honours List. And those rated as "Outstanding" provided us with useful, detailed data without delay and sometimes without being asked.

Other companies fail to respond to some or all of our requests for information, or provide only limited data. Some of them delay their response, then fail to provide usable information. Some omit the most important data. Red Cards are given to highlight persistent shortcomings in the provision of information by certain drug companies.

In 2015, few pharmaceutical companies embraced transparency by agreeing to share with health professionals all the data they hold, in particular data on adverse effects.

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Red cards (in alphabetic order)

**Allergan, Bayer Healthcare (Pharmaceuticals),
Biogen Idec,
Bristol-Myers Squibb,
Crinex, Gilead Sciences,
Meda Pharma, Menarini, Pfizer**

Still too little transparency on the part of drug companies in 2015. On the whole, pharmaceutical companies supply *Prescrire* with a lot of information, some new and some that we have obtained elsewhere. But they are less cooperative when asked to provide relevant, detailed documen-