

1981-2011: 31 years of Prescrire Drug Awards

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Awards for drugs, packaging and information: Prescrire's three annual awards are granted in total independence by *Prescrire's* Editorial Staff (rules available on our website: english.prescrire.org). These awards complement the annual review published at the beginning of each year in our French edition (see *Rev Prescrire* 2012, 32 (339): 29-61), and a review of new drugs and indications in 2011 to be published in the next issue of *Prescrire International*.

(1)	Pilule d'Or/Golden Pill Award	Honours list
1981 (n°10)	• VACCIN HEVAC B° (hepatitis B vaccine) (B)	• Androcur° (cyproterone) (RA) • Armophylline° (theophylline LP) (RA) • Cordium° (bepiridil) (RA) • Isoprinosine° (inosine acedoben dimepranol) (RA) • Pirilène° (pyrazinamide) (RA) • Tildiem° (diltiazem) (RA)
1982 (n°21)	(not attributed)	• Didronel° (etidronic acid) (RA) • Minirin° (desmopressin) (RA) • Nerfactor° (isaxonine) (RA)(2) • Vansil° (oxamniquine) (3)(RA)
1983 (n°31)	• LOPRIL° (captopril) (RA)	• Tigason° (etretinate) (RA)(3)
1984 (n°41)	(not attributed)	• Nizoral° (ketoconazole) (RA) • Orimètène° (aminoglutethimide) (RA) (3) • Ulcar° (sucralfate) (RA)
1985 (n°51)	(not attributed)	• Augmentin° (amoxicillin + clavulanic acid) (OAA)
1986 (n°61)	• ZOVIRAX° I.V. and tabs. (aciclovir) (B) and (RA)	• GHRH Clin Midy° (somatostatin) (RA) • Roaccutane° (isotretinoin) (RA)
1987 (n°71)	• LUTRELEF° (gonadorelin) (B) • DECAPEPTYL° (triptorelin) (RA)	• Introna° (interferon alfa) (RA) • Moscontin° (sustained release morphine) (RA) • Zovirax° cream (aciclovir) (OAA) • Rifadine° (rifampicin) (RA) • Tégrétole° (new indications) (carbamazepine) (RA)
1988 (n°81)	• LARIAM° (mefloquine) (B) • RETROVIR° (zidovudine) (B)	• Anexate° (flumazenil) (RA) • Nimotop° (nimodipine) (RA)
1989 (n°92)	• EPREX° (epoetin alfa) (B) • MECTIZAN° (ivermectin) (B)	• Malocide° (new indication) (pyrimethamine) (RA) • Nimotop° inj. (new indication) (nimodipine) (RA) • Sandostatin° (octreotide) (RA)
1990 (n°103)	(not attributed)	• Mopral° (omeprazole) (RA) • Narcan° (naloxone) (RA) • Pentacarinat° (pentamidine) (OAA)
1991 (n°114)	(not attributed)	• Aredia° (pamidronate) (RA) • Minirin° inj. (new indication) (desmopressin) (RA) • Lévocarnil° (L-carnitine) (RA) • Sandostatine° (new indication) (octreotide) (RA)
1992 (n°125)	• SURFEXO° (pulmonary surfactant) (RA)(3)	• Apokion° (apomorphine) (OAA) • Videx° (didanosine) (OAA)
1993 (n°136)	(not attributed)	• Avlocardyl° (new indication) (propranolol) (RA) • Daivonex° (calcipotriol) (OAA) • Sporanox° (itraconazole) (OAA)
1994 (n°147)	(not attributed)	• Botox°-Dysport° (botulinum toxin) (OAA) • Zophren° (new dosages) (ondansetron) (OAA)
1995 (n°158)	(not attributed)	• Chorhydrate de méthadone AP-HP° (methadone) (RA) • Retrovir° (new indication) (zidovudine) (RA) • Kogenate° - Recombinate° (recombinant factor VIII) (RA)
1996 (n°169)	• DIGIDOT° (antidigitalin antibodies)(B)(3)	• Cérédase° (alglucerase) (RA) (3) • Normosang° (hemin arginine) (RA) • Subutex° (buprenorphine) (RA) • Zocor° - Lodalès° (new indication) (simvastatin) (RA) • Zeclar° - Naxy° (clarithromycin); Clamoxyl° - Gramidil° (amoxicillin); Mopral° - Zoltum° (omeprazole); Ogast° - Lanzor° (lansoprazole) (same new indication) (RA)
1997 (n°180)	(not attributed)	• Elisor°-Vasten° (new indication) (pravastatin) (RA) • Novatrex° (new indication) (methotrexate) (OAA) • Vesanoïd° (new indication) (tretinoin) (RA)
1998 (n°192)	• CRIXIVAN° (indinavir) (RA)	• Cystagon° (mercaptamine) (RA) • Viagra° (sildenafil) (RA)
1999 (n°203)	(not attributed)	• Sustiva° (efavirenz) (OAA) • NorLevo° (levonorgestrel) (OAA)
2000 (n°214)	(not attributed)	• Remicade° (infliximab) (OAA)
2001 (n°225)	(not attributed)	• Estérasine° (C1 esterase inhibitor) (RA) (3) • Trolovol° (new indication) (penicillamine) (RA)
2002 (n°236)	(not attributed)	• Replagal° (agalgsidase alfa) (RA) (4) • Ceprotin°, Protexel° (human protein C) (RA) • Stromectol° (new indication) (ivermectin) (OAA)
2003 (n°247)	(not attributed)	• Carbaglu° (carglumic acid) (RA) • IVheBex° (hepatitis B immunoglobulin) (RA) • Meningitec° (conjugated meningococcal C vaccine) (OAA)
2004 (n°258)	(not attributed)	• Diacomit° (stiripentol) (OAA) • Fuzeon° (enfuvirtide) (OAA) • Morphine Aguetant° syrup (oral morphine) (OAA)
2005 (n°269)	(not attributed)	• Varivax° (chickenpox vaccine) (RA)
2006 (n°280)	• ORFADIN° (nitisinone) (B)	• Egaten° (triclabendazole) (RA)
2007 (n°292)	• CARBAGLU° (carglumic acid) (a second look) (B)	• Glivec° (imatinib) (chronic myeloid leukaemia, a second look) (RA) • Herceptin° (new indication) (trastuzumab) (OAA)
2008 (n°304)	(not attributed)	No awards for any new products or new indications
2009 (n°316)	(not attributed)	No awards for any new products or new indications
2010 (n°328)	(not attributed)	• Glivec° (imatinib) (inoperable and metastatic gastrointestinal stromal tumours, with more follow-up) (RA) see page 61
2011 (n°340)	(not attributed)	No awards for any new products or new indications

The table opposite lists the drugs along with their initial ratings in the New Products section of our French edition:
B = Bravo;
RA = Real Advance
OAA = Offers An Advantage

1- Year and issue of *la revue Prescrire* in which the annual awards were published.

2- Product no longer marketed in France, as of 5 December 2011.

3- Drug since withdrawn from the French market, because of adverse effects.

4- New data published after the inclusion of this drug on the Honours List led us to revise our rating (see French edition n°241 p. 498-499).



2011 Prescrire Drug Awards

Products evaluated during the previous year in the New Products section of our French edition are eligible for the Prescrire Awards for new drugs and indications (in 2011: issues 327 to 338).

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

This evaluation is based on rigorous procedures that include a thorough literature search, a large panel of reviewers (specific to each project) and a quality control system 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 Editorial Staff in total independence. *Prescrire* is financed exclusively by individual readers' subscriptions: 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 review articles published that year, and take into account any new data available since the initial articles were published. The rules governing the Drug Awards are available online, at english.prescrire.org.

"Therapeutic advance" is defined as better efficacy, fewer or less severe adverse effects (for similar efficacy), or safer or more convenient administration.

2011: a lean year. Once again this year, none of the new drugs we exam-

Pilule d'Or/Golden Pill Award

The "Golden Pill" award is granted to drugs that provide a major therapeutic advance for patients and healthcare professionals in a field in which no treatment was previously available.

NOT ATTRIBUTED in 2011

Honours list

Drugs included on the Honours List provide a clear advantage for some patients in comparison to existing therapeutic options, albeit with certain limitations.

NO INCLUSIONS in 2011

Noteworthy

These drugs made a modest improvement in patient care.

NONE LISTED in 2011

ined was awarded the "Golden Pill" Award (see above and page 78). In addition, for the first time since the Awards began in 1981, no new drugs or new indications for existing drugs made it to the Honours List or were even considered Noteworthy. Note that the selection criteria for the Awards have remained unchanged over these 31 years.

Three drugs nearly qualified for an award (for details, search for "ratings system" online at english.prescrire.org). Collagenases extracted from *Clostridium histolyticum* bacteria (Xiapex^o, *Prescrire Int* n° 122 pp. 285-287), and administered by local injection, may help patients with Dupuytren's disease when surgery for severe forms cannot be performed, as it reduces digital retractions in about 50% of cases. But little is known of the recurrence rate or the risk of developing autoimmune disorders in the long term.

For the treatment of vitamin E deficiency in the rare children with congenital or hereditary chronic cholestasis, oral pegylated vitamin E (*tocofersolan*)

(Vedrop^o, *Rev Prescrire* n° 333) avoids the need for painful intramuscular injections of vitamin E every 2 weeks. But its clinical assessment is inadequate, and none of the available trials used the marketed formulation of *tocofersolan*.

Mesalazine (Pentasa^o, *Prescrire Int* n° 119 p. 208), the standard anti-inflammatory salicylate, was finally authorised for the treatment of children with inflammatory bowel diseases, but the packaging is not suitable for certain children.

Running out of steam? 2011 was a dismal year for patients and healthcare professionals, given the dearth of new drugs providing real therapeutic advance.

Inadequate marketing authorisation procedures and a failing system of incentives to stimulate therapeutic advance call for urgent action from health authorities.

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2011 Prescrire Packaging Awards

The Packaging Awards focus on the quality of packaging for drugs evaluated during the previous year in the New Products section of our French edition (in 2011: issues 327 to 338).

Throughout the year, the editorial staff systematically examines the packaging of several hundred pharmaceutical products. This provides us with an opportunity to identify high-quality packaging and to detect dangerous packaging that is a potential source of confusion and errors, in order to inform our readers.

Painstaking analysis. Every aspect of the packaging is examined: the labelling on boxes, blister packs, vials, syringes; any devices provided for drug preparation or administration; caps and stoppers, and the legibility and quality of the information provided in the patient leaflet regarding the conditions of use, adverse reactions and interactions, and any recommended non-drug measures.

Independent rating. At the end of each year, the Packaging Awards are granted following a review of the year's standardised forms by the Prescrire Packaging Working Group, in total independence and with no input from drug or packaging manufacturers (rules available at english.prescrire.org).

Too many red and yellow cards in 2011. Prescrire has been examining drug packaging for three decades, representing more than 5000 packages analysed. This activity contributes to various projects, including the articles published in Prescrire, actions aimed at improving professional practice (such as the Preventing the Preventable programme at evitable.prescrire.org), and contributions to European public consultations.

This year's Packaging Awards highlight the poor overall quality of drug packaging in 2011.

The method used to prepare the Awards has remained unchanged over the years, meaning that the steady increase in the number of yellow and red cards simply reflects the state of the market. High-quality packaging is now so rare that the product to which the Packaging Award was granted in 2011 does nothing but to bring together all the basic requirements for quality packaging. The packaging in question was designed by *Établissement pharmaceutique of Assistance Publique-Hôpitaux de Paris (AP-HP) (EPHP) (a)*, which is no doubt more sensitive to the real needs of hospital practitioners than to the greed of BigPharma shareholders.

Even after France's Mediator° (*benfluorex*) scandal, health authorities are still failing to pay sufficient attention to the quality of drug packaging.

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a- EPHP is part of Ageps (Agence générale des équipements et des produits de santé) of AP-HP, Paris's public hospitals. Ageps provides various services, including evaluation and purchase of healthcare products, clinical research and development, and the manufacture and availability of drugs with marketing authorisations.



Packaging Award

• **Mexilétine AP-HP° capsules** Ageps-EHPH (*mexiletine*)

The labelling highlights information necessary to prevent medication errors, i.e. the international nonproprietary name (INN), the dosage, and the pharmaceutical form. The individual blister pockets of the blister packs are each labelled and precut (a). The packaging promotes correct preparation of the drug in daily practice, whether in the hospital or not.

a- A unit-dose blister pack is defined by the labelling of each blister pocket with the INN, the dosage, the pharmaceutical form (or the route of administration), as well as the batch number and the expiry date.



Yellow cards

(in alphabetical order)

• **Diarfix° capsules** Cristers (*racecadotril*) (Rev Prescrire n° 328)

• **Grazax° oral lyophilisates** Alk Abelló (*allergenic extract of Timothy grass pollen*) (Rev Prescrire n° 328)

• **Hexaquine° tablets** Du Gomenol (*quinine + thiamine*) (Rev Prescrire n° 337) (a)

• **Levofree° single-dose eyedrops** Chauvin (*levocabastine*) (Rev Prescrire n° 328). The printing on Levofree° single-dose units is easily rubbed off.

• **Lovavulo° Gé tablets** Codépharma (*ethinylestradiol + levonorgestrel*) (Rev Prescrire n° 327). Lovavulo° Gé blister packs mention the INN but in tiny, poorly legible characters.

The primary packaging (blister pack or single dose units) for these products does not clearly mention the name of the active ingredient.

• **Septidose° Gé unit-dose cutaneous solution** Neitum (*chlorhexidine*) (Rev Prescrire n° 336)

The route of administration is not clearly mentioned on the front of the box, even though confusion over the route of administration has been reported with other single-dose units containing various products used to treat infants. The packaging includes an obscure pictogram that is supposed to indicate the age of the patients.

a- The company announced that a label including the INN but accompanied by a much bigger brand name will be added, see Rev Prescrire n° 340 p. 156.



Red cards (by type of packaging defect, and then in alphabetical order)

Bulk bottles with potentially fatal contents:

- **Imeth° 10-mg tablets** Nordic Pharma (*methotrexate*) (Rev Prescrire n° 331)
- **Méthotrexate Bellon°** 2.5-mg tablets Sanofi Aventis (*methotrexate*) (Rev Prescrire n° 331)
- **Novatrex°** 2.5-mg tablets Pfizer (*methotrexate*) (Rev Prescrire n° 331)

Bulk bottles for these 3 products lack a child-proof safety cap, creating a risk of ingestion of a tablet that has accidentally fallen out of the bottle, and accidental ingestion of a lethal dose by a child (a).

a- The company stated that the risk was negligible compared with that of overdose due to dosing error, see Rev Prescrire n° 340 p. 156.

Patient leaflets that fail to provide adequate information to pregnant women and thus endanger their unborn children:

- **Adviltab rhume° tablets** Pfizer Santé Familiale (*ibuprofen + pseudoephedrine*) (Rev Prescrire n° 332)
- **Antarène Codéine° tablets** Élerté (*ibuprofen + codeine*) (Rev Prescrire n° 332)
- **Bi-Profénid° LP tablets** Sanofi Aventis (*ketoprofen*) (Rev Prescrire n° 327)
- **Compralfène° gel** Gifrer Barbezat (*diclofenac*) (Rev Prescrire n° 336)
- **Flector Tissugel Héparine° plasters** Genévrier (*diclofenac + heparin*) (Rev Prescrire n° 329)
- **Nifluril Enfants° suppositories** Bristol-Myers Squibb (*morniflumate*) (Rev Prescrire n° 336)
- **Profémigr° tablets** Sanofi Aventis (*ketoprofen*) (Rev Prescrire n° 327)
- **Tendol° gel** Népentès (*diclofenac*) (Rev Prescrire n° 336)
- **Voltarène Enfant° suppositories** Novartis Pharma (*diclofenac*) (Rev Prescrire n° 338)

The labelling of these nine nonsteroidal anti-inflammatory drug (NSAID)-containing products states that they are only contraindicated from the sixth month of pregnancy. The labelling fails to stipulate there is an increased risk of miscarriage and malformations with exposure in the first trimester, as well as life-threatening renal and cardiovascular fetal toxicity after NSAID exposure during the second trimester.

Paediatric suppositories examined in 2011 may be mistakenly used by pregnant women who are falsely reassured by their indication for paediatric use.

Contradictory dosing schedules on the boxes:

- **Colokit° tablets** Mayoly Spindler (*sodium phosphates*) (Rev Prescrire n° 329)
- The outer packaging includes a two-box treatment schedule with the words "date" and "hour" in the singular, whereas the 32 tablets must be ingested in eight sequences, each with 250 ml of water; this creates a source of confusion in the preparation and administration of this product, thus increasing the risk of adverse effects with this laxative (including life-threatening electrolyte disorders (b)).

b- According to the company, details about dosing schedules should be given during the visit prior to colonic investigation. Also a risk management plan is underway, see Rev Prescrire n° 340 p. 156.



Paediatric packaging unsuitable for children:

- **Picoprep° sachets of powder for oral solution** Ferring (*sodium picosulfate + magnesium oxide + citric acid*) (Rev Prescrire n° 330)
- There is no specific paediatric dosage or packaging: the labelling states that children under 9 years old should receive one-half or one-quarter of a sachet, creating a risk of dosing errors and adverse effects of laxatives (including life-threatening electrolyte disorders) (c).
- **Cozaar° preparation for oral suspension** Merck Sharp & Dohme (*losartan*) (Rev Prescrire n° 329)

Multiple sources of error during preparation of this product for hypertensive children, due to:

- The excess volume (273 ml) of solvent, and the excess capacity (40 ml) of the bottle provided for the reconstituted suspension;
- The need to "shake before use" is not mentioned on the bottle, but only on the patient leaflet; this can result in a solution that is not sufficiently homogeneous.
- The oral syringe is graduated in millilitres, representing a potential source of error when converting the prescribed dose (in mg) to the required volume (in ml).

c- The company announced that dosing spoon will be available in 2012, see Rev Prescrire n° 340 p. 156.

Adult medicines too readily accessible to children:

- **Humex toux sèche oxoméazine° syrup and oral solution** Urgo (*oxomemazine*) (Rev Prescrire n° 337)
- No child-proof safety cap is provided; the label represents what looks like a cream dessert, a starry night and a moon; and the graduated cups carry a risk of overdose.
- The multiple flaws of this self-medication product, part of an umbrella brand, create a risk of preventable overdose and misuse (for insomnia), especially in children.
- **Bipreterax° tablets** Servier (*perindopril arginine 10 mg + indapamide 2.5 mg*) (Rev Prescrire n° 327)
 - **Buccosoin° mouthwash solution** Merck Médication Familiale (*chlorhexidine + chlorobutanol, 42.8% ethanol*) (Rev Prescrire n° 335)
 - **Célestamine° tablets** Merck Sharp & Dohme (*betamethasone + dexchlorpheniramine*) (Rev Prescrire n° 331)
 - **Dolko° oral solution** Therabel Lucien (*paracetamol*) (Rev Prescrire n° 334)
 - **Eludrilpro° mouthwash solution** Pierre Fabre Médicament (*chlorhexidine + chlorobutanol, 42.8% ethanol*) (Rev Prescrire n° 338)
 - **Euphonyll toux sèche dextrométhorphane° syrup** Mayoly Spindler (*dextromethorphan*) (Rev Prescrire n° 330) (d)
 - **Flucalyptol toux sèche pholcodine° syrup** Zambon (*pholcodine*) (Rev Prescrire n° 327)
 - **Primalan° syrup** Pierre Fabre Médicament (*mequitazine*) (Rev Prescrire n° 337)
 - **Primpéran nourrissons et enfants° and Primpéran enfants° paediatric oral solutions** Sanofi Aventis (*metoclopramide*) (Rev Prescrire n° 328)

There is no child-proof safety cap on the bottles of these 10 products, creating a risk of overdose in children. Overdose exposes them to the adverse effects of the drugs concerned or their excipients (high ethanol concentration), including cardiovascular, hepatic and neurological disorders, depending on the substance ingested.

d- According to the company, a "feasibility study" for a safety cap will be conducted, see Rev Prescrire n° 340 p. 156.



2011 Prescrire Information Awards

The Information Awards focus on the quality of the information provided to *Prescrire* by the pharmaceutical companies whose products we examined in the New Products section of our French edition during the previous year (in 2011: issues 327 to 338).

Prescrire's reviews dealing with new drugs and indications are based on a thorough literature search for documents relating to the drug's pre-approval assessment, especially clinical trial reports.

In addition to textbooks and bibliographic databases, *Prescrire* editors search the websites of drug regulatory agencies, health economics institutions, health technology assessment agencies and other institutions specialising in the relevant therapeutic field. *Prescrire* regularly asks drug regulatory agencies to provide specific information and unpublished documents. We also search other independent journals belonging to the International Society of Drug Bulletins (ISDB), and any independent institutions that have evaluated the drug in question.

Assessing drug company transparency. We also request relevant information from the companies that market each drug we analyse in France, to ensure that we take into account all data, including unpublished data, used to justify marketing approval or to modify an existing marketing authorisation. These unpublished data such as expert reviews and Periodic Safety Update Reports or PSURs are held both by the regulatory agency that examined the application and by the company that obtained marketing authorisation for its product.

As is the case with the other *Prescrire* Awards, a systematic and totally independent process is used to grant the Information Awards (rules available on our website, at english.prescrire.org).

Rewarding accountable companies. Some drug companies respond to our requests for information in a timely manner and provide us with thorough and relevant data, including unpublished data. These companies are mentioned on the Honours List.

The companies rated as "Outstanding" provided us with exhaustive and detailed information without delay, sometimes without being asked.

Honours List (in alphabetical order)

- Outstanding: **Janssen-Cilag**
- Followed by: **Arrow Génériques, Chauvin, Kreussler Pharma, Mylan, Novex Pharma, Orphan Europe, Shire**



Red Cards (in alphabetical order)

- **Allergan, Bayer Schering, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Eisai, Ipsen Pharma, Menarini, Panpharma, Servier**



What do unhelpful companies have to hide? Other drug companies either fail to respond to our requests for information or provide only limited data. Some of them tend to delay their response as long as possible, i.e. only after publication of the opinion of the French Transparency Committee (that assesses the comparative effectiveness of new drugs and provides advice on drug reimbursement), or of the price in the *Journal Officiel*, or after the launch of their advertising campaign. They may also omit the most relevant data, claiming they are too busy, that the administrative services are too slow, that the clinical data are confidential, or that their headquarters raise objections. Other companies withhold information as a form of retaliation because they did not like one of our earlier product reviews.

"Red cards" for withholding information are a way of highlighting persistent shortcomings in the provision of information by certain drug companies and a way of encouraging more openness.

2011, following France's Mediator° scandal: a visible effort by some companies. The Mediator° (*benfluorex*) scandal alerted the French public that withholding information about drug adverse effects was unacceptable. Some companies, including some that were awarded "Red Cards" in the past, expressed their desire for change and even proposed to meet with the *Prescrire* team in order to better understand the nature of the information we expect to receive in response to our requests.

These meetings provided an opportunity to explain the *Prescrire* literature search methodology, which aims to take into account all evaluation data, and to highlight that transparency is important for pharmaceutical companies. A drug company's transparency is one of several criteria to be considered when choosing a drug, after efficacy, adverse effects, convenience and price.

In 2011, we noticed encouraging signs of more openness from some companies, which could ultimately benefit *Prescrire's* subscribers and their patients, but it is too early to measure their real impact.

Watch this space in 2012.

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Whenever we examine a new drug or indication, the review is accompanied by one of four pictograms rating the transparency of the company concerned for their response to our request for information about their product (for details search for "ratings system" online at english.prescrire.org).

