Adapted from ***Rev Prescrire*** **December 2004; 24 (256): 859-864**

Comparative advantages of new drugs: French authorities are not sufficiently demanding

- **We evaluate the therapeutic advantages of new drugs marketed in France in order to help prescribers and patients with day-to-day treatment choices.**
- **In France, the pharmacoeconomic Committee (*Commission de la Transparence*) assesses the medical benefits of new drugs in order to guide reimbursement policy.**
- **Two studies have compared pharmacoeconomic Committee ratings with *Prescrire*'s own ratings during the periods 1993-1998 and 1999-2004. More than 600 drugs and indications were examined, and the two studies presented consistent results.**
- **Overall, the pharmacoeconomic Committee is less demanding than *Prescrire* and is less concerned with convenience of use. *Prescrire*'s ratings are based on an explicit literature search and a systematic rating system; they also take convenience of use into account (including packaging quality), and their ratings are reached independently from the pharmaceutical industry. *Prescrire* also evaluates drugs not under consideration for reimbursement.**

The market is flooded with "new" drugs, only a few of which offer patients a tangible therapeutic advantage over existing alternatives.

Since 1981, *la revue Prescrire*, the French edition of this bulletin, has sought to provide health professionals with reliable information on which to base treatment choices. Each issue contains reviews of all available clinical data on new drugs. These review articles also feature an at-a-glance 6-level rating system for the degree of therapeutic advantage provided by the new product as compared to existing alternatives, ranging from "Bravo" to "Not acceptable" (see p. 50).

The French government is also interested in rating new drugs, if only for economic reasons. Two lists of drugs exist: those approved for use in health care institutions, and those that are reimbursed through social security. Drugs are included in these lists if the pharmacoeconomic Committee provides a favourable opinion (1,2). These opinions include an assessment of medical benefits, rated on a 6-level scale. The pricing committee also takes these ratings into account when negotiating the reimbursable price of a new drug.

This article examines the results of the two studies comparing the pharmacoeconomic Committee's ratings with those of *la revue Prescrire*.

Pharmacoeconomic Committee: an opinion aimed at government and based on company data

The methods used by *la revue Prescrire* to evaluate new medicines are fully transparent. They are described in the journal and on the Prescrire website, and are summarised in the inset on page 76.

The Committee's approach is somewhat different. According to French law, the Committee includes (our translation):
"1) Twenty permanent members with voting powers, appointed by the ministers of health and social security for twice-renewable three-year terms: a) a president; b) two vice-presidents; c) 17 permanent members chosen for their scientific expertise;
2) six substitute members, appointed similarly to permanent members, who have an advisory role at meetings and are called on, in the order of their nomination, to replace permanent members".

The Committee also includes "eight members with an advisory role, including health insurance representatives and a representative of the pharmaceutical industry".

Funding and transparency? The 2003 annual report of the French medicines agency provides no information on the operating budget of the pharmacoeconomic Committee (3). The Committee's rules were not available on the Agency's website as of October 2004.

Conflicts of interest managed case by case. According to French law, "*members of the Committee (…) and rapporteurs must provide the secretariat with a declaration mentioning any direct or indirect links they have with marketing authorisation holders, companies whose products may be examined by the Committee, and professional organisations operating in the pharmaceutical sector. They must undertake to report any changes in these links. These declarations are published in the Official Journal of the Ministry of Social Security.*

Members of the Committee cannot take part in discussions or votes if they have an indi- ▶▶

SURVEY

Prescrire's ratings: by health professionals for health professionals, to the benefit of patients

Our rating system, with its accompanying figure, offers an at-a-glance appraisal of all newly approved drugs in France (except for products used in general anaesthesia and diagnostics) and new indications evaluated in our New Products column. *La revue Prescrire* also examines drugs for which the companies concerned are not seeking social security refunding.

Six-level rating. The principles underlying our 6-level rating system are published in each issue (see p. 50): the first five are "bravo", "offers an advantage", "possibly helpful" "nothing new", and "not acceptable", while the sixth, "judgement reserved", indicates that the editorial team cannot reach a firm opinion for want of relevant data.

This judgement focuses on tangible benefits perceived by the patients in a well defined clinical use, i.e. the absolute value (benefits versus harm balance) based on a thorough analysis of adverse effects; and the relative value compared to other available treatments. Convenience of use is also taken into account.

The sale price is not taken into account in our rating system, as it is a negotiable element. We comment on the price, however.

The ratings are an integral part of the editorial process, following precisely the same collective process as the other parts of the review article.

Explicit methods. Our articles dealing with new drugs are subject to exactly the same methods as the Journal's other review articles. Our website (www.Prescrire.org) describes the editorial team collective work, the documentation search, in-house and external quality controls, and the choice of independent reviewers (each article is reviewed by 10 to 40 multidisciplinary health professionals) (see Prescrire Int 72, page 155 for details on our review panel).

Each issue also carries the names of the section editors and reviewers (see the back cover of this issue, for example).

Intellectual and financial independence. *Prescrire*'s articles are free of any influence by the pharmaceutical industry, thanks to strict and transparent collective editorial procedures, multiple quality controls, and a policy of zero conflict of interest with the pharmaceutical industry for our editors.

In addition, *la revue Prescrire* and *Prescrire International* are financed solely by their subscribers, carry no advertising whatsoever and receive no subsidies. It is published by a not-for-profit body, *Association Mieux Prescrire*; and the accounts are published each year in the March issue of our French edition *la revue Prescrire* [June issue of Prescrire International].

A thorough literature search. The literature search strategy is summarised at the end of each article, and always includes prospective screening of specialist journals; routine consultation of textbooks, independent bulletins and the websites of the American and European medicines agencies, the UK National Institute for Clinical Excellence, etc.; systematic search of bibliographical databases (well beyond Medline), and repeated questioning of the company concerned by a specialised editorial team (this is the only input requested from companies).

All statements are referenced. The reference lists are available to subscribers for at least 5 years (currently since Rev Prescrire issue 191) on request from our reference service.

1- Prescrire Editorial Staff "2003 Prescrire financial report" *Prescrire Int* 2004; **13** (71): 115.

► *rect or direct interest in the affair in question"* (**a**).

The timetable of Committee meetings, the agendas, and the minutes of past meetings were unavailable on the Agency's website (up to October 2004).

Opinions based on information submitted by the company, and reviewed by the company. In practice, the Committee bases its opinions on data supplied by manufacturers in support of their marketing applications. Its opinions are rarely referenced. No literature search is mentioned.

The Committee judges the degree of therapeutic advantage by *"taking into account the efficacy and tolerability of the new drug relative to available comparable drugs"* (2). Moreover, *"the company may, within eight days of receiving this opinion, ask to be heard by the Committee or present its written comments. The Committee may modify its opinion in light of these comments"*. Since 2001, the Committee's final opinions have been available on the Agency's website (4).

A six-level rating system. According to internal rules drawn up in 1990, the medical benefits can be graded on one of six levels:

"I-Major therapeutic advance;
II-Substantial improvement in efficacy and/or safety;
III-Modest improvement in efficacy and/or safety;
IV-Marginal improvement in efficacy and/or usefulness:
– in clinical terms: acceptability, convenience of treatment, compliance;
– a justified line extension;
– a potential advantage linked to pharmacokinetic properties or to a lower risk of drug interactions;
V-No advantage, but inclusion approved (2,5).
VI-Inclusion on list not recommended".

Initially hard to access

The pharmacoeconomic Committee was not explicitly required to publish its opinions for many years. Since 1996 sales representatives have been required to provide doctors with the most recent published Committee's opinions with all verbal presentations on new drugs (**b**)(6). Opinions reached before 2001 are not available on the website of the French medicines agency.

In 2001, a team in Bordeaux, France, compared Prescrire's ratings with the pharmacoeconomic Committee's ratings for the period 1993-1998 (7).

Among the 414 drugs rated by *la revue Prescrire*, 278 were also rated by the Committee. *Prescrire*'s rating was "judgement reserved" in 14 cases (not included). For the remaining 264 drugs, *Prescrire* and the Committee's judgements were identical in 105 cases, the Committee's rating was more favourable in 137 cases and less favourable in 22 cases (see table p. 78).

The ratings differed by two levels in 37 cases, three levels in six cases, and four levels in three cases. In only three cases (not specified) was the Committee's rating less favourable than Prescrire's.

The authors of this study stated that, in some cases (not specified), the Committee rated a drug more favourably solely on the basis of its indication, without considering the existence of similar treatment alternatives. The authors also pointed out that the time lag between the two ratings was highly variable (generally a few months), but that this did not appear to explain the discrepancies.

1999-2004: more accessible data

In March 1999 (issue 193), *la revue Prescrire* began to include, whenever possible, the pharmacoeconomic Committee's ratings in its reviews of new drugs.

A 5-year comparison. We were therefore able to compare the evaluations of new drugs and new indications featured in *Prescrire*'s reviews of "new products for ambulatory use" and "new products for hospital use" from March 1999 to February 2004 (French edition n°193 through n°247).

The following types of reports were excluded from this comparison: those subtitled "a second look" (except when the review also referred to an initial assessment published during the 5-year study period); drugs with temporary marketing authorisation (except when this was followed by full marketing authorisation, and when the drug was evaluated by the Committee); and drugs for which the company had not requested reimbursement.

Occasionally, the Committee's rating was not known when *Prescrire* went to press. If we subsequently reported the Committee's rating (as required by our editorial policy) and if the Committee's rating was also made available on the French medicines agency's website, we included the comparison. The literature search ended on 10 October 2004.

Linguistic problems in the Committee's ratings. Several problems arose when we attempted to interpret the pharmacoeconomic Committee's ratings.

Some ratings mentioned therapeutic advantages but did not provide a precise rating. We attempted whenever possible to overcome these ambiguities by rating the medical benefits as follows: a) the word "contribution" was considered to signify "improvement"; b) we noted the presence in the ratings of key qualifiers used to define the medical benefit levels: for example, language such as "*the benefit for patients… is important*" was considered to correspond to a level II rating, while "*considering the lack of alternative treatments, this drug meets a major need*" was rated as level I. In contrast, the statement or phrase "*occupies an important place*" could not be translated into a Committee rating, because it simply suggests a benefit without referring to existing therapeutic options.

In other ratings the Committee uses an odd concept of "*shared level of medical benefits*". We interpreted this to represent a lack of improvement as compared with existing treatment options. Some Committee ratings contained different ratings of therapeutic advantages for comparisons to different treatments. Whenever possible we chose the rating relative to what we considered as the reference treatment in our review article.

Too many missing or inconclusive ratings. 359 *Prescrire* evaluations were included (see table p. 78). *Prescrire* rated "judgement reserved" in 22 cases, and "unacceptable" in another 26 cases.

In 62 of these cases the Committee either provided no opinion or no rating in terms of therapeutic advantages. In one case (etanercept in rheumatoid arthritis) the Committee expressed disagreement with a product's approved indication: "For patients not previously treated with methotrexate and who have no contraindications to methotrexate, available data and uncertainties for long-term safety do not allow us to recommend routine first-line use of etanercept" (Prescrire Int 66).

The Committee and *Prescrire*'s evaluations were identical in 106 cases (30%) (**c**). The Committee was less favourable in 13 cases, with a rating difference of only one level in every case. The Committee was more favourable in 168 cases, with a rating difference of one level in 78 cases, two in 64 cases, three in 23 cases and four in three cases.

These figures must be interpreted with caution, because the precise rating difference depends on our interpretation of some of the Committee's opinions. Thus, in the case of glatiramer (Prescrire Int 69), the Committee stated that "*glatiramer has similar therapeutic advantages to interferons (level I)*". In contrast, *Prescrire* pointed out that "*glatiramer, unlike interferon beta-1a, does not delay the onset of disability (...), and is no better tolerated*"; and also that "*it exposes patients to serious adverse effects, and is less convenient to use*"; we therefore rated this preparation "Not Acceptable". The difference between ratings was thus maximal if the Committee's rating is considered to be level I, but far smaller if therapeutic advantages are considered to be "shared".

***Prescrire* more favourable in about 4% of cases.** In 13 (4%) of the 359 cases, *Prescrire* rated the contribution of the new drug more favourably than the pharmacoeconomic Committee.

In four cases we found an efficacy advantage: naratriptan; hepatitis A vaccine, valaciclovir in CMV disease; and etanercept in second-line treatment of rheumatoid arthritis.

In four cases convenience of use was improved: tinzaparin in pulmonary embolism; oral granisetron; follitropin beta, and valaciclovir in herpetic keratitis.

Three drugs provided an advantage in both efficacy and convenience: pamidronic acid in Paget's disease; bisoprolol in heart failure; and peginterferon alfa-2.

In two cases *Prescrire* found a safety advantage: lamotrigine and memantine.

Nearly half of *Prescrire*'s ratings that were higher than the Committee's were based on greater convenience of use. Note that we systematically examine the packaging of all new drugs (see our yearly packaging awards for new products) (8,9).

Committee's ratings 3 or 4 points higher in 7% of cases. In 90 cases (25%) Committee's ratings was at least two levels higher than *Prescrire*'s ratings.

In 26 cases (7%) the Committee's ratings were far more favourable than *Prescrire*'s, with a difference of 3 or 4 levels.

In two cases the Committee gave a level III rating (modest or moderate advantage), while *Prescrire* judged both drugs as "Not Acceptable". Both drugs were antibiotics with a higher potential for adverse effects than related substances, with ▶▶

a- Declared interests are published and revised annually in a document containing the declarations of all task force and members of the French medicines agency. The 2003 edition is available on the Agency's website, together with the names of pharmacoeconomic Committee members (refs 10,11).

b- Prescrire's sales rep monitoring network shows that this document is rarely offered spontaneously (4% of visits in 1998-2002) (ref 12).

c- In 83 of these 106 cases the level was V.

SURVEY

Pharmacoeconomic Committee vs *la revue Prescrire*'s ratings - 1993-1998 (ref 7)

Prescrire's rating	Committee's rating level of improvement	Number of Prescrire's rating (%)	Number of Committee's rating (%)
Bravo	I (major advance)	0	19 (7 %)
A real advance	II (substantial)	9 (3 %)	30 (11 %)
Offers an advance	III (modest)	29 (11 %)	40 (15 %)
Possibly helpful	IV (marginal)	73 (28 %)	79 (30 %)
Nothing new	V (none)	153 (58 %)	96 (37 %)
Not acceptable	VI	— (**a**)	— (**a**)
Total	**—**	**264 (100 %)**	**264 (100 %)**

a- The authors excluded the 'Not acceptable' rating from *Prescrire*.

Pharmacoeconomic Committee vs *la revue Prescrire*'s ratings - 1999-2004

Prescrire's rating	Committee's rating level of improvement	Number of Prescrire's rating (%)	Number of Committee's rating (%)
Bravo	I (major advance)	0	38 (11 %)
A real advance	II (substantial)	10 (3 %)	52 (14 %)
Offers an advance	III (modest) (**a**)	44 (12 %)	59 (16 %)
Possibly helpful	IV (marginal)	93 (26 %)	43 (12 %)
Nothing new	V (none)	164 (46 %)	104 (29 %)
Judgement reserved	0	22 (6 %)	38 (11 %) (**b**)
Not acceptable	VI	26 (7 %)	1
Avis non disponible	—	—	24 (7 %)
Total	**—**	**359 (100 %)**	**359 (100 %)**

a- In this period the word "moderate" was most often used for level III.
b- The Committee stated it could not give a rating in 19 cases: the opinion included no section on the medical benefit, or some vague comments (see text).

► no evidence of greater efficacy: telithromycin (drug interactions) and moxifloxacin (cardiac arrhythmias).

Strength of evidence. In three cases the Committee gave the highest rating (level I), whereas *Prescrire* considered the drugs to be "Nothing New".

One case was a conjugate vaccine against group C meningococci: the Committee awarded a level I rating to the three vaccines launched in 2001, while *Prescrire* praised the best-assessed of the three and considered the other two to offer no relative advantages.

In another case the rating difference was due to different interpretations of a clinical trial: the Committee stated that the HOPE trial indicated a "major" benefit for ramipril in patients with cardiovascular risk factors similar to those included in this trial, whereas *Prescrire* stated that no benefit had been shown in the subgroup of non-coronary diabetic patients.

The interpretation of a clinical trial also explained disagreements on verteporfin in occult age-related retrofoveolar macular degeneration: the Committee stated that "*the level I medical benefit is confirmed*" in this new indication, whereas *Prescrire* stated that the evidence was weak (improvement in visual acuity measured in a minority of patients in one subgroup in only one trial, with no evidence of an impact on daily life).

In 10 cases the Committee rated the product level I, whereas *Prescrire* considered it only "Possibly helpful". These differences usually reflected the Committee's reliance on surrogate outcomes or weak levels of evidence. This was the case in three evaluations of cancer treatments and once in a new indication for verteporfin (high myopia). For example, the Committee rated epoetin beta in oncology as level I, based on two unblinded trials showing a reduction in the number of patients requiring transfusion; however, there was no advantage over epoetin alfa, whose effects on quality of life or prevention of anemia are not documented.

The Committee awarded a level I rating in 12 cases, while *Prescrire* concluded the drugs provided "Nothing New", because of the weakness of the evidence. Four of these were cancer treatments.

Oncology: gaps and inadequacies. Anticancer drugs represented about 13% of all new products rated by *Prescrire* from 1999-2003. These drugs accounted for about 30% of cases in which *Prescrire* and the pharmacoeconomic Committee's ratings differed by three levels. Additionally, 20% of preparations not rated by the Committee were anticancer drugs.

Some opinions are clear cut, such as that for trastuzumab: "*considering the lack of information on survival and quality of survival during monotherapy, the absence of data in combination with other anticancer drugs such as paclitaxel, and its cardiotoxicity, it is difficult to situate Herceptin*". Other cases concerned new uses for hospital-approved drugs for which the Committee was not asked to give a new opinion (for example, paclitaxel in lung cancer).

The rating differences were greater for cancer treatments than in other medical fields.

Differences in timing did not influence results. The timing of evaluations did not appear to account for differences in results.

On average, the Committee's ratings preceded publication of *Prescrire*'s ratings by about one year. The interval was longer, on average (about 1.5 years), when the two ratings were similar, and shorter when *Prescrire*'s rating was more favourable (about 10 months) or much less favourable (about 10 months).

In all these categories the difference in timing was highly variable, with *Prescrire* rating drugs as much as 3 years prior to or as much as 13 years later than the Committee. For example, *Prescrire* examined the data on mycophenolate mofetil in cardiac transplantation in July 1999, and the Committee in December 2002. In contrast, *Prescrire* rated the atenolol + chlortalidone combination in 2000, shortly after the product was first marketed, but 12 years after the Committee released its rating.

The case of the coxibs clearly illustrates the lack of influence of the time interval on the difference in ratings. *Prescrire* rated rofecoxib as "Nothing New" in the treatment of osteoarthritis in July 2000. The

Committee rated this indication at level III in August 2000, then level IV in June 2004, before marketing authorisation was withdrawn in September 2004. For celecoxib, the ratings were the same as for rofecoxib; the dates were December 2000 for *Prescrire* and October 2000 (then June 2004) for the Committee. In the case of parecoxib, *Prescrire*'s rating was "Nothing New" in February 2004, and the Committee's rating was "no advantage" in September 2003.

Conclusion: the French pharmacoeconomic Committee is less demanding than Prescrire

Overall, the pharmacoeconomic Committee appears to be less demanding than *Prescrire* when it comes to assessing the evidence for therapeutic advantages.

Prescrire's ratings are based on a sound, systematic and transparent search strategy and an analysis totally independent of the pharmaceutical industry. *Prescrire*'s conclusions are generally in keeping with those of other independent bulletins, as shown in the "Opinion Elsewhere" section of review articles on new drugs. In addition, *Prescrire* gives more weight than the pharmacoeconomic Committee to convenience of use as a determinant of therapeutic advantage.

The Committee's rating is an important factor in drug price negotiations. During the period 1999-2004, the pharmacoeconomic Committee's opinions were often ambiguous and inconclusive. The routine practice of submitting opinions to manufacturers before publication may have contributed to these ambiguities, and to differences between the Committee and *Prescrire*'s evaluations. These differences almost always favoured the new drug.

These two studies help to identify factors that might improve the pharmacoeconomic Committee's performance: Committee members should be highly competent and independent of the pharmaceutical industry; high-quality independent documentary resources should be made available to the Committee; closer attention should be paid to drug packaging and conditions for use; a clear cut rating should be attributed to each product (even when the company does not seek social security reimbursement); and there should be rapid publication of the Committee's rating, independent from drug company endorsements.

The authorities should take these ratings into account when negotiating sale prices and reimbursement levels. They must also acknowledge the economic and health benefits to be derived from including the notion of therapeutic advantage in decisions regarding marketing approval.

Selected references from Prescrire's document watch.

1- Prescrire Rédaction "Médicaments hospitaliers. À quoi sert l'agrément aux collectivités" *Rev Prescrire* 2000; **20** (202): 68-71.
2- Prescrire Rédaction "Amélioration du service médical rendu (ASMR)" *Rev Prescrire* 1997; **17** (174): 425.
3- Agence française de sécurité sanitaire des produits de santé "Rapport annuel 2003" Saint-Denis 2004: 140 pages.
4- Prescrire Rédaction "Avis de la transparence: sur le site de l'Afssaps" *Rev Prescrire* 2001; **21** (222): 752.
5- Avouac B "L'évaluation du service médical rendu. Une nécessité pour la Commission de la Transparence" *Thérapie* 1992; **47**: 9-16.
6- Prescrire Rédaction "Nouveau décret sur la publicité" *Rev Prescrire* 1996; **16** (166): 695.
7- Dangoumau J et al. "L'évaluation des médicaments en France: comparaison de deux approches" *Thérapie* 2001; **56**: 307-314.
8- Prescrire Editorial Staff "Packaging awards 2003" *Prescrire Int* 2004; **13** (70): 62.
9- Prescrire Editorial Staff "Drug packaging: stil too many problems in 2003" *Prescrire Int* 2004; **13** (71): 112-113.
10- Agence française de sécurité sanitaire des produits de santé "Les déclarations d'intérêts des membres des conseils, commissions et groupes de travail 2003". Website http://www.afssaps.sante.fr consulted on 10 October 2004.
11- Agence française de sécurité sanitaire des produits de santé "Composition nominative de la Commission de la transparence - mise à jour: 02 octobre 2003". Website http://www.afssaps.sante.fr consulted on 10 October 2004.
12- Prescrire Editorial Staff "prescrire sales reps monitoring network" *Prescrire Int* 2003; **12** (66): 153 and (67): 197.