"Orphan" drug status: abuse of incentives

In 2015, we noticed a sharp increase in the number of new drugs or indications authorised with "orphan" drug status, increasing to 17 in 2015 from only 6 in 2014 and 9 in 2013.

Orphan drug status has been recognised in the European Union since 2000. The aim was to encourage the development of drugs for patients with rare diseases (mostly genetic), defined as 5 or fewer cases per 10 000 inhabitants (Rev Prescrire n° 380, 382). There are about 6000 or 7000 known rare diseases worldwide, affecting tens of thousands of people in total.

Regulatory and financial advantages. Companies that develop "orphan" drugs enjoy significant benefits, including an accelerated marketing authorisation (MA) process, an often limited application dossier (conditional authorisation, mainly bibliographic data) and a 10-year market monopoly.

"Orphan" drugs offer companies other financial incentives. Clinical trials are small and therefore generally less costly. Very high prices can be demanded because there is no therapeutic alternative and the patient population is small, greatly limiting health insurers' bargaining power. And marketing costs are lower because only a handful of specialists are likely to prescribe the drug.

Abuse. The past 15 years have seen the emergence of a vigorous "orphan" drug market, but patients have not always benefited. Some "orphan" drugs should even be avoided. Examples in 2015 include: *defibrotide*, a drug with uncertain utility in hepatic veno-occlusive disease (Prescrire Int n° 164); and *cabozantinib and sorafenib* (Prescrire Int n° 167, 168), two tyrosine kinase inhibitors that are more dangerous than beneficial in patients with thyroid cancer.

Some companies focus exclusively on very narrow markets or on niches abandoned by previous players. Thus, a year after the approval of Orphacol® (*cholic acid*) for two rare bile acid deficiencies, an EU marketing application was filed for Kolbam® (*cholic acid*) in three other rare bile acid deficiencies (Rev Prescrire n° 386). *Cholic acid*, which is extensively used as a food emulsifier, costs between 139 and 175 euros for a single 250-mg capsule in France depending on the product, despite the virtual lack of clinical studies.

Some "orphan" drugs are eventually authorised in several indications, expanding market share but not leading to significant price cuts. For example, *lenalidomide* is authorised in some forms of multiple myeloma and myelodysplastic syndromes (Prescrire Int n° 160), while *pasireotide* is authorised in Cushing's syndrome and for acromegaly in treatment failure (Prescrire Int n° 168).

Some rare diseases draw the attention of several drug companies. In 2015, two more vasodilators, *riociguat* and *macitentan*, were authorised for pulmonary hypertension, even though they have no advantages over *bosentan* or *sildenafil* (Prescrire Int n° 165, Rev Prescrire n° 379, 381). Similarly, two anti-CD20 monoclonal antibodies, *obinutuzumab* and *ofatumumab*, were authorised for the treatment of chronic lymphocytic leukaemia, even though they lacked any decisive advantages over *rituximab*, another anti-CD20 monoclonal antibody that has been available for many years (Prescrire Int n° 165).

In summary. The development of drugs with a favourable harm-benefit balance for patients with rare diseases and no other therapeutic options is clearly welcome. However, the overall dynamics of drug research is changing as companies seek to maximise profits by devoting more and more of their resources to "orphan" diseases. Companies know that this strategy allows them to demand exorbitant prices and to exert pressure on the authorities to reduce regulatory requirements. And that is a far cry from research designed to address the healthcare needs of the entire population.

▸ combination were comparatively evaluated in only 155 patients, even though an estimated 170 million patients worldwide have chronic hepatitis C. The European Medicines Agency (EMA) was particularly lax, taking these minimal data at face value and inferring that this antiviral combination had barely more adverse effects than placebo! (1)

Postmarketing discovery of serious harms. Marketing authorisation, even when based on very fragile clinical data, is rarely challenged once the drug is on the market. Yet knowledge about adverse effects accumulates during routine use. If an initially uncertain harm-benefit balance turns out to be clearly unfavourable, the drug should be withdrawn from the market. Unfortunately, regulators and governments rarely rise to the challenge.

For example, in 2015, cases of severe hyponatraemia were attributed to *aliskiren*, a renin-inhibiting antihypertensive drug that has no proven impact on the complications of hypertension but was linked to cardiovascular events and cases of renal failure in a placebo-controlled trial (Prescrire Int n° 166).

Some glucose lowering drugs with unproven efficacy on the complications of diabetes have been found to have serious, disproportionate adverse effects, including: intestinal obstruction and disabling joint pain with gliptins; and ketoacidosis (especially in patients with type 2 diabetes) with gliflozins (Prescrire Int n° 167, Rev Prescrire n° 386).

Because adverse effects are often poorly documented when marketing authorisation is initially granted, and because health authorities are overly lenient towards drug companies, it is up to patients and health professionals to report all possible adverse effects to their national pharmacovigilance networks in order to identify and prevent serious harms. It is also important to ensure, through collective action, that drugs with an unfavourable harm-benefit balance are not used.

Exorbitant prices endanger access to healthcare and patient safety

Following the example of *sofosbuvir*, prices for new anti-HCV antivirals marketed in the European Union in 2015 continued to soar. For example, in France, a 12- to 24-week course of treatment costs 50 000 to 100 000 euros with the *ledipasvir* + *sofosbuvir* combination, and about 67 000 to 134 000 euros with the *daclatasvir* + *sofosbuvir* combination (Prescrire Int n° 166).

The prices of drugs authorised for rare diseases are also disproportionate (see inset above). For example, *defibrotide* costs about 72 000 euros (excluding tax) for a 21-day course of treatment for hepatic veno-occlusive disease in a patient weighing 70 kg (Prescrire Int n° 164).

The monthly cost of *cholic acid* therapy for patients with certain bile acid deficiencies is about 20 000 euros for an adult weighing 60 kg (Prescrire Int n° 157).