INTERNATIONAL SOCIETY OF DRUG BULLETINS

# Newsletter

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## WELCOME TO THE FIRST ISDB NEWSLETTER OF 2023.

We report summaries of the online General Assembly, in November 2022 as well as of online meetings of the ISDB Executive Committee during November 2022 and March 2023.

A briefing paper outlines the aim of the ISDB Strategic Plan. The executive committee has launched two subgroups to reflect on ISDB's membership and on its mission and activities.

The newsletter includes some articles published by ISDB members or articles co-authored by staff of ISDB members.

The next newsletter is planned for Summer 2023. We welcome comments, suggestions and articles. Please send them to: rkessler@prescrire.org by end of June 2023.

# Online Ordinary General Meeting, November 17 2022

The online ISDB Ordinary General Meeting of Members (OGM) took place on November 17 2022 from 3 - 6 pm CET. The meeting was held online due to the Covid-19 pandemic, to enable the participation of as many members as possible. As the outgoing President Dick Bijl informed us by letter that he would be unable attend to attend for technical and personal reasons, the meeting was kindly moderated by Ciprian Jauca (Therapeutics Initiative, Canada), who facilitated our smooth and constructive discussions and exchanges. We are also very grateful to Therapeutics Initiative for the perfect technical organization of the meeting.

Altogether, 35 participants joined the meeting, representing 28 bulletins: 20 full members and 8 associate members.

The meeting was devoted to internal affairs, including presentations on:

- ISDB activities since the Paris OGM, October 2019, by Rita Kessler, Prescrire, France
- Financial report, by Luis Carlos Saiz, ISDB Treasurer, DTB Navarre, Spain
- Membership report, by Maria Font, InfoFarma, Italy
- Report on the Clinical Trials Working Group, by Nuria Homedes, Boletin Farmacos, USA

The presentations were sent to ISDB members by email on November 29 2022.

Participants were informed about the crisis faced by Australian Prescriber. The Australian government decided to stop funding NPS MedicineWise, the current publisher of Australian Prescriber, and to put the journal out to tender. It was decided to launch a campaign to support our Australian member. The ISDB committee was invited to send a letter in support of Australian Prescriber to the Australian Health minister. ISDB member organizations were invited to take action as well.

During the exchange session between members, it was suggested to initiate a strategic reflection on the future of ISDB, focusing on the ISDB's membership and on its mission and activities. Members also exchanged experiences on reconciling the funding of their respective bulletins with editorial independence.

**ISDB members also elected a new Committee.** 25 of the 31 full members with voting rights participated in the online election. All five candidates were elected:
- Nuria Homedes, Boletin Farmacos, USA
- Roberta Joppi, InfoFarma, Italy
- Rita Kessler, La revue Prescrire, France
- Barbara Mintzes, Therapeutics Initiative, Canada
- Luis Carlos Saiz, DTB Navarre, Spain

Before closing the meeting, members expressed their warm thanks and gratitude to Maria Font, InfoFarma (Italy), who recently retired, for her contribution to the ISDB over many years, during which she held various posts on the Committee.

# Feedback from ISDB Committee meetings

The Committee has held 3 online meetings since the Ordinary General Meeting on November 17 2022, on the following dates:
- November 24 2022
- January 19 2023
- March 23 2023

## The new Committee

In line with the ISDB Constitution, the first meeting of the incoming Committee, held on November 24 2022, was devoted to their appointment to the various Committee posts:
- Chairperson: Rita Kessler (Prescrire, France)
- General Secretary: Barbara Mintzes (Therapeutics Initiative, Canada)
- Treasurer: Luis Carlos Saiz (DTB Navarra, Spain)
- Nuria Homedes (Boletin Farmacos, USA), contact person for members from the Global South
- Roberta Joppi (InfoFarma, Italy) responsible for keeping members' records up to date

The Committee finalized a letter of support for Australian Prescriber, which was sent to the Australian Health Minister on November 28 2022. The minister responded on January 23 2023, stating that the Government is committed to safeguarding Australian Prescriber's editorial independence, quality standards, and role as a trusted information source. Both letters are available on the ISDB website www.isdbweb.org.

The Committee meetings in January and March 2023 were devoted to preparing the launch of the ISDB Strategic Plan. It was decided to launch two subgroups: one to reflect on the ISDB's membership and the other on ISDB's mission and activities. ISDB members were informed about the plans by email on February 8 2023. They were invited to communicate their willingness to participate in either subgroup.

The following members expressed their interest in participating in the discussion:

## Membership

- Carlos Durán, Excellencis, Ecuador
- Pierre Chirac, Prescrire, France
- Leire Leache, Boletín de Información Terapéutica de Navarra (BIT), Spain
- James Cave and David Phizackerley, DTB, UK
- Frans M. Helmerhorst, Ge-Bu, the Netherlands

## Value to its members: mission and activities

- Isidro Sia, RDU Update, Philippines, associate member
- Natalie Marty, Infomed, Switzerland
- Luca Iaboli, Farmaco-Logico, Italy, associate member
- María Francisca Aldunate González, ISPCH, Chile, associate member
- Pierre Chirac, Prescrire, France
- Juan Erviti, Boletín de Información Terapéutica de Navarra (BIT), Spain
- James Cave and David Phizackerley, DTB, United Kingdom
- Natalia Ceboterenco, MEDEX, Moldova
- Frans M. Helmerhorst, Ge-Bu, the Netherlands
- Jörg Schaaber, Pharma Brief, Germany

Online meetings will take place during 2023. The groups are expected to make recommendations by the end of 2023. More information on the ISDB Strategic Plan is available on page 3.

The Committee updated the ISDB website homepage and prepared the first issue of the newsletter for 2023.

# Developing a Strategic Plan for ISDB

## Document shared with ISDB Members on February 8, 2023

### Issues to be evaluated and addressed:

- Declining membership, while the number of groups that attempt to produce independent pharmaceutical information appears to be increasing
- Limited value of the organization to its members. Why should an organization join ISDB?
- Limited communication among ISDB members and between executive committee and membership: Sparse newsletter, outdated website
- Information about the organization disorganized and scattered.

### Methods

The Executive Committee can establish subcommittees to work on different issues. We propose to create two subcommittees, one dealing with membership issues, and the other with the mission, activities and organisational support for ISDB. Some ideas are listed below that each of these groups could discuss.

The subcommittees will work virtually, and some sharing of information between the two, either through the Executive Committee or directly. We anticipate that the groups will meet about four times in the next several months. Ideally, this task could be completed by the end of 2023.

The subcommittees should include representatives of the most well-established ISDB bulletins but also some from the global south. Each subcommittee should have a minimum of five members.

Each subcommittee will have a chairperson and they will jointly decide how they want to proceed. If necessary one or two members of the executive committee would join.

The final product would be a short paper to be shared with the entire membership.

The subcommittees can add to the issues mentioned below, or decide that they are irrelevant and propose alternatives.

### 1. Addressing membership

➥ Background:

According to the constitution, to apply for ISDB membership, institutions must fulfill the criteria in Box 1. The ISDB Constitution also defines information quality and independent information (Box 2).

Box 1

### Eligible ISDB members

4.1.1 Publishers of independent drug publications fulfilling all the following requirements and giving all the following undertakings may apply for membership of the Society:

- that they have editorial procedures and organisation that will, in the opinion of the Committee or the Society in General Meeting, ensure their independence and the quality of their content as defined in Article 2 above;
- that they contain no advertising relating to therapeutic or diagnostic activities;
- that they have published at least five issues;
- that they fully and unreservedly accept the Articles of the Society, in particular Articles 1 and 2, and its Rules;
- that they shall allow the quality of the publication and the independence of their editorial system to be periodically assessed by the Society;
- that they will inform the Committee of any changes in structure, working, financing or editorial organisation likely to modify their independence or the quality of their content;
- that they will pay the annual subscription as set out in Article 8 hereto.

4.4. Associate Member status Institutions or individuals sympathetic to the purposes of the Society, but not qualified to be members, may, at the absolute discretion of the Committee and on payment of the relevant subscription, be given the status of Associate Member of the Society. Associate Members shall have all the rights and obligations of members except those of voting and of standing for office and use of the Society's logo. Where appropriate, the term «member» in these Articles shall include an Associate Member.

4.2. Rights of members

a. The right of using the ISDB logo. Associate members cannot use the ISDB logo.

b. To receive the ISDB Newsletter

c. To use the ISDB communication network

d. To have the access to the full website

RULE IV - PUBLICATIONS WRITTEN FOR PATIENTS AND PUBLICATIONS PUBLISHED ELECTRONICALLY Publications aimed at patients or published electronically can become member publications provided they meet the criteria for membership.

Box 2

## ISDB definition of quality information and independent information

"Good-quality information": Information which fulfils the following two criteria: a. It is scientifically valid and clarifies current scientific consensus and distinguishes what is established from, what is not;

b. It helps the user of the information to optimise his or her therapeutic activity in the best interests of the patient or helping patients to make informed choices.

"Independent": A publication is independent if it fulfils the following three criteria: a. it is run by an independent editorial team; b. its organisational structure and financial resources are capable of guaranteeing the editorial team's independence. c. it does not accept any funding from the pharmaceutical industry or related healthcare industry.

RULE V - DEFINITION OF INDEPENDENCE The following definitions refer to the requirements of independence of a bulletin (Article 2)1 and the independence of the editorial system (Article 4.1.1)2 and specifically address conflict of interests (CoI). This rule was established at the Extraordinary General Meeting (EGM) 2 July 2016 in Leiden. It applies immediately on new ISDB members. Existing members will be entitled to a three year transition period to comply with the provisions of the rules, as described below.

V - 1. Definition: Conflict of interest (CoI) with the healthcare industry Any financial or advisory relationship (paid or unpaid) with the pharmaceutical industry or related healthcare products industry (e.g. medical devices or diagnostics), including the conduct of industry funded clinical trials. Declarations of CoI must cover the last three calendar years. Members may use the CoI forms provided by ISDB or their own forms as long as they cover a similar set of questions.

V - 2. Independent editorial team Members of the editorial team must be free from conflict of interest (CoI) with the healthcare industry. Their CoI declarations should be updated annually and publicly available.

V - 3. Organisational structure

(a) Institutional setup If the publication is part of a larger institution, safeguards must be in place to prevent any influence of the institution (or the governing board of a bulletin if applicable) on the editorial team, particularly regarding topic selection and article content.

(b) External authors If an editorial team makes use of external authors to write or draft articles: - The editorial team must have the autonomy to change the content or reject articles. - All authors who write articles which could influence therapeutic choices (e.g. drug and treatment reviews or guidelines) must be free from conflict of interest as defined above. - In exceptional circumstances a bulletin may publish an article (not influencing therapeutic choice) by an author who has a conflict of interest; in such a situation all CoI need to be declared at the end of the article.

(c) Reviewers of articles External reviewers of articles should declare their CoI.

➥ **Themes to be discussed:**

- In view of the growth in electronic publications in different formats, we need to clarify criteria for membership and for distinguishing Full members from Associate members.
  - For this exercise, it might be useful to scan the different types of publications - in paper and electronic- that are being produced by current ISDB members
  - Clarify the differences between Associate and Full members or others that the committee might consider appropriate
  - Revise the list of Full and Associate members to see if all members are classified correctly.
- Develop a preliminary list of potential additional members that could be invited to be part of ISDB in future
- Consider if ISDB should also include groups working on the assessment of medical devices.

### 2. Value of ISDB to its members

➥ **Background:**

ISDB's purpose and activities, as described in the constitution, are listed in Box 3.

➥ **Themes to be discussed:**

- Is the ISDB purpose still valid? Is there something we could add to make it more meaningful for its membership (i.e. provide information on policy direction of major regulatory agencies, ICH and WHO; policy advocacy, more extensive

and systematic sharing of drug evaluations between bulletins, etc.)

- ISDB does not currently carry out any training sessions for groups that want to produce independent information, although this has been an ISDB activity in past. According to the Constitution, this task is core to ISDB activities. If the group considers that it is still valid, there is a need to determine how it will be accomplished.
- Some training ideas that could be discussed:
    - Develop a list of existing bulletins that could assist others to grow and develop their own publications - this needs to consider language proficiency.
    - Develop a list of on-line or in-person courses to help those who are interested in producing independent information.
    - ISDB members could join efforts to develop an on-line course in English
    - Document the expertise of each ISDB member for the purpose of providing guidance to others.
    - Consider options for intensive training "how to edit and produce an independent drug bulletin" and more limited specific skills development or advancement that could be helpful for bulletins at a range of levels, for example on addressing uncertainty or on use of data from full clinical study reports, etc.
    - Consider exchange programs as a training option (a bulletin editor spends time working with an established bulletin and 'learning the ropes' on the job).
- Newsletters or listserv: consider if there is a need to maintain the publication of formal newsletters, whether a listserv could offer greater value to the membership, and/or other communication tools.
- Website. The website needs to be updated and redesigned. Much of the information is not up to date, and a lot of information is lacking. For examples, minutes of the Executive Committee meetings have not been uploaded. It is also important to consider if ISDB needs to have an Intranet. Probably the revamping of the webpage should occur after there is more clarity on the value that ISDB will offer to its members.

Box 3

**Purpose and Tools of ISDB**

Article 1 - PURPOSE

The purpose of the Society shall be:

a. to encourage and further the development of independent publications on drug and therapeutic information;

b. to promote international exchange of good-quality information concerning drugs and therapeutics;

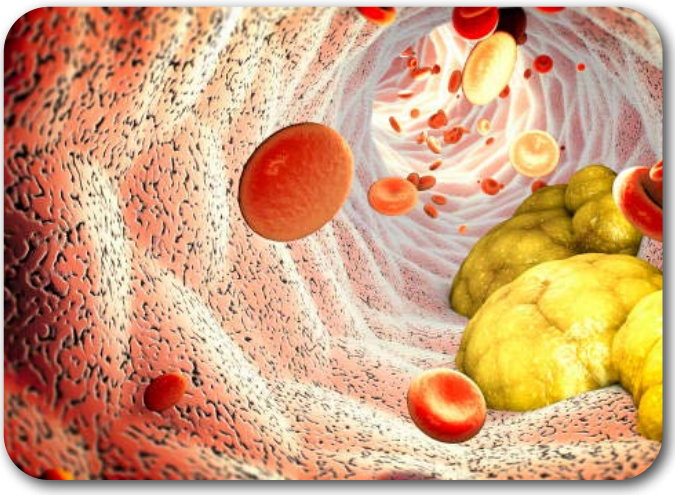
c. to engage in whatever ancillary activities the Committee considers desirable for the furtherance of these primary purposes.

RULE III - COMMUNICATION TOOLS: THE ISDB NEWSLETTER AND WEBSITE An official publication (Newsletter) of ISDB, issued at least 3 times a year, and a Website are the responsibility of the Committee of the Society. The Committee will serve as editorial board of both. The Newsletter will report events important for the Society, news from the various member publications, interesting articles, activities of ISDB, reports of the Committee etc. Both the Newsletter and the Website will serve as a way of communication between the members and the Committee as well as a way of transmitting important events which happened in and outside ISDB. The Website also has the purpose of presenting ISDB outside the Society. The contents of the Website should be updated monthly.

- ISDB documents are scattered; a centralised archive is needed. They could be stored on the website, for example in an Intranet section or the subcommittee could propose other options.
- Consider the need to hire a person/institution that can act as a secretariat to organize ISDB documents, manage communication tools (e.g. listserv and/or newsletter) and maintain communication with a webmaster that will update the webpage regularly. We currently use an external organisation to manage financial resources and it has worked very well. We would need to estimate of the number of hours required per month and its cost.

# A reanalysis of the FOURIER trial based on regulatory data challenges published mortality results of evolocumab

Article provided by Luis Carlos Saiz, DTB Navarra (Spain), co-author of the Fourier trial reanalysis and member of the ISDB committee



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An international research team including members of two ISDB bulletins [DTB Navarre (Spain) and Therapeutics Initiative (Canada)], has recently published in BMJ Open a reanalysis of mortality data from the FOURIER clinical trial. The article shows major discrepancies in death causes between the data reported in the final Clinical Study Report (CSR) submitted to health authorities for drug approval and those published in the New England Journal of Medicine (NEJM) in 2017, when its results were finally made public.

Evolocumab, a monoclonal antibody belonging to a new class of lipid-lowering drugs, was licensed to treat patients who fail to achieve optimal cholesterol levels with statin therapy. The FOURIER trial was designed to support the indication of evolocumab in reducing the cardiovascular risk in secondary prevention, assessing the impact of evolocumab versus placebo on cardiovascular outcomes in 27,564 patients with clinically evident atherosclerotic cardiovascular disease and LDL-C > 70 mg/dL on statin therapy. The study was carried out at 1,242 centres in 49 countries.

Results published in the NEJM showed that evolocumab helped lower cholesterol and was superior to placebo in reducing cardiovascular events. Given this apparent benefit, the FOURIER trial was stopped early, some 30 months earlier than the 56 months planned.

However, after detailed review of the mortality data in the CSR (a 25,000-page document) and subsequent reassignment of causes of death, the researchers found that mortality from myocardial infarction was numerically higher in the evolocumab-treated group (36 deaths) than in the placebo-treated group (27 deaths), in contrast to what was reported in the NEJM, 25 deaths with evolocumab versus 30 deaths with placebo. They also found that heart failure mortality was numerically higher in the evolocumab group (31 deaths) than in the placebo group (16 deaths), a previously unknown finding. Reanalysis of the data reveals that 360 of the 870 (41.4%) causes of death recorded over the duration of the trial were wrongly assigned according to the information in the CSR.

As readjudicated, the authors found that cardiovascular mortality was 20% higher in the evolocumab group relative to placebo, rather than the 5% published in the NEJM in 2017, although this difference was not statistically significant. Nevertheless, should this 20% point estimate was maintained throughout the full planned study duration, the increase in cardiovascular mortality from evolocumab might have reached statistical significance before the end of the prespecified follow-up.

As a limitation, despite the length of the CSR document, it does not include narratives on cases labelled as efficacy variable events (stroke, heart attack or non-fatal angina). Also, Case Report Forms were not available from regulators, which would be an essential improvement for future cases.

The restoration of the FOURIER trial was supported by the RIAT (Restoring Invisible and Abandoned Trials) initiative, an international effort to make public hidden scientific data, restore misreported trials and address biases in the publication of clinical research results.

According to the authors, it is very disappointing that regulatory agencies such as the EMA or Health Canada do not ask companies for the whole range of information linked to a trial. The FDA does, but it is not publicly accessible by default and it can only be requested under the Freedom of Information Act, which is a lengthy process taking several years. Therefore, this article highlights the urgent need for full clinical trial data to be made public in order to allow for independent risk-benefit assessment of drugs.

In this particular case, only a partial restoration has been possible so far. Because of that, the authors recommend

being cautious about prescribing evolocumab for patients with established atherosclerotic cardiovascular disease, until a full restoration of the FOURIER trial is available.

Finally, part of the research team has also recently published in TRIALS a second RIAT project focused on plasma rich in growth factors (PRGF) for knee osteoarthritis. In contrast to what was published in the original article, this reanalysis found no clinically or statistically significant benefit from PRGF compared to hyaluronic acid when a pain subscale score was estimated. In this case, the access to two unpublished study documents (original protocol and final report) was instrumental to identify and correct the non-prespecified primary endpoint used in the original paper. This restoration shows the urgency of relevant changes to trial reporting, oversight practices, and prompt intervention of ethics committees when needed.

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# Patients in Europe are ill informed about uncertainties in benefits of cancer medicines

From Barbara Mintzes, co-author of the BMJ article "Communication of anticancer drug benefits and related uncertainties to patients and clinicians: document analysis of regulated information on prescription drugs in Europe" (1) and member of the ISDB committee.

All patients need accurate information on benefits and harms of drug treatments, including gaps in evidence and ongoing uncertainties, to participate in shared informed treatment decisions. For cancer patients, who are often dealing with life-threatening conditions and treatments with serious toxicities, the need for accurate information is all the more pressing. Additionally, newer cancer drugs are often approved based on limited evidence, leading to greater uncertainty about outcome.

How well does patient information approved by the European Medicines Agency (EMA) inform patients about uncertainties and missing evidence on drug benefits?

Courtney Davis, King's College London, Huseyin Naci, London School of Economics and Political Science, and colleagues recently carried out a study of the information provided on drug benefits and related uncertainties in Patient Information Leaflets ('PILS' or 'patient leaflets') for 29 cancer treatments approved by the EMA for 32 indications from 2017 to 2019. [1] This study examined whether patient leaflets provide accurate and complete information on six key questions on the drug, how it was studied, and evidence of benefit. Information in patient leaflets are compared with regulators' assessments, as reported in the European Public Assessment Report (EPAR). The researchers also compared the EPAR with information for clinicians in Summary of Product Characteristics (SmPCs) and Public Summaries on the EMA's website.

## Limits to effectiveness not communicated

The results are damning: although all patient leaflets specified the drug class and mechanism of action, information on the indication and target patient population is often incomplete, with restrictions on the scope of the indication, such as disease stage, treatment sequence, or mutational status of patients' cancers, often missing. None of the patient leaflets reported whether there was evidence of a survival benefit or improved quality of life. Among the 32 assessed indications, 9 (28%) had evidence of improved survival times or quality of life at approval; the other 23 did not. Additionally, none on the patient leaflets provided any information on how the drug had been studied or what outcomes were measured in trials.

## Uncertainties raised in EMA assessments not shared

Concerns raised by EMA assessors and described in the EPAR were also rarely reported in patient leaflets. For example, EMA assessors had raised concerns about uncertain

therapeutic value for 47% of the approved indications. This was not reported in any patient leaflets or clinician information (SmPCs). EMA assessors also raised concerns about inappropriate or surrogate outcome measures for 47%; again there was no information in patient leaflets, and mention in only 3% of information for clinicians.

## Misleading implied efficacy

The Public Summaries sometimes provided information on trial outcomes, but this could be highly misleading. Gains in progression free survival are described in lay language as "living longer without their disease getting worse" although progression free survival does not necessarily translate to longer survival.

Nearly all patient leaflets stated a drug's mechanism of action. Statements that a drug "triggers the death of cancer cells ..." or "allow[s] the immune system to attack the cancer cells", for drugs without evidence of a survival or quality of life benefit, without any qualifying information on trial outcomes, misleadingly imply a high level of efficacy.

## Stricter regulation is needed to avoid misleading patients

Under EMA guidance, companies may provide more complete information on benefits in patient leaflets, as long as it is non-promotional and consistent with approved information for clinicians (the SmPC) but are not required to do so. In a news report on the study in *Lancet Oncology*, Marilys Corbex, WHO Regional office for Europe, highlights the importance of information for patients on "benefits, limits and potential harms of the treatments they are receiving and prescribing" especially given the minimal survival benefits of many new cancer medicines, and states that, "Stricter regulation is part of the solution but advocacy demanding better behaviour from the industry will also play a role." [2]

This study highlights the need to improve how drug benefits are communicated to patients in regulated patient leaflets. Regulators need to ensure that patient leaflets provide accurate information to answer the key questions patients have about their medicines, including how likely they are to benefit and what is and is not known about the drug's effects. For cancer drugs in Europe, this is clearly not happening. The EMA requires approved patient leaflets and regulates this information more than other regulators, even requiring a patient review for readability pre-approval. If the EMA allows patients to be misled about the benefits of cancer medicines because key information on uncertainty and limits to evidence of benefit is left out, this is likely also happening in other countries as well and for other drug classes.

### References

**1-** Davis C, Wagner AK, Salcher-Konrad et al. Communication of anticancer drug benefits and related uncertainties to patients and clinicians: document analysis of regulated information on prescription drugs in Europe. BMJ 2023;380:e073711. Available at: https://www.bmj.com/content/380/bmj-2022-073711

**2-** Gould E. EU cancer drug leaflets contain insufficient information. The Lancet Oncology. April 20, 2023. Available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00181-X/fulltext

# Prescrire's ratings of new drugs in 2022: a brief review

Only 11 of the 124 new marketing authorisations analysed and rated in our French edition in 2022 represented a notable therapeutic advance for patients.

Article published in *Prescrire International*, April 2023; **32** (247): 99-101

Every month, *Prescrire* publishes independent, comparative, systematic reviews of the latest developments in the European pharmaceutical market, including recent marketing authorisations for new active substances, new combinations, new pharmaceutical forms, and new indications. We also closely monitor news concerning adverse effects, market withdrawals (instigated by pharmaceutical companies or regulatory authorities), re-introductions of previously withdrawn products, re-evaluations of drugs already on the market, and the regulatory environment for health products. Our aim is to help subscribers distinguish between genuine advances and new products or new uses that are no better than existing treatments or that should never have been authorised, due to uncertainty over their harms or benefits or because they are clearly dangerous.

**No major therapeutic advances in 2022.** Prescrire examined 124 new marketing authorisations in 2022 in order to determine whether or not they advanced patient care (see the table opposite).

Thirty-four of these offered some degree of added benefit compared with existing treatments, at least for some patients, with 11 (9%) representing a notable advance (rated "Offers an Advantage"), and the remaining 23 (19%) a minimal advance (rated as "Possibly Helpful").

Half of the new authorisations we analysed in 2022 offered no proven advantages over existing treatment options (rated "Nothing New"). In 13 cases (10%), the harm-benefit balance could not be determined, because the clinical evaluation data provided insufficient evidence of their efficacy or potential serious adverse effects (rated "Judgement Reserved"). Finally, the evaluation data available on 14 authorisations (11%) showed them to be more dangerous than useful (rated "Not Acceptable").

**A few new authorisations worth using.** After the advances seen in 2021 with the first covid-19 vaccines, those observed in 2022 are far more modest, marking a return to the pattern generally seen before the pandemic.

A few new active substances are worth using, for example: *sacituzumab govitecan*, *tucatinib* and the combination of *pertuzumab* + *trastuzumab* for certain patients with breast cancer; as well as *nirmatrelvir* (combined with *ritonavir*) and *tocilizumab* for patients at risk of developing severe covid-19. The antibody *sotrovimab* was temporarily an advance for patients with covid-19, but not a durable advance due to the virus's variability. *Sodium oxybate* constitutes a notable therapeutic advance for children aged 7 years or older with narcolepsy, as was the case for adults.

**Dose strengths ill-suited to the recommended doses.** Some drugs *Prescrire* examined in 2022 are marketed at dose strengths that necessitate 2 to 4 injections in succession to achieve the recommended dose, for example: *bimekizumab*, supplied in pre-filled pens or syringes that contain 160 mg of the drug, yet the recommended dose for plaque psoriasis is 320 mg every 4 or 8 weeks (*Prescrire Int* n° 245); *natalizumab*, supplied in pre-filled syringes each containing 150 mg for subcutaneous administration, yet the recommended dose for multiple sclerosis is 300 mg per month (*Rev Prescrire* n° 464); and *tralokinumab,* marketed in pre-filled syringes containing only 150 mg of the drug, when the recommended dose is 600 mg, then 300 mg every 2 weeks, for certain patients with atopic dermatitis (*Prescrire Int* n° 239).

**A few welcome restrictive measures at European level.** A few welcome restrictive measures were taken in the European Union in 2022, in particular: the European Medicines Agency (EMA) issued a negative opinion on granting marketing authorisation for *aducanumab*, a drug with no demonstrated efficacy in Alzheimer's disease, leading the pharmaceutical company to withdraw its application (1); and authorisation for the use of *dapagliflozin* in type 1 diabetes was withdrawn. Authorisation for the use of *rucaparib* in relapsed ovarian cancer, recklessly granted in 2020 on the basis of a very tenuous evaluation, was finally revoked. And in late 2022, the EMA confirmed its earlier opinion recommending the withdrawal of products containing *amfepramone*. The dangers of this amphetamine have been known since the 1990s, and it had already been withdrawn in many countries, including France (2).

In contrast, *etifoxine* was not withdrawn from the European market, despite the fact that it has been known for many years to have an unfavourable harm-benefit balance.

**In summary: a disappointing year.** 2022 was a return to the bad old days for medicines in Europe. Therapeutic advances were few and far between. Most newly authorised products or indications offered no proven advantages over existing treatment options, or were excessively dangerous. And yet again, certain pharmaceutical companies gave too little consideration to the ease of use of their products, choosing to market them in pack sizes ill-suited to the doses to be administered.



► Translated from *Rev Prescrire* February 2023
Volume 43 N° 472 · Pages 146-147

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**1-** EMA "Withdrawal of application for the marketing authorisation of Aduhelm (aducanumab)" 22 April 2022: 2 pages.
**2-** EMA "EMA confirms recommendation to withdraw marketing authorisations for amfepramone medicines" 11 November 2022: 3 pages.

# Prescrire's ratings of new products and new indications over the past 10 years

| PRESCRIRE'S RATING | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|---|---|---|---|---|
| BRAVO | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| A REAL ADVANCE | 0 | 2 | 3 | 1 | 1 | 2 | 1 | 2 | 3 | 0 |
| OFFERS AN ADVANTAGE | 6 | 5 | 5 | 5 | 9 | 11 | 10 | 6 | 14 | 11 |
| POSSIBLY HELPFUL | 12 | 15 | 15 | 9 | 18 | 22 | 13 | 18 | 19 | 23 |
| NOTHING NEW | 48 | 35 | 43 | 56 | 45 | 50 | 61 | 55 | 51 | 63 |
| JUDGEMENT RESERVED | 9 | 10 | 6 | 5 | 4 | 5 | 9 | 17 | 12 | 13 |
| NOT ACCEPTABLE | 15 | 19 | 15 | 16 | 15 | 9 | 14 | 10 | 9 | 14 |
| TOTAL | 90 | 87 | 87 | 92 | 92 | 99 | 108 | 109 | 108 | 124 |

## OFFERS AN ADVANTAGE

- *Apremilast* (Otezla°) for oral ulcers associated with Behçet's disease (*Prescrire Int* n° 237).
- *Atidarsagene autotemcel* (Libmeldy°) in metachromatic leukodystrophy (*Prescrire Int* n° 243).
- *Azacitidine* (Onureg°) as maintenance therapy in acute myeloid leukaemia (*Prescrire Int* n° 244).
- *Nirmatrelvir + ritonavir* (Paxlovid°) in covid-19 (*Prescrire Int* n° 244).
- *Sodium oxybate* (Xyrem°) in narcolepsy with cataplexy from 7 years of age (*Prescrire Int* n° 241).
- *Pertuzumab + trastuzumab* (Phesgo°) in certain breast cancers (*Prescrire Int* n° 237).
- *Sacituzumab govitecan* (Trodelvy°) in certain breast cancers (*Prescrire Int* n° 241).
- *Sofosbuvir + velpatasvir + voxilaprevir* (Vosevi°) in hepatitis C in adolescents (*Prescrire Int* n° 246).
- *Sotrovimab* (Xevudy°) in covid-19 (*Prescrire Int* n° 239).
- *Tocilizumab* (Roactemra°) in severe covid-19 (*Prescrire Int* n° 242).
- *Tucatinib* (Tukysa°) in certain breast cancers (*Prescrire Int* n° 239).

## POSSIBLY HELPFUL

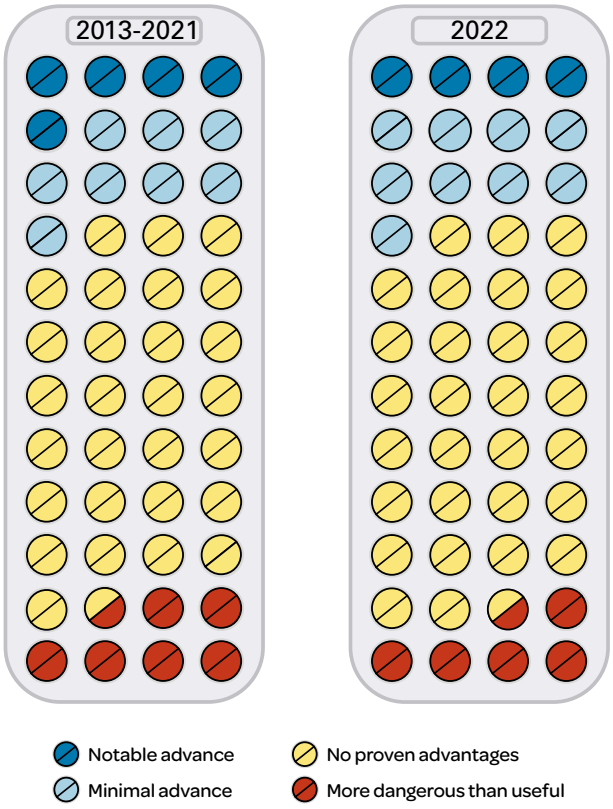
- *Aciclovir* solution (Aciclovir Accord°) in herpes virus or varicella zoster virus infections (*Rev Prescrire* n° 468).
- *Cannabidiol* (Epidyolex°) in epilepsy associated with tuberous sclerosis complex (*Prescrire Int* n° 242).
- *Casirivimab + imdevimab* (Ronapreve°) in early covid-19 (*Prescrire Int* n° 237).

- *Ceftazidime + avibactam* (Zavicefta°) in infections in infants and children (*Prescrire Int* n° 240).
- *Cenobamate* (Ontozry°) in focal seizures (*Prescrire Int* n° 244).
- Prolonged-release *potassium citrate and bicarbonate* (Sibnayal°) in distal renal tubular acidosis (*Rev Prescrire* n° 463).
- *Clopidogrel* (Plavix°) in combination with aspirin in ischaemic stroke (*Prescrire Int* n° 240).
- *Dobutamine* in pre-filled syringes (Dobutamine Sun°) in low cardiac output syndrome (*Rev Prescrire* n° 469).
- *Dolutegravir* (Tivicay°) in HIV infection from 4 weeks of age (*Prescrire Int* n° 240).
- *Fostemsavir* (Rukobia°) in multidrug-resistant HIV-1 infection (*Prescrire Int* n° 237).
- *Glecaprevir + pibrentasvir* (Maviret°) in hepatitis C from 3 years of age (*Prescrire Int* n° 244).
- *Ipilimumab* (Yervoy°) + *nivolumab* (Opdivo°) in certain inoperable pleural mesotheliomas (*Prescrire Int* n° 242).
- *Morphine* orodispersible tablets (Actiskenan°) in severe pain (*Rev Prescrire* n° 466).
- *Pegcetacoplan* (Aspaveli°) in certain patients with paroxysmal nocturnal haemoglobinuria (*Prescrire Int* n° 246).
- *Pembrolizumab* (Keytruda°) as 1st line treatment for advanced oesophageal cancers (*Prescrire Int* n° 243).
- *Pitolisant* (Ozawade°) in excessive daytime sleepiness linked to sleep apnoea (*Prescrire Int* n° 244).
- *Ravulizumab* (Ultomiris°) in paroxysmal nocturnal haemoglobinuria (*Prescrire Int* n° 242).
- *Rivaroxaban* (Xarelto°) in venous thromboembolism in children and adolescents (*Prescrire Int* n° 239).
- *Setmelanotide* (Imcivree°) in certain, very rare, genetic forms of obesity (*Prescrire Int* n° 244).
- *Sumatriptan* 3 mg/0.5 ml (Sumatriptan Sun°) in migraine (*Rev Prescrire* n° 468).
- *Tozinameran* (Comirnaty°) in the prevention of covid-19 in children from 5 years of age (*Prescrire Int* n° 236).
- *NVX-CoV2373 vaccine* (Nuvaxovid°) in the prevention of covid-19 in adults (*Prescrire Int* n° 238).
- *Venetoclax* (Venclyxto°) as 1st line treatment for acute myeloid leukaemia (*Prescrire Int* n° 243).

## JUDGEMENT RESERVED

- *Adalimumab* (Humira°) in ulcerative colitis from 6 years of age (*Prescrire Int* n° 240).
- *Dapagliflozin* (Forxiga°) in chronic kidney disease (*Prescrire Int* n° 239).
- *Dupilumab* (Dupixent°) in severe childhood atopic eczema from 6 years of age (*Prescrire Int* n° 236).

## Therapeutic advances in 2022 compared with the previous 9 years




► Translated from *Rev Prescrire* February 2023
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- *Fostamatinib* (Tavlesse°) in refractory chronic immune thrombocytopenia (*Prescrire Int* n° 239).
- *Idecabtagene vicleucel* (Abecma°) in multiple myeloma (*Prescrire Int* n° 243).
- *Ipilimumab* (Yervoy°) + *nivolumab* (Opdivo°) in certain colorectal cancers (*Rev Prescrire* n° 464).
- *Methylphenidate* (Ritaline LP°) in attention deficit hyperactivity disorder in adults (*Rev Prescrire* n° 465).
- *Osimertinib* (Tagrisso°) in certain lung cancers (*Prescrire Int* n° 245).
- *Pegvaliase* (Palynziq°) in phenylketonuria (*Prescrire Int* n° 239).
- *Pembrolizumab* (Keytruda°) in certain breast cancers (*Prescrire Int* n° 244).
- *Risdiplam* (Evrysdi°) in spinal muscular atrophy (*Prescrire Int* n° 242).
- *Selpercatinib* (Retsevmo°) in certain lung or thyroid cancers (*Prescrire Int* n° 236).
- *Vosoritide* (Voxzogo°) in achondroplasia (*Prescrire Int* n° 245).

## NOT ACCEPTABLE

- *Drospirenone + estetrol* (Drovelis°) for oral contraception (*Prescrire Int* n° 241).
- *Esketamine* (Spravato°) in depression with a high risk of suicide (*Prescrire Int* n° 238).
- *Icosapent ethyl* (Vazkepa°) in cardiovascular prevention (*Prescrire Int* n° 245).
- *Liraglutide* (Saxenda°) in obesity in adolescents (*Prescrire Int* n° 242).
- *Luspatercept* (Reblozyl°) in anaemia associated with myelodysplastic syndrome or with beta-thalassaemia (*Prescrire Int* n° 245).
- *Natalizumab* (Tysabri°) for subcutaneous use (*Rev Prescrire* n° 464).
- *Ozanimod* (Zeposia°) in multiple sclerosis (*Prescrire Int* n° 237).
- *Pemigatinib* (Pemazyre°) in cholangiocarcinoma (*Prescrire Int* n° 243).
- *Ponesimod* (Ponvory°) in multiple sclerosis (*Prescrire Int* n° 240).
- *Peanut protein* (Palforzia°) for oral desensitisation (*Prescrire Int* n° 238).
- *Relugolix + estradiol + norethisterone* (Ryeqo°) in uterine fibroids (*Prescrire Int* n° 244).
- *Roxadustat* (Evrenzo°) in anaemia associated with chronic kidney disease (*Prescrire Int* n° 245).
- *Opium tincture* (Dropizal°) in severe diarrhoea (*Rev Prescrire* n° 466).

# Members Events

### Therapeutics Initiative Best Evidence Webinar

UPCOMING: May 10 2023, 12:00 - 13:00 Pacific Time

"Completing the picture: the need for access to regulatory documents for better drug assessment"

With guest speaker: Dr. Juan Erviti, DTB Navarra, Spain

(free virtual event, registration required)

More info here