

Via electronic transmission

P. Nikiforos DIAMANDOUROS — The European Ombudsman

Prescrire's reply to the EMA opinion submitted in response to complaint
n° 1877/2010/FOR

Paris, 30 March 2011

Dear Sir,

Here is *Prescrire's* reaction to the opinion of the European Medicines Agency (EMA), issued on 31 January 2011, about the complaints we filed against the EMA. We have decided to maintain our 5 complaints for the reasons set out below.

Introduction:

Prescrire is an independent source of information on drugs.

Over the last few decades, several scandals involving drugs such as *rofecoxib* (Vioxx[°]) and *benfluorex* (Mediator[°]) have had devastating public health consequences for European populations. Other drugs, such as *rimonabant* (Acomplia[°]) and *buflomedil* (Fonzylane[°]), were withdrawn after being marketed for years. While they were on the market, these drugs caused serious adverse effects in thousands of patients. Yet they were all licensed by drug regulatory agencies, including the EMA.

These scandals have also shown that it is difficult to get access to information about drugs, especially the information held by drug regulatory agencies, confirming the need for transparency affirmed in 1996 in the Uppsala Declaration and the International Society of Drug bulletins (ISDB). These scandals have also shown that in order to evaluate a drug, it is necessary to ask questions and to examine, compare and cross-check information from multiple sources. For this reason, *Prescrire's* approach for decades has been to consult various essential sources of information on drugs: primary publication journals and reference works, other independent teams that evaluate medicines, pharmaceutical companies and drug regulatory agencies.

We are well aware that regularly questioning the drug regulatory agencies, including the EMA, creates work for their staff. This approach is all the more justified since only a small fraction of the information held by the regulatory agencies is made publicly available. The EMA's administrative processes, and especially reviews of drugs suspected of causing serious adverse effects, are too long in the face of the pressing need to safeguard patients and European populations. These drawn-out processes benefit the pharmaceutical companies that market the drugs in question. But they also delay the sharing of knowledge about these drugs' adverse effects and deprive healthcare professionals and patients of the opportunity to take this knowledge into account when deciding which treatments to use.

Throughout our requests for information, the EMA has regularly demonstrated its conception of the protection of commercial interests, which gives this protection priority over the transparency of clinical data.

Prescrire
83, boulevard Voltaire
75558 PARIS CEDEX 11
FRANCE

Tel. : (33) (0)1 49 23 72 80
Fax : (33) (0)1 49 23 76 48
contact@prescrire.org

Site internet
Web site
www.prescrire.org

Service aux Abonnés
Tel. : (33) (0)1 49 23 72 86
Fax : (33) (0)1 49 23 76 48
abonnements@prescrire.org

International
Subscription Department
Tel. : (33) (0)1 49 23 72 88
Fax : (33) (0)1 49 23 76 48
international@prescrire.org

Association Médex Prescrire

Organisme indépendant
de formation permanente
des soignants

Independent organization
continuing education
for health professionals

Aggrégation FMC, IFR et autres
Org. FC 11 751 711 075
N° TVA : FR 48 340647619
SIRET 340 647 619 00014
Code NAF : 8532
RFP CCP Paris
30041 00001 0061 2034 020 94
Association loi de 1901
n° 884331 - JO 21031/1987
(Statut sur demande)

The European Medicines Agency's role is to safeguard patients and European populations. The clinical data in its possession are common property and a matter of public interest. These data contribute to the knowledge of drugs, and especially of their adverse effects. They belong no more to pharmaceutical companies than to the entire community. In all circumstances, the importance of disclosing these data, in terms of public health, surpasses the importance of protecting commercial interests.

Complaint No 1: access to all the documents relating to the assessment report on the Risk Management Plan (RMP) for *rimonabant*.

Our first request on this subject dates back to 18 September 2008. Several exchanges with the EMA ensued, until 30 October 2008. *Prescrire* remained proactive throughout this process. Our request on 18 September 2008 was clear: all the PSURs (periodic safety update reports), the assessment reports produced by the CHMP for variations II/0008 and II/0011, and all of the documents relating to the RMP for *rimonabant*.

We also want to stress that, as outside parties subject to EMA's policies, and since the EMA website has no publicly accessible register listing all the documents produced and held by the agency, it is difficult to ask for a particular document when requesting access to literature, even for an experienced specialist team like *Prescrire*.

We recognise that the EMA gave access to the variation assessment reports II/0008 and II/0011, but not to their appendices. However these appendices appear useful, because they include the assessment reports of the rapporteur countries, which in theory are more detailed than the CHMP's variation reports. We had to work out for ourselves that the EMA only supplies the appendices of CHMP variation assessment reports if they are explicitly named in our requests. Otherwise, even though the appendices are listed in the "Attachments" section of the variation assessment reports, they are not supplied spontaneously. Our impression was that this showed lack of goodwill on the part of the EMA.

The EMA refused to give us access to the PSURs on *rimonabant*. We will come back to this point in the next section, which deals with our second complaint.

Let us return to our first complaint. We also asked for all of the documents relating to the RMP assessment report: a straightforward request. Yet the EMA asked us to clarify our request, probably because we had not asked for any specific documents. How can anyone know the exact title of documents that they do not know exist? The EMA then offered us 3 documents: "*risk management plans*"; "*initial scientific discussion*" and "*assessment reports on risk management plan and/or PSUR*". Again, as no public register lists the documents produced and held by the EMA about the RMP for *rimonabant*, we had to put our trust in the EMA. Further to our complaint being maintained, your inquiry will provide an opportunity to check the list of documents available on the subject at the time.

Regarding the item "assessment reports on risk management plan and/or PSUR", we initially thought that it referred to two documents: on one hand an "assessment report on risk management" and, on the other hand, one or more "PSURs". That is why we rephrased our request into three points "all PSURs"; "*risk management plan*" and "*assessment report on risk management plan*". We definitely did not intend to refuse the "assessment report on PSUR" part: we had asked for all of the documents in our initial request! The EMA's concealment of this long section of the Swedish assessment report is hard to justify, and the EMA acknowledged this in the opinion it issued about our complaints on 31 January 2011.

After receiving the 68-page Swedish document, 65 pages of which had been blacked out, we protested in a letter dated 21 October 2008. We repeated our request for all the documents, including the PSURs. On 30 October 2008, the EMA asked us again to clarify our request and to confirm that we did indeed want the "assessment report on PSUR" part of the Swedish assessment report. The EMA states in its opinion dated 31 January 2011 that *Prescrire* did not reply to this request for clarification. The reasons for this are simple: knowing that a few days earlier, on 23 October 2008, the CHMP had recommended the suspension of the marketing authorisations for *rimonabant*, we decided to put an end to this time-consuming and highly unproductive exchange with the EMA.

Complaint No 2: refused access to several PSURs.

The EMA has systematically refused over a period of several years to send PSURs, including the PSURs on *rimonabant*. At the time of the EMA's opinion dated 31 January 2011 on our complaints, we had not had a single PSUR on any drug from the EMA. We received the first PSUR on 08 March 2011, on *travoprost*, following a request on 21 December 2010. We were informed on 19 January 2011 that the PSUR would be sent. On 8 March, we received half of the requested PSUR on a CD-ROM. After we objected, the EMA supplied the second half of the PSUR. According to the EMA, it was a simple oversight.

In the end, it took over 2 years for the EMA to agree to send a PSUR. The fact that it agreed is a significant advance. It remains for the EMA to make all drug PSURs available online without delay, because requests from *Prescrire* or other organisations will frequently be made, and understandably so: the information about adverse effects given in Summary of Product Characteristics (SPCs) and in the EMA's "Steps taken after granting authorisation" tables is posted online some time after the source of the information and is too brief to enable independent drug evaluation teams to assess causality.

As for the turnaround time, we would like to share a few specific dates for the first PSUR that the EMA sent us in March 2011, which was a PSUR for *travoprost* (the request for this PSUR is unrelated to our complaints of 31 August 2010). This PSUR is a document that covers the period from 01 March 2006 to 28 February 2009. It is dated April 2009. After this date, the first CHMP safety variation was recommended on 23 September 2010. The European Commission validated this variation on 28 October 2010. Then the "Steps taken after granting authorisation" table for the drug was updated, which prompted our request for the PSUR in December 2010. If this PSUR had been available online immediately, we would have been able to read it in April 2009, 23 months sooner.

Third complaint: requests for packaging materials.

A drug's packaging is crucial to its correct and safe use. Teams like *Prescrire* that systematically analyse drug packaging are rare, but their work brings to light numerous features that can create confusion between drugs and cause medication errors. Some packaging items are dangerous, exposing patients to the risk of serious events or even death.

The EMA publishes the marketing authorisation annexes pertaining to labelling and the package leaflet on its website. But these documents do not allow examination of the drug's packaging. Pharmaceutical companies send the EMA colour mock-ups of the outer packaging and labelling. These items are not available in the marketing authorisation annexes however. The public has no access to the results of the EMA's examination of packaging items or to the results of the readability checks carried out on package leaflets. When Novartis, the company that markets *Sebivo*^o (*telbivudine*), refused to send the packaging to *Prescrire*, we decided to ask the EMA for the mock-ups of the boxes and blister labelling.

The EMA considers that the colour mock-ups included in marketing authorisation application dossiers are confidential. But we had no intention of obtaining packaging that predated the drug's market introduction. In our letter dated 23 April 2009, we were asking for the most recent version of these mock-ups held by the EMA. As *Sebivo*^o was authorised on 24 April 2007 and had already undergone 6 variations at the time of our request, we assumed that the EMA would have packaging materials dating from after its market introduction.

According to the procedure cited by the EMA for examining drug packaging (The Revised checking process of mock-ups and specimens of outer/immediate labelling and package leaflet), a sample of packaging materials must be sent to the EMA 15 days before market launch and before certain variations. It appears therefore that we should have requested copies of the specimens rather than mock-ups, although the EMA's opinion dated 31 January 2011 about our complaint does not clarify the procedure we should have followed. In any case, Mr Lönngren's two terse refusals were in no way explicit. He could have justified his reasons, indicating which Sebivo^o packaging materials were in the EMA's possession. The EMA could have sent us photographs of the specimens it held or, as the drug in question was Sebivo^o, a colour copy of the sides of the box and the blister labelling. We maintain that our exchange with Mr Lönngren does not reflect well on this administration.

Fourth complaint: requests for assessment reports relating to the European referral on *dextropropoxyphene*.

We confirm that the EMA sent us on 13 October 2010 the documents requested, but we maintain that the delay, on the grounds that these documents could only be released after a European Commission Decision had been adopted, is unacceptable. We would like to reiterate the facts relating to *dextropropoxyphene*.

Dextropropoxyphene was withdrawn in Switzerland in 2003, in Sweden in 2006, then in the United Kingdom. In spite of this, no decision was taken to conduct a European referral. After *Prescrire* wrote to the European Commission on 11 September 2007, the Commission launched a referral on combination products containing *dextropropoxyphene* and *paracetamol* in December 2007, pursuant to Article 31 of Directive 2001/83/EC. We are familiar with the kind of events that could have hindered the progress of this procedure: repeated "clock stops", refocusing the procedure to include products containing *dextropropoxyphene* on its own, the discovery of an injectable form in one member state, opposition from certain generic drugs manufacturers, etc. In the end, it took 3 years for the European decision to be issued. The last batches of products containing *dextropropoxyphene* will be withdrawn from the French market on 01 April 2011.

By arguing that it had to wait until the European Commission had reached a Decision, on a drug that was available on the market, the EMA further delayed access to the data, in a process that had already dragged on for too long. It benefited the pharmaceutical companies marketing these dangerous drugs, but not patients. Civil society might see in this an additional subterfuge to protect commercial interests. The refusal to send *Prescrire* the *dextropropoxyphene* review documents is just another example. We maintain our complaint about the unjustified delay in the EMA's response.

Fifth complaint: refused access to an assessment report on the review of the dangers of topical *ketoprofen*.

In this case, the EMA brandishes a similar argument for its refusal regarding *dextropropoxyphene*. It refers to Article 4(3) of Regulation (EC) No 1049/2001, concerning public access to administrative documents: "*access to a document, drawn up by an institution for internal use or received by an institution, which relates to a matter where the decision has not been taken by the institution, shall be refused if disclosure of the document would seriously undermine the institution's decision-making process, unless there is an overriding public interest in disclosure*".

The EMA therefore seems to consider that the request for the assessment report on topical *ketoprofen* is of insufficient public interest to justify its disclosure. We do not accept this argument.

Initially, the French drug regulatory agency (Afssaps) suspended the marketing authorisations for topical *ketoprofen* in France. France's Council of State (its highest judicial authority) then reversed the Afssaps decision. It cited as one of its arguments, the opinion of the co-rapporteur, appointed for the European procedure pursuant to Article 107 of Directive 2001/83/EC, that the marketing authorisations should not be withdrawn. The Council of State also mentioned that 20 of the member states consulted were not envisaging withdrawing the drug. However, when *Prescrire* asked for the co-rapporteur assessment report, it was refused by the EMA. So who informed the Council of State of the conclusions of the co-rapporteur assessment report? Why was *Prescrire* refused access to this information by the EMA?

The European Commission's Decision on this subject was taken on 29 November 2010, but we have still not received the co-rapporteur assessment report.

Ultimately, we consider that the EMA's attitude towards our request detracts from its remit to safeguard public health. Topical *ketoprofen* is still sold in Europe, exposing patients to serious cutaneous risks, yet it has no particular therapeutic value compared to other drugs of the same therapeutic group. Understandably, the pharmaceutical companies that market these products are pleased, but the next patients to fall victim to their adverse effects will regret the decision.

Conclusion:

Most of the requests mentioned in our complaints reflect maladministration practices by the EMA, which doubtless go beyond *Prescrire*'s requests for information:

- unacceptably long delays before disclosing information, particularly about adverse effects;
- insufficiently explicit responses, that rarely enable us to fine-tune our requests;
- blatant refusals to provide documentation.

Claiming that EMA documents cannot be released until the European Commission has made its Decision is yet another way of avoiding transparency. If the European Union accepts such a practice, it will be a serious setback for transparency. Civil society will see where the Community administrations' chosen priorities lie.

We have studied the EMA's new transparency rules from November 2010. We will observe their implementation and their limits. Because although these rules were supposed to bring out into the open certain types of document that the EMA had previously kept under wraps, they still only apply to a restrictive list of documents produced and held by the EMA, and therefore represent a limited interpretation of Regulation EC No 1049/2001 concerning public access to administrative documents.

We call on the EMA to provide public access through its website to a comprehensive register of all the documents it holds: all of those it produces and all of those it receives.

Information about the adverse effects of drugs is scientific data. The EMA has no right to refuse teams of healthcare professionals like *Prescrire* access to such data, on the pretext of their commercially confidential nature or the fact that an administrative procedure (the one conducted by the EMA and the Commission) is still underway.

We call on the EMA to provide immediate public access through its website to all supporting documents in its possession, relating to its recommendations.

We call on the EMA to provide public access to the raw data held in its databases, and especially the EudraVigilance database.

We call on the EMA to rapidly meet all its obligations in terms of transparency. For example, it is high time the Commissions' detailed agendas were released.

We call on the EMA to rapidly provide public access to the minutes and scientific opinions of all of its committees, working parties and other groups.

We call on the EMA to rapidly provide public access through its website to conflict of interest statements for all of its experts and participants of committees, working parties and other groups.

We call on the EMA to provide more constructive responses to concerned parties, and to help them determine how best to formulate their requests where appropriate.

To conclude our remarks, we would like to draw your attention to a recent request *Prescrire* submitted to the EMA. This is not another complaint, but an example that will doubtless help you to understand the scale of our dissatisfaction with the EMA. This request shows that the extent of the EMA's maladministration goes well beyond the requests for information submitted by *Prescrire* and other organisations.

Pioglitazone exposes patients to the risk of bladder cancer. This risk has been suspected for several years on the basis of animal studies. The risk in humans was subsequently raised by the Food and Drug Administration and added to the US Summary of Product Characteristics (SPC), according to the most recent version dated 31 August 2010 related to the renewal of the marketing authorisation. The European SPC still makes no reference to the risk in humans. On 18 January 2011, we asked the EMA for detailed data on this risk and the outstanding follow-up measures. The EMA replied on 18 March 2011, informing us of the follow-up measures, but provided no detailed data on the corresponding adverse effects. According to the EMA, the current data indeed reflect a safety signal. In March 2011, the EMA announced the start of an assessment procedure into this risk, pursuant to Article 20 of Regulation EC No 726/2004. We examined a few examples of Article 20 procedures: many long months separate the period when the risk is identified and the formal measures announced by the European Commission. *Pioglitazone*'s harm-benefit balance is clearly unfavourable. Its harms clearly outweigh any therapeutic value it provides. Why was immediate action not taken to suspend the marketing authorisations for *pioglitazone* pending the conclusions of the review?

Licensing drugs with unfavourable harm-benefit balances and not suspending marketing authorisations when a drug is suspected of posing a serious threat, are in themselves acts of serious maladministration. Pharmaceutical companies benefit, at the expense of the patients who remain exposed to these risks. As our requests show, the EMA persists in limiting access to information. There are concerns that this is one way in which the EMA gives priority to the interests of marketing authorisation holders.

This policy is seriously damaging to public health. On the other hand, a policy focused unequivocally on public health would lead to transparency on all clinical data, and especially data on adverse effects.

Thank you for your attention.

Best regards,

On behalf of *Prescrire*:

Olivier Huyghe