Proton pump inhibitors in general medicine. Comparison of routine practices with marketing authorization indications

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SUMMARY
Objective — To determine whether inaugural prescriptions for proton pump inhibitors (PPI) written by general practitioners in the Grenoble region are in non-compliance with the indications of the French drug marketing authorization.

Methods — The study was conducted on all inaugural PPI prescriptions written by general practitioners in Grenoble region between March 1 and March 31, 2004. Analyses were performed on a random sample of 600 representative prescriptions. A questionnaire was sent to the general practitioners who had written these prescriptions. There were 255 responses which could be analyzed.

Result — Among the 19,983 prescriptions for PPIs written in March 2004, 4,442 (22.8%) were first-time treatments. 85.9% of them were issued by general practitioners. The main reasons for prescription identified in the study sample were the association with other drugs [56.1%; 95%CI 50.0-62.2], gastroesophageal reflux disease [29.4%; 95%CI 23.8-35.0] and dyspepsia [11.4%; 95%CI 7.5-15.3]. The rate of non-compliance with the marketing authorization was 46.3% [95%CI 40.2-52.4], including 20.4% [95%CI 15.5-25.3] for inappropriate medical indications.

Conclusion — General practitioners were the principal prescribers of inaugural PPI treatments. Even after excluding prescriptions which were non-compliant because of a regulatory problem, one out of five prescriptions were written for inappropriate medical indications.

RÉSUMé
Inhibiteurs de la pompe à protons en médecine générale. Évaluation des pratiques au regard de l’autorisation de mise sur le marché
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Objectif — Mesurer la non conformité des instaurations d’inhibiteurs de la pompe à protons, au regard de l’autorisation de mise sur le marché.

Méthode — La population étudiée était l’ensemble des instaurations d’inhibiteurs de la pompe à protons par les médecins généralistes sur la région grenobloise du 01/03/2004 au 31/03/2004. Un tirage aléatoire a permis de sélectionner un échantillon représentatif de 600 prescriptions. Un questionnaire a été envoyé aux médecins généralistes à l’origine de ces prescriptions. Le nombre de dossiers exploitables était de 255.

Résultats — Sur les 19 983 prescriptions d’inhibiteurs de la pompe à protons de mars 2004, 4 442 prescriptions (22,8 %) étaient des instaurations de traitement. 85,9 % d’entre elles provenaient des médecins généralistes. Sur l’échantillon étudié, les principaux motifs de prescription étaient l’association à d’autres médicaments (56,1 % ; IC 95 % : 50,0-62,2), le reflux gastro-œsophagien (29,4 % ; IC 95 % : 23,8-35,0) et la dyspepsie (11,4 % ; IC 95 % : 7,5-15,3). Le taux de non conformité au regard de l’autorisation de mise sur le marché était de 46,3 % [IC 95 % : 40,2-52,4] dont 20,4 % [IC 95 % : 15,5-25,3] pour indication médicale non validée.

Conclusion — Les médecins généralistes étaient les principaux prescripteurs d’inhibiteurs de la pompe à protons en instauration de traitement. Même après exclusion des non conformités vis à vis de l’AMM, les indications médicales non validées représentaient une prescription sur cinq.

Introduction

In the protocol statement signed between French physicians and the national union of healthcare insurance funds and validated by the French ministry of health on March 23, 2006 (Journal Officiel, March 30, 2006), it was agreed that physicians would attempt to abide by the medical recommendations and therapeutic indications for reimbursable prescriptions for proton pump inhibitors (PPI). Few published studies have analyzed PPI prescription practices in general medicine. As early as 1995, one English team [1] observed an increase in PPI prescriptions, particularly for inappropriate indications such as non-ulcer dyspepsia or epigastric pain observed in the context of functional intestinal disorders. Conversely, another team [2] found that PPIs were underused, particularly in combination with non-steroidal anti-inflammatory drugs (NSAID) [2].

An evaluation of current practices, in comparison with defined recommendations, is a prerequisite to improve prescription practices. In the present context, the marketing approval process for reimbursable prescriptions serves as the legal reference. In France, marketing approval is proposed by French Agency for the safety of health products (AFSSAPS, Agence Française de Sécurité Sanitaire des Produits de Santé) and is awarded by the government. The medical reference corresponds to the official guidelines for good clinical practices elaborated by the High authority for health (HAS, Haute Autorité de Santé) or the AFSSAPS, but at the time of this study, the AFSSAPS recommendations excluded prescriptions combining PPI with NSAID [3].
In daily practice, it is easier to improve first-time prescriptions than renewals. The purpose of our study was thus to measure the proportion of non compliant inaugural prescriptions for PPIs in the Grenoble region in comparison with indications provided by the marketing authorization.

Methods

This study was designed to assess overall general medicine practices in the French administrative district of Isère which includes the city of Grenoble and environing areas. It was conducted within the framework of the agreement established in 2004 between general practitioners in Isère and the local healthcare insurance funds (general funds excluding mutual insurance funds) to audit overall practices in general medicine and specifically to examine compliance of prescriptions for PPIs within the official marketing authorization. All first-time prescriptions for PPI written between March 1 and March 31, 2004 for patients living in the Grenoble area and which were reimbursed by the funds were included for analysis.

Inaugural prescription for PPI was defined as a prescription for a PPI reimbursed by the health insurance fund to a person who had not been reimbursed for any anti-secretory agent during the year preceding the study. The study population was thus composed of patients treated with PPI by general practitioners in March 2004. A random sample of 600 representative prescriptions was drawn for analysis. The size of the sample was based on the hypothesis of 50% non compliance, 5% precision, and 5% alpha risk. This gave N=384 which was increased to 600 to account for potential non-responders.

Data were extracted from the health insurance fund reimbursement database and from a questionnaire sent in June 2004 to general practitioners who had prescribed PPIs for patients selected for the study sample. Data were collected by the Grenoble health insurance fund medical council and recorded using a standard grid. The grid, which listed patient symptoms and diagnostic criteria established by experts from the Grenoble University Hospital, was designed to describe as precisely as possible the diagnosis and the reasons for the first-time prescription of a PPI: gastroesophageal reflux disease (GERD), with or without endoscopy, with or without esophagitis, prevention or treatment of epigastric pain in a patient taking NSAID, prevention or treatment of gastroduodenal lesions in patients taking NSAID, non-specific epigastric pain, functional intestinal disorders, dyspepsia, other. The questionnaire was established in partnership between the university experts and the physician-councilors of the healthcare funds. The questionnaire did not ask the prescriber to report the diagnosis which had been established, but rather to answer a series of open or multiple-choice questions concerning the patient: age, gender, specialist’s opinion prior to prescription, family history of ulcer, patient’s personal medical history, existence and results of a recent gastroscopy performed within the last three months or earlier, presence of a hospital stay within recent months, prior treatments, detailed symptoms. The physicians could make the questionnaire anonymous by striking out their identity and that of the patient. Data were recorded anonymously.

Prescriptions were compared with the medical indications and doses stated in the marketing authorization document in vigor during the study period [4]. In March 2004, marketing approval had been awarded for PPI for the following medical conditions: ulcerative disease, GERD with or without esophagitis, treatment and prevention of gastroduodenal lesions in patients...
tak ing NSAID. For the prevention of gastroduodenal lesions in patients taking NSAID, the marketing authorization specifically states that PPIs are indicated for “patients at risk (age >65 years, history of gastroduodenal ulcer)”. Although the marketing authorization indications were limited to the prevention of gastroduodenal lesions and did not mention the prevention of secondary effects of NSAID (including epigastric pain), we considered that a PPI prescribed because of a prior history of intolerance to NSAID was in compliance with the marketing authorization. We based this assumption on the following facts:

- the marketing authorization did not establish an all-inclusive list of “patients at risk”;
- there is no medical standard detailing the indications for PPIs in combination with NSAID (the AFSSAPS excluded this topic from its guidelines issued in 1999 [3]),
- certain experts propose lowering the NSAID dose or prescribing another drug and the adjunction of omeprazole, keeping in mind that comparative studies designed to demonstrate the efficacy of omeprazole for the treatment of NSAID-related dyspepsia also included GERD patients, so that “the degree of efficacy of omeprazole must be considered as relative” [5].

PPIs do not have marketing approval for patients with dyspepsia, non-specific epigastric pain, functional intestinal disorders, and as a therapeutic test. The AFSSAPS does not recommend use of PPIs for these indications [3].

Prescriptions for PPIs were considered non-compliant with the marketing authorization indications if one of the following three criteria was satisfied:

1. The medical indication was not in compliance with the marketing authorization: systematic combination of PPI and NSAID without the presence of a risk factor or history of NSAID-related epigastric pain, combination with a corticosteroid without presence of GERD, dyspepsia, non-specific epigastric pain, functional intestinal disorder, therapeutic test.

2. Prescription of a drug whose marketing authorization does not include a medical indication warranting the prescription of a PPI: at the time of this study, rabeprazole and esomeprazole did not have marketing authorization for the prevention of NSAID-related gastroduodenal lesions and the marketing authorization for pantoprazole mentioned only non-selective NSAID.

3. The dose was not in compliance with the marketing authorization: there is no marketing authorization for high-dose PPI for first-intention treatment of GERD without esophagitis and for the prevention of NSAID-related gastroduodenal lesions; with one exception: omeprazole 20 mg has marketing authorization for the prevention of NSAID-related gastroduodenal lesions.

Each prescription of a PPI identified as non-compliant was assigned to one of these three categories as detailed in figure 1.

Independently of their compliance with the marketing authorization, PPI prescriptions written for GERD were examined in light of the guidelines for good clinical practices published for endoscopic procedures where it is stated that an upper endoscopy procedure should be performed for all patients aged over 50 years presenting with GERD [6, 7].

The reimbursement database of the healthcare insurance fund registered 19,893 prescriptions for PPIs in March 2004. Among these, 4,542 (22.8%) were first-time prescriptions. Among these 4,542 first-time prescriptions, 3,900 (85.9%) were written by general practitioners. The study sample was randomly selected from these 3,900 prescriptions.

### Statistical analysis

Excel was used for data processing, using the chi-square test to compare sex ratios and Fisher’s exact test to compare ages. Results are presented as percentage, with the 5% alpha risk interval of confidence for small sample size.

## Results

Responses were received for 281 of the 600 questionnaires sent to the physicians who had written prescriptions for the patients selected for the study sample. Among these, 255 could be analyzed. For the 600 questionnaires, mean patient age was 50.5 years and the M/F sex-ratio was 1.4. For the 255 analyzed questionnaires, mean patient age was 51.2 years and the M/F sex-ratio was 1.4. There was no difference for patient age (P=0.23) or for M/F sex-ratio (P=0.75).

For 235 of the 255 first-time prescriptions written by general practitioners [92.2%; 95%CI: 88.9-95.5], the general practitioner had made the decision to prescribe without knowledge of a prior opinion from a specialist.
Reasons for the prescription (Table I)

Among the 255 prescriptions for PPI, 75 [29.4%; 95%CI: 23.8-35.0] were written to institute a first-time treatment by PPI. Among these 75 patients, 31 (41.3%) were over 50 years old and did not had an endoscopy.

Combination with selective or non-selective NSAID, aspirin at any dose, and corticosteroids was noted for 143 of the 255 prescriptions [56.1%; 95%CI: 50.0-62.2] of the first-time prescriptions for PPIs. Combination of a PPI with NSAID (excluding coxibs), aspirin, or corticosteroids accounted for 127 of the 255 prescriptions [49.8%; 95%CI: 43.7-55.9] of the first-time prescriptions for PPIs. Other findings noted for these 127 prescriptions were: history of ulcer in 7 patients (5.5%), history of previous intolerance to NSAID in 89 patients [70.1%; 95%CI: 62.2-78.0], age over 65 years in 19 patients [15.0%; 95%CI: 8.8-21.2], and another reason for prescribing in 12 patients (9.5%; 95%CI: 4.4-14.6).

Epigastric pain and functional intestinal disorders without GERD were noted for 29 patients, 11.4% of first-time prescriptions for PPIs [95%CI: 7.5-15.3]: 11 patients with functional intestinal disorders (38% of these 29 patients), 13 patients with epigastric pain without GERD history of ulcer (45% of these 29 patients), and 5 patients with epigastric pain and a history of ulcer (17% of 29 patients). Among the 18 patients with epigastric pain, 13 (72.2%) had never been reimbursed for a prescription of an anti-acid agent.

Other reasons for prescribing were noted for 8 patients (3.1%), including six cases where the prescription was to test the effect on pharyngeal, pulmonary or thoracic symptoms with no prior digestive tract work-up (endoscopy, pHmetry, manometry).

Non-compliance of prescriptions with the marketing authorization (Table II)

For 118 of the 255 first-time prescriptions for PPI treatment [46.3%; 95%CI: 40.2-52.4], the prescription was not in compliance with the marketing authorization. Considering that a history of intolerance to NSAID also constituted non-compliance with the marketing authorization, 81.9% of the prescriptions (209/255) [95%CI: 77.2-86.6] were not in compliance with the marketing authorization. According to the marketing authorization indications, the medical reasons put forward to explain the first-time prescription of a PPI were inappropriate for 52 of the 255 prescriptions [20.4%; 95%CI: 17.5-25.3].

Among the 122 prescriptions for a combination of first-time PPI with a NSAID (coxibs excluded) or aspirin, 37 [30.3%; 95%CI: 25.1-35.5] were non-compliant: 9/122 (7.4%) because the indication was inappropriate, 9/122 (7.4%) because the indication for the other drug was inappropriate while the indication for the PPI was, and 19/122 [15.6%; 95%CI: 9.2-22.0] because the dose was outside the indicated range.

A combination with coxibs was non-compliant with the marketing authorization for 5 of 16 prescriptions [31.3%], including 3 prescriptions (18.8%) because the coxib prescription was inappropriate.

Regarding GERD (75 prescriptions), first-time PPI treatments were non-compliant with the marketing authorization for 34/75 prescriptions (45.3%) of the GERD patients [95%CI: 34.0-56.4]. In these cases, the prescription was inappropriate because of the dose.

Discussion

We report the results of a cross-sectional study on inaugural prescriptions for PPI treatment written by general practitioners. The prescriptions studied are representative of 86% of all institutions of PPI treatments in the Grenoble area. General practitioners wrote most of the primary prescriptions for PPIs and in 92% wrote the prescription without seeking the opinion of a specialist.

The data presented here are comparable with the data collected in 1991 where 90% of these type of prescriptions were written by general practitioners.

Three measures were taken to avoid diagnostic biases:

1) The study was limited to first-time prescriptions of PPI. This should enable collection of more reliable data compared with secondary prescriptions for continued or discontinued treatments.

2) The responses were anonymous. The selection bias of non-responders (53% of the sample) might be expected to compromise the representativeness of the data set. It can be noted however that such bias would under-estimate the results, considering that physicians writing inappropriate prescriptions would respond less readily to a survey questionnaire designed to audit prescription practices than physicians writing appropriate prescriptions. Similarly, even if the rate of prescriptions for inaugural treatment with PPI non-compliant with the marketing authorization had been 0% among the non-responders, the overall rate of non-compliance for the entire sample would have been, at least, 19.7% (118/600).

3) There is an information bias regarding the real reason for instituting PPI treatment. We attempted to limit the impact by not considering the diagnosis reported by the prescriber, evaluating the reason for prescribing PPI on the basis of the responses to the items on the questionnaire.

Ideally, it would have been best to couple the questionnaire responses with a physical examination of the patient (at a time as close as possible to the date of the prescription). This would have provided concrete evidence that the reason for prescribing, deducted from the analysis of the responses to the questionnaire items, was indeed the reason for which the physician had written the prescription. This would have nevertheless been highly

Table II. – Rate of inappropriate inaugural prescriptions for PPIs written by general practitioners in the Grenoble region in March 2004, according to the marketing authorization indications.

<table>
<thead>
<tr>
<th>Prescription Category</th>
<th>N</th>
<th>% [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate prescriptions</td>
<td>137</td>
<td>53.7 [47.6-59.8]</td>
</tr>
<tr>
<td>Inappropriate prescriptions(a)</td>
<td>118</td>
<td>46.3 [40.2-52.4]</td>
</tr>
<tr>
<td>non-compliant medical indication(b)</td>
<td>52</td>
<td>20.4 [15.5-25.3]</td>
</tr>
<tr>
<td>non-compliant drug(c)</td>
<td>12</td>
<td>4.7 [2.1-7.3]</td>
</tr>
<tr>
<td>non-compliant dose(d)</td>
<td>54</td>
<td>21.2 [16.2-26.2]</td>
</tr>
<tr>
<td>Total</td>
<td>255</td>
<td>100</td>
</tr>
</tbody>
</table>

Source: Medical service of the Grenoble health fund.

(a) Only one reason by prescription: in the event of comorbidity, the condition in compliance with the marketing authorization indications was retained, or by default the main disease.

(b) Example: epigastric pain.

(c) Example: according to the marketing authorization indications, pantoprazole combined with coxib was inappropriate because the indication was for non-selective NSAID only. Raabeprazole was no authorized for the prevention of NSAID-related gastroduodenal lesions.

(d) Example: pantoprazole 40 mg used for GERD without esophagitis.
resource-intensive without truly eliminating the selection bias related to non-response.

In France, there is no legal basis for a claim against a physician who writes a prescription which does not comply with the marketing authorization statement. The prescription is however not reimbursed by the healthcare insurance funds and could be challenged more readily in court [9]. For that reason, the physician has a legal requirement to add the notation “NR” (non remboursable) (articles L. 162-4 and R. 162-1-7 of the French social security code). Marketing authorization is established on the basis of studies presented by the drug manufacturer at a given date (the date of the marketing authorization), while the AFSSAPS and the High authority for health (HAS, Haute Autorité de Santé) elaborate evidence-based medical standards approved by a pluridisciplinary committee of experts. Consequently, the marketing authorization indications do not reflect the latest scientific evidence used to establish recommended medical practices. This type of discordance can be confusing for physicians whose practices are supposed to be in compliance with both marketing authorization indications and recommended medical practices. Thus, for this study, the choice of the marketing authorization as the standard reference for determining the appropriateness of physician prescriptions is controversial. Unfortunately, there was no other official reference for comparison since the guidelines for good clinical practices issued in 1999 excluded concomitant prescription of PPI and NSAID [3].

The prescription of NSAID – aspirin – corticosteroids – coxibs was a leading cause of inaugural prescriptions for PPI in the Grenoble area (56% of prescriptions in the study sample). These first-time prescriptions for PPIs were not in compliance with the marketing authorization 30% of the time, but only 7.4% were inappropriate because of the medical indication. For combination treatments associating NSAID (excluding coxibs), aspirin or a corticosteroid with PPI, 70% of the prescriptions were written for patients who had a history of clinical intolerance to NSAID and no other risk factor. Consequently, these prescriptions concerned the prevention or treatment of NSAID-related epigastric pain or dyspepsia more than the prevention or treatment of gastroduodenal lesions. This is a point for which the current marketing authorization indications present two problems:

1. Prevention or treatment of NSAID-related epigastric pain with a PPI was not taken into consideration by the authorization statement which only mentions prevention or treatment of gastroduodenal lesions without considering the adverse effects of NSAID. There is however no evidence of a link between the risk of lesions and subjective digestive signs [10-12]. If the presence of a history of clinical intolerance to NSAID is considered to constitute non-compliance with the marketing authorization, the rate of inappropriate prescriptions, considering all first-time prescriptions for PPIs, would have been 82% instead of 46%.

2. The marketing authorization statement does not give a sufficiently detailed description of the situations for which the risk of gastrointestinal lesions is great enough to warrant the prescription of a PPI. Only three situations are mentioned: age above 65 years, history of ulcer, and digestive bleeding. Other risk factors are mentioned in the literature including use of anti-coagulants or anti-aggregates [13], severe cardiovascular morbidity, and presence of Helicobacter pylori which could increase 6-fold the risk of ulcer and bleeding ulcer [14].

Sturkenboom et al. [2] reported that among patients receiving a prescription for a NSAID, 86.6% had a risk factor for ulcerative disease and that among those with two or more risk factors, and 81.2% were not given prophylactic treatment. Thus PPIs and NSAIDs are prescribed uselessly for some patients and insufficiently for others.

The prevention or treatment of NSAID-related epigastric pain, as well as the prevention of gastroduodenal lesions are primary reasons for inaugural treatments with PPIs. Thus, considering that no change in the French marketing authorization for PPIs can be expected in the near future, the regulatory authorities (HAS or AFSSAPS) should elaborate recommendations of specific medical practices.

The inaugural prescriptions for PPIs in patients with GERD were not in compliance with the marketing authorization in 45% of the cases because of the dose of the formulation prescribed. Institution of a treatment with a PPI was appropriate, but not the dose. However, for patients with mild to moderate reflux, there is evidence suggesting that amines or anti-histamine agents (anti-H2) can be a legitimate first-intention treatment in combination with dietary measures [15]. In our data set there was no information concerning the frequency of symptoms or the presence or not of prior treatments before instituting treatment with a PPI. In their study, Naunton et al. [16] gave anti-H2 agents as the first-intention treatment for less than 60% of patients with mild reflux symptoms. According to these authors, use of PPI as a first-intention treatment would hinder the identification of patients who would respond to anti-H2 agents and as a consequence increase overall expenditures. Anti-H2 agents improve symptoms significantly in 50 to 70% of patients [17, 18]. If no improvement is observed after two weeks of treatment, a PPI could be prescribed. The AFSSAPS proposes this strategy uniquely for typical GERD in patients presenting symptoms for less than once a week [3].

The marketing authorization document for PPIs states that low doses should be used for first-time prescriptions for patients with GERD without esophagitis. This is in agreement with the recommended clinical practices issued by the AFSSAPS for patients aged less than 50 years with typical GERD. It is not however in agreement with the AFSSAPS guidelines for other situations after endoscopy where the recommended dose of PPI is either half of the standard dose or the standard dose, even without esophagitis [3]. Marketing authorizations in other countries recommend the standard dose for these indications.

Independently of the marketing authorization, patients aged over 50 years presenting their first symptoms of reflux should, according to current guidelines [6, 7] undergo an endoscopic exploration before introducing a PPI. The objective here is to avoid missing an esophageal neoplastic or preneoplastic lesion (Barrett’s esophagus) which would require regular endoscopic and pathological surveillance. The same is true for patients with symptoms considered to be warning signals. Among the first-line prescriptions for PPI for patients with GERD, 41.3% were written for patients aged over 50 years who did not had an endoscopic exploration. The sample size was too small here to extrapolate this finding to all first-line treatments for GERD, but evidence from an earlier French study suggests that routine practices are not compliant with recommendations for endoscopic explorations in 48% of patients [19].

For 11.4% of patients, the reason for prescribing a PPI was the presence of dyspepsia or functional intestinal disorders. The proportion of dyspepsia cases identified in an English study on the indications for new prescriptions for PPIs increased from 16% in 1991 to 32% in 1995 [1]. In this situation, if the patient does not have GERD, prescription of a PPI non-compliant with both the marketing authorization and the AFSSAPS guidelines.

Regarding the over-prescription of PPIs, our findings are in agreement with those reported by Nauton et al. [16] in 2000. These authors also found that physicians failed to comply with the consensus statements because they over-prescribed PPIs without adequately testing the effect of anti-H2 agents, failed to sufficiently reevaluate the need for continuing the PPI treatment, and were insufficiently convinced of the effect of eliminating drugs exacerbating reflux.
Under-use of PPIs, i.e. situations where a prescription of a PPI would be legitimate but is not written, was beyond the scope of the present study. It would nevertheless be interesting to conduct a study in France to assess appropriate use of PPIs.

There are logical explanations for the practices observed in the present study:

— official guidelines have not been issued in France concerning good clinical practices for the use of PPI in combination with NSAID and corticosteroids, in particular for the prevention or treatment of NSAID-related epigastric pain;

— the marketing authorization mentions a multitude of products and indications (five INN and eight proprietary names for PPI, 21 different indications, six for ulcerative disease, twelve for GERD and esophagitis, three for combinations with NSAID);

— General practitioners are insufficiently aware of the marketing authorization indications and the good clinical practices guidelines concerning PPI prescriptions,

— failure of the regulatory obligation to add the notation "NR" (not reimbursable) for all prescriptions outside the marketing authorization indications.

In conclusion, our work demonstrated that even after excluding non-compliant prescriptions related to drug dose or to a specific INN, one out of five prescriptions for first-time PPI treatments were based on medical indications which failed to comply with either the marketing authorization nor with the AFSSAPS guidelines. Any attempt to improve prescription practices should be focused on general practitioners since they wrote the large majority of inaugural prescriptions for PPIs. It would also be useful to obtain more information on prescription practices among specialists and public institutions.

To be successful, a program designed to improve overall prescription practices must meet two prerequisites:

— non-compliance with accepted standards should be demonstrated and published. Demonstrating this non-compliance was the object of our audit of current practices.

— prescription rules should be clarified officially, particularly for combination prescriptions with NSAID. The question is whether this is a mission of the HAS or the AFSSAPS?

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