SUMMARY

STUDY TITLE

Description of the Use of Quetiapine Extended Release (XR) in Real-life Practice in France: QUIéTUDE Observational Study

SCIENTIFIC COMMITTEE

The scientific committee for the study consists of 2 members:

Prof. Bruno Falissard, *Psychiatrist and Methodologist*

Prof. Pierre-Michel Llorca, *Psychiatrist*

CONTEXT

The Quiétude study was set in place at the request of the health authorities in order to assess the use of quetiapine, in real-life practice, although limited data on the role of the proprietary medicinal product in the management of psychiatric disorders are available in France.

The purpose of this study is to provide a description of the use of Xeroquel® in France, following its marketing authorisation, for patients with schizophrenia or bipolar disorder.

This study report presents the whole of analyses: it covers the results of the inclusion report and completed it with the results of the longitudinal study.

OBJECTIVES

Primary objective

- To describe the demographic and clinical characteristics of the patients as well as the prescription conditions of Xeroquel® in actual practice in patients receiving the treatment for the 1st time, irrespective of the indication.

Secondary objectives

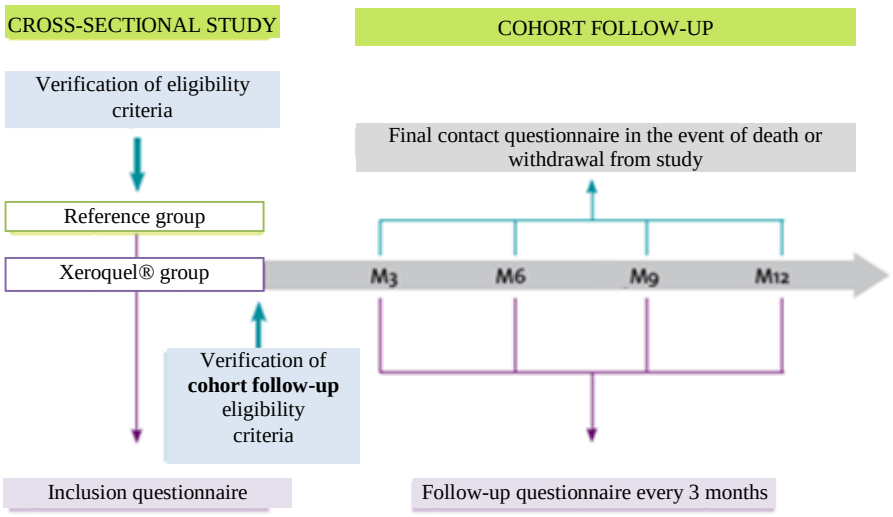
- 1) To assess the patients' health status and the use of medical resources up to one year post initiation of Xeroquel® for the treatment of schizophrenia or acute-phase bipolar disorder (not described in this report).

- 2) To assess the representativeness of the patients treated with Xeroquel® among all patients with schizophrenia or acute-phase bipolar disorder and to identify the existence of potential channelling bias.

METHODS

General study plan

This was a prospective, national, observational, pharmacoepidemiological study conducted in both hospital-based and private psychiatric practices, comprising two stages, a cross-sectional study and cohort follow-up over 1 year.



For the cross-sectional study, 1400 patients were expected to be included by 275 psychiatrists, including:

- 1100 patients treated with Xeroquel® (all indications combined) comprising the **"Xeroquel® group"**
- 300 patients treated with a treatment other than Xeroquel® (150 patients presenting a diagnosis of schizophrenia and 150 patients presenting with a diagnosis of acute-phase bipolar disorder) comprising the **"reference group"**

For the cohort follow-up, the protocol required that between the 1100 patients treated by Xeroquel® in the cross-sectional study, 500 patients presenting a diagnosis of schizophrenia and 500 patients presenting with a diagnosis of acute-phase bipolar disorder were followed for a maximum of one year. The follow-up visits were performed every 3 months, during naturalistic visits (about 3-6-9-12 months)

Study population

The study population consisted of eligible patients included in the study by the participating investigating sites according to two groups:

Patients treated with Xeroquel®: patients for whom treatment with Xeroquel® was initiated on the day of inclusion (± 1 month) for all diseases combined (schizophrenia, bipolar disorder, MDD, other).

Patients in the reference group: patients with schizophrenia who started treatment with an atypical antipsychotic other than Xeroquel® or patients with acute-phase bipolar disorder whose treatment belongs to the following classes of drugs:

- Antiepileptic drugs (valproic acid and lamotrigine)
- Atypical antipsychotics other than Xeroquel®
- Antidepressants

Eligibility criteria in the cross-sectional study

> Eligibility criteria for patients in the "Xeroquel® group":

The study was conducted exclusively on incident patients (initiation of Xeroquel®) at inclusion.

Inclusion criteria:

1. Treated with Xeroquel® at initiation, all indications combined (incident patient)
2. Patient consenting to take part in the study

Exclusion criteria:

1. Patient participating in a clinical trial
2. Pregnant women

> Eligibility criteria for patients in the "reference group":

Inclusion criteria:

1. Patients with schizophrenia who have started treatment with an atypical antipsychotic drug other than Xeroquel® or patients with acute-phase bipolar disorder whose treatment belongs to the following classes of drugs:
    - Antiepileptic drugs (valproic acid and lamotrigine)
    - Atypical antipsychotics other than Xeroquel®
    - Antidepressants
2. Patient consenting to take part in the study

Exclusion criteria:

1. Patient participating in a clinical trial
2. Pregnant women

Eligibility criteria in the longitudinal study

Inclusion criteria for the cohort:

1. Patient from the "Xeroquel® group" [cross-sectional phase corresponding to patients treated with Xeroquel® at initiation (all indications combined)], consenting to take part in the study.
2. Aged over 18 years
3. Diagnosed with bipolar disorder or schizophrenia according to DSM IV criteria

Exclusion criteria for the cohort:

1. Patient participating in a clinical trial
2. Pregnant women

Exposure assessment

The population of interest of the cross-sectional study was formed from patients starting Xeroquel® treatment (all indications combined).

The patients included in the longitudinal study are treated with Xeroquel® at inclusion in the cohort and over the 1-year follow-up period. The patients continue to be followed up in the cohort (exposure to treatments post-Xeroquel®) for a year, even if they stop treatment. The ITT (intention to treat) principle was applied: patients having stopped treatment were not excluded from the analyses.

A reference group was also formed: patients with schizophrenia who have started treatment with an atypical antipsychotic drug other than Xeroquel® or patients with acute-phase bipolar disorder whose treatment belongs to the classes of drugs defined in the inclusion criteria.

Primary and secondary endpoints

The primary endpoint was the description of the combined Xeroquel® population (all indications) and of the prescription conditions.

The secondary endpoints are as follows:

- Assessment of the patients' health status up to one year post initiation of Xeroquel® for the treatment of schizophrenia or acute-phase bipolar disorder.

- The use of medical resources up to one year post initiation of Xeroquel® for the treatment of schizophrenia or acute-phase bipolar disorder.

- The representativeness of the patients treated with Xeroquel® among all of the patients with schizophrenia or bipolar disorder.

Required population size

In order to address the primary endpoint, based on a proportion (p) of 50% (null hypothesis), with an accuracy (i) of 5% and assuming a normal distribution ($\varepsilon = 1.96$ when $\alpha = 5\%$), 384 patients were required.

The size of the population sample was increased by 30% in order to take into account patients lost to follow-up: 500 patients per indication (500 patients with schizophrenia and 500 patients with bipolar disorder), i.e. 1000 patients in total. This population was also increased by 10% to allow for the use of Xeroquel® in indications other than schizophrenia or bipolar disorder.

Based on this estimate, 1100 patients (all indications combined) were to be included in the study for the Xeroquel® group.

In addition, in order to meet the secondary objective, it was necessary to include 150 patients with schizophrenia and 150 patients with bipolar disorder in the reference group who were not treated with Xeroquel®, in order to be able to compare them with patients treated with Xeroquel®.

IMPLEMENTATION OF THE STUDY

Recruitment of investigators

The study was conducted among a representative sample of psychiatrists prescribing Xeroquel® who were selected from the CEGEDIM professional database and stratified by type of facility and region of practice. The study protocol provided for the initiation of 425 psychiatrists in order to obtain 275 active physicians.

In total, out of all physicians contacted following the two rounds of enrolment:

- 589 agreed to participate (acceptance rate of 12%)
- 520 initiations were conducted (objective: 425, i.e. a rate of 122.4%)
- 269 physicians included at least one patient:
    - Investigator activity rate: 269/520 = 51.7% of investigators initiated in the study
    - Investigator activity rate compared to target: 269/275 = 97.8%

The first site was initiated on 07 December 2012; the last site on 14 October 2013.

Inclusion of patients

The first inclusion in the study took place on 11 December 2012 (FPI: first patient in). The sites were able to include patients having initiated their treatment with Xeroquel® from the date on which they were enrolled in the study.

The initial inclusion period was 6 months. In June 2013, 173 physicians were active and had included 870 patients. Given the rate of inclusions and the distribution of patients included into groups of interest significantly different from the protocol hypotheses, an extension of the inclusion period was proposed in order to meet the protocol targets for each group.

The last patient was included on 30 November 2013. The length of the inclusion period was 11.5 months.

Finally, 2303 patients were included in the study by 269 active physicians, i.e. an average of 8.6 patients/physician.

Patient follow-up

As the last patient was included on 30 November 2013, the one-year follow-up period for each patient included in the cohort ended on 30 November 2014. The last patient follow-up visit in the study took place on 19 December 2014.

Out of the 2303 patients included in the study, 1475 patients were included in the cohort and 1418 (96%) had at least one follow-up visit.

RESULTS

In total, 2303 patients were included in the Quiétude study: 1877 in the Xeroquel® group, 425 in the reference group not treated with Xeroquel® and one patient included without allocation to a group and excluded from the analyses.

Following a review of the data, the analysis population was comprised of 1825 and 399 patients in each of the groups, respectively.

Primary endpoint: combined population starting Xeroquel® treatment

Among the 1825 patients treated with Xeroquel®, 52.8% were diagnosed with bipolar disorder (n=963), 36.1% with schizophrenia (n=659) and 8.6% with major depressive disorder.

The mean age of patients included in the study was 45 years. Overall, the male to female ratio was close to parity (52% female and 48% male). Nearly 49% of the patients had a BMI equating to being overweight or obese.

Regarding professional status, 32% of patients were employed.

The distribution of sociodemographic characteristics and professional activity differed, however, according to the diagnosis.

The patients with schizophrenia were adults aged 41 years on average, predominantly male (65%), with 20% having a professional activity. Schizophrenia involved paranoid disorders in 48% of cases and schizoaffective disorders in 28% of cases.

The patients with bipolar disorder were adults aged 47 years on average, predominantly female (62%), with 40% having a professional activity. Patients suffered from type I bipolar disorder in 44% of cases, and type II in 52% of cases.

The severity of the disorders, as determined by the CGI-S scale, was known at the time of initiation of treatment with Xeroquel® (CGI-S ≥ 4 for 90% of patients).

Patients receiving Xeroquel® in the context of the Quiétude study were rarely patients receiving *de novo* treatment for their psychiatric disease. At initiation of treatment with Xeroquel®, the mean length of the disease was 11.4 years for all patients (median of 8.4 years).

During the last 12 months prior to their inclusion in the study, 80% of patients had medicine-based psychiatric treatment (77% of patients with schizophrenia and 82% of patients with bipolar disorder).

Primary endpoints: Xeroquel usage conditions

Xeroquel®was prescribed in the context of its MA and within reimbursement coverage for all patients with schizophrenia and for 98% of patients with bipolar disorder. Patients with MDD received Xeroquel® in the context of the MA, however not covered by reimbursement. The 46 patients who received Xeroquel® for other diseases (2.5%) corresponded to those patients receiving the treatment off-label.

The dosage prescribed at initiation was compliant with the SmPC: administration once daily on average and in the evening for 90% of the patients. The median daily posology at initiation of Xeroquel® was 300 mg for the total population, with the exception of patients with MDD (150 mg). Only a proportion (6%) of the patients received the maximum dosage of 800 mg/day and 10 patients received a greater dosage (0.5%).

- The daily dosage was bimodal for the "schizophrenia" group, with 2 frequency peaks (300 and 600 mg/day for 36% and 28% of patients, respectively) and a mean dose of 421 mg/day. This trend was identical to that of patients presenting other disorders.
- In the "bipolar disorder" group, the mean daily dosages at initiation of Xeroquel® varied depending on the type of ongoing episode: in the case of manic episodes, it was 493 mg (median 600 mg); in the case of mixed episodes, it was 311 mg (median 300 mg); in the case of hypomanic episodes, it was 289 mg (median 300 mg); and, in the case of depressive episodes, it was 251 mg (median 300 mg).

A titration was performed for 42% of patients (49% of patients with bipolar disorder and 35% of patients with schizophrenia).

During follow-up, only 33% of patients with schizophrenia and 34% of patients with bipolar disorder had a change in Xeroquel® dosage. Changes in dosage tended to occur, in the majority of cases, during the three first months of treatment, it was in majority an increase in dosage.

Changes in dosage were observed in similar proportions for patients with or without titration at initiation.

The dosages prescribed during the one-year patient follow-up period are similar to those described at treatment initiation and remain close to the lower limit of the range described in the SmPC. Over-dosing was detected in only 3% of all patients followed up. Nearly 54% of patients with schizophrenia and 47% of patients with bipolar disorder received Xeroquel® at a dosage lower than that described in the SmPC, during the study.

At the initiation of Xeroquel®, 66% of patients had a concomitant prescription for a pharmacological psychiatric treatment (78% of patients with MDD, 60% of patients with schizophrenia and 68% of patients with bipolar disorder). On average, 2.1 treatments (median of 2) were prescribed. The most frequent concomitant treatments were antidepressants (45%), anxiolytics (45%) and antipsychotics (except lithium) (32%). The majority of patients in the schizophrenia group had received antipsychotic drugs (except lithium) (55%) and the majority of patients with bipolar disorder and MDD had received antidepressants (49% and 80%). Among all groups, anxiolytic drugs had been prescribed for between 41 and 46% of patients.

During follow-up, continued treatment with Xeroquel® was not accompanied by simpler concomitant treatments. There was rather a trend towards an increase in these treatments, in terms of prescriptions and number of concomitant treatments, both among patients with schizophrenia and patients suffering from bipolar

disorder. Concomitant treatments were mainly added between inclusion and 3 months, then, to a lesser extent, over the rest of follow-up.

Few temporary treatment discontinuations were reported for Xeroquel® during the study: 5% for patients with schizophrenia and 6% for patients with bipolar disorder. The total duration of treatment in the context of the study was 11 months on average for all patients (median 12 months). 11% of patients with schizophrenia and 15% of patients with bipolar disorder stopped treatment permanently during the year of follow-up in the study, usually for reasons relating to poor compliance or tolerability.

Secondary endpoint: Assessment of health status in the 12 months following initiation of Xeroquel®

The therapeutic strategy, including treatment with Xeroquel®, enables a significant reduction in disease severity (improvement in CGI-S score of up to 1.6 points for patients with schizophrenia and up to 2 points for patients with bipolar disorder).

Few patients suffered from relapses of their disorder during follow-up, whether according to physician reports or as defined in the protocol, respectively 14 and 18% of patients with schizophrenia and 17% and 14.5% of patients with bipolar disorder.

Among the patients with schizophrenia, 78% attended an appointment for psychiatric disorders during the year of follow-up (8.3 appointments on average for the patients concerned) with a ratio of 0.5 appointments per month of follow-up. 13% of patients were hospitalised for psychiatric disorders.

Among the patients with bipolar disorder, 80% attended an appointment for psychiatric disorders during the year of follow-up (8.6 appointments on average for the patients concerned) with a ratio of 0.6 appointments per month of follow-up. 11% of patients were hospitalised for psychiatric disorders.

Description of adverse events and adverse drug reactions

1057 adverse events were reported in the context of the study for 446 patients (31.5%). These events were considered related to Xeroquel® (adverse drug reaction) for 188 patients (13.3%) (306 ADRs). The most common ADRs were drug ineffective (23%), sedation (23%), somnolence (16%) and weight increase (14%). The last two ADRs are described as very common (1 in 10 patients) in the SmPC. 26 ADRs were considered serious (8.5% of all 306 ADRs, for 19 patients), i.e. 1.3% of patients in the cohort.

Two cases of exposure during pregnancy were reported during the study: 1 female patient with schizophrenia and 1 female patient with bipolar disorder. Five cases of death were reported during the study. None of the deaths occurring were related to intake of Xeroquel®.

Secondary endpoint: Representativeness of patients having initiated treatment with Xeroquel®

Patients with schizophrenia had similar profiles irrespective of their treatment group (Xeroquel®/reference). The only significant differences were observed in patient sub-groups:

- Within the working population, a greater proportion of persons "working in a protected environment" was observed in patients initiating Xeroquel® (40% *versus* 17%).
- There was a similar level of unemployment in the 2 groups. In the case of inactivity, there was a greater proportion of invalidity in the group treated with Xeroquel® (66% *versus* 51%).
- The level of management in a public hospital department was higher (41% *versus* 29%).
- In the case of hospitalisation, the duration of hospitalisation at inclusion was greater in the group treated with Xeroquel® (28.4 days *versus* 16.5 days in the reference group).

The proportions of the different types of schizophrenia were different between the two groups of patients.

A greater proportion of patients in the Xeroquel® group suffered from schizoaffective disorder (27.9% *versus* 17.5%) while patients in the reference group suffered more from paranoid schizophrenia (50.7% *versus* 48.0% in the Xeroquel® group) or disorganised schizophrenia (14.8% *versus* 11.2%).

The assessment of the severity using the CGI-S scale showed that the patients' disorders were significantly more severe for patients initiating Xeroquel® than for patients in the reference group.

The patients with bipolar disorder in the Xeroquel® and reference groups were comparable in terms of age, male to female ratio, education level, professional activity, type of accommodation and the place of treatment. The patients in the Xeroquel® and reference groups were comparable in terms of the distribution of type I/II bipolar disorder, the profile of episodes occurring during the 12 months prior to inclusion and the manifestation of psychiatric disorders during the preceding 12 months.

The patients' disorders were significantly more severe (CGI-S scale) in the case of patients in the Xeroquel® group than for patients in the reference group.

The difference in treatment facility between the 2 groups (slightly more patients were followed up in a day hospital/part-time treatment centre in the reference group than in the Xeroquel® group) should be compared to the profiles of patients included by each investigator. Physicians practising in a private medical practice and in a clinic included more patients on average in the Xeroquel® group whereas physicians practising in a hospital department included more patients in the reference group on average.

As the Quiétude study was conducted soon after the availability of Xeroquel®, a channelling bias was to be expected (Xeroquel® reserved for patients with the most severe disease).

The existence of a channelling bias in the study was, however, not demonstrated. Although the profiles of the patients were more severe in the group of patients with schizophrenia, other factors, such as age and type of episode, should also be taken into account. Patients who were normal to mildly ill appeared to be exposed less to the product, in accordance with the indication of an acute episode before commencing treatment with Xeroquel®.

Treatment with Xeroquel® was prescribed more to patients with bipolar disorder presenting a depressive episode compared to those presenting a hypomanic episode and was prescribed less to those whose disease was milder.

DISCUSSION

The combined Xeroquel® treatment population corresponds to that expected in the context of its MA and its prescription indications (SmPC), namely: schizophrenia, bipolar disorder (manic and depressive episodes and prevention of relapses) and major depressive disorder. A very low proportion of patients (2.5%) received treatment for other psychiatric disorders.

Among the reimbursed indications (schizophrenia and bipolar disorder), the beneficiary population mainly corresponds to bipolar patients (59%), in keeping with current knowledge on the product.

Patients with schizophrenia included in the Quiétude study and receiving treatment with Xeroquel® are comparable to patients in the reference group in this study or observational studies conducted in France on the same type of disorder. The comparison between patients initiating Xeroquel® and the reference group revealed a similar disease history (number of episodes during the preceding months, prior suicide attempts, psychiatric comorbidities, duration of the disease) and confirmed that the combined Xeroquel® population corresponded clinically to the expected population.

The patients with bipolar disorder initiating Xeroquel® treatment were similar to patients in the reference group in terms of both the sociodemographic front as well as the length of the disease. The Quiétude study population was also comparable with patients in the observational studies published.

The results revealed an initiation of treatment at a relatively low dose (the recommended doses for schizophrenia are 600 to 800 mg/day), close to the lower limit of the range recommended by the SmPC, even at the end of the titration period.

The titration period recommended by the SmPC was not performed for all patients according to the information reported by the physicians. The implementation of a progressive dosage adjustment applied to 42% of the patients, with a difference in execution between patients with schizophrenia (35%) and patients with bipolar disorder (49%). The execution of a titration at the start of the study was not documented for all patients and did not always seem appropriate to the practice environment, especially private practice. It was offset by initiation of treatment at low doses.

During follow-up, only 33% of patients with schizophrenia and 34% of patients with bipolar disorder had a change in Xeroquel® dosage. Changes in dosage tended to occur, in the majority of cases, during the three first months of treatment and it was in majority an increase in dosage.

The dosages prescribed during the one-year patient follow-up period are similar to those described at treatment initiation and remain close to the lower limit of the range described in the SmPC. Overdose was detected in only 3% of all patients followed up. Nearly 54% of patients with schizophrenia and 47% of patients with bipolar disorder received Xeroquel® at a dosage lower than that described in the SmPC, during the study. These results indicate that physicians attempt to find the minimum effective dosage rather than prescribing immediately as per the SmPC.

Use of Xeroquel® at dosage strengths below those recommended in the SmPC has been observed in the literature and reported in countries where quetiapine has been available for several years.

Xeroquel® was prescribed in combination with on average 2 concomitant psychiatric treatments. Xeroquel® was prescribed in combination with another antipsychotic agent for 15% of patients with bipolar disorder and 33% of patients with schizophrenia. Combination of multiple antipsychotic treatments is also reported in the literature. Management of patients using a combination of antipsychotic agents with other treatments appears to be widespread practice among physicians in actual prescribing conditions.

The therapeutic strategy, including treatment with Xeroquel®, enables a significant reduction in disease severity (improvement in CGI-S score of up to 1.6 points for patients with schizophrenia and up to 2 points for patients with bipolar disorder). Few patients suffered from relapses of their disorder during follow-up, whether according to physician reports or as defined in the protocol, respectively 14 and 18% of patients with schizophrenia and between 17% and 14.5% of patients with bipolar disorder.

1057 adverse events were reported in the context of the study for 446 patients (31.5%).

The adverse events and adverse drug reactions reported are in keeping with the known safety profile for Xeroquel® and do not constitute new alerts.

As the Quiétude study was conducted soon after the availability of Xeroquel®, a channelling bias was to be expected (Xeroquel® reserved for patients with the most severe disease). The existence of a channelling bias in the study was, however, not demonstrated. The profile of patients receiving Xeroquel® represents the ranking attributed to Xeroquel® by physicians within the arsenal of treatments available for these diseases.

Among the 7715 physicians who made up the sampling frame, the 269 physicians who contributed to the study presented characteristics comparable to those of other physicians in the database. In particular, they were distributed homogeneously and in a representative fashion throughout France and in the various healthcare pathways.

The representativeness of the participating investigators conferred a certain reliability on the study regards description of the patients in the Xeroquel® group.

The significant number of active sites and the representativeness of the sites prescribing Xeroquel® participating in the study indicate a representativeness of the study population in relation to the target population (treatment with Xeroquel®).

CONCLUSION

The Quiétude study, conducted in France on a large sample of patients treated with Xeroquel®, enabled the modes of use of the medicinal product in France to be described, even though this treatment has been on the market since November 2011.

The patients receiving treatment were close to the expected population from a sociodemographic standpoint. However, the study revealed certain usage characteristics from a clinical point of view. Xeroquel® was most frequently prescribed for moderately to seriously ill patients with schizophrenia presenting schizoaffective disorders or for moderately to severely ill patients with bipolar disorder during depressive episodes. This appears to correspond to the positioning of the product more than one year after its release in France.

The study demonstrated appropriate use in the context of the indications and usage conditions in the SmPC, both in terms of posology and usage indication. The execution of a titration at the start of the study was not documented for all patients and did not always seem appropriate to the practice environment, especially private practice. As in other studies describing real-life prescribing patterns, Xeroquel® was prescribed at somewhat low dosage strengths and was used as multiple agent therapy in two-thirds of cases. In contrast to the clinical trials, treatment discontinuations during the first year were infrequent as 86.9% of patients were still receiving treatment at one year.

The therapeutic strategy, including treatment with Xeroquel®, enabled a significant reduction in the severity of the disorder (improvement in CGI-S score). Few patients experienced relapse of their disorder during follow-up. The adverse events and adverse drug reactions reported are in keeping with the known safety profile for Xeroquel® and do not constitute new alerts.

The Quiétude study offers a high quality response to the requests of the French health authorities with very satisfactory precision, by assessing patient characteristics and usage conditions in a large patient sample size.