

## Analyse coût-efficacité des stratégies de prise en charge des patients schizophrènes : place d'un antipsychotique atypique sous forme injectable à libération prolongée

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**Résumé.** La schizophrénie est une maladie chronique qui nécessite un traitement au long cours. La continuité du traitement est un élément clé de la prise en charge permettant une réduction du nombre de rechutes et du nombre de ré-hospitalisations. Les antipsychotiques atypiques administrés quotidiennement permettent un gain de tolérance, d'efficacité et une amélioration de l'observance par rapport aux neuroleptiques conventionnels. Objectifs – L'objectif de cette étude médico-économique est d'évaluer si le bénéfice clinique attendu de rispéridone injectable à libération prolongée (LP), selon une hypothèse de prix, s'accompagne ou non d'un surcoût pour l'assurance maladie. La rispéridone injectable LP a été comparée à l'olanzapine et à l'halopéridol décanoate. Méthode – Une modélisation pharmaco-économique de type coût-efficacité comparant ces 3 alternatives thérapeutiques, pendant 2 ans, a été réalisée. L'hypothèse principale est qu'une amélioration de l'observance grâce à une forme injectable à libération prolongée entraîne une augmentation de l'efficacité. La perspective adoptée est celle de l'assurance maladie. Les probabilités de transition et les coûts estimés ont été déterminés à l'aide de données publiées et d'avis d'experts. Seuls les coûts directs ont été pris en compte. Le critère d'efficacité retenu est le taux de patients traités avec succès, celui-ci étant défini comme le maintien du traitement pendant 2 ans. Résultats – Parmi les patients traités par rispéridone injectable à LP, 82,7 % sont toujours traités avec succès à 2 ans 74,80 % et 57,3 % respectivement pour olanzapine et halopéridol décanoate. Le coût direct par patient traité pendant 2 ans avec rispéridone injectable LP est de 14 055 €. Ce coût est de 14 351 € avec olanzapine et de 17 203 € avec halopéridol décanoate. Conclusion – Les résultats observés dans cette modélisation montrent que le traitement par un antipsychotique atypique sous forme injectable

à libération prolongée permet une meilleure continuité du traitement, réduit les rechutes, le niveau des ressources consommées et par conséquent permet une diminution des coûts.

**Mots clés :** Antipsychotiques ; Arbre de décision ; Coût-efficacité ; Schizophrénie.

### Cost-effectiveness analysis of schizophrenic patient care settings : impact of an atypical antipsychotic under long-acting injection formulation

**Summary.** Schizophrenia is a disease affecting the young adults and amounts to approximately 300 000 people in France (12). The French public psychiatric sector takes care of approximately 150 000 adults schizophrenics : 50 % benefit from ambulatory care, 50 % are in partial or full-time hospitalization care. Schizophrenia represents the first diagnosis that psychiatric sectors take in charge (4). The costs associated with schizophrenia, mainly hospital costs, are important and were estimated at 2 % of the total medical costs in France (5). In the French social welfare system, the social costs (pensions, allowances, managements of custody or guardianship by social workers) are also to be taken into account : it amounts to a third of the global direct cost. Schizophrenia also generates indirect costs (losses of productivity and premature deaths) which would be at least equal, or even more important, than direct medical costs (11, 19). The non-compliance to the antipsychotic treatment is a major problem with people suffering from schizophrenia. Indeed the lack of compliance to the treatment, estimated at 20 to 40 % (14), is a major handicap for schizophrenic patient stabilization. The poor level of compliance is due to many various causes :

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adverse effects that are considered unbearable, medicine viewed as persecutory, negation of the disease, nostalgia for the productive phases of the disease, lack of social support, complexity of the prescription, relapse itself (10). Compliance is thus influenced by the patient's clinical features, local provision of health care and the specific nature of the drug (adverse effects, pharmaceutical formulation). The atypical antipsychotics present fewer extrapyramidal side effects and reduce the cognitive deficits associated with the disease, which results in improved compliance. Long-acting injectable antipsychotics allow a better therapeutic compliance and thus better efficacy of the treatment. Several studies have shown a significant improvement in compliance related to the pharmaceutical formulation of antipsychotics. Hospitalization and relapse risks are lower in compliant than in non-compliant patients. Objectives – The main objective of this pharmacoeconomic analysis is to evaluate the impact in terms of medical benefits and costs of the following strategies : 1. Risperidone long-acting injection : first long-acting injectable atypical antipsychotic ; 2. Haloperidol depot : long-acting injectable conventional neuroleptic ; 3. Olanzapine : atypical antipsychotic available commercially in oral formulation. Methods – The target population defined for the study are young schizophrenic patients treated for at least 1 year and whose disorder has not been diagnosed for longer than 5 years. The time horizon is 2 years. A cost-effectiveness analysis is performed. The perspective adopted is the French Health System. The main hypothesis of the model is that an increase in compliance linked to the use of long-acting injectable formulation could lead to an increased efficacy and a modification of the cost-effectiveness ratio. A decision tree was built. Six periods of follow-up are identified with a duration of 4-months per period. The tree contains 3 principal arms, each one corresponding to a specific treatment : risperidone LA injection, haloperidol decanoate and olanzapine. For each arm, at the chance node, two health states are identified : either the patient responds favourably to the treatment or does not respond favourably and requires a switch to another drug treatment. After a period of response, the patient can either remain in the same state or experiences a clinical deterioration. If the patient presents a clinical deterioration, he can either go back to a positive response state after a period of intensive follow-up or remain in an insufficient response state ; in this case, a change of antipsychotic treatment is necessary. In the model, a patient should receive four different treatments before a long-term hospitalization takes put in place. According to the market authorization labelling, clozapine is proposed only as a 2<sup>nd</sup> or 3<sup>rd</sup> line therapeutic option, so when at least one or two successive neuroleptics have failed. The efficacy data used in the model are provided by clinical research recently published. These studies estimate the efficacy of oral risperidone, LA risperidone, olanzapine, and treatment by haloperidol. When available data in the literature were insufficient, the opinion of experts was sought. The effectiveness criteria is the rate of patients treated successfully : patients responding to the initial treatment with the possibility of experiencing one or two episodes of clinical deterioration but without requiring a switch to another drug during 2 years of follow-up. The base case is as follows : efficacy for oral risperidone is used for the LA ris-

peridone strategy, increased by 10 % within the first 4 months of follow-up ; efficacy for oral haloperidol is used for haloperidol depot, increased by 5 % within the first 4 months of follow-up ; for olanzapine, observed data in clinical trials were applied. The hypotheses for long acting forms are rather conservative because the increase of efficacy which can be expected for the long-acting injectable formulations varies between 5 % to more than 30 % according to the literature data. The analysis of sensibility includes three scenarios : scenario 1 : for LA risperidone, 5 % of patients treated successfully improvement in regard to oral risperidone instead of 10 % in the base case ; scenario 2 : for haloperidol depot, 10 % of patients treated successfully improvement in regard of oral haloperidol instead of 5 % in the base case ; scenario 3 : the results of an open trial conducted within the framework of the LA risperidone license are used, leading to an increase of up to 13,3 % of the rate of successfully treated patients, compared to oral risperidone literature data. As for the side effects, only extrapyramidal symptoms were considered. Other side effects are described in the literature such as the obesity or the occurrence of a diabetes ; these effects were not taken into account in the model, their impact on the coverage of schizophrenic patients and on resources utilisation being poorly known. Only direct medical costs were considered in the pharmacoeconomic analysis. Two types of costs were identified : hospital costs and community care costs. The stays in overnight hospitalisation and day hospitalisation were derived from the Disease Related Groups (DRG) and valued from the data of the National Cost Study (Étude Nationale de Coûts ; 1999). The DRGs corresponding to the diagnosis of schizophrenia are the DRG 627 (complete hospitalization) and DRG 819 (day hospitalisation). Ambulatory care : procedures and visits, were valued in euros in reference with the tariffs for reimbursement issued in the Naming General of the Professional Acts (NGAP) and published by the French National Health Insurance (Year 2001). Medication consumption was quantified by using the daily dosage specified in the the MAA and the French prescription database IMS-Dorema. The cost of medicines was valued from tariffs 2001 (SEMPEX). LA risperidone price being not fixed to date, the reserved hypothesis is a 141,62 € retail price. As schizophrenia is listed among the diseases reimbursed at a 100 % rate by the Health insurance, out of pocket expenses by patient are not considered in the analysis. The cost for the extrapyramidal effects was attributed to all the strategies. This cost was calculated according to the rates of extrapyramidal effects occurrence collected in the literature. Globally, in the published studies, the incidence of the side effects for the patients treated by olanzapine or risperidone is similar. It was thus decided by the experts to use the same rate of occurrence for extrapyramidal effects for olanzapine and risperidone (20 %). This rate is 40 % for haloperidol decanoate, 10 % for oral clozapine. For the cost estimation, the expenses for treating a schizophrenic patient for two years were taken into account. Results – The results show that in two years, LA risperidone is more effective than the two other antipsychotics. After 2 years, the rate of patients treated successfully is 82,7 % for LA risperidone, 74,8 % for olanzapine and 57,3 % for haloperidol depot. The 2 year-cost per patient treated by LA risperidone is 14 055 €. This cost is 14 351 €

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