Development of a Regulatory Post-Marketing Studies Database

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Objectives

Post-marketing surveillance for adverse effects has become an essential element of new drug and medical devices development in the European Union and the USA. The objective of this study is to present an overview of the content of a database gathering the details of Post-Marketing Studies (PMS) requested by the European Medicines Agency (EMA, EU), the Food and Drug Administration (FDA, USA) and the Haute Autorité de Santé (HAS, France).

Methods

All drug approvals published by the EMA, the FDA, and the HAS between January 1, 2005 and November 10, 2011 were reviewed to retrieve PMS. The information was categorized as follows: product description (brand name, INN, indication, etc.), study type, description of study, and information source.

Table 1. Example of a product with PMS requested by the EMA, HAS, and FDA

Brand name (INN)	MAH	Indication	Agency	Opinion's nature	Opinion's date	SMR	ASMR	Study type	Detail of Study type	Description of study	Population	Information sources
Elaprase (idursulfase)	Shire	Mucopolysaccharidoses	EMA	Approval	08/01/2007	Not Applicable	Not Applicable	Observational	Long-term clinical endpoints	The MAH commits to evaluate the following long-term clinical endpoints primarily through the HOS. These data will be re-evaluated annually and outcomes reported and discussed within the Annual Reassessments: - Assessment of long-term pulmonary morbidity (e.g., incidence of infections, pulmonary function status), and mortality - Assessment of long-term cardiovascular morbidity (e.g., incidence of events, and echocardiography data, where available), and mortality - Assessment of long-term urinary GAG excretion patterns - Assessment of long-term antibody levels, isotype, and correlation to other therapeutic parameters	ND	http://ec.europa.eu/health/documents/community-register/2007/2007010816808/anx_16808_en.pdf
Elaprase (idursulfase)	Shire	Indicated for the long-term treatment of patients with Hunter syndrome	HAS	Opinion	14/03/2007	Substantial	Level II	Observational	Registry	Following a request from the Directorate General for Health, the Transparency Committee wishes to establish a register of patients with Hunter syndrome in France. The aim of this register will be to assess, over the long term, the impact of ELAPRASE treatment on morbidity and mortality (particularly neurological morbidity and the clinical consequences of development of anti-idursulfase antibodies), on the quality of life and on the organization of care. It should also have a part in improving knowledge about the disease and its management. An independent scientific committee will be responsible for the production of this register.	Children	http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-04/elaprase_ct_4169.pdf
Elaprase (idursulfase)	Shire	Mucopolysaccharidoses	FDA	Approval	24/07/2006	Not Applicable	Not Applicable	Observational	Observational survey	Shire commits to evaluating long-term safety and efficacy data in an observational survey (the Hunter Outcome Survey, HOS) of patients with Hunter syndrome being treated with ELAPRASE. In addition to clinical and laboratory tests that are part of standard medical care for patients with Hunter syndrome, the survey will collect data from patients on the six-minute walk test, from a subset of centers that will have the training and facilities to collect the data in a standardized and reproducible manner, and urinary GAG levels approximately every 6 to 12 months for at least 15 years. Assessments and data collected in the HOS will include those listed in Table 1 of the Hunter Outcome Survey protocol summary version 1.0, dated October 31, 2005, and in the Safety Specification and Pharmacovigilance Plan documented in the ELAPRASE BLA. For pediatric patients in the HOS, data to be collected will include standardized and replicated height, weight, and head circumference measurements in conjunction with deformity assessments and patients' method of feeding. The survey will be designed to take advantage of any opportunity to evaluate the effect of ELAPRASE on female reproduction, pregnancy, and lactation. The HOS data will be analyzed at yearly intervals and the results will be submitted in the IND annual reports.	ND	http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/125151s0000_Ltr.pdf

Results

- For the FDA, we reviewed 676 original approvals and 929 supplements and included, respectively, 199 and 110 drugs approved with PMS.
- For the EMA, we reviewed 333 marketing authorizations and included 33 files with PMS.
- For the HAS, 3549 opinions were published in this interval with only 174 opinions with PMS.
  See an example of entry, Table 1.

- Many requests of the HAS were long-term follow-up studies. About 43% of the PMS requested by the FDA were pediatric studies. The EMA also requires pediatric studies but under a Pediatric Investigation Plan (PIP). Since 2005, 21 PIPs have been requested.
- Whatever the agency, all kinds of indications are covered by the PMS, e.g., treatment of sepsis, asthma, malaria, depressive disorder, etc.

Conclusion

The Post-Marketing Requirements (PMR) Database will be a unique source of centralized information about post-marketing studies requested in Europe and in the USA. It will be useful to observe the current trends in requirements to anticipate the demands, and to integrate the studies as early as possible in the product development process. The database will be available online in an independent website, with access by subscription.

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