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Expert Opinion

Managing the teratogenic risk of thalidomide and lenalidomide: an industry perspective

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Celgene has developed and operated pregnancy prevention programs since 1998 with the first approval of thalidomide in the US. With the development and marketing of lenalidomide, an analog of thalidomide, the company further advanced its risk management activities, which now cover several territories across the globe. To date, the program is a success in as much as it has minimized the risk of fetal exposure and subsequent development of fetal malformations. Nonetheless, the company understands the need to provide a mechanism for intervention and remediation when at-risk behaviors are identified, and this forms an integral part of the risk management processes. The implementation of the thalidomide and lenalidomide pregnancy prevention program partners patients, healthcare professionals, regulators and the company in a spirit of shared responsibility. This paper also presents the authors' experience and perspective on the challenges of managing a pregnancy prevention program, which at its core aims at ensuring that the product's benefits outweigh the risk of fetal exposure.

Keywords: lenalidomide, pregnancy prevention, risk management, thalidomide

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1. Introduction

1.1 Background

Thalidomide (α-phthalimidoglutaramide) was marketed in the 1950s and early 1960s as a sedative–hypnotic agent, gaining rapid popularity as a purportedly safe alternative to barbiturates [1]. Peripheral neuropathy was an initial concern [2], but this was superseded by an epidemic of phocomelia, an extremely rare congenital abnormality that was associated with maternal thalidomide usage [3-5]. Between the period of thalidomide's first marketing to its worldwide withdrawal in 1961, an estimated 10,000 children were born with a range of defects and disabilities, including severe congenital deformities, as a result of the drug's unrecognized teratogenic effects [2,6].

Thalidomide displays a broad spectrum of pharmacological and immunological activity and has been used in clinical practice to treat a wide range of diseases, including hematological malignancies. In 1998, Celgene's brand of thalidomide (Thalomid®, Celgene, Warren, NJ, USA) received the FDA approval to treat moderate to severe erythema leprosum nodosum. It was subsequently approved for use in combination with dexamethasone for the treatment of newly diagnosed multiple myeloma based on response rates. To prevent the risk of fetal exposure to thalidomide and to ensure benefits outweighed the teratogenic risk, Celgene worked closely to meet the FDA requirements on the development of a risk management program (RMP), the System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S*®). Under the *S.T.E.P.S* program, all prescribers, pharmacists and patients who prescribe, dispense and receive thalidomide, respectively, are required to enroll in this restricted distribution program, regardless of what disease is being

treated. Because of *S.T.E.P.S*, thalidomide is now available in the US to the medical community. Details of the *S.T.E.P.S* program have been described elsewhere [7].

With the development and marketing of lenalidomide, a second-generation immunomodulatory drug structurally related to thalidomide and potentially teratogenic in humans, Celgene similarly worked with the FDA to develop an RMP, RevAssist®. Details of the RevAssist program have been described elsewhere [8]. Lenalidomide was first approved in the US in 2005 for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities. In 2006, it was also approved in the US for the treatment of multiple myeloma in combination with dexamethasone in patients who have received at least one prior therapy. Lenalidomide is only available in the US through RevAssist, which shares many features with the *S.T.E.P.S* program. However, there are important differences between the two programs, among which are the availability of lenalidomide through contracted pharmacies (a limited number of US specialty pharmacies).

The *S.T.E.P.S* and RevAssist programs in the US have provided Celgene with the experience to develop and implement thalidomide and lenalidomide risk management programs in ex-US territories. Both US programs are resource intensive and perceived as putting a heavy workload on the prescribers and pharmacies and also require significant electronic and telecommunication interaction for patients, prescribers, pharmacies and Celgene with the system. As Celgene expanded into other territories, these risk management programs were further refined and streamlined, taking into consideration the national legal and regulatory framework whilst maintaining their effectiveness in achieving their cardinal goal of preventing fetal exposure.

The objective of this paper is to present the range of Celgene's global experience in managing effective risk management programs, particularly a pregnancy prevention program (PPP) in patients on thalidomide or lenalidomide, within the context of existing regulatory guidelines and directives, and underscore that RMPs such as ours that require additional tools beyond routine pharmacovigilance build on core objectives through the participation of stakeholders, culminating in the development of country-specific RMPs.

1.2 Objective of the thalidomide and lenalidomide pregnancy prevention program

Thalidomide's teratogenicity is species-specific, dose-specific and influenced by gestational age. The lowest doses and the shortest treatment period where characteristic birth defects in human fetuses are observed is 25 mg/day for 2 – 3 days and 50 mg/day for only 1 day [9]. There is a significant risk of birth defects when thalidomide is administered during the period of embryonic organogenesis, principally between 20 and 36 days post-fertilization or 34 – 50 days after the last menstrual cycle [10].

The primary objective of the thalidomide and lenalidomide PPP is the prevention of fetal exposure in women treated with the drug(s) as well as female partners of male patients.

2. Core content of the pregnancy prevention program

The identification and description of the risk(s) and the series of steps necessary for mitigating the risk are key drivers in the development of any risk management programs, which must be feasible if they are to successfully achieve their goals.

To achieve the primary PPP goal of preventing fetal exposure, no single element operating in isolation is deemed sufficient to mitigate risk. However, this is achieved through a series of in-built PPP steps which operate in parallel within the pre-planned risk mitigation strategy. Four PPP elements can be discerned that are discussed in the following sections.

2.1 Participant education

Patients and healthcare professionals are provided with information on the risks of thalidomide and lenalidomide especially with regard to the potential of fetal exposure and the resultant severe life-threatening congenital malformations. Additional educational materials for the healthcare professional and the patient have been developed, specifically re-emphasizing the key messages for minimizing the potential for fetal exposure to the drug.

Healthcare professionals play a key role in providing adequate education and counseling to the patient on the teratogenic risks associated with thalidomide and lenalidomide. It is a requirement that healthcare professionals prescribing/dispensing thalidomide or lenalidomide advise patients on the drug's fetal risks and the measures that must be in place to mitigate the risk. Patients must agree to adhere to the conditions of the PPP in order to be eligible to receive the drug. The educational component of the program is designed with the objective of improving both the healthcare provider's and patient's knowledge about the teratogenic risk and facilitating modification of patient behavior through the promotion of informed uptake of use of effective forms of contraception. Promotion of behavioral change in terms of choices relating to the selection of contraceptives and their consistent use is influenced by multiple factors. However, it is our belief that adequate targeted education provided by healthcare professionals, underscoring the scientific rationale for the need of contraception, does promote patient acceptance and motivation to use contraceptives. In 134 females of childbearing potential (FCBPs) surveyed in the US lenalidomide RevAssist program, 97% reported being aware of the need to use two forms of birth control methods when engaged in heterosexual intercourse, and all the women reported to be using birth control methods as per program requirements [8].

2.2 Target risk population and monitoring

The main target groups for prevention of pregnancy are FCBP and male patients with partners who are FCBP. It is,

therefore, important to define and identify who is an FCBP and who is a female not of childbearing potential in order to tailor messaging around the thalidomide and lenalidomide teratogenic risk. In addition, information on what constitutes adequate contraception must be provided for each category of reproductive potential in accordance to what is available in a country. As part of the PPP of the thalidomide and lenalidomide risk management, FCBP must undergo monthly pregnancy testing and the drug only dispensed if the pregnancy test is negative. A false positive pregnancy test result in the program, where the majority of female patients receiving thalidomide or lenalidomide are older and have hematological malignancies, is not uncommon. A study in aging women examining factors affecting β hCG testing performance standards showed that serum β hCG increases with age in non-pregnant women [11]. There has been at least one case report of elevated β hCG in a nongravid, premenopausal patient with MM, where immunochemical investigations demonstrated that myeloma cells expressed immunoreactive β hCG, which may explain the positive pregnancy test results in a nongravid woman [12]. In a US study of the thalidomide *S.T.E.P.S* program, positive pregnancy tests were registered in 72 out of the ~ 6000 FCBPs, with 69 (95.8%) of these tests found to be false positives [13].

2.3 Controlled distribution

A component of the PPP involves the description of the process of drug distribution from the point of prescription to final dispense of the product to the patient. Thalidomide and lenalidomide are available with a prescription from a healthcare professional, and in most cases this is an oncologist/hematologist with an understanding of the pregnancy prevention program.

The drugs are made available through a restricted distribution program, which range from various degrees of restriction of drug use (e.g., to hematologists/oncologists with demonstrated evidence of having trained on the pregnancy prevention program) and fulfillment of important in-built steps that assure safe use, such as a negative pregnancy test in FCBP, before the drug is dispensed. The locally implemented country-specific controlled distribution program is arrived at after consultations with the relevant stakeholders, for example, regulators, healthcare professionals and thalidomide victims' groups where these exist. In addition, Celgene has over the years come to recognize the positive impact of the Named Patient Program, operating prior to post-marketing launch where this is possible within the national regulations, as a means of working with stakeholders to test the practicability of implementing the post-marketing RMP.

2.4 Evaluation of the pregnancy prevention program effectiveness

Once risk management plans/programs are in place, it is imperative, through a process of continuous evaluation, to measure whether the program is achieving its primary objective. Through Celgene's pharmacovigilance activities and a program requirement for healthcare professionals and patients to report all suspected and confirmed pregnancies in female patients or female partners of male patients, the company is able to directly assess the effectiveness of the pregnancy prevention program. In some of the programs, for example, RevAssist and *S.T.E.P.S* in the US, periodic surveys of patients and prescribers are performed as an integral part of the program. Through these surveys, information on patient and prescriber understanding of the program can be assessed. An analysis of the results of the lenalidomide surveys from December 2005 to December 2006 showed that > 95% of FCBP and males on the drug demonstrated understanding of the teratogenic risks potentially associated with lenalidomide and the behaviors necessary to minimize the risk [8]. Where the survey results suggest poor understanding of the program goals, there is active follow-up with the patient and prescriber. Follow-up in most of these cases revealed an error in response rather than lack of understanding around the teratogenic risk of lenalidomide and measures necessary to mitigate that risk. Additional surveys to measure program effectiveness and compliance are ongoing in multiple countries.

FCBPs constitute about 3 – 5% of the population on thalidomide or lenalidomide. By April 2010, about 300,000 patients worldwide had been exposed to the Celgene thalidomide, with four confirmed fetal exposures in female patients. So far, there has not been a report of *in utero* exposure resulting in congenital malformation as a result of exposure to Celgene thalidomide. By June 2010, there were > 140,000 patients worldwide who had been exposed to lenalidomide. During this period, there were two confirmed fetal exposures to lenalidomide in pregnant female patients within the post-marketing setting. Similarly, there has not been a report of *in utero* exposure resulting in congenital malformation as a result of exposure to lenalidomide.

3. Operating the pregnancy prevention program: lessons learned

Celgene operates pregnancy prevention programs across multiple countries and regions with diverse regulatory environments, ranging from well-developed regulation or national guidelines (e.g., in North America and the EU [14,15]) to a complete absence of national pharmaceutical regulation on risk management programs that go beyond routine pharmacovigilance as a means of ensuring a product's benefits outweigh its risks. Celgene mandates all its territories to adopt a PPP for lenalidomide and thalidomide even if there is no local regulatory expectation, and as a matter of policy discusses the proposed PPP with national regulatory agencies. Currently, thalidomide and lenalidomide PPPs are under development or have been implemented in > 50 countries, and they take into account the established local medical practices and regulations and even cultural considerations.

3.1 Corporate commitment

Celgene's commercial model is built around RMPs, and the majority of the company's sales relate to products under an RMP, specifically a pregnancy prevention program. An RMP implementation requires corporate commitment and is labor-intensive on all participants: the patient, prescriber, pharmacies and the company. Celgene has had to build a personnel network dedicated to supporting PPP activities at a corporate and local affiliate level and has defined dedicated personnel to take responsibility for running the programs. This network of Celgene staff is responsible for the development and maintenance of PPP activities, closely liaising with other functions within the safety and regulatory departments. Adequate resourcing of risk management activities is a critical factor in program success. Irrespective of whether the implemented system is an intensive, multi-component, integrated program such as RevAssist and *S.T.E.P.S* or one that is less onerous and dependent on augmented communication of the teratogenic risk and pregnancy minimization measures, operating a pregnancy prevention program with a global reach does require additional resources that go way beyond those that are usually allocated for routine pharmacovigilance.

3.2 Definition of core PPP standards

Nested levels of decision-making are integral through any risk management program, and coordination at all strata within the company to ensure understanding, consistency and planning of activities should be clearly defined. Celgene has a global governance structure that through interactions with internal and external stakeholders has facilitated to delineate the company's core thalidomide and lenalidomide PPP standards. These core standards are the starting point in any country's PPP development.

3.3 Implementing the program: global standards but with a local flavor

Implementation of core standards differs from region to region or country to country. Country-specific programs are implemented in accordance with the healthcare system organization and in sync with the national legal or regulatory environment and cultural considerations, among others. The responsibilities and accountabilities around the execution of the PPP take into consideration the individual roles of prescribers and pharmacists within the framework of their roles in providing healthcare. For example, in the UK and Ireland, pharmacies must be registered with Celgene in order to dispense thalidomide. In addition, they must agree to implement and audit the use of a Prescription Authorization Form (PAF) or ensure that the contents of the PAF are incorporated into the institution's standard prescription. The PAF requires both the prescribing physician and the pharmacist to document and confirm that the key elements of the PPP have been undertaken. The results of the self-audit are reported periodically to the national competent authorities and to the European Medicines Agency (EMEA). In some countries, pharmacists do not play a prominent role in program execution as the prescribing physician is accountable for all aspects of the PPP.

Further, local legal or regulatory considerations might be a source of conflict with the public health imperative championed by the company; for example, due to local privacy laws in some US states, follow-up on outcomes that are a subject of an identified risk (pregnancy in the case of the PPP) might present particular difficulties. Nonetheless, the company routinely undertakes intensive measures to obtain outcome data and relevant follow-up information. This is an undertaking that requires significant resource mobilization and cooperation with healthcare professionals who are the source of information. It is important that regulatory authorities understand and appreciate this challenge as companies must balance their actions for acquiring data that informs decisions on the effectiveness of the program against individual rights that are protected and enshrined within the national legal framework.

3.4 Balancing practicality with burden

Steps that assure safe use of a product, which are integral in a specific risk management program, should not be burdensome on the healthcare system, but at the same time ought to be designed in such a way that they realistically and effectively mitigate the risk of interest. In the US RevAssist and *S.T.E.P.S*, all physicians, pharmacists and patients who prescribe, dispense and receive the drug, respectively, are required to enroll in the pregnancy prevention program, regardless of the disease being treated. The system also ensures that results from the required pregnancy tests are documented and linked to prescription activation and dispensing through an interactive voice response system or via telephone customer service contact prior to dispensing the drug [15]. Besides, patients and prescribers must complete required surveys to demonstrate knowledge of program goals and identify changes in risk status. Patient surveys are either monthly or six monthly depending on a patient's reproductive risk category. Physicians are required to complete a survey for each prescription to be written for each patient to minimize risk of fetal exposure. In the US, PPP healthcare professionals must devote time and resources to ensure all requirements of the program are met. Taking into consideration the healthcare delivery environment and issues relating to patient data protection in ex-US territories, Celgene has worked with regulators and other stakeholders to develop less resource-intensive programs outside the US. These programs do not require monthly surveys and have fewer transactional elements between the users and the supporting technology platforms, but nonetheless do have mechanisms that allow for the collection and assessment of data relevant to evaluate program effectiveness, with opportunity to intervene when corrective measures are required.

3.5 Stakeholder input

The success of any RMP hinges on the realization and appreciation of the local regulatory environment and

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