1. Abstract

Title

An Observational, Prospective Post-Marketing Surveillance Program to Evaluate the Safety Profile of Intravitreal Ozurdex® in the Treatment of Visual Impairment due to Diabetic Macular Edema by Actively Identifying and Evaluating the Occurrence of Adverse Events and Serious Adverse Events Information.

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Keywords

Post marketing surveillance, diabetic macular edema, intravitreal, visual impairment, adverse events.

Rationale and background

India is second to China in having the maximum number of diabetics. This significant proportion of diabetes in India indicates an increase in diabetic retinopathy or diabetic macular edema (DME) cases. The increase of such cases is directly proportional to the duration of diabetes.

Ozurdex® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion or central retinal vein occlusion; non-infectious uveitis affecting the posterior segment of the eye; and DME. Ozurdex® is an intravitreal implant containing 0.7 mg (700 mcg) dexamethasone in the Novadur® solid polymer sustained-release drug delivery system.

As a part of Allergan's commitment to the Regulatory Authority of India, this post-marketing surveillance (PMS) program was planned to be conducted to collect safety information from Indian patients who received intravitreal Ozurdex® injection for the treatment of visual impairment due to DME.

Research question and objectives

The objective of this PMS program was to evaluate the safety profile of Ozurdex® by actively identifying and evaluating the occurrence of adverse events (AEs) and serious adverse events (SAEs) for a 1-year period in adult Indian patients (≥18 years of age) who received at least one intravitreal Ozurdex® injection for the treatment of visual impairment due to DME.

Study design

This was an observational, prospective PMS program to evaluate the safety profile of intravitreal Ozurdex® by actively identifying and evaluating the occurrence of AEs and SAEs information.

On the Visit 1/Baseline visit, an informed consent was signed. No study medication was provided as part of the study as this is a non-interventional study of usual clinical practice. However, the marketed intravitreal Ozurdex® injection was administered to the patient at the discretion of the treating physician/investigator if he/she considered that the patient would benefit with the injection. The injection was administered by the physician/investigator either in the same visit or in the subsequent visit. The date of the injection was recorded in the pre-designed case report form (CRF). During subsequent follow-up visits/telephonic contact, the study investigator collected information pertaining to AEs/SAEs in a pre-designed CRF.

Setting

The planned duration of the study was one year. The study was conducted in the Indian population during usual clinical practice. Approximately 20 sites across India were planned to be included based on the enrollment potential.

Subjects and study size, including dropouts

This study included Indian adult patients aged ≥18 years who had a visual impairment due to DME. Approximately 250 patients were planned to be screened and enrolled into the study from approximately 20 sites across India.

Variables and data sources

Medical records of the patient were used which served as a data source for determining the exposures, effects and outcomes.

The following variables were collected in the CRF during patient assessment:

Patient demography
Medical history
Concomitant medications
Ophthalmic history
Concomitant ophthalmic medications
Information on pregnancy
Date of the last intravitreal Ozurdex® injection (if applicable)
Date of the present intravitreal Ozurdex® injection
AEs/SAEs/ adverse drug reactions (dates of AE/SAEs, if available)

The data collected on the CRF (demographic and other baseline data) were transferred into a clinical database. For continuous data, number of non-missing records, mean, standard deviation, median, minimum, maximum and the two-sided 95% confidence interval of the mean were to be

presented. For categorical data, number of non-missing records and percentages were to be presented.

Results

The study was designed to collect safety information for a duration of 1 year in patients receiving Ozurdex® and to analyze the AEs and SAEs. A total of 250 patients were enrolled from 19 sites across India. All the 250 patients were treated with marketed intravitreal Ozurdex® injection at the discretion of their treating physician/investigator.

The mean age of patients enrolled was 60.2 (± 9.39) years. Of the 250 enrolled patients, a total of 84 patients (33.6%) had received prior Ozurdex® treatment. Ninety-one patients (36.4%) had at least one relevant ophthalmic condition at the time of enrollment with a mean duration of 1.7 (±2.64) years. Of the enrolled 250 patients, majority of the patients reported Type 2 diabetes mellitus (188 [75.2%]) and hypertension (154 [61.6%]). Overall, 249 (99.6%) of the patients had reported the intake of concomitant medications during the study. Majority of the patients were taking metformin (114 [45.6%]), glimepiride (76 [30.4%]), and other anti-diabetic medications.

A total of 22 treatment emergent adverse events (TEAE) were reported in the 0-364 days follow up period from 7 (2.8%) patients. Ophthalmic TEAEs were reported by 4 (1.6%) patients. Of the 7 (2.8%) patients who reported TEAE's, 3 (1.2%) patients had TEAEs that were considered as treatment-related and 3 (1.2%) patients had TEAEs that were severe in intensity.

Three (1.2%) patients reported 12 serious TEAEs during the study with majority of the events related to cardiac disorders. Other SAEs included pyrexia, dyspnea, acute hepatic failure, septic shock, fluid overload and acute kidney injury. The most common reason for SAE was in-patient hospitalization or prolongation of existing hospitalization (11 [91.7%]). There were two deaths reported in the study (0.8%). One male patient [redacted] was noted with severe myocardial infarction 32 days after the last intravitreal Ozurdex® injection which resulted in death. Another male patient [redacted] was noted with severe acute hepatic failure 101 days after the last intravitreal Ozurdex® injection. The patient was hospitalized. However, the patient developed septic shock and cardiac arrest which resulted in death which occurred 120 days after the last intravitreal Ozurdex® injection. All the events were considered as not related to treatment with Ozurdex®.

Discussion

Considering the observational nature of this study and voluntary reporting of the AEs, the proportion of patients reporting AE was relatively low. The treatment related TEAEs were reported in 1.2% of patients enrolled. The TEAEs that were considered to be related to Ozurdex® treatment were increased intraocular pressure and glaucoma, while all other events were considered as not related to Ozurdex® treatment. The treatment related TEAEs were either mild or moderate in severity. The event of glaucoma was reported as ongoing at the time of this report. The treatment with Ozurdex® was considered safe with few treatment related TEAEs. The safety results of this study confirm that Ozurdex® is safe for the treatment of visual impairment due to DME and the safety profile of Ozurdex® derived from this study is consistent with the current Prescribing Information of Ozurdex® Intravitreal Implant.

Marketing Authorization Holder

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