Direct Healthcare Professional Communication

04 October 2018

Ozurdex® 700 micrograms intravitreal implant (dexamethasone): silicone particle observed on implant during inspection

Dear Healthcare Professional,

Allergan Pharmaceuticals Ireland, Westport, Co. Mayo, Ireland in agreement with the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency (MHRA) would like to inform you of the following:

Summary

- During a routine manufacturing inspection, a silicone particle approximately 300 microns in diameter was observed in dispensed Ozurdex implants. The silicone particle has been confirmed to originate from the needle sleeve.

- Some batches of Ozurdex already distributed in the EU are affected by this defect. Most batches have 2% to 4% defective units, but defect rates as high as 22% have been reported.

- Ozurdex batches known to be affected are being recalled from the EU market. Refer to appendix 1 for the list of recalled batches. In the UK, an electronic recall notice will be issued by MHRA.

- Remaining batches in which additional testing has not identified the defect will be recalled once sufficient new stocks of Ozurdex that are reliably known to be free of this defect become available in each country. Allergan will provide an update, via a direct mailing, by the 19th of October 2018 to advise when new stock will be available for each market.

- Until unaffected product is available, clinicians are advised to consider alternative treatments if available and use Ozurdex only if no other treatment is suitable, taking each patient's individual clinical condition into account.

- The decision on whether to use Ozurdex should be made by the treating ophthalmologist based on an assessment of the benefits of Ozurdex treatment, the additional potential risks of injecting the silicone particle along with Ozurdex, and the risks of delaying treatment if other therapies are either not appropriate or not available.

- It is recommended that Ozurdex should only be used after a full discussion of the defect, its potential added risks, and any alternative available options with the patient.

- If treatment with Ozurdex is continued, regular monitoring and extra vigilance for adverse events is required and any adverse events that are considered related to Ozurdex implant should be promptly reported to the Yellow Card Scheme.

Background and clinical implications on the safety concern

During a routine in-process inspection, a loose particle of silicone was observed on a sampling of Ozurdex implants. The particle is from the needle silicone sleeve. The silicone sleeve is an intrinsic part of the Ozurdex product, and the particle is not an external contaminant. The particle size is approximately 300 microns in diameter. Subsequent testing of retained samples has identified that batches already distributed in the EU are affected. However,

due to the nature of the testing it cannot be ruled out that other batches also contain a silicone particle and the root cause of the particle presence has not yet been definitively identified.

Clinical implications:

The risks associated with the injection of the silicone along with the Ozurdex implant cannot be precisely ascertained due to a lack of adequate information. Likewise, experience with other silicone substances injected into the eye cannot be directly extrapolated to this scenario. However, for some patients the immediate need and benefit of Ozurdex implant may outweigh the total risk of the injection of Ozurdex including the additional potential risks of injecting the silicone particle.

- **Obscuration of vision by particle:** the silicone particle is not expected to degrade, and it will remain permanently in the vitreous cavity unless removed. The particle is likely to move within the visual axis, it may act in the same way as an endogenous vitreous opacity (floater).

- **Intraocular inflammation:** in sensitive patients this potential risk cannot be ruled out and it is difficult to predict if patients may react to this particular silicone particle. Monitoring for potential intraocular inflammation through routine eye exam at routine intervals for Ozurdex-treated patients is recommended.

- **Corneal adverse reaction:** in patients that have an opening between the anterior and the posterior segment of the eye (eg, following capsulotomy or iridectomy) the particle could potentially migrate to the anterior chamber. While the potential of particle migration through such an opening is low, the possibility cannot be ruled out, thus signs of corneal adverse reactions should be monitored.

If Ozurdex is used, **extra-vigilance from clinicians and patients** is required. Clinicians need to inform patients of the defect. Symptoms and signs for patients and clinicians to be aware of include:

- Uncontrolled or persistent inflammation in patients treated with the Ozurdex implant which are not in keeping with conventional disease course normally seen after treatment with intravitreal Ozurdex therapy.
- A permanent dense floater in the field of vision present more than 12 months after last Ozurdex treatment that is not attributed to underlying ocular diseases.
- Any signs of corneal adverse reactions associated with a small (~300 micron) foreign body in the anterior chamber that is not degrading.
- Any increases in intraocular pressure in patients who did not previously experience increased intraocular pressure with Ozurdex.
- Observation of a blue particle (~300 microns) in the vitreous or in the anterior chamber upon examination.

Routine Ozurdex product safety reviews conducted by Allergan do not indicate an adverse event trend associated with the presence of a silicone particle with over 1.5 million units distributed worldwide. Although a few ocular inflammation adverse events have been found in EudraVigilance database, these are difficult to interpret given the likelihood of events being attributed to underlying ocular disease. There is currently no evidence to indicate an association between intraocular inflammation and the silicone particle. However, there may be an element of underreporting given that this defect has not been identified before. No additional risks associated with off-label use are anticipated.

Allergan will issue an update to clinicians by the 19th October when it will be possible to provide a reasonable estimate of when their marketplace can be supplied with defect free stock.

Allergan Pharmaceuticals Ireland has identified a corrective action that eliminates creation of the particle and are in the process of confirming this corrective action prior to releasing any further product. Allergan is recommending, in association with MHRA, that current stocks of Ozurdex product be replaced with new stock once product without the possible silicone particle becomes available.

Call for reporting

Ozurdex is a medicine. Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme.

Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle▼

It is easiest and quickest to report ADRs online via the Yellow Cards website - https://yellowcard.mhra.gov.uk/ or via the Yellow Card app available from the Apple App Store or Google Play Store.

Alternatively, prepaid Yellow Cards for reporting are available:

- by writing to FREEPOST YELLOW CARD (no other address details necessary)
- by emailing yellowcard@mhra.gov.uk
- at the back of the British National Formulary (BNF)
- by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789 or
- by downloading and printing a form from the Yellow Card website (see link above)

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

ADRs may also be reported to Allergan.

Company contact point

It is anticipated that there may be patients where other alternatives are NOT available or suitable. In the scenario where the remaining batches for which the defect has not been detected are exhausted, clinicians can request access to quarantined stock on an individual patient supply basis from Allergan. Please contact Customer Services at:

Phone: +44 (0)808 238 1500 Option 1
Email: ukcustomerservices@allergan.com

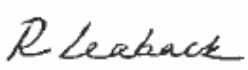
Adverse events: UK_Medinfo@allergan.com

You may also contact our medical information department at:

Allergan Ltd, Marlow International, The Parkway, Marlow, SL7 1YL, United Kingdom
Tel: +44 1628 494026
Email: UK_Medinfo@allergan.com

if you have any questions about the information contained in this letter or the safe and effective use of Ozurdex.

Yours Faithfully,



Richard Leaback
Country Medical Director