Cherubino Ltd.
Since 1906
YOUR HEALTH AT HEART

NOTICE OF OUT OF STOCK AND SPECIAL HANDLING INSTRUCTIONS

USE A 5 MICRON FILTER NEEDLE WITH VIALS OF ERWINASE® FROM BATCHES 174* AND 177*

Dear Healthcare Professional:

Cherubino ltd would like to inform you of the following:

Summary

- Jazz Pharmaceuticals (Jazz), which distributes ERWINASE on a world-wide basis, is experiencing an immediate shortage of ERWINASE due to an unanticipated manufacturing issue that has delayed the scheduled release of an additional batch of the product. Our current estimate is that we could have an ERWINASE product outage of up to 4 weeks.[1]

- ERWINASE is the only approved treatment for patients with acute lymphoblastic leukaemia (ALL) who have experienced hypersensitivity to E. Coli-derived asparaginase treatments.

- To reduce the length of the potential product outage, previously unreleased ERWINASE vials from batches 174 and 177 (see Dear HCP letters dated May and June 2016) are now being made available for use with a 5-micron filter needle (the "Newly Released Vials"). The Newly Released Vials contain particulate matter, which appears as a black discolouration, on the underside of the stopper.

    - Particulate matter was observed bound to the stopper of some vials during routine inspection of ERWINASE batches 174 and 177. These vials were not released at the time the rest of batches 174 and 177 were released.

    - Transference studies conducted by Jazz showed that the particulate matter bound to the stoppers on vials from these batches did not transfer to the product during reconstitution.

- Jazz Pharmaceuticals has assessed the overall benefit-to-risk ratio of administering ERWINASE from the Newly Released Vials for the treatment of acute lymphoblastic leukaemia as positive.

[1]The content relating to the existence and length of product outage, here and elsewhere in the document, is subject to change, depending on the facts at the time the Dear HCP letter is issued.

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- Carefully inspect each vial. If you observe particulate matter anywhere other than on the underside of the stopper (for example, on or in the product), discard the vial.
- If you do not observe particulate matter anywhere other than on the underside of the stopper, reconstitute the product as set forth below.
- After reconstitution, carefully inspect the reconstituted product. If you discover particulate matter after reconstitution, discard the vial.
- If there is no visible particulate matter in the product after reconstitution, **as an additional precaution, use a standard 5-micron filter needle to withdraw the reconstituted product from the vial prior to administration.**
- The Newly Released Vials can be identified by the following label, attached to the carton:

USE 5 MICRON FILTER NEEDLE SEE NOTICE OF SPECIAL INSTRUCTIONS

PLEASE READ THE FOLLOWING ADDITIONAL INFORMATION ABOUT THE RELEASED VIALS

Recommendations for Preparation

ERWINASE is used in combination with other anti-neoplastic agents to treat acute lymphoblastic leukaemia. It may also be used in other neoplastic conditions where depletion of asparagine might be expected to have a useful effect. Patients receiving treatment with L-asparaginase from *Escherichia coli* and who develop hypersensitivity to that enzyme may be able to continue treatment with ERWINASE as the enzymes are immunologically distinct.

During routine visual inspection of ERWINASE batches 174 and 177, particulate matter was observed bound to the stopper of some vials. These vials were identified and segregated and were not released (See Dear HCP Letters dated May and June 2016). The remaining vials in both batches were released with special handling instructions to use a 5 micron filter needle post-reconstitution.

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Transference studies demonstrated that the particulate matter bound to the stopper in the vials from these batches did not transfer to the product during reconstitution. To reduce the length of the potential product outage, the vials of ERWINASE from batches 174 and 177 that were previously segregated due to the presence of visible particulate matter on the stopper (the "Newly Released Vials") will now be made available for use with a standard 5-micron filter needle .

Before reconstitution, carefully inspect each vial. If you observe particulate matter anywhere other than on the underside of the stopper (for example, on or in the product), discard the vial.

If you do not observe particulate matter anywhere other on than the underside of the stopper, reconstitute the product as set forth below. After reconstituting the product from the Newly Released Vials, carefully inspect the product to confirm that no particulate matter is visible in the reconstituted solution. Section 6.6 of the SMPC (Special precautions for disposal and other handling) instructs health care providers that "If there are any visible particles or protein aggregates present the reconstituted solution should be rejected." In the event that you discover particulate matter in reconstituted product, discard the product. Use of reconstituted product containing particulate matter may pose a safety risk to patients.

If the reconstituted product does not contain particulate matter, use a standard 5-micron filter needle to withdraw the reconstituted product from the vial prior to administration as an additional precaution. This is intended to further minimise the potential risk of exposure to particulate matter. A study has demonstrated that filtration through a 5-micron filter needle after reconstitution has no effect on ERWINASE activity or purity.

Jazz Pharmaceuticals has assessed the overall benefit-to-risk ratio of administering ERWINASE from the Newly Released Vials for the treatment of acute lymphoblastic leukaemia as positive, particularly with the additional precaution of using a 5-micron filter needle to withdraw the reconstituted product from the vial.

The Newly Released vials have been approved under a Batch Specific Variation for release in the UK by the Medicines & Healthcare Products Regulatory Agency (MHRA.

In the event that you need to discard a vial of ERWINASE, please contact the Customer Services department for replacement.

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Call for Reporting

In the event of any adverse reaction to ERWINASE, please report side effects directly to:

Malta Medicines Authority,
Sir Temi Zammit Building,
Malta Life Sciences Park,
San Gwann SGN 3000
OR
www.medicinesauthority.gov.mt/adrportal

Company contact point

If you have any questions about this letter or any other enquiry, please contact the below:

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Yours sincerely,

Mrs. Luisa De'Piro O'Connell B.Pharm (Hons)
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