

**Newly Released Vials consist of lot numbers: 183aG117, 183aG217, 184aG117, 184aG217, 185aG117 and 185aG217*

SPECIAL HANDLING INSTRUCTIONS
VIALS OF ERWINASE® FROM BATCHES 183a, 184a and 185a* should be used with a 5-micron filter needle

Dear Healthcare Professional:

Jazz Pharmaceuticals UK Limited would like to inform you of the following:

Summary

- Jazz Pharmaceuticals (Jazz) is experiencing an immediate shortage of ERWINASE due to an ongoing 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 1 week.¹ in January 2018
- 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, some previously unreleased ERWINASE vials from batch 183, 184 and 185 (see Dear HCP letters dated August 2017, September 2017 and November 2017 respectively) 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 and/or present on the lyophilized cake during routine inspection of ERWINASE batch 183G, 184G and 185G. These vials were not released at the time the rest of batch 183, 184 and 185 was released.
 - These vials have gone through an additional round of inspection in order to remove the vials with visible particulate matter on the lyophilised cake.
- 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.
- 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), do not administer the product and retain for collection.
- If you do not observe particulate matter anywhere other than on the underside of the stopper, reconstitute the product as set forth below.

¹The 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.

- After reconstitution, carefully inspect the reconstituted product. If you discover particulate matter after reconstitution, do not administer the product and retain for collection.
- 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 batch 183, 184 and 185, particulate matter was observed bound to the stopper and/or present on the lyophilized cake of some vials. These vials were identified and segregated and were not released (See Dear HCP Letters dated August 2017, September 2017 and November 2017). The remaining vials in both batches were released with special handling instructions to use a 5 micron filter needle post-reconstitution.

To reduce the length of the potential product outage, the vials of ERWINASE from batch 183, 184 and 185 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 following an additional round of inspection in order to remove the vials with visible particulate matter on the lyophilised cake.

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), do not administer the product and retain for collection.

If you do not observe particulate matter anywhere other 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, do not administer the product and retain for collection. 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.

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

¹Tel +44 (0)1865405019

Fax +44 (0)1865594353

Customerservices.uk@jazzpharma.com

Adverse Event Reporting

In the event of any adverse reaction to ERWINASE, Healthcare professionals are asked to report any suspected adverse reactions via HPRC Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie

Company contact point

If you have any questions about this letter or any other enquiry, please contact Medical Information at the following address:

Tel +44 (0)845 0305089

Medinfo-uk@jazzpharma.com

This information is being sent to you with the agreement of the Health Products Regulatory Authority (HPRA)."

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Yours sincerely,

A handwritten signature in black ink, appearing to read "Kelvin Tan". The signature is fluid and cursive, with a large loop at the end.

Dr Kelvin Tan
Vice President Medical Affairs
Jazz Pharmaceuticals

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NOTICE OF SPECIAL HANDLING INSTRUCTIONS

VIALS of ERWINASE[®] from BATCH 183a* 184a* and 185a* should be used with a 5-micron filter needle

(additions to the current Summary of Product Characteristics in **bold + italics**)

Vials from BATCH 183a, 184a 185a can be identified by the following label, attached to the carton:

<p>USE 5 MICRON FILTER NEEDLE</p> <p>SEE NOTICE OF SPECIAL INSTRUCTIONS</p>

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), do not administer the product and retain for collection.. If you do not observe particulate matter anywhere other than on the underside of the stopper, reconstitute the product as follows.

The contents of each vial should be reconstituted in 1 ml to 2 ml of sodium chloride (0.9%) solution for injection. Slowly add the reconstitution solution against the inner vial wall, do not squirt directly onto or into the powder. Allow the contents to dissolve by gentle mixing or swirling maintaining the vial in an upright position. Avoid froth formation due to excessive or vigorous shaking.

After reconstituting the product, carefully inspect the product to confirm that no particulate matter is visible in the reconstituted solution.

The solution should be clear without any visible particles. Fine crystalline or thread-like wisps of protein aggregates may be visible if shaking is excessive. If there are any visible particles or protein aggregates present the reconstituted solution should be rejected.

If the reconstituted product does not contain particulate matter, then a standard 5-micron filter needle should be used to withdraw the reconstituted product from the vial prior to administration as an additional precaution.

The solution should be administered within 15 minutes of reconstitution. If a delay of more than 15 minutes between reconstitution and administration is unavoidable, the solution should be withdrawn into a glass or polypropylene syringe for the period of the delay. The solution should be used within 4 hours.

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Additional information

There are two centrally licensed products Spectrila (EU/1/15/1072/001 EU/1/15/1072/002) and Oncaspar (EU/1/15/1070/001) available. Both of these products are indicated as a component of antineoplastic combination therapy for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years and adults. Spectrila contains 10,000 units of asparaginase and Oncaspar contains 750 units of pegaspargase. However Spectrila and Oncaspar may not be suitable in patients who are hypersensitive to the active substance, any native (non-pegylated) E. coli-asparaginase preparation, or to any of the excipients listed in section 6.1 of the product information.

Please see the links below for further information.

Spectrila

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002661/human_med_001954.jsp&mid=WC0b01ac058001d124

Oncaspar

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003789/human_med_001949.jsp&mid=WC0b01ac058001d124