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{Healthcare Professionals address}
{reference}

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Dear

Direct Healthcare Professional Communication on the restriction of the indication for ZERIT® (stavudine) due to potentially severe side effects

Summary

- The indication for stavudine (Zerit® Hard Capsules and Powder for Oral Solution) has been restricted. Stavudine should only be used when there are no alternatives, and for the shortest period of time possible.
- Post-marketing safety reports and published literature have increased awareness and characterisation of stavudine's safety profile, including lactic acidosis, lipoatrophy and peripheral neuropathy.
- A new evaluation has concluded that there is an increased risk of potentially severe toxicity in patients receiving stavudine, compared with alternative HIV treatments.

Further information on the safety concern

Toxicities such as lactic acidosis, lipoatrophy and peripheral neuropathy have been identified as side effects associated with stavudine use:

1. Cases of lactic acidosis, with an estimated fatality rate of 30-50%, have been reported with stavudine. This can occur within the first few months of treatment, but also much later. The incidence of stavudine-associated lactic acidosis has been around 1% in cohort studies and randomised controlled trials.[1]
2. There is an increased risk of lipoatrophy in patients receiving stavudine, as compared with other nucleoside reverse transcriptase inhibitors (NRTIs). In a recent study, 42% of patients on stavudine had more than 20% loss of extremity fat (by DEXA scan) at 96 weeks. The corresponding figure for zidovudine was 27% and 9 % for tenofovir, as well as for the control group without NRTI. The incidence and severity of lipoatrophy are cumulative over time and often not completely reversible on stopping stavudine.[2]
3. Peripheral neuropathy is reported in up to 20% of patients treated with stavudine. Those with a history of neuropathy or with other risk factors (for example excessive alcohol

intake, concomitant medications such as isoniazid, and renal impairment) are at particular risk.[3,4].

Due to these safety problems with stavudine, the benefit/risk remains favourable only in selected individuals where there are no appropriate alternative treatment options, and for the shortest period of time possible.

In consideration of this, the Summary of Product Characteristics (SPC) for Zerit® Hard Capsules and Powder for Oral Solution has been updated (see Annexes).

The information in this communication has been agreed with the European Medicines Agency and the Irish Medicines Board (IMB).

Further information on recommendations to healthcare professionals

Given the potential risks of using stavudine a benefit/risk assessment for each patient must be made and an alternative appropriate therapy carefully considered whenever possible. Patients must be appropriately informed of any potential risks.

Call for reporting

Please report suspected adverse reactions with any medicine to the Irish Medicines Board (IMB) using the online form at www.imb.ie or using the freepost Yellow Card system. In addition, suspected adverse reactions, pregnancy, overdose and unexpected benefits for stavudine (Zerit) may be reported to Bristol-Myers Squibb Pharmaceuticals Ltd. via telephone at +44 1895 523740 or via email at medical.information@bms.com.

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

Yours sincerely

Pascal King
Acting Medical Director - Ireland

Annexes

Revised wording for ZERIT ®(stavudine) Powder for Oral Solution SPC:

ZERIT® Powder for Oral Solution

4.1 Therapeutic Indication:

Zerit is indicated in combination with other antiretroviral medicinal products for the treatment of HIV infected adult patients and paediatric patients (from birth) only when other antiretrovirals can not be used. The duration of therapy with Zerit should be limited to shortest time possible (See section 4.2)

4.2 Posology and method of administration

For patients starting therapy with Zerit, the duration should be limited to shortest time possible followed by a switch to an alternative appropriate therapy whenever possible. Patients continuing treatment with Zerit should be assessed frequently and switched to an alternative appropriate therapy whenever possible. (See section 4.4)

ZERIT® Hard Capsules

4.1 Therapeutic Indication:

Zerit is indicated in combination with other antiretroviral medicinal products for the treatment of HIV infected adult patients and paediatric patients (over the age of 3 months) only when other antiretrovirals can not be used. The duration of therapy with Zerit should be limited to shortest time possible (See section 4.2)

4.2 Posology and method of administration

For patients starting therapy with Zerit, the duration should be limited to shortest time possible followed by a switch to an alternative appropriate therapy whenever possible. Patients continuing treatment with Zerit should be assessed frequently and switched to an alternative appropriate therapy whenever possible. (See section 4.4)

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1. Lactic Acidosis International Study Group. Risk factors for lactic acidosis and severe hyperlactataemia in HIV-1-infected adults exposed to antiretroviral therapy. AIDS 2007; 21:2455-2464.
2. Riddler SA, Haubrich R, DiRienzo AG, et al, for the AIDS Clinical Trials Group Study A5142 Team. Class-sparing regimens for initial treatment of HIV-1 infections. N Engl J Med 2008; 358: 2095-2106.
3. Cherry CL, Skolasky RL, Lal L, et al. Antiretroviral use and other risks for HIV-associated neuropathies in an international cohort. Neurology 2006; 66:867-873.
4. Smyth K, Affandi JS, McArthur JC, et al. Prevalence of and risk factors for HIV-associated neuropathy in Melbourne, Australia 1993-2006. HIV Medicine 2007; 8:367-373.