臺北醫學大學附設醫院
TAIPEI MEDICAL UNIVERSITY HOSPITAL

藥物不良反應工作小組藥物安全警訊通告 107.06

食品藥物管理署(TFDA)用藥安全資訊風險溝通：

Dolutegravir於懷孕期間服用可能導致嬰兒先天性神經管缺陷

摘要說明：

Tsepamo study 為一進行中觀察性研究，初步結果顯示於服用含 dolutegravir 成分藥品期間懷孕或懷孕初期，產下先天性神經管缺陷（如脊柱裂）嬰兒的風險較高。神經管缺陷是在懷孕初期因脊髓、大腦與相關結構未能正常成型所發生的先天性缺陷。

此研究共納入 11,558 位感染 HIV 女性，其中 426 位服用 dolutegravir 之女性所生產之嬰兒有 4 位發生神經管缺陷事件(0.9%)，與服用其他藥物相比風險較高(0.1%，N=14/11,173)。目前該研究中並無於懷孕較後期開始使用含 dolutegravir 成分藥品而產下神經管缺陷嬰兒的報告案例(N=0/2824)。

此研究尚有約 600 名服用 dolutegravir 之懷孕中婦女，預計於一年後發布最終研究結果，美國 FDA、歐盟 EMA 及澳洲 TGA 均將持續監視並調查此風險。

醫療人員注意事項：

1) 歐盟 EMA 建議預防性措施如下：
   - ✓ 不應處方含 dolutegravir 成分藥品予計畫懷孕的婦女。。
   - ✓ 育齡婦女於使用含 dolutegravir 成分藥品期間應採行有效之避孕措施。
2) 處方含 dolutegravir 成分藥品於具有生育能力的女性時：
   - ✓ 應評估其臨床效益與風險，並考慮使用其他替代藥品的臨床效益與風險。
   - ✓ 用藥前應進行懷孕檢查，以確認病人是否懷孕。
   - ✓ 應告知病人於服用含 dolutegravir 成分藥品期間懷孕或懷孕初期使用該藥品，產下先天性神經管缺陷（如脊柱裂）嬰兒的風險較高，用藥期間應持續採行有效的避孕措施。
3) 提醒正在服用 dolutegravir 的女性在未經醫療人員的評估下不建議自行停藥。
4) 醫療人員若懷疑病人因為使用藥品導致不良反應發生時，請立即線上通報藥物不良反應及登入於藥物過敏/不良反應記錄中。

院內品項：

Tivicay ® (Dolutegravir) 50 mg/tab 汰威凱膜衣錠

Triumeq ® (Lamivudine, Abacavir, Dolutegravir) (300,600,50) mg/tab 汰威凱膜衣錠

北醫藥物不良反應工作小組　敬啟
臨床藥學組　呂懷恩 藥師
(分機 8443/8444)

Dolutegravir 成分藥品安全資訊風險溝通表

日期：107/06

藥品成分	Dolutegravir
藥品名稱 及許可證字號	衛生福利部核准含 dolutegravir 成分藥品製劑許可證共 2 張。 查詢網址：https://www.fda.gov.tw/mlms/H0001.aspx
適應症	與其他抗反轉錄病毒藥物合併用於治療成人及 12 歲以上青少年的人類免疫不全病毒(HIV)感染症。
藥理作用機轉	Dolutegravir會與HIV嵌合酶的活性部位結合，進而抑制嵌合酶的作用，並阻斷反轉錄病毒去氧核醣核酸(DNA)之嵌合過程中的鏈轉移步驟。
訊息緣由	美國 FDA、歐盟 EMA 及澳洲 TGA 陸續發布警訊指出，一項正在進行的觀察性研究初步結果顯示，於服用含 dolutegravir 成分藥品期間懷孕或懷孕初期使用該藥品，可能有產下先天性神經管缺陷（如脊柱裂）嬰兒的潛在風險之安全性資訊。網址： 美國 FDA： https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm608168.htm 歐盟 EMA： http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/05/news_detail_002956.jsp&mid=WC0b01ac058004d5c1 澳洲 TGA: https://www.tga.gov.au/alert/dolutegravir
藥品安全有關資訊分析及描述	1. 一項正在進行的觀察性研究初步結果顯示，於服用含 dolutegravir 成分藥品期間懷孕或懷孕初期使用該藥品，產下先天性神經管缺陷（如脊柱裂）嬰兒的風險較高。 2. 神經管缺陷是在懷孕初期因脊髓、大腦與相關結構未能正常成型所發生的先天性缺陷。目前該研究中並無於懷孕較後期開始使用含 dolutegravir 成分藥品而產下神經管缺陷嬰兒的報告案例。 3. 此研究預計於一年後發布最終研究結果，美國 FDA、歐盟 EMA 及澳洲 TGA 均將持續監視並調查此風險。目前歐盟 EMA 建議預防性措施如下： ● 不應處方含 dolutegravir 成分藥品予計畫懷孕的婦女。 ● 育齡婦女於使用含 dolutegravir 成分藥品期間應採行有效之避孕措施。

食品藥物管理署 風險溝通說明	◎ **食品藥物管理署說明：** 1. 經查，我國核准含 dolutegravir 成分藥品之中文仿單已於「特殊族群之使用」刊載「目前懷孕婦女使用 dolutegravir 的資料有限，未知 dolutegravir 對於人體懷孕的影響。」、「只有在預期效益大於對胎兒風險的狀況下，才可於懷孕期間使用。」等相關警語，惟未提及於服用含 dolutegravir 成分藥品期間懷孕或懷孕初期使用該藥品，產下先天性神經管缺陷（如脊柱裂）嬰兒的風險較高。 2. 本署現正評估是否針對該成分藥品採取相關風險管控措施。 ◎ **醫療人員應注意事項：** 處方含 dolutegravir 成分藥品於具有生育能力的女性時： 1. 應評估其臨床效益與風險，並考慮使用其他替代藥品的臨床效益與風險。 2. 用藥前應進行懷孕檢查，以確認病人是否懷孕。 3. 應告知病人於服用含 dolutegravir 成分藥品期間懷孕或懷孕初期使用該藥品，產下先天性神經管缺陷（如脊柱裂）嬰兒的風險較高，用藥期間應持續採行有效的避孕措施。 ◎ **病人應注意事項：** 1. 於服用含 dolutegravir 成分藥品期間懷孕或懷孕初期使用該藥品，產下先天性神經管缺陷（如脊柱裂）嬰兒的風險較高，故用藥前應進行懷孕檢查確認是否懷孕，用藥期間亦應持續採行有效的避孕措施。 2. 用藥前或用藥期間，若發現懷孕、覺得自己可能懷孕或計畫懷孕，請盡快告知醫療人員。 3. 若對藥品或避孕方式有任何疑問，請諮詢醫療人員。切勿於諮詢醫療人員前自行停藥，自行停藥可能會導致 HIV 感染惡化。若您已懷孕，擅自停藥且未以其他替代療法治療時，可能會造成 HIV 病毒增加及病毒擴散至胎兒。 ◎ 醫療人員或病人懷疑因為使用（使用）藥品導致不良反應發生時，請立即通報給衛生福利部所建置之全國藥物不良反應通報中心，並副知所屬廠商，藥物不良反應通報專線 02-2396-0100，網站：https://adr.fda.gov.tw；衛生福利部食品藥物管理署獲知藥品安全訊息時，均會蒐集彙整相關資料進行評估，並對於新增之藥品風險採取對應之風險管控措施。

Juluca, Tivicay, Triumeq (dolutegravir): FDA to Evaluate - Potential Risk of Neural Tube Birth Defects

[Posted 05/18/2018]

AUDIENCE: Infectious Disease, Health Professional, Patient

ISSUE: Serious cases of neural tube birth defects involving the brain, spine, and spinal cord have been reported in babies born to women treated with dolutegravir used to treat human immunodeficiency virus (HIV). Preliminary results from an ongoing observational study in Botswana found that women who received dolutegravir at the time of becoming pregnant or early in the first trimester appear to be at higher risk for these defects.

Neural tube defects are birth defects that can occur early in pregnancy when the spinal cord, brain, and related structures do not form properly. To date, in this observational study there are no reported cases of babies born with neural tube defects to women starting dolutegravir later in pregnancy. We are investigating this new safety issue and will update the public when we have more information.

BACKGROUND: Dolutegravir is an FDA-approved antiretroviral medicine used in combination with other antiretroviral medicines to treat HIV, the virus that can cause acquired immunodeficiency syndrome (AIDS). Dolutegravir works by blocking integrase, an HIV enzyme, to prevent the virus from multiplying and can reduce the amount of HIV in the body. Stopping dolutegravir without first talking to a prescriber can cause the HIV infection to become worse. Approved in 2013, dolutegravir has been on the market for 5 years, and is available as a single ingredient product under the brand name Tivicay and as a fixed dose combination tablet with other HIV medicines under the brand names Juluca and Triumeq.

RECOMMENDATION: Patients should not stop taking dolutegravir without first talking to your health care professional because stopping your medicine can cause the HIV infection to worsen. In addition:

- If you are already pregnant, stopping your dolutegravir-containing regimen without switching to alternative HIV medicines could cause the amount of virus to increase and spread HIV to your baby.
- If you take a dolutegravir-containing regimen at the time of becoming pregnant and during the first trimester of pregnancy, there is a risk that your baby may develop neural tube defects. Neural tube defects happen early in pregnancy, before many women even know they are pregnant. For this reason, women of childbearing age should talk to their health care professional about other non-dolutegravir-containing antiretroviral medicines.
- You should tell your health care professional if you are pregnant or are planning to become pregnant before you start a dolutegravir-containing regimen. Your health care professional may discuss other treatment options with you.
- Women of childbearing age who decide to take a dolutegravir-containing regimen should consistently use effective birth control (contraception) while on HIV treatment. Women should talk to their health care professionals about an effective birth control method to use while taking a dolutegravir-containing regimen.
- Before you start a dolutegravir-containing regimen you will need a pregnancy test to determine if you are already pregnant.

Healthcare professionals should inform women of childbearing age about the potential risk of neural tube defects when a dolutegravir-containing regimen is used at the time of conception and early in pregnancy. In addition:

- Healthcare professionals should weigh the benefits and the risks of dolutegravir when prescribing antiretroviral medicines to women of childbearing age. Alternative antiretroviral medicines should be considered. Discuss the relative risks and benefits of appropriate alternative antiretroviral therapies.
- If the decision is made to use dolutegravir in women of childbearing age, health care professionals should reinforce the consistent use of effective birth control.
- Perform pregnancy testing before initiating a dolutegravir-containing regimen in women of childbearing age to exclude pregnancy.

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

- Complete and submit the report Online: **www.fda.gov/MedWatch/report (https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home)**
- **Download form (/Safety/MedWatch/HowToReport/DownloadForms/ucm2007307.htm)** or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178

[05/18/2018 - **Drug Safety Communication (/Drugs/DrugSafety/ucm608112.htm)** - FDA]

More in Safety Alerts for Human Medical Products (/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/default.htm)

2018 Safety Alerts for Human Medical Products (/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm590808.htm)

2017 Safety Alerts for Human Medical Products (/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm535957.htm)

18 May 2018
EMA/295960/2018

New study suggests risk of birth defects in babies born to women on HIV medicine dolutegravir

While EMA review is ongoing, dolutegravir should not be used in women seeking to become pregnant

The European Medicines Agency (EMA) is evaluating preliminary results from a study which found 4 cases of birth defects such as spina bifida (malformed spinal cord) in babies born to mothers who became pregnant while taking dolutegravir. While EMA is assessing the new evidence it has issued the following precautionary advice:

- Dolutegravir HIV medicines should not be prescribed to women seeking to become pregnant.
- Women who can become pregnant should use effective contraception while taking dolutegravir medicines.

The study, which looked at babies born to 11,558 HIV-infected women in Botswana, showed that 0.9% of babies (4 of 426) whose mothers became pregnant while taking dolutegravir had a neural tube defect, compared with 0.1% of babies (14 of 11,173) whose mothers took other HIV medicines. Final results are expected in about a year.

Women who have been prescribed dolutegravir should not stop taking their medicine without first consulting their doctor.

EMA will update the recommendations as necessary when it concludes its assessment.

Information for patients

- Preliminary data show that taking dolutegravir for HIV before pregnancy may increase the risk of birth defects such as spina bifida (malformed spinal cord).
- If you are taking dolutegravir and you can become pregnant you should use an effective contraception.
- If you are taking dolutegravir and wish to become pregnant please talk to your doctor about whether dolutegravir remains the most appropriate treatment.
- If you are pregnant and using dolutegravir, you should consult your doctor. Do not discontinue dolutegravir without consulting your doctor, as this may harm you and your unborn child.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

- Tell your doctor if you become pregnant, think you might be pregnant or are planning to become pregnant. Your doctor will review your treatment.
- If you have any questions about your treatment or contraception, speak to your doctor or pharmacist.

Information for healthcare professionals

- Preliminary results from an observational study revealed an increased risk of neural tube defects in infants born to women who took dolutegravir at the time of conception. No cases were reported in infants born to women who started dolutegravir later during pregnancy.
- Reproductive toxicology studies have not shown any relevant findings. Likewise, other data on the use of dolutegravir in pregnancy, including data from the Antiretroviral Pregnancy Registry (APR), clinical trials and post-marketing use have not indicated a risk of neural tube defects.
- As a precaution, healthcare professionals in the EU are advised of the following:
  - Do not prescribe dolutegravir for women of child bearing potential who are trying to become pregnant.
  - Exclude pregnancy in women of child bearing potential before starting dolutegravir.
  - Advise women of child bearing potential who are taking dolutegravir to use effective contraception throughout treatment.
  - If pregnancy is confirmed in the first trimester while a woman is taking dolutegravir, switch to an alternative treatment unless there is no suitable alternative.
- Healthcare professionals in the EU will be sent a dear healthcare professional letter concerning these recommendations.

More about the medicine

Dolutegravir is an integrase inhibitor. This means that it blocks an enzyme called integrase that is needed by the HIV virus to make new copies of itself in the body. When it is given with other medicines, it helps to prevent the spread of HIV and keep the amount of the virus in the blood at a low level. Dolutegravir does not cure HIV infection or AIDS, but it may hold off damage to the immune system and the development of infections and diseases associated with AIDS.

In the EU, dolutegravir has been authorised since 2014. It is marketed on its own as Tivicay and in combination with lamivudine and abacavir as Triumeq. Further information on these medicines can be found here. Another medicine, Juluca, a combination of dolutegravir and rilpivirine has received a positive opinion by the Committee for Medicinal Products for Human Use (CHMP) and is currently awaiting a decision by the European Commission.

More about the procedure

The review of dolutegravir was carried out in the context of a safety signal. A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation.

The review was carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines.