

季度藥訊 Quarterly Drug Newsletter

2009 No. 4

本季度藥訊的內容主要摘錄自世界各國藥政部門所公佈及在本澳所收集有關藥物安全性的資訊，目的是通知本澳的衛生專業人士最新的藥物安全性資訊，從而推廣安全及合理用藥。

The content of this Quarterly Drug Newsletter originates as compilation of the adverse drug reactions (ADR) and drug safety issues published by various drug regulatory authorities as well as those reported locally. With this information, we aim at disseminating the latest adverse drug reaction alerts, safety and efficacy issues to our healthcare professionals with the ultimate goal to encourage safe and rational use of pharmaceuticals.

熱點關注藥物 DRUGS OF CURRENT INTEREST

熱點關注藥物泛指一些近期在國內外及本地曾被報告發生藥物不良反應的藥物，以及最近獲批准進口本澳的新藥，訂定熱點關注藥物的目的是提醒衛生專業人士尤其關注及通報該等藥物所引起的不良反應，如閣下察覺病人在服用以下及其他藥物後產生任何不良反應，請向藥物事務廳通報。

Generally speaking, 'Drugs of Current Interest' are defined as those drugs of which adverse drug reaction(s) (ADRs) was (were) experienced and had been reported recently at international, national and local levels. In addition, drugs that have received recent approval for importation into Macao are also being incorporated into this list. The purpose of including this column serves to remind all healthcare professionals to pay special attention to ADRs and report them. If you observe any adverse reaction on your patient subsequent to the use of the following or any other drugs, please report all suspected reactions to the Department of Pharmaceutical Affairs.

Abacavir	Drotrecogin alfa	Methylphenidate
Adalimumab	Entecavir	Metoclopramide
Aliskiren	Erlotinib	Moxifloxacin
Allopurinol	Eszopiclone	Metoclopramide
Atorvastatin	Etanercept	Moxifloxacin
Azacitidine	Etoricoxib	Mycophenolate mofetil
Bisphosphonates	Ezetimibe	Norfloxacin
Bevacizumab	Ezetimibe/Simvastatin	Oseltamivir
Botulinum toxins	Flucloxacillin	Phenytoin
Bortezomib	Fluoroquinolones	Propranolol
Carbamazepine	Fosaprepitant dimeglumine	Raltegravir
Carbimazole	Fulvestrant	Rimonabant
Certolizumab pegol	Gadobenate dimeglumine	Rituximab
Clopidogrel	Heparin sodium	Rosiglitazone
Darunavir	Iloprost trometamol	Simvastatin
Decitabine	Infliximab	Sunitinib malate
Deferasirox	Ivabradine	Tinzaparin sodium
Desflurane	Lamotrigine	Tiotropium bromide
Diacerein	Lapatinib	Trabectedin
Didanosine	Levofloxacin	Zanamivir
Docetaxel	Leukotriene inhibitors -montelukast	Zonisamide

通報及聯絡資料 Reporting and Contact Information:

通報表格：在 http://www.ssm.gov.mo/design/services/serpt_chn.pdf 下載或向藥物事務廳索取。

網上通報：登入 <http://www.ssm.gov.mo>。

如有任何疑問，請致電 85983517(辦公時間)或傳呼 85008068(非辦公時間)。

Report form: access http://www.ssm.gov.mo/design/services/serpt_chn.pdf to download or obtain from Dept. of Pharmaceutical Affairs. Internet reporting: access <http://www.ssm.gov.mo>. Any query, call 85983517(office hrs) or pager 85008068 (off-duty hrs).

有關 deferasirox (商品名: Exjade®)安全性的最新資訊

Latest safety update on deferasirox (Exjade®)

資料來源: 美國食物及藥物管理局

Source: United States Food and Drug Administration (USFDA)
<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm183840.htm>

美國食物及藥物管理局 (USFDA) 通知衛生專業人士一則關於 deferasirox (商品名: Exjade®)安全性的最新資訊。Exjade 是一口服鐵螯合劑, 用於治療 2 歲以上因患慢性貧血接受輸血而造成鐵質過多的病人。最新資料顯示 60 歲以上患有骨髓異常增生綜合症(myelodysplastic syndrome, MDS) 的病人在使用 Exjade 後, 可能會出現較多不良反應和增加死亡率。因此, USFDA 正和美國諾華公司(Novartis)商討在此藥品的處方資訊的禁忌症、警告和注意事項中加入新資訊, 以提醒醫療專業人員, 急性腎衰竭和胃腸道出血等不良反應雖然罕見, 但對於患有與血液相關的惡性腫瘤和/或血小板過低的老年病人, 是有可能致命的。

The United States Food and Drug Administration (USFDA) notified healthcare professionals about the latest safety update on deferasirox (Exjade®). The main points are summarized as follows: Exjade, an oral iron chelator, is approved for patients aged two and older with chronic anemia and iron overload as a result of receiving blood transfusions. New data suggests there may be a greater number of adverse events and deaths in patients using Exjade who are over sixty years old who have myelodysplastic syndrome (MDS). Hence, USFDA is working with Novartis, USA to add new information in the contraindications, warnings, and precautions sections of the prescribing information, to alert healthcare professionals of the risks and adverse events, including acute renal failure and gastrointestinal hemorrhages that in rare cases, especially in older patients with blood-related malignancies and/or low platelet counts, have been fatal.

有關 sitagliptin(商品名: Januvia®)及 sitagliptin/metformin (商品名: Janumet®)安全性的最新資訊

Latest safety update on sitagliptin (Januvia®) and sitagliptin/metformin (Janumet®)

資料來源: 美國食物及藥物管理局

Source: United States Food and Drug Administration (USFDA)
<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm183800.htm>

美國食物及藥物管理局 (USFDA) 通知衛生專業人士一則關於 sitagliptin(商品名: Januvia®)及 sitagliptin/metformin (商品名: Janumet®)安全性的最新資訊, 並要求 sitagliptin (商品名: Januvia®)及 sitagliptin/metformin (商品名: Janumet®)的製造商在上述藥物的說明書內標示有關病人在服用 sitagliptin 後可引發急性胰臟炎的資訊。在 2006 年 10 月至 2009 年 2 月期

間,USFDA 共接獲 88 宗關於 sitagliptin 與急性胰臟炎有關的上市後通報個案,當中包括 2 宗病人在服用 sitagliptin 後引致嚴重的出血性或壞死性胰臟炎。因此,該局建議主診醫生在首次處方該藥予病人或在增加 sitagliptin 或 sitagliptin/metformin 劑量時,應謹慎地監測病人有否出現胰臟炎。由於沒有關於患有胰臟炎病史的病人服用 sitagliptin 的研究報告,因此仍未得知此藥會否令上述病人增加發生胰臟炎的風險,倘若有必要處方 sitagliptin 給予此類病人時,醫生應慎用該藥,並對病人施以適當的監測。

The United States Food and Drug Administration (USFDA) notified healthcare professionals about the latest safety update on sitagliptin(Januvia®) and sitagliptin/metformin (Janumet®). She had requested the manufacturer of sitagliptin (Januvia®) and sitagliptin/metformin (Janumet®) to include revisions about post-marketing reported cases of acute pancreatitis in patients treated with these medications. So far, among the eighty-eight cases of acute pancreatitis received by the USFDA between October 2006 and February 2009, there were two cases of hemorrhagic or necrotizing pancreatitis in patients using sitagliptin. Hence, it is recommended that the prescribing physicians should monitor patients carefully for the development of pancreatitis after initiation or dose increases of sitagliptin or sitagliptin/metformin. Sitagliptin has not been studied in patients with a history of pancreatitis. Therefore, it is not known whether these patients are at an increased risk for developing pancreatitis and the medication should be used with caution and appropriate monitoring should be implemented for patients with a history of pancreatitis.

有關鎮靜安眠藥 (sedative hypnotics or sleep aid medications)安全性的最新資訊

Latest safety update on sedative hypnotics (sleep aid medications)

資料來源: 加拿大衛生部

Sources: Health Canada

http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2009/2009_161-eng.php

加拿大衛生部 (Health Canada) 通知衛生專業人士一則關於鎮靜安眠藥安全性的最新資訊。近期用於失眠短期治療的鎮靜安眠藥(處方藥)標籤內容已被更新。最新標籤資料描述了有關病人服用這些藥物時所出現複雜的睡眠相關行為,例如在睡夢中說話、步行、煮食、進食和駕駛,而事後病人一般不會記起。新標籤內容強調病人應適當地使用這些藥物,尤其是不應與酒精併用,此外也不應過量服用。當與其他引起嗜睡的藥物如其他鎮靜劑和安眠藥、抗組胺藥、抗驚厥藥、麻醉性止痛藥以及用於治療抑鬱或焦慮的藥物併用時,應謹慎使用。醫生應鼓勵病人和他們的親人留意上述睡眠相關行為,病人也應向醫療專業人士報告任何懷疑的事件。對於曾發生上述複雜睡眠相關行為的病人,為了這些病人和其他人免受傷害,應考慮停止使用安眠藥。因為突然停藥可能會產生戒斷症狀,因此,病人須獲醫生同意後才可停藥。具有可引發上述複雜睡眠相關行為風險的安眠藥包

括氟馬西平(flurazepam)、硝泮地平(nitrazepam)、替馬西平(temazepam)、三唑侖(triazolam)、佐匹克隆(zolpiclone)、唑吡坦(zolpidem)及扎來普隆(zaleplon)。

Health Canada notified healthcare professionals about the latest safety update on sedative hypnotics, which are also known as sleep aid medications. Recent changes are implemented onto the labeling information of prescription sedative hypnotics (sleep aid medications) used in the short-term treatment of insomnia. The new labeling describes reports of complex sleep-related behaviors that have occurred while patients using these drugs were not fully awake, such as talking, walking, cooking, eating, and driving. Patients typically did not remember these events afterwards. Besides, it also emphasizes the proper use of these medications. In particular, sedative-hypnotic medications (sleep aid medications) should not be taken with alcohol, and patients should not take more than the prescribed dose. Caution should be used when taking sleep aid medications at the same time as other drugs that can cause drowsiness, such as other tranquilizers or sleeping pills, antihistamines that cause drowsiness, anticonvulsants, painkillers that contain narcotics, and medicines used to treat depression or anxiety. Patients and people close to them are encouraged to be aware of these types of sleep-related behaviours. Patients should report any suspected events to their health care professional. Discontinuing sleep aid medication should be considered for patients who report complex sleep-related behaviors, due to the risk of harm to the patient and to others. Individual patient should only discontinue these type of medications after consulting with their physicians, as abrupt discontinuation may cause withdrawal symptoms. The sleep-aid medications with potential risk of complex sleep-related behaviors include flurazepam, nitrazepam, temazepam, triazolam, zolpiclone, zolpidem, and zaleplon.

有關 rituximab(商品名: Rituxan®)安全性的最新資訊

Latest safety update on rituximab(Rituxan®)

資料來源：美國食物及藥物管理局
加拿大衛生部

Source : United States Food and Drug Administration (USFDA)
Health Canada

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm187791.htm>
<http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM187792.pdf>
http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2009/rituxan_5_hpc-cps-eng.php

美國食物及藥物管理局 (USFDA) 及加拿大衛生部 (Health Canada) 通知衛生專業人士一則關於 rituximab(Rituxan®)安全性的最新資訊。資料顯示患有類風濕性關節炎的病人服用 rituximab 會增加發生進行性多灶性白質腦病 (progressive multifocal leukoencephalopathy, PML) 的風險, PML 是一種罕見的、進展性的且會導致死亡或嚴重殘障的中樞神經系統去鞘性疾病。有報告指 PML 曾出現在患有類風濕性關節炎病

人中, 當中包括使用 rituximab 以外的免疫抑制劑治療類風濕性關節炎的病人。早前有兩名分別 51 歲和 73 歲接受 rituximab 治療的類風濕性關節炎的女病人死亡, 她們在 rituximab 治療期間或之前已同時具有以化療和放射治療口咽部惡性腫瘤及/或患有長期淋巴細胞減少症的危險因子。第三宗 PML 個案涉及一名已患有血清陰性類風濕性關節炎(seronegative rheumatoid arthritis)三年, 並接受 rituximab 治療的 73 歲病婦。目前所得資訊指出患有類風濕性關節炎的病人服用 rituximab 會增加罹患 PML 的風險, 因此, 當接受 rituximab 治療的病人表現出新發的神經症狀時, 醫生應懷疑病人可能產生了 PML, 並須作出相應的臨床跟進, 包括轉介病人至神經內科專家就診、安排腦部 MRI 掃描及腰椎穿刺。

The United States Food and Drug Administration (USFDA) and Health Canada notified healthcare professionals about the latest safety update on rituximab (Rituxan®). Data suggests that patients with rheumatoid arthritis (RA) who are also receiving rituximab have an increased risk of developing progressive multifocal leukoencephalopathy (PML), which is a rare, progressive, demyelinating disease of the central nervous system that may lead to death or severe disability. PML has been reported in patients with RA, including those treated with other immunosuppressive medications in the absence of rituximab. Previous to this, two female RA patients died who aged 51 and 73 years old respectively, were treated with rituximab and also had predisposing risk factors including oropharyngeal malignancy treated with chemotherapy and radiation therapy and/or long standing lymphopenia prior to and during rituximab treatment. The third case of PML involved a 73 year-old female patient with seronegative rheumatoid arthritis for 3 years and was treated with rituximab. Information to date suggests that patients with RA who receive rituximab have an increased risk of PML. Hence, physicians should consider PML in any patient being treated with rituximab who presents with new onset neurologic manifestations. Consultation with a neurologist, brain MRI, and lumbar puncture should be considered as clinically indicated.

有關 exenatide(商品名: Byetta®)的最新資訊

Latest update on exenatide(Byetta®)

資料來源：美國食物及藥物管理局

Source : United States Food and Drug Administration (USFDA)

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm188703.htm>

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm188656.htm>

美國食物及藥物管理局 (USFDA) 通知醫療專業人士一則有關 exenatide (Byetta®) 處方資訊的更新, 上市後藥物監測報告指出此藥物可能會引起腎功能改變, 包括急性腎衰竭和腎功能不全。Byetta® 是一種仿腸降血糖素 (incretin-mimetic), 通過輔助飲食和運動來控制血糖, 獲准用於 2 型糖尿病的成年病人。

在2005年4月至2008年10月期間，USFDA共接到78宗使用Byetta[®]的病人發生腎功能改變的報告(62宗急性腎衰竭和16宗腎功能不全)，其中63名病人(80%)停用Byetta[®]後，39名病人(50%)表示停藥後症狀有改善，當中1名病人重新使用Byetta[®]後再次發生腎功能改變。然而，在這些案例中有些病人曾經患有腎病，或者有一個或以上發生腎病的危險因子。醫生在處方此藥時，應考慮以下資料：

- 與病人討論服用 Byetta[®]有可能引起腎功能改變、服藥的臨床效益、使用其他糖尿病療法的風險評估以及不控制糖尿病的危險性。
- 監控病人腎功能改變症狀的出現，如血清肌酐升高、排尿改變(如顏色、頻率和量)、不能解釋的四肢腫脹、血壓上升、嗜睡、食慾改變、中或下背部隱痛。
- 當發生原因不明的腎功能損傷時應考慮停用 Byetta[®]。
- 應了解腎功能改變可能是糖尿病導致，而並不一定由 Byetta[®]引起。
- 告知病人高血壓和胰臟炎等慢性疾病以及非甾體消炎藥、利尿藥和抗高血壓藥也可能增加發生腎功能改變的風險。
- 同時應教導病人留意上述腎功能改變的症狀，使他們在發生任何不尋常的症狀時，能夠察覺和通知他們的主診醫生。

The United States Food and Drug administration (USFDA) notified healthcare professionals of revisions to the prescribing information for exenatide (Byetta[®]) to include information on post-marketing reports of altered kidney function, including acute renal failure and insufficiency. Byetta, an incretin-mimetic, is approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

From April 2005 through October 2008, FDA received 78 cases of altered kidney function (62 cases of acute renal failure and 16 cases of renal insufficiency), in patients using Byetta. Byetta was discontinued in 63 of 78 (80%) patients, with 39 (50%) patients reporting improved signs and symptoms after discontinuation of the drug. One patient experienced recurrent altered kidney function after re-initiation of Byetta. Some cases occurred in patients with pre-existing kidney disease or in patients with one or more risk factors for developing kidney problems. Prescribers should consider the following:

- Discuss with patients the possibility of developing altered kidney function with Byetta, taking into account the clinical utility of Byetta, the risks/benefits of other antidiabetic therapies, and the risks associated with uncontrolled diabetes mellitus.
- Monitor for the emergence of signs and symptoms of altered kidney function, such as increased serum creatinine, changes in urination (color, frequency, amount), unexplained swelling in the extremities, increases in blood pressure, lethargy, changes in appetite or digestion, or dull ache in the mid to lower back.
- Consider discontinuation of Byetta if kidney dysfunction cannot be explained by other causes.

- Understand that altered kidney function can be a consequence of diabetes, independent of any risk associated with Byetta.
- Discuss with patients that chronic conditions such as hypertension and pancreatitis as well as medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), diuretics, and antihypertensives, can increase the risk of developing altered renal function.
- Inform patients of the signs and symptoms of altered kidney function so they are aware of and able to notify their healthcare professional if they experience any unusual signs or symptoms.

有關 clopidogrel 與 omeprazole 相互作用的最新資訊

Latest update on interaction between clopidogrel and omeprazole

資料來源：美國食物及藥物管理局

Sources : The United States Food and Drug Administration (USFDA)
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm190787.htm>

美國食物及藥物管理局(USFDA)通知公眾關於抗血栓藥物氯吡多(clopidogrel bisulphate)和用於減少胃酸的質子泵抑制劑奧美拉唑(omeprazole)相互作用的安全性的最新資訊。最新資料顯示，當 clopidogrel 與 omeprazole 同時使用，clopidogrel 的療效會減少。為防止心臟病復發和中風而服用 clopidogrel 預防血栓的病人，如果同時使用 omeprazole，則得不到充分的抗血栓效果。

Omeprazole 抑制將 clopidogrel 轉化為活性代謝物的藥物代謝酶(CYP2C19)，研究比較了單獨服用 clopidogrel 的病人以及併用 clopidogrel 和 omeprazole 病人的抗血栓效果以及他們血中 clopidogrel 的活性代謝物，結果發現相比那些單獨使用 clopidogrel 的病人，無論同時或者相隔 12 小時併用 clopidogrel 及 omeprazole 的病人，其體內的活性代謝物減少大約 45%，而 clopidogrel 對血小板的效果最多減少 47%。

由於預期其他具強力抑制 CYP2C19 作用的藥物也有相似的效果，所以應避免與 clopidogrel 併用，這些藥物包括：西咪替丁(cimetidine)、氟康唑(fluconazole)、酮康唑(ketoconazole)、伏立康唑(voriconazole)、依曲韋林(etravirine)、非氨酯(felbamate)、氟西汀(fluxetine)、氟伏沙明(flvoxamine)和噻氯匹定(ticlopidine)。由於其他質子泵抑制劑抑制藥物代謝酶的程度不同，因此並不知道這些質子泵抑制劑干擾 clopidogrel 作用的程度。但是，作為 omeprazole 組成成分的埃索美拉唑(esomeprazole)，也會抑制 CYP2C19，因此也應該避免與 clopidogrel 併用。

對衛生專業人士的建議：

- 由於對 clopidogrel 的活性代謝物和抗血栓作用的影響，應該避免 omeprazole 與 clopidogrel 併用。為防止心臟病復發和中風而服用 clopidogrel 預防血栓的病人，如果同時使用 omeprazole，則可能得不到充分的抗血栓效果。
- 分開服用 clopidogrel 和 omeprazole 並不會減少兩藥

的相互作用。

- 因為可能有相似的相互作用，應避免併用 clopidogrel 及下列藥物：esomeprazole、cimetidine、fluconazole、ketoconazole、voriconazole、etravirine、felbamate、fluoxetine、luvoxamine 和 ticlopidine。
- 除了 omeprazole 和 esomeprazole 外，現時 USFDA 並沒有足夠關於 clopidogrel 與其他質子泵抑制劑的相互作用資料，因此，衛生專業人士和病人在開始治療前應考慮所有治療方案。
- 沒有證據顯示其他減少胃酸的藥物包括大部分 H2 阻斷劑，如雷尼替丁 (ranitidine)、法莫替丁 (famotidine) 和尼扎替丁 (nizatidine) 或制酸劑會干擾 clopidogrel 的抗血栓作用。
- 了解病人所服用的非處方藥物，注意病人可能正服用 omeprazole 和 cimetidine。

The United States Food and Drug administration (USFDA) is alerting the public to new safety information concerning an interaction between clopidogrel, an anti-clotting medication, and omeprazole, a proton pump inhibitor (PPI) used to reduce stomach acid. New data show that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced. Patients at risk for heart attacks or strokes who use clopidogrel to prevent blood clots will not get the full effect of this medicine if they are also taking omeprazole.

Omeprazole inhibits the drug metabolizing enzyme (CYP2C19) which is responsible for the conversion of clopidogrel into its active form (active metabolite). The new studies compared the amount of clopidogrel's active metabolite in the blood and its effect on platelets (anti-clotting effect) in people who took clopidogrel plus omeprazole versus those who took clopidogrel alone. A reduction in active metabolite levels of about 45% was found in people who received clopidogrel with omeprazole compared to those taking clopidogrel alone. The effect of clopidogrel on platelets was reduced by as much as 47% in people receiving clopidogrel and omeprazole together. These reductions were seen whether the drugs were given at the same time or 12 hours apart.

Other drugs that are potent inhibitors of the CYP 2C19 enzyme would be expected to have a similar effect and should be avoided in combination with clopidogrel. These include: cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine. Since the level of inhibition among other PPIs varies, it is unknown to what amount other PPIs may interfere with clopidogrel. However, esomeprazole, a PPI that is a component of omeprazole, inhibits CYP2C19 and should also be avoided in combination with clopidogrel.

Considerations for Healthcare Professionals

- The concomitant use of omeprazole and clopidogrel should be avoided because of the effect on clopidogrel's active metabolite levels and anti-clotting activity. Patients at risk for heart attacks or strokes, who are given clopidogrel to prevent blood clots, may not get the full protective anti-clotting effect if they also take omeprazole.
- Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction.

- Other drugs that should be avoided in combination with clopidogrel because they may have a similar interaction include: esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine.
- At this time FDA does not have sufficient information about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole to make specific recommendations about their co-administration. Healthcare professionals and patients should consider all treatment options carefully before beginning therapy.
- There is no evidence that other drugs that reduce stomach acid, such as most H2 blockers ranitidine, famotidine, nizatidine, or antacids interfere with the anti-clotting activity of clopidogrel.
- Talk with your patients about the OTC medicines they take. Be aware that patients may be taking omeprazole and cimetidine.

有關含 gadolinium 造影劑的最新資訊

Latest update on gadolinium-based contrast agents

資料來源：歐盟藥物監管局

Sources : European Medicines Agency (EMA)

<http://www.emea.europa.eu/pdfs/human/press/pr/73981809en.pdf>

<http://www.emea.europa.eu/pdfs/human/press/pr/75243109en.pdf>

歐盟藥物監管局(EMA)通知衛生專業人士以下關於含 gadolinium 造影劑的最新資訊：

USFDA 在 2007 年曾發出公告指出含 gadolinium 造影劑與腎性全身性纖維化(Nephrogenic Systemic Fibrosis, NSF) 或 腎 性 纖 維 化 皮 膚 病 (Nephrogenic Fibrosing Dermopathy, NFD)具關聯性，EMA 轄下的人用藥物委員會(CHMP)近期亦提出下列建議，用以減少病人在使用含 gadolinium 造影劑後發生腎性全身性纖維化的風險：

- i) 對於高風險的含 gadolinium 造影劑(如 Omniscan[®], OptiMARK[®], Magnevist[®])，該局建議禁用於患有嚴重腎病的病人、正準備或近期接受過肝臟移植的病人以及小於 4 星期的新生兒。CHMP 亦建議在使用含 gadolinium 造影劑前須以實驗室指標檢測病人的腎功能，婦女在掃描後 24 小時內須暫停授乳。
- ii) 對於中度風險(如 MultiHance[®])和低度風險(如 ProHance[®])的含 gadolinium 的造影劑，CHMP 建議在說明書中加入對於患有嚴重腎病以及接受肝臟移植的病人須謹慎使用的資訊。並且建議在使用含 gadolinium 造影劑前以實驗室指標檢測病人的腎功能，婦女在掃描後 24 小時內須暫停授乳。

CHMP 建議在所有含 gadolinium 造影劑的說明書中加入：

- 由於老年人的腎功能受損，以致不能將 gadolinium 排出體外，因此可能會增加發生 NSF 的風險。
- 沒有證據顯示起用血液透析能夠幫助未曾進行過血液透析的病人預防或治療 NSF。
- 須記錄所使用造影劑的類型及劑量。

目前的資料顯示，如果採取上述減低風險的措施，CHMP 認為使用這些造影劑的風險是可以接受的。

The European Medicines Agency (EMA) notified healthcare professionals about the latest update on gadolinium-based contrast media. Summaries are listed as follows:

Apart from the USFDA reported evidence for a causal relationship between these contrast agents and the development of Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD) in patients with moderate to end-stage renal disease, the Committee for Medicinal Products for Human Use (CHMP) under the European Medicines Agency (EMA) has recently adopted the following recommendations aiming to minimize the risk of NSF with these contrast agents in patients at risk of developing the condition :

- i) For high-risk gadolinium-containing contrast agents (Optimark[®], Omniscan[®], Magnevist[®]) the Committee recommended contraindications in patients with severe kidney problems, in patients who are scheduled for or have recently received a liver transplant and in newborn babies up to four weeks of age. The CHMP advised that patients should always be screened for kidney problems using laboratory tests before use. The CHMP also recommended that women should discontinue breastfeeding for at least 24 hours after a scan.
- ii) For medium- (MultiHance[®]) and low-risk agents (ProHance[®]), the CHMP recommended adding new warnings in the prescribing information concerning their use in patients with severe kidney problems and patients receiving a liver transplant. The CHMP advised that screening patients for kidney problems using laboratory tests is generally recommended before administration of these gadolinium-containing contrast agents and that the decision to continue or suspend breastfeeding for at least 24 hours after a scan should be taken by the doctor and the mother.

The CHMP also recommended that the prescribing information of all gadolinium-containing contrast agents should include:

- a warning that the elderly may be at particular risk of NSF due to impaired ability of their kidneys to clear gadolinium from the body;
- a statement that there is no evidence to support the initiation of haemodialysis to prevent or treat NSF in patients not already undergoing haemodialysis.
- a statement that the type and dose of contrast agent used should be recorded.

Based on currently available data, and with these risk minimization measures in place, the CHMP considers that the balance of benefits and risks of these agents is acceptable.

有關含西布曲明藥物的最新資訊

Latest update on sibutramine-containing medications

資料來源：美國食物及藥物管理局

Sources : United States Food and Drug Administration (USFDA)
<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm191655.htm>

美國食物及藥物管理局 (USFDA) 通知衛生專業人士關於含西布曲明(sibutramine) 藥物的最新資訊：

近期 SCOUT(Sibutramine Cardiovascular OUTcome

Trial)臨床研究的初步資料顯示，相對使用安慰劑的病人，使用 sibutramine 的病人出現較多的心血管事件(心臟病發、中風、心臟停止或死亡)。上述研究結果顯示，相對於服用安慰劑(10%)，服用 sibutramine 的病人發生較多的心血管事件(11.4%)，此差異較預期高，說明了 sibutramine 可能會增加心血管疾病的風險。這項研究進一步強調了在現行 sibutramine 藥品標籤上建議曾有冠心病(心臟病)、充血性心臟衰竭、心律不整或中風等病史的病人中避免服用 sibutramine 的重要性。在美國食物及藥物管理局(USFDA)和歐洲藥物管理局(EMA)對這些減肥藥物進行安全性的回顧評價期間，衛生專業人士應該：

- 留意個別病人的病史，持續評估 sibutramine 對病人的效益及風險。
- 教育病人和消費者應與衛生專業人士討論 sibutramine 是否適合他們。

The United States Food and Drug Administration (USFDA) notified healthcare professionals about the latest updates on sibutramine-containing medications. Summaries are listed as follows:

Preliminary analysis of the primary endpoint for the recent SCOUT (Sibutramine Cardiovascular OUTcome Trial) clinical study suggest that patients using sibutramine have a higher number of cardiovascular events (heart attack, stroke, resuscitated cardiac arrest, or death) than patients taking placebo. The reported cardiovascular events were 11.4% in patients taking sibutramine compared to 10% of patients using a placebo. This difference is higher than expected, suggesting that sibutramine is associated with an increased cardiovascular risk in the study population. This study findings highlight the importance of avoiding the use of sibutramine in patients with a history of coronary artery disease (heart disease), congestive heart failure (CHF), arrhythmias, or stroke, as recommended in the current sibutramine labeling. In the interim while the USFDA & EMA are conducting safety reviews on this class of anti-obesity medicines, prescribers should

- take into account individual patient medical history and continue to evaluate the benefits and risks of sibutramine for their patients.
- educate patients and consumers to discuss with their healthcare professional about whether sibutramine is right for them.

有關 sirolimus (Rapamune[®]) 的最新資訊 Latest safety update sirolimus (Rapamune[®])

資料來源：加拿大衛生部

Sources : Health Canada

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2009/rapamune_4_hpc-cps-eng.php

加拿大衛生部(Health Canada)及加拿大惠氏藥廠(現屬於輝瑞藥廠)通知衛生專業人士關於各種用於檢測 sirolimus (Rapamune[®])血液谷濃度(血中最低濃度, trough concentration)的實驗方法所得出的結果不能互換。如 sirolimus 的藥物說明書所述，在治療藥物監測(TDM)中，建議使用高效液相色譜法(HPLC)作為測定 sirolimus 血

液谷濃度的參考方法，而臨床上一般是使用色譜法和免疫分析法來測量 sirolimus 的全血濃度。惠氏藥廠指出，由於不同實驗室的檢測結果可能不同以及有機會受所使用血液樣本是新鮮或冰凍的影響，因此這些不同方法得出的 sirolimus 血液谷濃度是不能互換的。同樣地，在不同平台之間轉換，不管是在免疫分析平台之間或在免疫分析與 HPLC 之間，都會產生臨床上顯著的不同結果，因此需要根據所用的檢測方法調整目標範圍以確定 sirolimus 的血液谷濃度。由於檢驗方法對所得的數值有直接影響，因此，醫生和其他衛生專業人士應該注意實驗室用於測量 sirolimus 的全血濃度的檢驗類型和方法。醫生應時刻清楚 sirolimus 的檢測方法和參考範圍的任何改變。若因使用不同的檢測方法而導致不適當調整 sirolimus 的劑量，可能會引起移植排斥反應(如果給與病人的劑量過低)或毒性(如果給與病人的劑量過高)。

Health Canada and Wyeth (Pfizer), Canada would like to inform all healthcare professionals about the fact that different laboratory assays used to measure the trough concentrations of sirolimus (Rapamune®) generate results that are not interchangeable. High Performance Liquid Chromatography (HPLC) is the recommended therapeutic drug monitoring (TDM) reference method to determine the trough concentrations of sirolimus (Rapamune®) as described on the product monograph of sirolimus. In clinical practice, sirolimus whole blood concentrations are being measured using both chromatographic and immunoassay methodologies. Wyeth described that the concentration of the sirolimus trough values obtained by these different assays are not interchangeable. As assay results may vary from one laboratory to another and may also be affected by whether fresh or frozen blood samples are used. Similarly, switching between platforms, whether between immunoassay platforms or between immunoassay and HPLC, can produce differing results that may be clinically significant. Adjustments to the targeted range should be made according to the assay being used to determine the sirolimus trough concentration. Hence, prescribers and other healthcare professionals should be aware of the type of assays and methods being used in the laboratory to measure the sirolimus whole blood concentration because these have a direct impact on the values obtained. Physicians should stay informed of any changes to the assay methods or reference range for sirolimus. Improper adjustment to the dose of sirolimus based on the use of differing assay methods can lead to allograft rejection (if the patient is underdosed) or toxicity (if the patient is overdosed).

有關 valproate sodium 及相關藥物(valproic acid 和 divalproex sodium)安全性的最新資訊

Latest safety update on valproate sodium and other related products (valproic acid and divalproex sodium)

資料來源：美國食物及藥物管理局

Sources : United States Food and Drug Administration (USFDA)
<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm192788.htm>

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm192649.htm>

美國食物及藥物管理局(USFDA)通知衛生專業人士關於 valproate sodium 及相關藥物(valproic acid 和 divalproex sodium)安全性的最新資訊。這類藥物除了傳統上用於癲癇症外，近年亦將用法延伸至雙極症(憂鬱-躁狂症)和偏頭痛，故會增加胎兒暴露於 valproate sodium 及相關藥物的機會，從而增加接受 valproate 治療婦女所誕下的嬰兒出現出生缺陷的風險，這些缺陷包括神經管缺陷、面顱外形缺陷、心血管畸形以及其他身體器官的畸形。北美癲癇藥物(NAAED)懷孕登記處的資料顯示，服用 valproate(單一藥物療法)的癲癇婦女誕下的嬰兒出現主要器官缺陷的比率，較服用其他抗癲癇藥物婦女高出近 4 倍。基於上述資料，USFDA 對衛生專業人士作出下列建議：

1. 在懷孕早期服用 valproate，會增加嬰兒的主要器官出現缺陷的風險。
2. 如果病人考慮接受 valproate 治療，需告知她們的疾病風險以及服用這些藥物的風險。
3. 懷孕期間服用 valproate 會增加包括神經管缺陷等主要器官缺陷的風險。
4. 對於懷孕期間出現的癲癇症和雙極症(憂鬱-躁狂症)，若不治療或不適當治療將增加孕婦及其胎兒出現併發症的風險。
5. 在懷孕前及懷孕首三個月服用葉酸能減少先天性神經管缺陷的風險。
6. 對於服用 valproate 期間懷孕的婦女，產前檢查能夠發現神經管缺陷和其他主要器官缺陷。
7. 對處於生育年齡及須服用 valproate 的女性病人作出下列建議：
 - 在懷孕期間服用 valproate 會增加誕下先天缺陷嬰兒的風險，尤其神經管缺陷，這是懷孕早期服用 valproate 最常見的先天缺陷。基於這個原因，除非認為對她們的治療是必須的，否則她們不應該服用 valproate。
 - 教導並不打算懷孕的婦女採取有效的避孕措施以及與她們討論其他治療癲癇方法的相對效益與風險。
 - 在服用 valproate 期間採取有效的避孕措施。
 - 在服用 valproate 時，如果她們準備懷孕或經已懷孕，應立即與主診醫生聯絡，討論其他治療方案。
 - 即使懷孕，她們亦不應在沒有告知主診醫生的情況下自行停止服用 valproate。突然停用 valproate 會產生嚴重的問題。不治療癲癇症或雙極症(憂鬱-躁狂症)會對孕婦和胎兒構成危害。

The United States Food and Drug Administration (USFDA) would like to remind all healthcare professionals about the latest drug safety information on valproate sodium and related products (valproic acid and divalproex sodium). Apart from the traditional use of this class of drugs in epilepsy, recent extension of approved uses in treating bipolar disorder and migraine headaches also increase the

risk of prenatal exposure to valproate sodium and related products. Subsequently, this leads to an elevated risk of birth defects including neural tube defects, craniofacial defects, cardiovascular malformations and malformations involving other body systems in babies born to female patients on valproate treatments. Data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry shows that the rate of major malformations in babies born to women with epilepsy taking valproate (monotherapy) is almost 4 times higher than the rate of major malformations in babies born to women with epilepsy taking a different antiepileptic drug. In light of the above, USFDA recommends the following actions for healthcare professionals to bear in mind that :

- 1) valproate use during early pregnancy increases the risk of major malformations in the baby.
- 2) if these patients are considering being treated with or taking valproate, inform about both the risks of their medical condition and the medicines used to manage their condition.
- 3) valproate use during pregnancy can increase the risk of major malformations including neural tube defects.
- 4) untreated or inadequately treated epilepsy or bipolar disorder during pregnancy increases the risk of complications in both the pregnant mother and her developing baby.
- 5) taking folic acid before and during the first trimester of pregnancy can decrease the risk for congenital neural tube defects.
- 6) there are prenatal diagnostic testing available to detect neural tube defects and other malformations to female patients who become pregnant while taking valproate.
- 7) providing the following advice to their female patients of childbearing age who are on valproate that
 - taking valproate during their pregnancy increases the chance of having a baby with a birth defect especially neural tube defects, such as spina bifida, are the birth defects most often seen with valproate use in early pregnancy. For this reason, they should generally not take valproate unless it is considered essential for her treatment.
 - effective contraception for women who are not planning a pregnancy and discussion about relative risk and benefits of appropriate alternative therapies.
 - use effective birth control (contraception) while taking valproate.
 - if they are planning a pregnancy or who become pregnant while taking valproate should contact their healthcare professionals immediately to discuss other treatment options for them.
 - they should not stop their valproate therapy without talking to their prescribing physician, even in pregnant women. Stopping valproate suddenly can cause serious problems. Not treating epilepsy or bipolar disorder can be harmful to women and their developing babies.

有關含 diclofenac 藥物的最新資訊

Latest update on diclofenac containing medications

資料來源：美國食物及藥物管理局

Sources : United States Food and Drug Administration (USFDA)

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm193047.htm>

<http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM193101.pdf>

美國食物及藥物管理局 (USFDA) 通知衛生專業人士一則關於更新含雙氯滅痛(diclofenac)藥物說明書的資訊，根據美國恩多製藥公司(Endo Pharmaceuticals)和諾華製藥公司(Novartis Pharmaceuticals)收到的上市後通報，使用 diclofenac 後所出現的肝毒性個案中，有些在首個月發生，有些在治療後兩個月內發生，也有在使用 diclofenac 治療的任何階段發生。上市後監測所接獲的嚴重肝病個案包括肝壞死、黃疸、暴發性肝炎(伴有或不伴有黃疸)，以及肝衰竭，上述個案中，一些病人最終死亡或者進行了肝移植。基於以上事實，生產商向醫生作出下列建議：

- 對於需要長期接受 diclofenac 治療的病人，由於嚴重肝毒性可能在沒有可判斷的先兆症狀下發生，醫生應定期測量病人血中的轉氨酶(transaminases)。目前並不清楚首次及繼後測量轉氨酶的最理想時間，基於臨床試驗資料和上市後的經驗，應在開始 diclofenac 治療 4-8 星期內檢驗轉氨酶。然而，嚴重肝毒性可以在 diclofenac 治療的任何階段發生。
- 如不尋常的肝功能測試結果持續出現或惡化，同時出現與肝病一致的臨床症狀，或者出現全身性症狀，如嗜紅血球增多、皮疹、腹痛、腹瀉、尿顏色變黑等，應立即停用 diclofenac。
- 為了減少在兩次測量轉氨酶之間，發生嚴重肝損傷的可能性，醫生應告知病人肝毒性的警示症狀，如噁心、疲倦、嗜睡、腹瀉、痕癢、黃疸、右上腹柔軟以及流感樣症狀，並告知出現這些症狀時應採取的適當措施。
- 為了使服用 diclofenac 治療的病人發生與肝臟有關的不良反應的潛在風險減至最低，應考慮最短的療程及使用最低有效劑量。
- 在處方 diclofenac 時應注意可能併用已知具潛在肝毒性的其他藥物(如抗生素、抗癲癇藥物等)。

The United States Food and Drug administration (USFDA) notified healthcare professionals about revisions to the prescribing information of diclofenac containing products. According to the postmarketing reports received by Endo Pharmaceuticals and Novartis Pharmaceuticals, USA, cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of therapy, but can occur at any time during treatment with diclofenac. Postmarketing surveillance has also reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation. In view light of the above, the

manufacturers offered the following recommendations for the prescribing physicians :

- For those patients who are receiving long-term diclofenac treatment, physicians should measure patients' transaminases periodically because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are unknown. Based on clinical trial data and postmarketing experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac. However, severe hepatic reactions can occur at any time during treatment with diclofenac.
- If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, abdominal pain, diarrhea, dark urine, etc.), diclofenac should be discontinued immediately.
- To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms), and the appropriate action patients should take if these signs and symptoms appear.
- To minimize the potential risk for an adverse liver related event in patients treated with diclofenac, the lowest effective dose should be used for the shortest duration possible.
- Caution should be exercised in prescribing diclofenac with concomitant drugs that are known to be potentially hepatotoxic (e.g., antibiotics, anti-epileptics).

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