NORTHERN IRELAND
MEDICINES MANAGEMENT

HSC Health and Social Care Board

September 2018

Safety Update: Errors with tacrolimus and other solid organ transplant immunosuppressants

Transplant immunosuppression

Organ transplant rates continue to increase resulting in many more people in Northern Ireland living with an organ transplant. The kidney transplant programme in Belfast has seen immense growth over the last 6 - 8 years, more than doubling the number of kidney transplants being performed each year. There are over 300 patients with liver transplants in NI. Every person with a life-transforming organ transplant requires to take immunosuppressive ("anti-rejection") drugs, e.g. tacrolimus, for the rest of their life.

"Dosage or formulation errors with these drugs can have serious, potentially fatal, consequences"
(Dr Henry Brown, Consultant Nephrologist at the Belfast Trust)

Over the past couple of years there have been several incidents where patients have been prescribed or dispensed the wrong strength or formulation. This has caused either under-dosing or over-dosing of immunosuppressive drugs and potential or actual harm to patients including in one case the death of a liver transplant recipient. It is therefore extremely important that patients receive the **correct strength and formulation** of these drugs. There are differences in the bioavailability of the drug between brands potentially resulting in changes in blood drug level that may impact on risk of rejection or side effect. Additional information is contained in the shared care guideline.

Further dispensing errors involving tacrolimus

HSCB issued a Quality and Safety Learning Letter "Prescribing and Dispensing High Risk Drugs, e.g. immunosuppressants such as tacrolimus" in **June 2015** to all general practitioners, community pharmacies and Trusts.

The letter shared the learning from a serious adverse incident where a patient who had undergone an organ transplant inadvertently received the wrong strength (under-dose) of the immunosuppressant tacrolimus (Advagraf®) and sadly died as a result of subsequent organ rejection.

Unfortunately, since this letter was issued, there have been further serious adverse incidents reported to the HSCB which involved tacrolimus (Advagraf® and Prograf®). See table below:

Drug Prescribed	Drug dispensed in error
Advagraf® 0.5mg	Prograf® 0.5mg
Advagraf® 1mg	Prograf® 1mg
Prograf® 5mg	Prograf® 0.5mg
*Tacrolimus MR 1mg	Prograf® 1mg
Prograf® 0.5mg	Prograf® 5mg
Prograf® 1mg	Prograf® 1mg out of date
Prograf® 1mg	Advagraf® 1mg

***Oral tacrolimus: prescribe by brand**

HSCB and MHRA guidance advise that oral tacrolimus products should be prescribed and dispensed by brand name only. Check if any patients are currently prescribed generic tacrolimus and establish the correct brand, or if an unlicensed oral liquid, who it is manufactured by.

Drug interactions and configuration of drug warnings on GP clinical systems

There have been a number of adverse incidents involving drug interactions reported to HSCB. For example, two incidents occurred in which a clinically significant interaction between tacrolimus and clarithromycin was missed. One case resulted in patient harm (acute kidney injury), which was picked up at a renal review appointment as tacrolimus levels had been affected by the clarithromycin. In the second adverse incident there was no patient harm as the patient read their tacrolimus alert card which highlighted the interaction and subsequently spoke to secondary care who advised them not to take it.

Following review of these and the other similar incidents, a significant contributing factor was that the configuration settings for drug interactions had been adjusted by the practice to suppress the users' alert levels.

Practices are asked to check system settings across all computers and users within the practice to ensure they are in line with BNF advice with respect to visible warnings that appear on the screen when prescribing a medication. These may act as a reminder of possible clinically significant interactions or give the prescriber an opportunity to discuss and educate patients on possible side effects to be watchful for.

Refer to the shared care guideline for tacrolimus for full section on drug interactions.

Common Drug Interactions	**The interactions listed below relate to tacrolimus. Consideration should be given to the other agents used as part of a regime.** Tacrolimus is metabolised by cytochrome P450 and interacts with many drugs that are metabolised by this group of liver enzymes. **The following drugs should not be initiated by GP unless discussed with specialist:** **Antibiotics:** erythromycin and clarithromycin increase tacrolimus levels; rifampicin decreases tacrolimus level. **Anti-epileptics**: carbamazepine, phenobarbital and phenytoin decrease tacrolimus levels. **Antifungals:** fluconazole; itraconazole, posaconazole and voriconazole increase tacrolimus levels. **Anti-obesity drugs**: orlistat decreases tacrolimus levels.

Robot serious adverse incident (SAI)

A recent SAI investigation of a dispensing error in a community pharmacy involved a robotic system where the wrong strength of Prograf® was dispensed. The robotic system correctly picked a full original box of 50 x Prograf® 5mg capsules and a skillet manually labelled as Prograf® 5mg capsules.
The contents of the skillet were added to the full original box at the assembly of the prescription. The pharmacist then undertook the final check and dispensed the prescription to the patient.
Unfortunately, due to human error, the skillet manually labelled Prograf® 5mg picked by the robotic system actually contained Prograf® 0.5mg. This error was not picked up on at the assembly of the prescription or the accuracy check. The patient was dispensed both strengths of Prograf®.
This incident would not have occurred if the pack of Prograf® was not split — see below.

Prescribe and dispense as whole packs of tacrolimus

Tacrolimus products are considered "special containers" and should therefore only be prescribed and dispensed in multiples of that container (as these packs should not be split).
Split packs contributed to at least one identified error and can cause patient confusion.
See Code Book for further information on special container status.

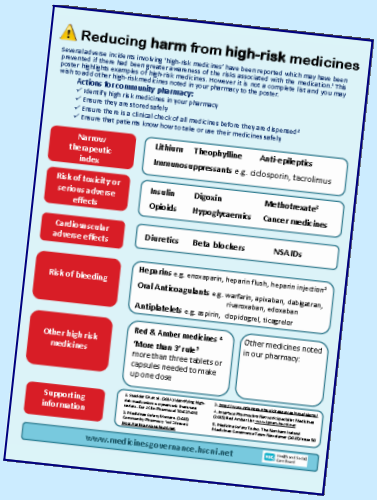
Example: Prograf® - Only pack of 50		
Quantity on prescription	**Quantity to be coded and paid**	**Pack used for payment**
14	50	50
28	50	50
56	50	50
84	100	50
112	100	50
156	150	50
180	200	50

Important - Final accuracy check

Unfortunately in a number of tacrolimus incidents the final accuracy check did not prevent medication errors.

Community pharmacists have a key role in patient safety by ensuring that medicines are prescribed and administered safely. The final check of prescribed medicines is a crucial 'safety net' in preventing patient harm.

Action for community pharmacies:



- Ensure robust standard operating procedures (SOPs) are in place to cover the dispensing and supply of high risk drugs such as tacrolimus
- Ensure all staff follow the processes indicated in the pharmacy's accuracy checking SOPs
- Pharmacists should ensure that split, unsealed packs and skillets have not been used
- Ensure all staff are vigilant to expiry dates
- Ensure stock is rotated so that the earliest expiry date is at the front and used first
- Check patients' understanding of their medication and, if you have any concerns, contact the prescribing GP
- Consider additional measures to highlight high risk drugs, e.g. shelf edging, computer alerts, separating stock. HSCB High Risks drugs poster is available here: http://www.medicinesgovernance.hscni.net/primary-care/high-risk-medicines/.

Long time - no see!

60% of dispensing errors reported to the HSCB are selection errors, a number of which have included medicines that are less commonly used. The most common error is Prograf® 0.5mg and 5mg. Even if the prescription is scanned onto the computer, the correct strength might not appear in the personal list of medicines, particularly if it has not previously been dispensed.

Lessons learned

Prograf® is a high-risk drug, available in three strengths: 0.5mg, 1mg and 5mg. The 0.5mg and 5mg strengths are frequently dispensed in error. The following lessons have been learned:

- The importance of a well-informed patient / carer in the safety chain
- Unintentional under-dosing or overdosing can have serious consequences for the patient
- Ensure full packs of tacrolimus are not split
- Brand name prescribing of tacrolimus is essential
- IT solutions such as robots and barcodes are not failsafe — final checks should still be robust.

The patient knows best

In a number of reported tacrolimus incidents it was the **patient** who recognised that they should not have been prescribed a different strength. The patients reported their concerns to the pharmacist and the medication was changed.

Patients are provided with the following advice when their treatments are started or changed:

- Check your prescription before you leave the GP or pharmacy. If there are any changes that you did not expect, speak with a member of staff
- Contact your transplant team if you are still unsure. Do not be afraid to speak up if there is any confusion or uncertainty
- Be familiar with the appearance of any medicines that you take regularly. If something looks different from what you were expecting, speak with a member of the pharmacy staff or another healthcare provider before taking any doses.

Commonly prescribed immunosuppressive drugs

MUST be prescribed by BRAND:

There are differences in the bioavailability of the drug between brands potentially resulting in changes in blood drug level that may impact on risk of rejection or side effect.
GP practices should search for patients prescribed these immunosuppressant generically and contact the community pharmacy to establish which 'brand' the patient is currently taking before changing the prescription for future supplies.

Tacrolimus

Formulation:	once a day sustained release or twice a day
Trade names:	Prograf® (twice per day) Advagraf® (once a day) [these are the most commonly prescribed brands]; Adoport® (twice per day), Capexion® (twice per day), Envarsus® (once per day), Modigraf® (twice per day), Tacni® (twice per day), Vivadex® (twice per day).
Strength:	0.5mg, 1mg, 5mg (most common in NI). Also available: 0.2mg, 0.75mg, 2mg, 3mg, 4mg
Doses:	range from 0.5mg bd to 10mg bd and may be a whole number (X)mg or X.5mg

Ciclosporin

Formulation:	twice a day
Trade names:	Ciclosporin (non-proprietary); Capimmune®; Capsorin®; Deximmune®; Neoral®) [the most commonly prescribed brand]; Vanquoral®.
Strength:	10mg, 25mg, 50mg, 100mg.
Doses:	range from 25mg bd to 200mg bd, usually in multiples of 25mg.

Sirolimus

Formulation:	once daily
Trade names:	Rapamune®
Strength:	0.5mg, 1mg, 2mg
Doses:	1mg to 6mg daily

Prescribe by brand unless advised otherwise by secondary care:

Mycophenolate mofetil

Formulation:	twice a day, though can be prescribed three or four times per day
Trade names:	Cellcept® [the most commonly prescribed brand]; Mycophenolate mofetil (non-propriety); Myfortic® (modified formulation)
Strength:	250mg and 500mg; 180mg and 360mg for Myfortic®.
Doses:	250mg bd to 1g bd

May be prescribed generically:

Azathioprine

Formulation:	once daily
Trade names:	Azathioprine (non-proprietary); Imuran®
Strength:	25mg, 50mg
Doses:	25mg to 200mg daily

Additional information on each of these drugs is contained in the shared care guideline.

Pharmacy shelf-edgers

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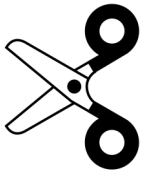

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