

Prescriber Update

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Contents

Safe Prescribing of Direct-Acting Antivirals for Treatment of Hepatitis C – It’s Complicated	50
Gardasil 9 – The Next Generation Human Papillomavirus (HPV) Vaccine	52
The Medsafe Files – Episode Two: Clinical Trials	54
MARC’s Remarks: September 2016 Meeting	55
M MEDICINES MONITORING	55
Sudden Unexpected Death in Infants (SUDI): No Causal Link to Vaccination	56
Adverse Event Reporting for Medical Devices	58
Recent Approvals of Medicines containing a New Active Ingredient	58
Don’t get HIT: Heparin -induced Thrombocytopenia	59
Drug-induced Photosensitivity	60
Quetiapine – Not Without Side Effects	61
<i>Prescriber Update</i> Quiz 2016	62
Quarterly Summary of Recent Safety Communications	63

Safe Prescribing of Direct-acting Antivirals for Treatment of Hepatitis C – It's Complicated

Key Messages

- ⌘ Direct-acting Antivirals (DAAs) are used for the treatment of hepatitis C infection.
- ⌘ Viekira Pak, Viekira Pak-RBV and Harvoni are funded by PHARMAC.
- ⌘ Beware of the many potential drug interactions when prescribing or dispensing DAAs.

Direct-acting antivirals (DAAs) are recently approved medicines indicated for the treatment of hepatitis C infection. The World Health Organization (WHO) now recommends DAA regimens for the treatment of persons with hepatitis C infection, rather than regimens with pegylated interferon and ribavirin¹. The *NZ Society of Gastroenterology HCV Treatment Guidelines* and PHARMAC funding have been updated to align with the WHO recommendations^{2,3}.

What are DAAs?

DAAs are used for the treatment of hepatitis C infection with the goal of curing the patient. DAAs work by blocking the action of hepatitis C virus proteins required for viral replication.

Treatment regimens with DAAs have a short treatment duration (usually 12 weeks), are administered orally and are very effective (sustained virological response rates of $\geq 90\%$)¹.

There are a number of DAAs approved in New Zealand. This article focuses on Viekira Pak, Viekira Pak-RBV and Harvoni, which are funded by PHARMAC.

Viekira Pak contains ombitasvir, ritonavir and paritaprevir in a combination tablet packaged together with dasabuvir tablets. Viekira Pak-RBV also contains ribavirin in the same package.

Harvoni is a combination tablet containing ledipasvir and sofosbuvir.

In some countries DAAs are marketed under different brand names and in different combinations. Be aware that patients who have been importing DAA products from overseas may be taking a different combination from those funded in New Zealand.

Things to remember when prescribing DAAs

Genotype of hepatitis C

Prior to starting the treatment, determine the hepatitis C virus genotype and measure the viral load, as this will direct the choice of DAA and the treatment duration (Table 1).

Interactions

DAAs are known to interact and postulated to interact with a substantial list of medicines. These interactions may be severe. Comorbidities are common in patients with hepatitis C so it is important to know what other medicines the patient is taking. Be careful when prescribing DAAs with medicines metabolised or transported by^{4,5,6}:

- CYP3A4
- Organic Anion Transporting Polypeptides (OATP) family and Organic Cation Transporter 1 (OCT1)
- Breast Cancer Resistance Protein (BCRP)
- P-glycoprotein (P-gp) in the intestine
- glucuronidation (UGT1A1)
- CYP2C19
- CYP1A2.

The University of Liverpool provides an online interactions tool that is quick and easy to use (see below).

What do I need to look out for?

Hepatitis B reactivation has also been reported in temporal association with DAA treatment. The Medicines Adverse Reactions Committee (MARC) recently reviewed the information on this possible risk. Although patients may get flares of hepatitis B at any time, the MARC considered that patients who are being prescribed DAAs should be assessed, tested and closely monitored for hepatitis B (www.medsafe.govt.nz/profs/adverse/Minutes167.htm#3.2.4).

Advise patients to report any signs and symptoms of hepatotoxicity with Viekira Pak or Viekira Pak-RBV to their healthcare professionals. Patients who develop evidence of hepatic decompensation with the use of Viekira Pak or Viekira Pak-RBV should discontinue treatment^{4,5}.

Table 1: Summary table for Viekira Pak, Viekira Pak-RBV and Harvoni^{4,5,6}

	Viekira Pak	Viekira Pak-RBV	Harvoni
Genotypes	Genotype 1b	Genotype 1a	All genotypes
Contraindications	Hypersensitivity to any component		
	Severe hepatic impairment		
	Patients taking other medicines with significant interactions		
		Pregnant women or patients with a pregnant partner	
		Severe pre-existing cardiac disease	
	Haemoglobinopathies		
Interactions	http://hep-druginteractions.org/checker		
Main adverse effects	Fatigue, nausea, itchy skin, insomnia, anaemia		Fatigue, nausea, headache, rash
	Hypersensitivity reactions including tongue and lip swelling		Symptomatic bradycardia when co-administered with amiodarone
	Hepatic decompensation and hepatic failure		

Please report any adverse reactions with DAAs, including interactions, to the Centre for Adverse Reactions Monitoring (CARM). These are new medicines and the safety profile has not yet been fully identified. Reports can be submitted on paper or electronically (<https://nzphvc.otago.ac.nz/>). These reports will help CARM and Medsafe identify any trends or patterns in New Zealand that may require action to ensure DAAs continue to be used safely.

Where can I look for more information?

Links to some useful resources are provided below.

- Detailed prescribing information is contained in the medicine data sheets: www.medsafe.govt.nz/Medicines/infoSearch.asp
- Information on PHARMAC funding including application forms: www.pharmac.govt.nz/medicines/my-medicine-has-changed/hepatitis-c-treatments/
- The University of Liverpool interactions checker tool: <http://hep-druginteractions.org/checker>
- The Best Practice Advocacy Centre (BPAC): www.bpac.org.nz/2016/hepc/
- NZ Society of Gastroenterology HCV Treatment Guidelines: www.nzsg.org.nz/cms2/uploads/Hepatitis%20C%20Guidance_FINAL%20July%2011.pdf

- The Hepatitis C webpage on the Ministry of Health website: www.health.govt.nz/our-work/diseases-and-conditions/hepatitis-c
- The Hepatitis Foundation of New Zealand: www.hepatitisfoundation.org.nz/
- WHO *Guidelines for the Screening, Care and Treatment of Persons with Chronic Hepatitis C Infection*: www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/

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Gardasil 9 – The Next Generation Human Papillomavirus (HPV) Vaccine

Key Messages

- ⌘ Gardasil 9 vaccine is the new HPV vaccine which protects against nine HPV strains.
- ⌘ The efficacy of Gardasil 9 was greater than Gardasil in clinical trials.
- ⌘ There is an increased rate of injection site reactions with Gardasil 9 compared to Gardasil, but otherwise, the safety profile appears to be very similar.

Gardasil 9, the next generation human papillomavirus (HPV) vaccine, provides protection against the four HPV subtypes found in Gardasil (HPV 6, 11, 16 and 18) and an additional five subtypes (HPV 31, 33, 45, 52 and 58).

HPV infection

HPV is the most common sexually transmitted infection worldwide. The lifetime risk for HPV infection is greater than 50%. Most HPV infections are asymptomatic and 90% of HPV infections are cleared within 24 months¹.

Infection with one of the numerous low-risk HPV types may result in genital warts. Infection with high-risk types can cause cancer, particularly in the 10% of infections that are not cleared. The risk of cancer is increased with smoking and infection with multiple cancer-causing HPV subtypes¹.

The different cancer types where at least some cases can be associated with HPV infection and the incidence rate in New Zealand are shown in Table 1.

Table 1: New Zealand cancer registrations in 2013²

Cancer	Incidence per 100,000 per year	Number of registrations 2013
Cervical cancer	6.3 (Mortality rate 1.4)	158
Vulvar cancer	1.5	56
Vaginal	0.7	23
Penile	0.6	19
Anal	1.0 in men, 1.2 in women	32 in men, 38 in women
Oropharyngeal	0.4 in men, 0.1 in women	11 in men, 5 in women
Tonsil	1.6 in men, 0.3 in women	48 in men, 9 in women

Infection with HPV can be avoided by vaccinating with the HPV vaccine and/or using condoms. Although there is a screening programme for cervical cancer, there are no screening programmes for other cancers caused by HPV infection. The screening programme is not 100% effective, and women still die from cervical cancer (Table 1).

The prevalence of different subtypes of HPV varies between regions. For Australia and New Zealand, 86.5% of HPV-induced cervical cancer is caused by the HPV subtypes included in the Gardasil 9 vaccine¹.

Efficacy of Gardasil 9

Gardasil 9 was approved for use in New Zealand based on clinical studies which included more than 15,000 subjects who received at least one dose of Gardasil 9^{3,4,5,6,7,8,9}. Medsafe's assessment of these studies has been published (www.medsafe.govt.nz/publications/OIAContents.asp).

In the pivotal study, Gardasil 9 was compared with Gardasil using a three-dose regimen in females aged 16 to 26 years³. Gardasil was used as the comparator since it would have been unethical to use a placebo. The study was conducted at multiple sites, including sites in New Zealand. Gardasil 9, like Gardasil, is only effective if given prior to first sexual contact/exposure to HPV. Therefore, the results of this study were analysed according to whether there was evidence that the clinical trial subjects were HPV-uninfected. The incidence of high-grade cervical, vulvar and vaginal disease in the HPV-uninfected group was 2.4 per 1,000 person-years

in the Gardasil 9 group and 4.2 per 1,000 person-years in the Gardasil group³.

The efficacy results from the pivotal study were extrapolated (immunologically bridged) to younger girls and boys^{4,5}. Gardasil may also be administered at the same time as meningococcal and Tdap vaccines^{6,8}.

The immunogenicity of Gardasil 9 in females who had already been vaccinated with Gardasil was also assessed⁷. In this study, saline was used as the placebo comparator. The frequency of injection site reactions was 9.1 in every 10 subjects given Gardasil 9 and 4.4 in every 10 subjects given the placebo. The frequencies of systemic adverse events were 3.1 in every 10 of the Gardasil 9 subjects and 2.6 in every 10 of the placebo group⁷.

The immunological response to a two-dose schedule of Gardasil 9 has also been investigated in a non-inferiority trial. Two timing intervals were assessed at 6 months and 12 months. Non-inferiority was demonstrated for both time points. Antibody titres were higher when the two doses were separated by a period of 12 months rather than 6 months¹⁰.

The long-term efficacy of Gardasil 9 is still to be determined. Of interest, studies on Gardasil have now reported data for up to nine years since vaccination with no decrease in efficacy¹¹.

Safety of Gardasil 9

An integrated safety analysis of all the clinical studies has been published¹². The most common adverse events were injection site reactions, headache and pyrexia. Twenty of the 15,875 subjects given Gardasil 9 discontinued the vaccination course because of an adverse event. Recent safety concerns with Gardasil have focused on postural orthostatic tachycardia syndrome (POTS) and complex regional pain syndrome (CRPS). Two subjects were diagnosed with POTS, one did not have recurrent episodes, and in the other subject, the events occurred more than three years after vaccination. The two cases of CRPS were attributed to a previous injury.

Other concerns have been raised regarding the use of Gardasil. It has been suggested that vaccination with HPV vaccine may promote promiscuity. Several studies have been conducted, and to date, none has reported any change in sexual behaviour after vaccination^{13,14}.

Overall, Gardasil 9 has improved efficacy, and the safety profile is consistent with that for

Gardasil. There was an increase in the number of injection site reactions compared to Gardasil, but this is expected as the vaccine contains an increased number of antigens.

Please continue to report all suspected adverse reactions to CARM (<https://nzphvc.otago.ac.nz/>).

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The Medsafe Files – Episode Two: Clinical Trials

Key Messages

- ⌘ Approval is required before a clinical trial using a ‘new medicine’ may commence in New Zealand.
- ⌘ The application process is administered by Medsafe; the applications are considered by a committee of the Health Research Council of New Zealand.
- ⌘ An ethics approval system applies to all clinical trials.
- ⌘ All clinical trials are expected to be conducted in accordance with internationally accepted Good Clinical Practice (GCP) standards.

Approval is required from the Director-General of Health before a clinical trial using a ‘new medicine’ or ‘investigational product’ may commence in New Zealand. The application and approval process for clinical trials is delegated to and administered by Medsafe.

A ‘new medicine’ is a medicine for which consent for distribution in New Zealand has not been granted or the approval has lapsed. In some circumstances, a substance that is commonly used as an ingredient in food, dietary supplement or cosmetic is used in a clinical trial. That substance, when administered to human beings for a therapeutic purpose, as defined by the Medicines Act 1981, as part of a clinical trial, is considered to be a new medicine and approval for the trial under Section 30 of the Medicines Act 1981 is required. ‘Investigational product’ is defined in the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP). Definitions of the regulatory status of medicines are on the Medsafe website (www.medsafe.govt.nz/Medicines/registration-situation.asp).

Clinical trial approval process

Section 30 of the Medicines Act 1981 authorises the Director-General of Health to approve a clinical trial and to allow importation of a ‘new medicine’. All applications, except for bioequivalence trials, are considered by a committee of the Health Research Council of New Zealand (HRC) and the approval is given

on the recommendation of this committee. The HRC maintains two committees to consider clinical trial applications involving a new medicine.

- The Standing Committee on Therapeutic Trials (SCOTT) considers applications for pharmaceutical-type medicines.
- The Gene Technology Advisory Committee (GTAC) considers applications for gene and other biotechnology therapies.

Medsafe notifies the applicant of the committee’s decision within 45 days of receiving the application. If the decision is to approve the trial, an approval letter will be issued. The Medsafe approval letter serves as a customs clearance document to import an investigational product. If the decision is for a provisional approval or to decline an application, the reasons will be provided to the applicant.

Interface with ethics

An ethics approval system applies to all clinical trials conducted in New Zealand. This is a separate process administered by the New Zealand Health and Disability Ethics Committee. At present, medical devices do not require approval under the New Zealand Medicines legislation. However, the Health and Disability Ethics Committee approval should be obtained for clinical trials of medical devices.

Good Clinical Practice

All clinical trials in New Zealand are expected to be conducted in accordance with internationally accepted GCP standards (www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html). In order to achieve compliance with the New Zealand law, some requirements of the GCP guidance have been modified as outlined in Part 11 of the Guideline on the Regulation of Therapeutic Products in New Zealand (www.medsafe.govt.nz/regulatory/Guideline/GRTPNZ/Part11.pdf).

Compliance with other legislation such as the Hazardous Substances and New Organisms Act 1996 or the Misuse of Drugs Act 1975 may also be required.

MARC's Remarks: September 2016 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 8 September 2016 to discuss a number of medicine-related safety issues.

The MARC discussed the safety of **metformin** use in pregnancy. The MARC considered that the data sheets should describe the benefits and risks of harm of using metformin in pregnancy. This will enable healthcare professionals to make an educated decision when prescribing metformin to pregnant women. Likewise, the MARC considered that consumers should have access to consumer-specific information that explains the risks and benefits of treatment with metformin during pregnancy.

The MARC discussed the use of **fluconazole** in pregnancy. This will be further discussed at a future meeting when more information becomes available.

The MARC discussed Medsafe's proposed monitoring and communication for the National Immunisation Schedule change to **Gardasil 9** as a two-dose schedule and considered this to be adequate. Further information on Gardasil 9 can be found in this edition of *Prescriber Update*: www.medsafe.govt.nz/profs/PUArticles.asp

Finally, the MARC reviewed the available information on the possible risk of hepatitis B reactivation with **direct-acting antivirals** for hepatitis C. The MARC recommended that healthcare professionals be advised of this risk. Further information can be found in this edition of *Prescriber Update*: www.medsafe.govt.nz/profs/PUArticles.asp

Further information on this meeting is on the Medsafe website (www.medsafe.govt.nz/profs/adverse/Minutes167.htm)

WE NEED YOUR HELP!

Please send your reports for these potential safety issues* listed in the table below.



MEDICINES
MONITORING

Medicine	Potential Safety Issue	Active Monitoring Ends
Rivaroxaban, Dabigatran, Apixaban	Hair loss (Alopecia)	31 December 2016

- **M²** is a Medsafe scheme designed to collect more information on potential safety signals for specific medicines.
- Safety signals are identified from reports of adverse medicine reactions sent to the Centre for Adverse Reactions Monitoring (CARM). For further information see the Medsafe website.
- The **M²** scheme does not replace routine adverse reaction reporting. Find out how to report at: www.otago.ac.nz/carm or www.medsafe.govt.nz



New Zealand Government



* The appearance of a possible safety issue in this scheme does not mean Medsafe and CARM have concluded that this medicine causes the reaction.

Sudden Unexpected Death in Infants (SUDI): No Causal Link to Vaccination

Key Messages

- ⌘ Through chance alone, up to nine cases of SUDI per year are expected in the month after vaccination of infants.
- ⌘ The number of cases of SUDI reported to CARM after vaccination is lower than the expected rate due to chance alone.
- ⌘ Observational studies investigating the risk of SUDI after vaccination have not found an association.

Sudden unexpected death in infants (SUDI), also known as sudden infant death syndrome (SIDS) or cot death, continues to be a leading cause of death in infants worldwide¹. SUDI is defined as the sudden unexpected death of an infant <1 year of age, with the onset of the fatal episode apparently occurring during sleep that remains unexplained after a thorough investigation including performance of a complete autopsy and review of the circumstances of death and the clinical history².

A number of risk factors for SUDI have been identified. The Ministry of Health provides advice on safe sleep practices to reduce the risk of SUDI³. In the general population, there is concern that an increased risk of SUDI occurs after vaccination, but is this warranted?

Data on infant deaths are published by the Ministry of Health and Statistics New Zealand^{4,5}. The latest data published by the Ministry of Health is for 2012. In 2012 the infant mortality rate was 4.7 per 1000 live births per year (total of 294 infant deaths). The rate of SUDI was 0.6 per 1000 live births per year (total of 36 cases)⁶.

Using the 2012 figures for SUDI, around three cases are expected per month. Infants are given three sets of vaccines in the first year of life, at 6 weeks, 3 months and 5 months. Therefore, up to nine reports of cases of SUDI occurring within a month of vaccination may be expected each year through chance alone. This is an estimate because not all children are vaccinated, and the risk of SUDI varies, with the peak incidence being at two to three months². Furthermore, the

number of SUDI cases in New Zealand is small and rates may fluctuate from year to year⁶.

On average, the Centre for Adverse Reactions Monitoring (CARM) receives two to four cases of infant death after vaccination each year. Reporters do not necessarily think that there is a link between the death and vaccination but wish to record the event in the national database. In these cases, the time period between vaccination and the death has been reported at less than 12 hours and up to 30 days. The infants in the reports were aged between 6 weeks and 25 weeks.

It should be noted that cases are often reported to CARM before the coronial investigation, and therefore in some cases, a cause of death may be ascertained later. CARM encourages reporters to send further information on these cases but acknowledges that this may not always be available to the reporter. Other risk factors for SUDI, such as parental smoking, are rarely described in the CARM reports.

A number of observational studies have investigated a possible link between vaccination and SUDI. There are some limitations to these studies such as:

- the healthy vaccinee effect (whereby sick children who may be more at risk of SUDI are not vaccinated)
- the difficulty of identifying unvaccinated controls
- the difficulty of verifying that the death was due to SUDI
- the inability to fully control for other risk factors such as age
- the concurrent timing of campaigns to promote safe infant sleeping practices with the initiation of vaccination programmes.

Although the suspicion of a possible association between the newer hexavalent vaccines was raised by a German group based on three cases⁷, observational studies have either failed to find a causal link or have in fact found that vaccination reduced the risk of SUDI (Table 1).

Table 1: Summary of more recently published observational studies of sudden infant death syndrome following vaccination. [This is not a comprehensive summary of all studies published on this topic]

Study	Dates	Data source	Number of subjects	Analysis	Results	Conclusions
Mueller-Nordhorn ¹	1968–2009	Centers for Disease Control in the US, US Immunisation Survey, National Infant Sleep Position Survey.	US population-wide.	Poisson regression model (ecological study).	IRR 0.92 (0.87–0.97) per 10% increase in DTP immunisation coverage after adjusting for infant sleep position.	Increased DTP immunisation coverage was associated with decreased SIDS mortality.
Traversa ⁸	1999–2004	Population of children resident in Italy, cases identified through death certificates.	604 cases of sudden unexplained death.	Self-controlled case series methodology.	A limited increase in risk after the first dose of hexavalent vaccine only RR: 2.0 (1.2–3.5).	The limited increase after the first dose may be partly explained by residual uncontrolled confounding effect of age.
Kuhnert ⁹	1987–2001	Reanalysis of German study on sudden infant death (GeSID), the confidential enquiry into still births and deaths in infancy (CESDI) study and the New Zealand cot death study (NZCD).	GeSID-333 cases and three controls per case CESDI – 154 cases and up to four controls per case NZCD – 393 cases.	Case-control and self-controlled case series models were used to re-analyse the data.	Numerous outcomes showing no difference between vaccinated and non-vaccinated subjects.	No increase or decrease in SIDS associated with vaccination.

IRR, incidence rate ratio; RR, rate ratio; DTP, Diphtheria-Tetanus-Pertussis

In conclusion, the available evidence continues to show no causal link between vaccination (immunisation) and SUDI.

Please continue to report all adverse events following immunisation to CARM (<https://nzphvc.otago.ac.nz/>). Recording these cases in the national database enables the event to be reviewed and the quality and safety of vaccines to be monitored.

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Adverse Event Reporting for Medical Devices

Key Messages

- ⌘ Adverse event reporting is important as it helps Medsafe monitor the safe use of medical devices.
- ⌘ Anyone can report adverse events, including patients, healthcare professionals, and New Zealand suppliers/manufacturers of the medical device.
- ⌘ Medsafe is currently updating the medical device adverse event reporting forms to assist with the ease of reporting.

Medsafe monitors the safety of medical devices through adverse event reports. Recent concerns associated with the use of surgical mesh have highlighted the importance of adverse event reporting. Improving reporting of device adverse events was a key finding in a recent report published by the Government Health Select Committee (www.parliament.nz/resource/en-NZ/51DBSCH_SCR69220_1/2ebf5e03f6fae9f78e731ff8ebf8e8ded2df857f).

Adverse Event Reporting

Any adverse events suspected to be due to the use of a medical device should be reported to Medsafe. Medsafe accepts reports from patients and their carers or relatives, healthcare professionals, New Zealand suppliers/manufacturers of the medical device, Accident Compensation Corporation (ACC) and overseas regulators.

To simplify the reporting procedure, Medsafe is currently redesigning the adverse event reporting

forms (the current reporting form is available from the Medsafe website www.medsafe.govt.nz/regulatory/devicesnew/9AdverseEvent.asp). There will be separate reporting forms for patients/consumers, healthcare professionals and suppliers/manufacturers. A consumer reporting form is currently in development and will be published on the Medsafe website shortly.

Adverse event reports are reviewed by Medsafe to determine the appropriate course of action. This can include working with the supplier/manufacturer to address the adverse event and publish communications.

Communications

Medsafe publishes monitoring communications when potential safety concerns are identified with devices. Often Medsafe is seeking additional information from the users of the device (www.medsafe.govt.nz/safety/EWS/monitoring-communications.asp).

More detailed information may also be published, for example, for surgical mesh (www.medsafe.govt.nz/hot/alerts/Surgical_Mesh_Implants_September_2016.pdf).

Recalls and corrective actions are also published on the Medsafe website (www.medsafe.govt.nz/hot/recalls/recallsearch.asp).

Please report any adverse events in relation to medical devices to Medsafe (www.medsafe.govt.nz/regulatory/DevicesNew/9AdverseEvent.asp).

Recent Approvals of Medicines containing a New Active Ingredient

For period 16 July to 15 October 2016

Trade Name (Active ingredient)	Dose form and strength	Therapeutic area
Cyramza (ramucirumab)	Concentrate for infusion 100 mg/10 mL and 50 mg/50 mL	Advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma
Sirturo (bedaquiline)	Tablet 100 mg	Multi-drug resistant tuberculosis

The data sheets for currently marketed prescription medicines are published on the Medsafe website (www.medsafe.govt.nz/profs/Datasheet/dsform.asp).

Don't get HIT: Heparin-induced Thrombocytopenia

Key Messages

- ⌘ HIT is a rare but potentially fatal condition.
- ⌘ Morbidity and mortality can be reduced by early recognition, withdrawal of heparin and treatment with a non-heparin anticoagulant.
- ⌘ Consider HIT in patients presenting with new onset thrombocytopenia, thrombosis, or anaphylaxis during or following heparin treatment.
- ⌘ HIT can occur with unfractionated heparin (UFH) and low molecular weight heparin (LMWH).
- ⌘ Avoid warfarin in patients with HIT until non-heparin anticoagulation has been stabilised and platelet counts have returned to normal.
- ⌘ Lifelong avoidance of heparin is recommended for most patients.

What is HIT?

Heparin-induced thrombocytopenia (HIT) is a potentially fatal antibody-mediated adverse reaction that occurs in up to 5% of patients exposed to heparin^{1,2}. A mortality rate of 2–20% has been reported¹.

Thrombocytopenia (a platelet count of $<150 \times 10^9/l$ or a $\geq 50\%$ reduction in platelets) occurs in $>90\%$ of patients with HIT³. In 60% of cases, thrombocytopenia occurs 5 to 10 days after

exposure to heparin^{3,4,5}. However, the onset can be rapid (30%) with an immediate fall in platelets, or delayed (10%) where thrombocytopenia can occur up to three weeks post-exposure to heparin^{3,4,5}.

Approximately 25% of cases will have thrombosis at the time of their diagnosis³. However, it is estimated that up to 50% of patients with untreated HIT will develop a thrombotic complication^{2,3,4}. These include skin necrosis, pulmonary embolism, mesenteric ischaemia, ischaemic limb necrosis, gangrene, acute myocardial infarction, and stroke⁴.

HIT may also present with anaphylaxis, even in the absence of thrombocytopenia³.

Diagnosis

Diagnosis is based on the presence of clinical features of HIT (as described above) and laboratory confirmation of HIT antibodies^{1,2}. The presence of risk factors (Table 1) increases the possibility of HIT. However, differentiating HIT from other causes of thrombocytopenia can be difficult. Clinical prediction tools, such as the 4Ts probability scale (www.uptodate.com/contents/clinical-presentation-and-diagnosis-of-heparin-induced-thrombocytopenia#H13466287) can be used to estimate the probability of HIT in an individual patient, and provide guidance on the management until laboratory confirmation of the diagnosis is available^{2,3}.

New Zealand case reports

Since 2000, the Centre for Adverse Reactions Monitoring (CARM) has received 51 reports

Table 1: Risk factors for HIT^{2,3,4}

Risk factor for HIT	Details
Previous history of HIT	Particularly if heparin is reused for more than four days.
Type of heparin	A meta-analysis of 15 controlled trials reported the following risks for HIT ⁶ : <ul style="list-style-type: none"> • UFH – 2.6% (95% CI 1.5-3.8) • LMWH – 0.2% (95% CI 0.1-0.4)
Heparin dose	HIT has been reported with all heparin doses. A higher incidence of HIT has been reported with therapeutic doses than prophylactic doses of heparin.
Gender	Multiple studies have reported that women have a higher risk of HIT than men.
Indication for heparin	A higher risk of HIT in surgical patients, compared to medical patients, has been reported.
Age	HIT appears to be rare in patients aged <40 years.

CI, confidence interval; UFH, unfractionated heparin; LMWH, low molecular weight heparin

consistent with HIT including 28 reports that documented the presence of HIT antibodies. Both UFH (31) and LMWH (29) were implicated; nine reports documented usage of both UFH and LMWH (enoxaparin).

The majority of reports were in men (31) with a mean age of 67 years. Most cases (80%) were serious including seven cases considered to be life-threatening and two cases of death. Thrombotic complications were confirmed in seven reports: pulmonary embolism (three), deep vein thrombosis (two), intracardiac thrombosis (one) and peripheral gangrene (two). In one report, a patient who had received warfarin prior to the diagnosis of HIT required a below knee amputation after developing venous gangrene of the foot.

Management

Specialist advice should be sought from a haematologist if HIT is suspected¹. Management includes stopping all sources of heparin and starting a non-heparin anticoagulant to prevent ongoing thrombosis.

Warfarin should NOT be used until the patient has been adequately anticoagulated and platelet levels have normalised (due to a risk of venous gangrene resulting from the rapid lowering of protein C levels)¹.

Heparin should be avoided in the future, except in exceptional circumstances and upon the advice of a haematologist. Patients should be advised that they are allergic to heparin and should avoid it in the future^{1,2}.

All cases of HIT should be reported to CARM, so that heparin allergy can be added to the Medical Warnings System.

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2. Linkins LA. 2015. Heparin induced thrombocytopenia. *BMJ*. 350: g7566.
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4. Salter B, Weiner M, Trinh M, et al. 2016. Heparin-induced thrombocytopenia: a comprehensive clinical review. *Journal of the American College of Cardiology*. 67(21): 2519–2532.
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Drug-induced Photosensitivity

As summer approaches, be aware that there may be a risk of drug-induced photosensitivity.

Drug-induced photosensitivity is an adverse skin reaction induced by sun exposure in some patients taking particular medicines¹. As the skin absorbs ultraviolet (UV) radiation this can cause a chemical change to a medicine that is present in the skin resulting in a phototoxic or photoallergic reaction².

Phototoxic reactions are more common than photoallergic reactions³. These reactions are due to cellular damage from the altered medicine in sun-exposed areas and are dose-dependent. Phototoxic reactions can appear within minutes to hours after exposure⁴. Clinical presentation varies from mild burning and stinging to exaggerated sunburns with erythema and oedema of the sun exposed areas. Hyperpigmentation may also occur^{1,4}.

Photoallergic reactions have an immunological basis^{3,4}. The UV radiation transforms the medicine into an antigen that triggers an allergic response. These reactions are typically delayed, developing after 24 to 72 hours. The presentation is generally of eczematous dermatitis which can spread across the whole body beyond the exposed areas^{2,4}.

Which medicines cause photosensitivity in New Zealand?

The top 10 medicines suspected to have caused photosensitivity reactions reported (between April 1965 and September 2016) to the Centre for Adverse Reactions Monitoring (CARM) are:

1. Doxycycline (89 reports)
2. Hydrochlorothiazide (62 reports)
3. Amiloride (61 reports)
4. Amiodarone (49 reports)
5. Chlorpromazine (39 reports)

6. Trimethoprim (18 reports)
7. Co-trimoxazole (18 reports)
8. Tetracycline (12 reports)
9. Bendrofluazide (11 reports)
10. Enalapril (11 reports)

See Dermnet (www.dermnetnz.org/topics/drug-induced-photosensitivity/) for a list of medicines that can cause photosensitivity.

Management

For patients who have experienced a photosensitivity reaction, medicine discontinuation and sunlight avoidance remain the mainstay of treatment. Depending on the severity of the reaction, topical or systemic corticosteroids can be used for symptom alleviation.

Not everyone will experience photosensitivity reactions but sensible precautions for patients taking medicines that can cause photosensitivity include^{1,2}:

- limiting exposure to strong sunlight (eg, at the beach and between 10 am and 4 pm)

- using broad spectrum sunscreens containing zinc oxide or titanium oxide, as they filter out more UVA
- wearing sunglasses with UVA filters
- wearing protective clothing (eg, long sleeve shirt, hat)
- taking medicine at night, if the pharmacokinetic properties allow.

Further information is available at the New Zealand Dermatological Society (www.dermnetnz.org/topics/drug-induced-photosensitivity/).

Please continue to report any adverse reactions to CARM. Reports can be submitted on paper or electronically (<https://nzphvc.otago.ac.nz/>).

References

1. Moore DE. 2002. Drug-induced cutaneous photosensitivity. *Drug Safety*. 25(5): 345–372.
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Quetiapine – Not Without Side Effects

Key Messages

- ⌘ Use of quetiapine, an atypical antipsychotic, has been increasing in recent years.
- ⌘ Potentially serious adverse reactions are associated with quetiapine and other atypical antipsychotics.

Quetiapine is indicated in adults for the treatment of acute and chronic psychoses including schizophrenia, and bipolar disorder¹. In recent years, use of quetiapine in the primary care has been gradually increasing, and there is also an awareness of potential quetiapine misuse internationally and in New Zealand.

All atypical antipsychotics may cause potentially serious side effects, such as¹:

- metabolic changes (eg, weight gain, hyperglycaemia)
- mood or behaviour changes (eg, anxiety, irritability, in extreme cases suicidal thoughts and self-harm)

- movement disorders (eg, tardive dyskinesia)
- cardiovascular effects (eg, QT interval prolongation)
- hepatic changes (eg, increased liver enzymes, hepatitis)
- haematological changes (eg, neutropenia, agranulocytosis)

See quetiapine data sheets for further information (www.medsafe.govt.nz/Medicines/infoSearch.asp).

From 1 January 2011 to 30 September 2016, the Centre for Adverse Reactions Monitoring (CARM) has received 47 adverse reaction reports associated with quetiapine use. Please continue to report any adverse reactions to CARM. Reports can be submitted on paper or electronically (<https://nzphvc.otago.ac.nz/>).

References

1. AstraZeneca Limited. 2015. *Seroquel Data Sheet* 16 November 2015 URL: www.medsafe.govt.nz/profs/Datasheet/s/seroqueltab.pdf (accessed 17 October 2016).

TEST YOUR KNOWLEDGE

Have you read your copies of *Prescriber Update* in 2016?

Have you kept up to date with emerging safety signals?

Test your knowledge with the end-of-year *Prescriber Update* quiz.

Answers to the quiz are at the bottom of page 63.

1. A negative blood test for IgE specific to penicillin excludes penicillin allergy in adults?

True False

2. Which of the following medicines may cause hearing loss?

a) Tobramycin b) Terbinafine c) Furosemide d) All of them

3. Which of the following is false?

- a) Patients taking medicines that can cause photosensitivity should cover up with dark clothing, wear a wide-brimmed hat and long-sleeved shirts and trousers.
- b) Patients taking medicines that can cause photosensitivity should use a water-resistant, broad spectrum, topical sunscreen agent (SPF 50+).
- c) Photosensitivity reactions typically appear as unexpected sunburn or a dry and blistering rash on sun-exposed skin.
- d) Photosensitivity reactions are not expected to be an adverse effect from the use of the antidepressant venlafaxine.

4. Which medicine is least likely to be associated with serotonin syndrome?

a) Dextromethorphan b) Escitalopram c) Ondansetron d) Methotrexate

5. Which group reported the most adverse reaction reports in 2015?

a) Hospital doctors b) Nurses c) Community pharmacists d) General practitioners

6. Name THREE medicines most commonly reported to CARM because they are suspected to have caused lung injury?

7. In patients taking spironolactone with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB), serum potassium levels and renal function should be monitored regularly. Which of the following is true?

- a) After initiation and dose increase of spironolactone, ACEi or ARB.
- b) At least ONCE within the first year of starting spironolactone, ACEi or ARB.
- c) Every 3 months.
- d) Monitoring is not required.

8. Medicine-induced gynaecomastia occurs as a result of which mechanism?

a) Hypogonadism b) Decreased testosterone levels
c) Increased prolactin levels d) All of the above

9. Which of the following is true?

- a) HIT only occurs with unfractionated heparin.
- b) Warfarin should be used as first-line treatment for HIT.
- c) Heparin should be avoided in the future in patients with a history of HIT.
- d) HIT always presents with thrombotic complications.

10. Which of the following is true?

- a) Viekira Pak is used for genotype 1a hepatitis C virus.
- b) Viekira Pak is used for genotype 1b hepatitis C virus.
- c) Viekira Pak-RBV is used for genotype 1b hepatitis C virus.
- d) Viekira Pak-RBV is used for all known genotypes of hepatitis C virus.

Quarterly Summary of Recent Safety Communications

The early warning system provides current and historical information on safety concerns for medicines and medical devices. These warnings are intended to help consumers and healthcare professionals make informed decisions about their use of medicines and medical devices.

More information about the early warning system can be found on the Medsafe website (www.medsafe.govt.nz/Projects/B2/EWS.asp).

Consumer information leaflets provide information about medicines and medical devices or medical conditions to consumers.

Date	Communication	Topic
11 November 2016	Consultations	Outcome of consultation on proposed changes to the data sheet format
28 October 2016	Medicines	Influenza Vaccine Composition
27 September 2016	Medical Devices	Surgical Mesh - Implementation of Government Response to Health Committee Recommendations
22 September 2016	Consultations	Change to warning statements on labels of OTC loratadine and desloratadine medicines
9 September 2016	Alert Communication	Consumer Level Recall – GlucaGen® HypoKit 1 mg solution for injection

If you would like to receive Medsafe’s early warning communications you can subscribe at www.medsafe.govt.nz/profs/subscribe.asp

Quiz Answers

- 1. False. A positive blood test for IgE specific to penicillins is highly predictive of penicillin allergy in adults, but a negative result does not adequately exclude penicillin allergy.
- 2. d)
- 3. d)
- 4. d)
- 5. b)
- 6. Any of the following: Nitrofurantoin, Methotrexate, Amiodarone, Leftunomide, Docetaxel, Adalimumab, Cyclophosphamide, Clozapine, Prednisone.
- 7. a)
- 8. d)
- 9. c)
- 10. b)

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Data sheets, consumer medicine information, media releases, medicine classification issues and adverse reaction forms can be found at www.medsafe.govt.nz

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