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Tamoxifen: CYP2D6 interactions and variable clinical response

Recent evidence suggests there is a potential risk for higher rates of disease recurrence and death related to breast cancer in women taking tamoxifen concomitantly with CYP2D6 inhibitors. It is noted in the literature that CYP2D6 inhibitors such as selective serotonin reuptake inhibitors (SSRIs) are commonly used concomitantly with tamoxifen.

The interaction centers on endoxifen. Endoxifen is an important active metabolite that contributes significantly to the efficacy of tamoxifen and is produced by the metabolism of tamoxifen via CYP2D6. Drugs that inhibit CYP2D6 can therefore lead to reduced plasma concentrations of endoxifen and reduced action.

A study involving over 1,200 women found that the 2-year breast cancer recurrence rate was 1.9 times higher in patients receiving both tamoxifen and a CYP2D6 inhibitor, compared to those receiving tamoxifen only (13.9% vs 7.5%). In addition the breast cancer recurrence rate was 2.2 times higher in women receiving a moderate to potent CYP2D6 inhibitor.

A more recent population based cohort study (n=2430) found an increased risk of death related to breast cancer in women taking tamoxifen and concomitant paroxetine. A dose response relationship was apparent, with relative increases in death related to breast cancer associated with increased time of overlapping tamoxifen and paroxetine treatment. The authors estimated that overlapping treatment with paroxetine for 41% of tamoxifen therapy (the median in the study) could result in one additional breast cancer death at five years for every 20 women who need both medicines. An association did not extend to other SSRIs in this study such as citalopram, escitalopram, sertraline, mirtazapine and venlafaxine.

Advice for prescribers:
- Avoid concomitant use of potent CYP2D6 inhibitors in women taking tamoxifen for breast cancer (e.g. paroxetine).
- If antidepressant treatment is required, preference should be given to those that show little or no inhibition of CYP2D6.

Further information about this interaction is available in two recently published reviews. Medsafe is currently working with manufacturers to provide more information about this interaction in applicable medicine data sheets.

References

Leflunomide – if in doubt wash it out

Leflunomide is a disease modifying anti-rheumatic drug indicated for the treatment of rheumatoid arthritis and active psoriatic arthritis.

Leflunomide can cause serious and potentially life-threatening adverse reactions involving the liver, blood, lungs and skin. Due to its immunosuppressant effects leflunomide can also cause life-threatening infections, particularly when given in combination with other immunosuppressant medicines. As leflunomide has a very long half life (usually 1-4 weeks), adverse reactions can occur or persist long after leflunomide is discontinued.

Prescribers are reminded that if serious adverse reactions occur, leflunomide must be stopped and a cholestyramine or charcoal wash-out procedure initiated immediately. In addition, rheumatology advice should be sought for all patients experiencing serious adverse reactions to leflunomide.

Prescribers are encouraged to familiarise themselves with the prescribing information for leflunomide, available on the Medsafe website at: www.medsafe.govt.nz/profs/Datasheet/dsform.asp.

Safety information has recently been added to the data sheet including:

- Side effects may occur more commonly if leflunomide is given concomitantly with other hepatotoxic or haematotoxic medicines. Monitoring guidelines contained in the leflunomide data sheet should be carefully followed.

- Interstitial pneumonitis may occur more frequently with concomitant use of methotrexate.

- A wash-out procedure should be used for all serious adverse reactions. This information is included in a new subsection of the data sheet “Washout procedure for severe adverse reactions”.

As with all medicines, healthcare professionals are encouraged to continue to report all suspected serious or unexpected adverse reactions to leflunomide to CARM.

References


Paracetamol toxicity in children – let’s reduce the risk

Reports over the last 12 months describing serious adverse reactions in children due to paracetamol toxicity highlight the importance of using this medicine appropriately.

Paracetamol liquid remains one of the most commonly used medicines for minor illnesses in children. However toxicity can easily occur if there is confusion over the strength of paracetamol liquid used or the need to calculate or measure the dose.

National Poisons Centre data suggests the number of unintentional chronic overdoses involving paracetamol has increased in children over the last five years. A further breakdown by age indicates this increase is greatest in children aged 0–2 years.

The risk of unintentional overdosing in children can be reduced by:

- Prescribing small volumes of paracetamol liquid to be dispensed. Young children are likely to be most at risk of chronic overdosing due to rapidly changing weight, variability in weight versus age, and wide dosing ranges.

- Prescribing paracetamol for each child rather than providing a large volume of liquid for several children or an entire family.

- Reducing the need for parents to calculate doses and convert to the number of mL to administer. A specific dose should always be stated on the prescription.

Healthcare professionals are reminded to inform parents that paracetamol should only be given to children for the treatment of pain and pyrexia, and to ensure the correct dose is given at the correct frequency.

Prescribers are also advised to consider limiting the volume of paracetamol liquid prescribed to children to a maximum of 200mL per dispensing. This approach may help to reduce the number of poisonings needing hospitalisation and will reduce the risk of parents using expired medicine.

Key messages

- The number of unintentional chronic overdoses involving paracetamol has increased in children over the last five years.

- Parents and caregivers need to be informed about the importance of giving paracetamol for the treatment of pain and pyrexia, at the correct dose, and not to exceed the recommended frequency. Parents should also be reminded to check the dose on the bottle each time before giving.

- Prescribers should also consider limiting the volume of paracetamol liquid prescribed for children, such as a maximum of 200 mL per dispensing.

- All paracetamol containing liquids should be fitted with child resistant caps.

- Accurate measuring devices reduce the risk of unintentional overdosing and should be provided wherever possible. Checking that parents understand how to use these correctly is also important.
**DRESS syndrome: remember to look under the skin**

DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) is an adverse reaction term that is currently used to describe a hypersensitivity reaction with an estimated mortality of up to 10%.¹

Prompt clinical recognition and discontinuing suspected medicines helps to minimise morbidity and mortality associated with this syndrome.

DRESS syndrome is a delayed type IVb hypersensitivity reaction thought to be mediated by antiviral T cells.² It is a severe, idiosyncratic multisystem reaction to a drug, characterised by fever, skin rash, lymphadenopathy, haematolocal abnormalities and internal organ involvement.

**Symptoms and diagnosis**

DRESS syndrome most commonly manifests two to eight weeks after starting the offending medicine, with a mean onset of three weeks.¹ Upon re-challenge with the associated medicine symptoms may recur within one day; however symptoms may also flare up three to four weeks after stopping the medicine, even after initial improvement.

Patients routinely develop fever early on in the disease process, followed by the development of rashes. These may vary from a very mild exanthem to extensive blistering and skin loss, but is more often a pruritic, macular erythema which may contain papules, pustules or vesicles. Systemic involvement commonly manifests as lymphadenopathy, hepatitis, pericarditis, interstitial nephritis or pneumonitis. Autoimmunity may develop as a sequelae to DRESS.

If DRESS syndrome is suspected, prescribers are reminded to look beyond the skin as the severity and extent of skin involvement does not always correlate with the extent of internal organ involvement.¹

Diagnosis can be difficult due to the variable presentation of the syndrome and is more often obtained by exclusion. Symptoms such as rash, fever, and organ involvement can be attributed to a wide range of other causes. In addition, the long latency period following initiation or after stopping the medicine creates difficulties in diagnosis.

The European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples (RegiSCAR) is a consortium created to reduce the burden of severe cutaneous reactions. This consortium has produced diagnostic criteria to assist in the diagnosis of DRESS syndrome.

RegiSCAR inclusion criteria for potential cases require at least 3 of the following:³

- Hospitalisation
- Reaction suspected to be drug related
- Acute skin rash
- Fever about 38 degrees Celsius
- Enlarged lymph nodes at two sites
- Involvement of at least one internal organ
- Blood count abnormalities such as low platelets, raised eosinophils or abnormal lymphocyte count.

In addition a Japanese group consider human herpes virus 6 (HHV-6) reactivation to be diagnostic. However as this is likely to occur two to three weeks after the onset of the rash, a diagnosis may be missed if reactivation is not measured at the correct time. Experts also debate whether reactivation is part of the syndrome or should be interpreted as a complication.⁴

Differential diagnoses include other cutaneous drug reactions such as Stevens Johnsons Syndrome (SJS) and toxic epidermal necrolysis (TEN). Acute infection, neoplastic and other immunological disorders such as Kawasaki disease or juvenile rheumatoid arthritis also need to be excluded.

**Risk factors**

Medicines most commonly associated with DRESS syndrome are anticonvulsants, antibiotics (particularly beta-lactams), and allopurinol. Other medications that are known to be associated with DRESS include non-steroidal anti-inflammatory drugs, captopril, mood stabilisers, and antiretrovirals.⁵

The incidence of DRESS with anticonvulsants has been reported at 1 in 1000 to 1 in 10,000 exposures.⁵ The risk of allopurinol induced DRESS is increased in patients with renal impairment and concomitant use of thiazide diuretics. The syndrome is thought to be caused
by an allopurinol metabolite oxypurinol, which increases in concentration in renal impairment or with the use of diuretics.\textsuperscript{6,7}

Genetic factors are also important. The risk of DRESS may be as high as 25\% for individuals who have a first degree relative who has experienced this syndrome.

**Management**

Treatment of DRESS involves early recognition followed by prompt cessation of all suspected medicines. Prompt cessation is vital to minimise associated morbidity and mortality. Supportive care is then recommended including local and systemic treatment to relieve symptoms.

Systemic corticosteroids have been used in the treatment of DRESS with some researchers reporting dramatic improvement in their patients following treatment. Systemic steroids may need to be continued for several months, with very slow tapering of the dosage, to avoid flare. However there are no data available from randomised clinical trials to support this treatment. Intravenous immunoglobulin has also been reported as being effective; however again there are no trial data to support this.

**Summary & key messages**

- DRESS syndrome is a severe reaction to a drug with an estimated mortality of up to 10\%.
- Early recognition of symptoms is vital to minimise morbidity and mortality.
- The extent of skin involvement and its severity does not always correlate with the extent of internal organ involvement. Remember to look beneath the surface.
- Drugs most commonly associated with DRESS are anticonvulsants, allopurinol, antibiotics, antiretrovirals.
- The risk is higher in people who have a first degree relative who has had the syndrome co-infection with HHV6, EBV or CMV may act as a trigger for the full blown syndrome.
- Management involves prompt cessation of the associated medicine and providing supportive treatment.

**References**


**Statin interactions: reports of serious myopathy**

Prescribers are reminded of the potential for serious adverse reactions when statins are prescribed with medicines that inhibit the CYP3A4 isoenzyme.

Recent reports to the Centre for Adverse Reactions Monitoring (CARM) indicate that the concomitant treatment with medicines that interact with simvastatin or atorvastatin has led to serious myopathies. These reports have included life-threatening and fatal cases of rhabdomyolysis. In some cases more than one interacting medicine was prescribed.

The adverse reaction reports describe common situations such as:

- The use of macrolides for acute infection without stopping the patient’s regular simvastatin.
- Initiating diltiazem in patients taking over 40 mg simvastatin daily.
- A lack of clarity in the treatment plan when care of the patient is transferred from primary to secondary care.

The metabolism of simvastatin and atorvastatin is affected by inhibitors of CYP3A4, such as macrolide antibiotics, azole antifungals, ciclosporin, amiodarone, protease inhibitors and grapefruit juice. Although diltiazem is considered
to be a weak inhibitor of CYP3A4, the risk of adverse reactions increases with higher doses of statin.

A comprehensive list of medicines that interact with simvastatin or atorvastatin can be found in the medicine data sheets at: http://www.medsafe.govt.nz/profs/Datasheet/dsform.asp

To further inform prescribers about the management of clinically important statin interactions, the New Zealand Royal College of General Practitioners has published advice on its website: http://www.rnzcgp.org.nz/assets/documents/Publications/JPHC/June-2009/JPHCJune09Insert24WEB.pdf

Acknowledgement: Thank you to Dr Ruth Savage, CARM, New Zealand Pharmacovigilance Centre.

**Clozapine: impacts on the colon**

Prescribers are reminded of the importance of treating constipation in patients taking clozapine to prevent potentially life-threatening complications.

Clozapine is indicated for use in patients with treatment-resistant schizophrenia. Constipation is a very common adverse effect related to clozapine use, occurring in 14-60% of patients. In rare cases complications can be fatal.1

Clozapine has potent anticholinergic effects. Although many anticholinergic medicines can cause gastrointestinal (GI) hypomotility, clozapine has a much more potent effect through its interaction with multiple receptors, including anticholinergic and serotonergic receptors.1

Clozapine can impair motility throughout the GI tract causing intestinal obstruction, bowel ischaemia, necrosis, perforation, toxic megacolon, and related aspiration pneumonia.1,3-7

Risk factors include recent initiation of clozapine treatment,1 higher clozapine doses,1 concomitant use of anticholinergics (e.g. benztropine and tricyclic antidepressants),1,3 and concurrent illness.1

Since 2007, when Medsafe last issued advice on this topic,7 CARM has continued to receive reports of clozapine-induced GI hypomotility-related adverse reactions. From 1 April 2007 to 31 March 2011, CARM received 14 reports of GI hypomotility for which clozapine was assessed as causally associated; two reports were life-threatening and two reported a fatal outcome.

Prior to initiation of treatment with clozapine, a gastrointestinal history and abdominal examination should be performed.1 Patients should be warned about the risks of constipation and given information on diet, exercise and fluid intake.1,3,6

Pre-existing constipation should be addressed before starting treatment with clozapine.1

Any patients taking clozapine should be asked about their bowel habits regularly, especially in the first few months of treatment.1,2,7 However the risk continues with ongoing use; therefore all patients taking clozapine need to be asked about their bowel habits on an ongoing basis.

Appropriate laxatives should be prescribed to treat constipation and need to be reviewed regularly.1 A combined stimulant and softening laxative may be helpful as a first-line treatment.1 However stimulant laxatives should be avoided if intestinal obstruction has already developed; these patients need to be referred urgently for treatment.1

The most commonly reported signs and symptoms of serious complications include: moderate to severe abdominal pain, abdominal distension, vomiting, paradoxical “overflow” diarrhoea, reduced appetite, nausea.1,4-6 Patients with these signs and symptoms require urgent medical referral and treatment as complications such as septic shock can occur.

**Key messages:**

- Clozapine can impair motility of the entire GI tract
- Constipation can lead to life-threatening complications
- Ask clozapine patients about bowel function
- Before prescribing clozapine:
  - Treat pre-existing constipation
  - Advise patients about the risks of constipation
  - Provide advice about diet, exercise and fluid intake
- Refer patients early
- Prescribe laxatives for constipation and regularly review treatment.
References


Seeing drug induced glaucoma?

Prescribers are reminded that glaucoma can be caused by many medicines (see table opposite).

Glaucoma is characterised by optic nerve damage and visual field loss resulting primarily from increased intraocular pressure. It can generally be classified as angle-closure or open-angle glaucoma.

**Angle-closure glaucoma** is a medical emergency and confers a risk of blindness within days of onset if left untreated. The most common symptoms of angle-closure glaucoma include sudden, severe eye pain, eye redness and decreased or cloudy vision. Other symptoms include nausea and vomiting, rainbow-like halos around lights and feeling of swelling in the eyes. Symptoms may initially occur intermittently.

Most cases of drug-induced angle-closure glaucoma occur in susceptible patients such as those with a pre-existing abnormally narrow angle or patients with other risk factors for glaucoma (see table opposite).

Proposed mechanisms for drug-induced glaucoma include sudden dilation of the pupil, forward movement of the iris/lens diaphragm or swelling of the ciliary body, lens or vitreous body. In susceptible patients, these events may result in further narrowing or blockage of the angle; thereby triggering angle-closure glaucoma.4

**Open-angle glaucoma** is the most common type of glaucoma. It generally presents with a gradual and painless loss of vision.4

<table>
<thead>
<tr>
<th>Medicines associated with drug-induced glaucoma</th>
<th>Risk factors for glaucoma1,4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids (inhaled and topical)</td>
<td>Narrow angle or shallow anterior chamber</td>
</tr>
<tr>
<td>Adrenergic agonists (ephedrine and bronchodilators)</td>
<td>Previous angle closure</td>
</tr>
<tr>
<td>Serotonin re-uptake inhibitors</td>
<td>Family history</td>
</tr>
<tr>
<td>Medicines with anticholinergic effects (such as TCAs and tiotropium)</td>
<td>Severe hypermetropia</td>
</tr>
<tr>
<td>Sulpha-based medicines (such as topiramate and cotrimoxazole)</td>
<td>Advanced age</td>
</tr>
<tr>
<td></td>
<td>Female gender</td>
</tr>
<tr>
<td></td>
<td>Ethnicity (higher prevalence in Asian and Hispanic)</td>
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<tr>
<td></td>
<td>Use of substances that cause pupil dilation</td>
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</tbody>
</table>

As at 31 December 2010, CARM had received 20 reports of suspected drug-induced glaucoma or worsening glaucoma. These reports were associated with a variety of medicines including glucocorticoids, phenylephrine, venlafaxine, ipratropium, and ipratropium combined with salbutamol. Most cases involved patients with additional risk factors for glaucoma such as advanced age or female gender.

All patients with suspected angle-closure glaucoma should be referred to an ophthalmologist immediately, as rapid diagnosis and treatment to reduce intraocular pressure is vital to saving a patient’s vision. Patients with existing open angle glaucoma should already be under ongoing...
ophthalmological review and should advise their ophthalmologist about any new medication being taken.

Healthcare professionals should be mindful of the potential for glaucoma to be caused by medicines. If symptoms of intermittent angle closure are reported, any suspect medicines should be tapered or discontinued as soon as possible. Specialist advice should be sought if this is not possible.

Healthcare professionals are encouraged to report all suspected cases of drug-induced glaucoma from any medicine, to the Centre for Adverse Reactions Monitoring (CARM).

References

Watch out for amiodarone’s eye effects

Amiodarone use is associated with the development of ophthalmological adverse effects including optic neuropathy (which occurs rarely) and corneal deposits (which occur in most patients).

All patients experiencing new or worsening visual symptoms whilst taking amiodarone should be referred for ophthalmological assessment. Amiodarone should be stopped if optic neuropathy is confirmed due to the potential for progression to permanent visual loss.1

Optic neuropathy can present with decreased visual acuity, decreased colour vision, an afferent pupillary defect and/or visual field loss. Drug induced optic neuropathies usually occur in both eyes, either simultaneously or in close proximity, and improves or resolves when the offending medicines are discontinued.2

The Centre for Adverse Reactions Monitoring (CARM) has received 51 reports of eye-related adverse reactions to amiodarone up to April 2011. These include 3 reports of optic neuropathy, 19 reports of corneal deposits and 12 reports of abnormal vision.

Reports to CARM highlight the variable presentation of amiodarone associated optic neuropathy. One case involved a 63-year-old woman who developed sudden onset of left sided visual loss two weeks after stopping amiodarone (which she had received for six weeks prior to successful cardioversion). A second case involved a 67-year-old man who first noticed visual changes four months after starting amiodarone. Initial examination found reduced visual acuity in the right eye. One year later this had progressed to complete visual loss in the right eye and substantial visual loss in the left eye.

Consistent with CARM reports, the published literature indicates that amiodarone associated optic neuropathy usually occurs within 12 months of starting amiodarone (median time to onset of 4 months).3 Visual loss can be acute or gradual, with approximately 65% of cases presenting with evidence of bilateral optic neuropathy.

Patients treated with amiodarone may also be predisposed to anterior ischaemic optic neuropathy due to their underlying cardiovascular risk factors. The differentiation of this cause of visual loss from a drug induced optic neuropathy can be difficult but both diseases can result in severe visual loss.

Amiodarone monitoring guidelines in New Zealand recommend that baseline eye examinations be performed in patients with pre-existing visual impairment.4 Follow-up eye examinations are recommended for all patients who develop visual symptoms while taking amiodarone.

Prescribers are reminded to enquire about visual symptoms during follow-up visits and to continue to report suspected serious and/or unexpected adverse reactions to amiodarone to CARM.

References
Prescribers are reminded that the proposed changes to the Medicines Regulations described in the March edition of *Prescriber Update* are not yet in force. This means that the maximum period of supply is six months for oral contraceptives and three months for all other prescription medicines.

The Ministry of Health will inform healthcare professionals of the date these changes will come into force.

Further information about the proposed changes to the Medicines Regulations is available at: [http://www.medsafe.govt.nz/profs/PUArticles/ChangestoMedicinesRegulations.htm](http://www.medsafe.govt.nz/profs/PUArticles/ChangestoMedicinesRegulations.htm)

**PASSIONATE ABOUT THE SAFETY OF MEDICINES?**

**Call for Appointments to the Medicines Adverse Reactions Committee**

*Applications are being sought for appointments to the Medicines Adverse Reactions Committee (MARC) – a Ministerial advisory committee*

Expressions of interest are currently being sought for four positions on the Medicines Adverse Reactions Committee (MARC).

The MARC is an independent expert advisory committee that advises the Minister of Health on medicines safety issues. The advice provided by the MARC is an important component of the regulatory framework for safeguarding public health in New Zealand.

Applications are being sought from the following candidates who have the desire to contribute to the enhancement of medicines safety in New Zealand:

**Practising clinicians** in New Zealand with:
- At least five years experience in their vocational field or area of expertise; and
- Excellent critical appraisal skills; and
- A sound knowledge of medicines.

In particular, a candidate is sought with expertise in the use of biological medicines or medicines that act on the immune system, including vaccines.

**Laypersons** (non-healthcare professionals) in New Zealand with:
- Experience in representing consumer interests.

Appointments to the Committee are made by the Minister of Health and are generally for a three-year term.

For further information about this committee, including the Terms of Reference and Responsibilities and Expectations of the MARC, go to the Medsafe website at: [http://www.medsafe.govt.nz/profs/MARC/MARC.asp](http://www.medsafe.govt.nz/profs/MARC/MARC.asp) or contact Medsafe on (04) 819 6800 and ask to be put through to the MARC Secretary.

All candidates who wish to be considered for appointment to the MARC must complete an application form. A copy of the application form is available at: [http://www.medsafe.govt.nz/profs/MARC/vacancies.asp](http://www.medsafe.govt.nz/profs/MARC/vacancies.asp)

The completed application form should be submitted together with a current *curriculum vitae* by **Wednesday 29 June 2011** to:

MARC Secretary  
Medsafe  
PO Box 5013  
Wellington

Or by e-mail to the Manager of the Clinical Risk Management Branch at Medsafe:  
[joanne_hart@moh.govt.nz](mailto:joanne_hart@moh.govt.nz)
WE NEED YOUR HELP!

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

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Potential safety issue</th>
<th>Active monitoring ends</th>
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<tbody>
<tr>
<td>Rivaroxaban</td>
<td>Atrial fibrillation</td>
<td>1 September 2011</td>
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<tr>
<td>Simvastatin</td>
<td>Joint pain &amp; swelling</td>
<td>1 September 2011</td>
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<tr>
<td>Quetiapine</td>
<td>Cardiomyopathy</td>
<td>1 September 2011</td>
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* The M scheme does not replace routine adverse reaction reporting. Find out how to report at: http://www.otago.ac.nz/carm or http://www.medsafe.govt.nz

INTENSIVE MEDICINES MONITORING PROGRAMME

Which medicines are currently being monitored?

- Varenicline (Champix)
- Dapoxetine (Priligy)

Where to report

Please report all adverse events occurring with IMMP medicines to: IMMP, NZ Pharmacovigilance Centre, PO Box 913, Dunedin 9054. Use the reporting form provided with each edition of MIMS New Ethicals or download it from either the NZ Pharmacovigilance Centre or Medsafe websites: [http://carm.otago.ac.nz/reporting.asp](http://carm.otago.ac.nz/reporting.asp) or [www.medsafe.govt.nz/Profs/adverse.asp](http://www.medsafe.govt.nz/Profs/adverse.asp)

Further information on IMMP is available at: [http://carm.otago.ac.nz/index.asp?link=immp](http://carm.otago.ac.nz/index.asp?link=immp)
Reporting form for Adverse Reactions to Medicines, Vaccines and Devices and all Clinical Events for IMMP

PATIENT DETAILS

Surname: First Name/s: 
Address: 
NHI No: 
Date of Birth: 
Sex: 
Ethnicity: 

ALL MEDICINES IN USE *ASTERISK SUSPECT MEDICINE/S* Include over-the-counter (OTC) and alternative medicines

<table>
<thead>
<tr>
<th>Medicine or Vaccine+batch no. (and brand name if known)</th>
<th>Daily Dose</th>
<th>Route</th>
<th>Date Started</th>
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<th>Reason for Use</th>
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DESCRIPTION OF ADVERSE REACTION OR EVENT

Date of onset: ________________

Recovered ☐ Not yet recovered but improved ☐ Not yet recovered ☐ Unknown ☐ Fatal ☐ Date of Death: ________________

Severe? - Yes ☐ No ☐ Rechallenged? - No ☐ Yes ☐ Result: ________________

OTHER FACTORS - Please tick or specify as appropriate

Renal disease ☐ Allergy ☐ Other Medical Conditions: __________________________

Hepatic disease ☐ Nutritional Suppl or OTC use ☐ Industrial Chemicals ☐

REPORTER - Please tick as appropriate: Doctor ☐ Pharmacist ☐ Dentist ☐ Nurse ☐ Other ☐

Name: 
Address: 
Signature: __________________________
Phone: __________________________ Date: ________________

Send completed form to CARM
Freepost 112002, CARM, PO Box 913, Dunedin 9054 or Fax: (03) 479 7150
Prescriber Update is published and distributed by Medsafe in the interests of safer, more effective use of medicines and medical devices.

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