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NSAIDs can SCAR (Severe Cutaneous Adverse Reaction)

NSAIDs are medicines widely used for the relief of pain and inflammation and are commonly purchased over-the-counter in addition to being prescribed. Non-steroidal anti-inflammatory drugs (NSAIDs) can cause severe cutaneous adverse reactions (SCARs) in rare cases.

SCARs include bullous eruptions, erythema multiforme, epidermal necrolysis, toxic epidermal necrolysis and Stevens Johnson syndrome. The Centre for Adverse Reactions Monitoring (CARM) has received a number of reports of SCARs associated with NSAIDs (Figure 1).

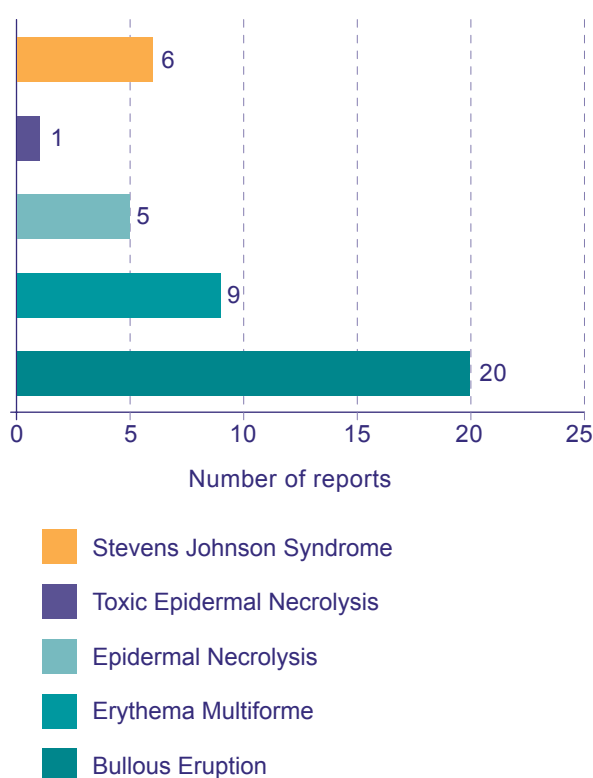


Figure 1: CARM reports of severe cutaneous adverse reactions associated with NSAIDs

SCARs may cause permanent sequelae such as disfigurement, blindness and death. Importantly, these reactions may occur without warning.

The overall risk of SCARs associated with the use of NSAIDs is extremely low. The highest reported incidence is with celecoxib at six cases per 1 million person-years¹. In New Zealand, the NSAIDs most commonly reported to cause SCARs are piroxicam, naproxen, diclofenac, celecoxib and ibuprofen (Figure 2).

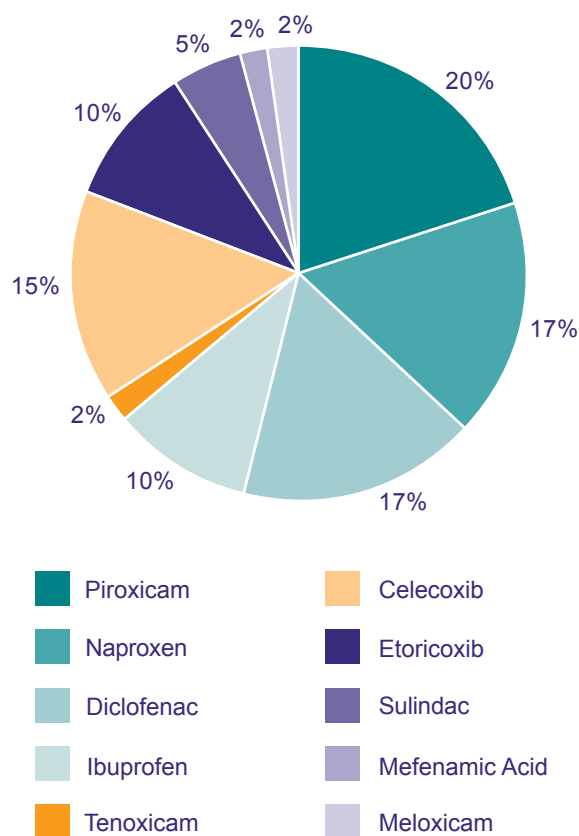


Figure 2: NSAIDs associated with severe cutaneous adverse reactions reported to CARM

SCARs are idiosyncratic and independent of dose or duration of use. People who appear most at risk are older patients, women and those early in the course of therapy. The onset of these reactions generally occurs within the first month of treatment¹.

Prescribers should advise patients of the signs and symptoms of SCARs. Patients should be advised to consult their doctor at the first appearance of a skin rash, new onset fever without explanation, mucosal lesions or any sign of hypersensitivity. If a SCAR occurs, NSAID treatment should be discontinued immediately²⁻⁴.

Key Messages

- NSAIDs are associated with a risk of severe cutaneous adverse reactions.
- Patients should be advised to seek medical advice immediately if signs or symptoms of a serious skin reaction occur.
- NSAID treatment should be discontinued if a severe skin reaction occurs.

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Beware – Peanut Oil is Present in Some Medicines!

Healthcare professionals are advised to consider the potential for allergic reactions to occur when prescribing or dispensing medicines to patients with a known peanut allergy.

Peanut oil (also known as arachis oil) is present in a number of medicines available in New Zealand (Table 1). The Centre for Adverse Reaction Monitoring (CARM) has recently received a report of an allergic skin reaction in a patient after receiving her first dose of a medicine. The patient had a known peanut allergy but only discovered later that the medicine contained peanut oil.

The peanut oil used in medicines is highly refined and the majority, if not all, of the peanut protein is removed during manufacturing¹. However, as life-threatening allergic reactions can occur with minimal exposure to peanut, caution is recommended with the use of medicines containing peanut oil in patients with a known peanut allergy.

Medsafe is working with the sponsors of medicines containing peanut oil to improve labelling. A list of medicines containing peanut oil can be obtained from the Product/Application search section on the Medsafe website www.medsafe.govt.nz/regulatory/DbSearch.asp

Table 1: Medicines containing peanut oil that are approved for use in New Zealand

Name of Medicine (Classification)	Active Ingredient	Indications
Utrogestan Tablets (Prescription)	Progesterone	Adjunctive use with oestrogen in post-menopausal women with an intact uterus (HRT).
Metvix Topical Cream (Prescription)	Methyl aminolevulinate	Treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses on the face and scalp.
Sustanon Solution for Injection (Prescription)	Testosterone	Testosterone replacement therapy in males.
Deca-Durabolin (Prescription)	Nandrolone	Treatment of osteoporosis. Palliative treatment of selected cases of disseminated breast cancer.
Cerumol Ear Drops (Pharmacy only)	Chlorobutanol Paradichlorobenzene Orthodichlorobenzene Arachis oil	
Polytar Liquid Topical Solution (General sale)	Cade oil Pine tar Coal tar	
Colpermin (General sale)	Peppermint oil	
Blackmores Flexagil Pain Relief Topical Cream (General sale)	<i>Symphytum officinale</i>	

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Osteonecrosis: A Pain in the Jaw

Osteonecrosis of the Jaw (ONJ) has been associated with a number of medicines and is a potentially debilitating condition that is difficult to treat. Prescribers are advised to recommend oral hygiene measures and closely monitor patients who are at risk of experiencing ONJ.

ONJ is characterised by the presence of necrotic, exposed bone in the jaw. The jaws are particularly sensitive to osteonecrosis due to high bone turnover resulting from daily activity and the presence of teeth¹.

Patients usually experience pain, possible secondary swelling, painful lesions, tooth mobility, ulceration and various dysaesthesias. However, patients can also be asymptomatic.

Medicines associated with the development of osteonecrosis include:

- bisphosphonates (both oral and intravenous)
- corticosteroids
- angiogenesis inhibitors such as bevacizumab (Avastin) and sunitinib (Sutent)
- denosumab (Prolia), a new medicine for osteoporosis.

Patients may be considered to have bisphosphonate-related ONJ if they have current or previous treatment with a bisphosphonate and have exposed or necrotic bone in the maxillofacial region that has persisted for more than eight weeks with no history of radiation therapy to the jaws².

Additional factors that may have an additive impact on the risk of ONJ are invasive dental procedures, radiotherapy, renal insufficiency, alcohol use, smoking, obesity, increasing age, anaemia, diabetes, rheumatoid arthritis and vitamin D deficiency³.

To date, the Centre for Adverse Reactions Monitoring (CARM) has received a total of 28 reports of ONJ that they considered to be related to the medicine. Alendronic acid was suspected in 13

cases, pamidronic acid in 11 cases and zoledronic acid in seven cases (some cases involved more than one suspect medicine).

Bisphosphonate-induced ONJ is estimated at 0.1% for patients with cancer being treated for associated bone problems that have not had invasive dental procedures⁴. The incidence of ONJ associated with oral bisphosphonate treatment is much lower, possibly in the region of one in 60 thousand⁵.

In a literature review of case reports, the minimum onset time was 10 months with zoledronic acid, 18 months with pamidronic acid and three years with oral bisphosphonate treatment⁶. The average cumulative minimum dose prior to diagnosis was 49mg for zoledronic acid, 2,217mg for pamidronic acid and 13,870mg for oral bisphosphonates⁶.

Despite the association of these medicines with ONJ, the benefits of bisphosphonate treatment are still considered to outweigh the risks of experiencing this condition.

Key Advice for Healthcare Professionals⁷

- Advise the patient to complete any necessary dental treatment prior to starting any of the medicines outlined above.
- Ensure that all relevant healthcare professionals, especially dentists, are aware that the patient is taking a medicine associated with ONJ.
- Monitor patients for signs and symptoms associated with ONJ.

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Warning: Adulterated Sildenafil Found to Contain Gliclazide

The dangers associated with buying medicines online have again been highlighted with the discovery of hidden and potentially harmful ingredients in a dietary supplement marketed for erectile dysfunction.

All batches of Vigour 800 were recently seized after testing confirmed that the product contained high levels of the prescription medicine sildenafil (110mg). Worryingly, further testing showed that the product also contained 3mg of a commonly used anti-diabetic medicine, gliclazide.

The undeclared presence of 110mg of sildenafil may prove dangerous to those people who should not take PDE-5 inhibitors, such as those with underlying cardiovascular disorders or those being treated with glyceryl trinitrate, isosorbide salts, sodium nitroprusside, amyl nitrite or nicorandil.

The quantity of gliclazide found in Vigour 800 is considered unlikely to result in a clinically significant effect. However, the discovery of gliclazide within a dietary supplement is concerning.

Medsafe has regularly highlighted the dangers of importing products purchased via the internet and last year participated in a global operation against counterfeit medicines.

Unfortunately, the discovery of products containing undeclared medicines continues to increase. Many of the products were marketed via the internet and sold to unsuspecting New Zealanders who believed they were buying natural remedies.

Healthcare professionals are encouraged to ask their patients about any products they may be taking, including dietary supplements and alternative remedies, particularly if they present with unexplained symptoms or adverse reactions.

Please contact the Medsafe Compliance Management Team on (04) 819 6800 if you are suspicious that a product may have been adulterated.

Reversible Cerebral Vasoconstriction Syndrome – Medicine Induced?

A recent Medsafe review confirmed that cases of Reversible Cerebral Vasoconstriction Syndrome (RCVS) have been reported in association with the use of the serotonergic medicines. Cases of RCVS have been reported with duloxetine, sertraline, citalopram, paroxetine, fluoxetine and sumatriptan. However, this data is currently inadequate to confirm a causal association.

RCVS should be considered in the differential diagnosis of thunderclap headaches when other causes have been excluded.

RCVS is thought to be under-reported for many reasons including lack of awareness of the condition and difficulties in confirming the diagnosis. The current data on RCVS comes primarily from case series conducted in Taiwan, France and the US¹⁻³. The case series included 262 patients who experienced RCVS.

Medsafe has added '*thunderclap headache/RCVS with serotonin reuptake inhibitors or triptans*' to the **M** monitoring scheme. Prescribers are asked to report all cases of recurrent thunderclap headaches or suspected RCVS associated with these medicines to the Centre for Adverse Reactions Monitoring (CARM). Prescribers should report cases even if an angiogram has not been performed.

What is RCVS?

RCVS is a unifying term used to describe a diverse range of conditions characterised by recurrent thunderclap headaches and reversible segmental cerebral arterial vasoconstriction on angiogram. Conditions include Call-Fleming syndrome, benign angiopathy of the CNS, postpartum angiopathy or idiopathic thunderclap headache.

Clinical Presentation⁴

RCVS classically presents with sudden-onset and severe headaches that recur over a 1–3 week period. The headaches may be accompanied

Table 1: Vasoactive substances associated with the development of RCVS⁴

Serotonergic drugs	Selective serotonin reuptake inhibitors and triptans
Illicit drugs	Cannabis, cocaine, ecstasy, amphetamines and LSD
Ergots	Ergotamine, methergine, lisuride and bromocriptine
Sympathomimetic drugs	Ephedrine and diet pills
Immunosuppressants	Tacrolimus, cyclophosphamide and interferon- α
Others	Nicotine patches, ginseng, indomethacin, binge drinking and oral contraceptive pills

by nausea, vomiting and photophobia. Most headaches are bilateral and involve the occipital region. Patients with a history of headaches (including migraines) describe the headache as different from their usual headache.

Neurological complications occur in up to 50% of patients. Complications include seizures, cortical subarachnoid haemorrhage, ischaemic stroke and intra-cerebral haemorrhage.

RCVS is more common in women and in middle aged people (median age of 40–60 years). Up to 80% of patients have identifiable triggers such as exertion, cough, defecation or sexual activity.

Diagnosis of RCVS

The diagnosis of RCVS should be made by a specialist. All three of the following events are required for the diagnosis of RCVS.

1. History of multiple thunderclap headaches.
2. Demonstration of segmental vessel constriction (string and beads appearance) of the cerebral arteries and its reversibility (complete or marked normalisation of arteries within 12 weeks of onset by initial and repeated cerebral angiography).
3. Exclusion of other causes of thunderclap headaches such as aneurysmal subarachnoid haemorrhage, cervicocerebral arterial dissection or primary angiitis of the CNS.

In patients presenting with thunderclap headaches, a normal CT scan and lumbar puncture does not exclude RCVS. If the patient presents with unexplained recurrent headaches and is using a vasoactive agent, a CT angiography (CTA) or magnetic resonance angiography (MRA) may be necessary to further investigate the cause.

Possible causes of RCVS¹⁻³

Although RCVS can occur spontaneously, a number of potential secondary causes have also been identified. Vasoactive substances (50% of cases) and the post-partum state (9% of patients) are the secondary causes most commonly implicated (Table 1).

Treatment options

There is general agreement that all patients require supportive care, withdrawal or correction of possible secondary causes and avoidance of further triggers.

Prognosis

The majority of patients recover fully. However, neurological deficits were found to be permanent in 3–9% of patients in a prospective case series⁵.

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Complementary Corner: Butterbur and Liver Toxicity

Healthcare professionals are advised that reports of liver toxicity associated with Butterbur have been received overseas.

The UK Medicines and Healthcare products Regulatory Agency has recently issued a safety alert warning consumers about the risks of liver toxicity associated with the use of products containing butterbur¹.

Butterbur, *Petasites hybridus*, is a member of the ragweed family that is native to the northern United States and Canada. Butterbur is traditionally used for the treatment of hay fever, migraine and asthma.

Butterbur contains unsaturated pyrrolizidine alkaloids that are known to be hepatotoxic in humans and in preclinical studies have been shown to be carcinogenic and mutagenic². Pyrrolizidine alkaloids may be present in low concentrations in all parts of the plant.

It is possible to reduce the unsaturated pyrrolizidine alkaloids to low levels during the manufacturing process. However, cases of liver toxicity have been reported with extracts of butterbur where the pyrrolizidine alkaloids had been removed and only small amounts remained¹.

A search of the World Health Organization's pharmacovigilance database, VigiBase, revealed reports of adverse reactions involving the liver in association with products containing *Petasites hybridus*³. VigiBase reports include nausea, anorexia and pruritus to hepatic enzymes increased, hepatic necrosis, hepatocellular damage, jaundice, hepatitis and hepatic failure.

In the literature, 40 cases of liver toxicity in association with butterbur have been reported¹. Cases included nine of acute hepatitis and two of liver failure requiring transplantation.

Healthcare professionals are encouraged to ask patients about their use of complementary and alternative medicines and to report any suspected adverse reactions to the Centre for Adverse Reactions Monitoring (CARM).

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Statins, Ciclosporin and the Risk of Myopathy

Patients taking a statin with ciclosporin may be at increased risk of statin-related adverse events. In patients currently taking ciclosporin, who also required lipid-lowering therapy, statins should be used with care. Prescribers should use the lowest possible dose and monitor for adverse reactions and the effectiveness of treatment.

Dyslipidaemia is common in patients who have undergone solid organ transplantation. Dyslipidaemia is estimated to occur in up to 80% of renal, pancreas, and heart transplant recipients and up to 45% of liver transplant patients. In addition, immunosuppressant therapy, including corticosteroids and ciclosporin, have all been associated with dyslipidaemia^{1,2}. For these reasons, it is common for transplant patients to require statin therapy. PHARMAC data indicates that approximately one third of patients taking ciclosporin are also taking a statin.

Pharmacokinetic studies confirm that ciclosporin interacts with all statins to increase the plasma levels of the statin^{3,4}. Ciclosporin is an inhibitor of CYP3A4 as well as several membrane transporters, including OATP2 and P-glycoprotein⁵. The metabolic pathways of statins include CYP3A4, OATP2 and P-glycoprotein (Table 1). It has been suggested that the risk of myopathy is lower with non-lipophilic statins because of their inability to enter muscle cells and to alter membrane structure⁶.

Myopathies are the most severe adverse reaction to statin therapy. The risk of myopathy increases with increasing plasma levels of statins⁷. Clinical

Table 1: Characteristics of statins available in New Zealand²

Statin	Equipotent doses (mg/day)*	CYP metabolism	P-glycoprotein substrate	OATP2 substrate	Lipophilic
Atorvastatin	5	3A4	Yes	Yes	Yes
Pravastatin	20	None	Yes	Yes	No
Rosuvastatin	?	2C9 (minor)	No	Yes	No
Simvastatin	10	3A4	Yes	Possibly	Yes

*Equivalent dose to reduce LDL-cholesterol from baseline by 25–30%.

studies have estimated the following incidence of myopathies in patients taking statins⁶.

- Myopathy – 5 patients per 100,000 person-years
- Rhabdomyolysis – 1.6 patients per 100,000 person-years
- Myalgia or myositis – 2–7% of patients
- Elevated creatine kinase – 11–63% of asymptomatic patients.

Other risk factors for statin-induced myopathy include female gender, a decline in renal or hepatic function, low body mass index, hypothyroidism and a personal or family history of symptoms associated with rhabdomyolysis.

In New Zealand, PHARMAC fully subsidises simvastatin, atorvastatin and pravastatin. Rosuvastatin has consent for distribution in New Zealand but is not currently subsidised.

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Nitrofurantoin – Do the Benefits Outweigh the Risks Long-Term?

Reports of suspected adverse reactions to the Centre for Adverse Reactions Monitoring (CARM) show that long-term (greater than six months) use of nitrofurantoin is associated with pulmonary toxicity.

CARM have received over 60 reports of serious pulmonary reactions following the use of nitrofurantoin. Pulmonary reports include pulmonary fibrosis (20), interstitial pneumonia (13), pulmonary infiltration (9) and interstitial lung disease (8). All of these conditions can have severe or fatal consequences^{1,2}. Pulmonary function may be permanently impaired even after treatment has been discontinued.

Nitrofurantoin is indicated for the treatment and prophylaxis of urinary tract infections. Long-term prophylaxis therapy is deemed as up to six months³. However, data provided by PHARMAC suggests that up to 5% of patients may be taking nitrofurantoin for longer than six months. Nitrofurantoin should **not** be prescribed beyond six months unless the expected benefits clearly outweigh the risks.

If the benefits of long-term use for an individual patient are considered to outweigh the risks, patients should be instructed to report the development of persistent cough or shortness of breath. Nitrofurantoin should be discontinued at the first signs of pulmonary toxicity³.

Key Messages

- Nitrofurantoin treatment should not be prescribed beyond six months unless the benefits outweigh the risks.
- Patients receiving long-term nitrofurantoin treatment should be monitored for changes in pulmonary function.
- Nitrofurantoin treatment should be discontinued at the first sign of pulmonary damage.

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MARC's Remarks: March 2012 Meeting

The latest meeting of the Medicines Adverse Reactions Committee (MARC) took place on 8 March 2012.

The MARC reviewed the safety of funded **anti-epileptic medicines** when used during **pregnancy**. The safety of valproate and topiramate in pregnancy has been reviewed previously and was therefore not included in this review. The MARC agreed that updates to the data sheets of some anti-epileptic medicines were appropriate. Overall the MARC concluded that the expected benefits of anti-epileptic treatment in pregnancy continue to outweigh any risks for the mother and child.

The MARC reviewed the risk of **reversible cerebral vasoconstriction syndrome (RCVS)** associated with use of **serotonergic agents**. The MARC considered that raising awareness of RCVS would aid in determining if there is an association with serotonergic agents. An article describing RCVS has been included in this edition of *Prescriber Update*¹. The MARC recommended that this issue be added to the **M** scheme.

The clinical significance of the pharmacokinetic interaction between **ciclosporin** and **statins** was reviewed by the MARC. The MARC agreed that there is currently insufficient data to determine

the relative risk of an interaction between ciclosporin and each individual statin. The MARC deemed that patients should be prescribed the lowest possible dose and monitored closely for effectiveness. Further information can be found in this edition of *Prescriber Update*².

Further information relating to these matters is available from the MARC meeting minutes www.medsafe.govt.nz/profs/adverse/Minutes149.htm

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Somatropin – Is There an Increased Risk of Mortality?

Healthcare professionals are reminded that the recommended daily dose of somatropin should not be exceeded and somatropin must not be used when there is any evidence of activity of a tumour.

Medsafe recently conducted a review of somatropin following the publication of a paper showing increased risk of mortality in patients treated with somatropin. Medsafe concluded that the study had significant limitations and the benefits of somatropin treatment continue to outweigh the risks when used for approved indications and at the approved doses.

Somatropin is a recombinant human growth hormone that promotes growth during childhood and adolescence. In New Zealand, somatropin is indicated in children for growth disturbance due to insufficient secretion of growth hormones, Turner syndrome, chronic renal insufficiency and Prader-Willi syndrome.

A long-term population-based study in France of patients treated with somatropin during childhood found that patients receiving high doses of somatropin had a higher risk of mortality than patients on the low-dose regimen¹. The study found that bone tumour-related and cerebrovascular disease-related mortality was increased.

The French study is part of a larger European study called the 'Safety and Appropriateness of Growth hormone treatments in Europe' (SAGhE).

A second paper from the SAGhE study did not support the observations of the French study.

The second SAGhE paper examined mortality and cause of death in patients treated with somatropin in Belgium, The Netherlands and Sweden². Not a single case of death caused by cancer or cardiovascular disease was observed in the study.

Following the results from the French study, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) completed a review of the risks and benefits of somatropin³. The CHMP considered all available data on the safety of somatropin and concluded that the benefits of somatropin continue to outweigh the risks.

Medsafe supports the conclusions of the CHMP that the benefits of somatropin continue to outweigh the risks for the approved indications and doses.

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Metal-on-Metal Replacement Hip Implants

Medsafe and the New Zealand Orthopaedic Association support recent advice issued by the UK Medicines and Healthcare products Regulatory Agency on the management of patients who received metal-on-metal hip replacements.

DePuy ASR

In August 2010, DePuy Orthopaedics issued a hazard alert to New Zealand surgeons that data from the UK National Joint Registry showed revision rates of 13% for ASR hip replacements¹.

As DePuy had ceased supplying these hip replacements in New Zealand in December 2009, there was no need to recall un-implanted hip replacements. However, in the rest of the world, un-implanted ASR hip replacements were recalled.

The alert advised surgeons to contact their patients and recommended monitoring and follow-up of those with the ASR hip replacement¹. Medsafe understands a total of 525 devices have been implanted in 400 New Zealand patients.

DePuy did not recommend the prophylactic revision of ASR replacement hips in asymptomatic patients. This is consistent with expert advice issued both in New Zealand by the New Zealand Orthopaedic Association and internationally.

Stryker MITCH TRH

In April 2012, Stryker issued a hazard alert regarding its MITCH TRH modular head and cup when used in conjunction with un-cemented Stryker Accolade femoral stems². The UK National Joint Registry showed this combination had significantly higher revision rates than other total hip prostheses.

The issue with the MITCH TRH related primarily to loosening of the femoral stem and is not related to the issue experienced with the DePuy ASR.

The alert recommended surgeons follow up with patients and advise them of this issue². Although 106 MITCH modular heads and cups have been implanted, Medsafe understands only 41 were used in combination with the Stryker Accolade femoral stem.

Stryker ceased supply of MITCH TRH modular heads and cups in New Zealand in August 2011.

Summary

The majority of patients who receive a metal-on-metal hip replacement do well with the implant and are thought to be at low risk of developing serious problems.

In a small number of patients a soft tissue reaction may occur due to a build-up of microscopic metal debris through wear at the articular surface of the joint. Surgeons have been informed that this issue can be monitored by measuring trace amounts of cobalt and chromium in affected patients.

Further information and recommendations for management of patients with metal-on-metal replacement hip implants is published on the Medsafe website www.medsafe.govt.nz/hot/recallactionnoticesnew/metalonmetalhipimplants/metalonmetalhipimplants.asp

References

1. DePuy Orthopaedics. 2010. DePuy ASR™ Articular Surface Replacement and ASR™ XL Acetabular System. *Hazard Alert* 26 August 2010. URL: www.medsafe.govt.nz/hot/RecallActionNoticesNew/MetalOnMetalHipImplants/NZ%20ASR%20Hazard%20Alert%20Letter%20Final%20_2_.pdf (accessed 24 May 2012).
2. Stryker Australia & New Zealand. 2012. MITCH TRH modular heads. *Hazard Alert* 12 April 2012. URL: www.medsafe.govt.nz/hot/RecallActionNoticesNew/Stryker%20MITCH%20Recall%20notice.pdf (accessed 24 May 2012).

SMARS Launch

Medsafe has been working to provide more information to the public about New Zealand reports of suspected adverse reactions to medicines.

Suspected medicine adverse reaction reports received in New Zealand will be available by the end of June via a searchable database. The suspected medicine adverse reaction search (SMARS) will be located on the Medsafe website www.medsafe.govt.nz

SMARS is designed to increase transparency and address the growing public need for access to information.

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
Sildenafil	Thromboembolism	30 September 2012
Cetirizine	Severe Mood Disorder	30 September 2012
SRIIs	Thunderclap headache/RCVS	31 December 2012
Triptans	Thunderclap headache/RCVS	31 December 2012
Lithium	Diabetes mellitus	31 December 2012
Lansoprazole, Pantoprazole, Omeprazole	Hypocalcaemia	31 December 2012

- **M²** is a new 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.

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