

Medicines update: removal of Special Authority status

The requirement for Special Authority approval for subsidy will be removed from the following medicines:

1 October 2014 Perhexiline maleate (Pexsig)
 Nicorandil (Ikorel)
 Mycophenolate mofetil (MMF; Cellcept)
 Bicalutamide (Bicalaccord)

1 February 2015 Imiquimod (Aldara, Apo-Imiquimod cream 5%)

Antianginal medicines: perhexiline maleate (Pexsig), nicorandil (Ikorel)


From 1 October 2014, Special Authority approval for the subsidy of nicorandil and perhexiline will cease and these medicines will be subsidised without restrictions. Nicorandil acts as both an arterial and venous vasodilator and is indicated for the prevention of angina. Perhexiline is indicated for the treatment of angina, although its mechanism of action has not been fully elucidated. Nicorandil and perhexiline would normally be used under specialist guidance where other treatment options have been previously trialled or excluded.

Nicorandil may cause skin flushes, headaches, dizziness and nausea, and rarely oral or perianal ulceration. The concurrent use of nicorandil and phosphodiesterase-5 inhibitors (sildenafil, tadalafil and vardenafil), should be avoided due to risks of severe hypotension.¹

Patients prescribed perhexiline must have their blood levels of perhexiline monitored.² Patients exhibit a wide range of hepatic clearance, possibly arising from mutations in the CYP2D6 gene,³ and can exhibit dose accumulation which increases the risk of toxicity and adverse effects. Monitoring should begin

at the end of the first week of dosing with plasma levels kept between 0.15 – 0.60 micrograms/mL.² Dosing should only increase if levels are below this range and two to four weeks have passed since beginning or increasing dosage. The use of perhexiline is not recommended in patients with impaired renal or hepatic function,² and it should be used with caution in patients with diabetes as it can cause hypoglycaemia.² Adverse effects can include altered liver function tests and neuropathy with longer term use.²

As angina is caused by underlying cardiovascular disease, the aim of treating patients with stable angina should be to reduce cardiovascular risk as well as provide angina symptom management. The New Zealand Primary Care Handbook recommends that all people with angina should be treated with aspirin, a statin, a beta-blocker and considered for an ACE inhibitor unless contraindicated.⁴ Beta-blockers, calcium-channel blockers and nitrates can also be used for the management of angina symptoms.

 For further information, see: www.health.govt.nz/publication/new-zealand-primary-care-handbook-2012

and: "The medical management of stable angina pectoris", BPJ 39 (Oct, 2011).

Immunosuppressant: mycophenolate mofetil (MMF; Cellcept)

The immunosuppressant mycophenolate mofetil will be funded without the need for Special Authority approval from 1 October 2014. Previously this had been available to transplant recipients or other patients requiring immunosuppression that had tried or were intolerant to azathioprine, cyclophosphamide or corticosteroids. Mycophenolate mofetil will now be available subsidised for patients with other conditions requiring immunosuppression such as lupus nephritis, vasculitis and for prophylaxis of acute transplant rejection. The


use of mycophenolate mofetil during pregnancy has been reported to cause congenital malformations and appropriate contraception should be planned.¹

Patients should be advised of the symptoms of bone marrow suppression, such as unexplained bruising, bleeding, and the risk of infections, and to report if these develop.⁵ It may be useful to flag clinic notes for these warning signs. Patients should be monitored with weekly full blood counts for the first month of use, reducing to twice monthly for the following two months and then monthly for subsequent use.¹ The use of live vaccines is not recommended within six months of the use of mycophenolate mofetil.⁵

Prostate cancer treatment: bicalutamide (Bicalacord)

Bicalutamide is a non-steroidal anti-androgen medicine for the treatment of patients with advanced prostate cancer, used in combination with castration or gonadorelin analogue therapy. From 1 October 2014 the requirement for Special Authority will be removed. However, this medicine is unlikely to be initiated in primary care as it indicated for the treatment of prostate cancer only.

Due to the biological role of testosterone, its inhibition during androgen deprivation therapy has a wide range of adverse effects including breast pain (in males) and gynaecomastia, hot flushes, metabolic changes including weight gain, and alterations in sexual function.⁶ Patients should be advised of these effects and to report their occurrence.

 For further information, see: "Diagnosis and management of prostate cancer in New Zealand men", available from: www.health.govt.nz/publication/diagnosis-and-management-prostate-cancer-new-zealand-men-recommendations-prostate-cancer-taskforce

Warts and superficial skin lesions: imiquimod (Aldara, Apo-Imiquimod cream 5%)


Imiquimod is an immune response modifier, used topically for the treatment of genital and perianal warts, and superficial pre-malignant and malignant skin conditions such as solar keratoses (actinic keratoses), basal cell carcinoma and squamous cell carcinoma. With the listing of a generic branded product, imiquimod cream (5%) will be fully funded with no restrictions from 1 February 2015.

Imiquimod is used for the topical treatment of superficial pre-malignant and malignant skin conditions. Surgical excision

is the recommended treatment for basal cell carcinoma by the Cancer Council of Australia and British Association of Dermatologists.^{7,8} Similarly, for the treatment of squamous cell carcinoma, surgical excision is usually performed as it allows for accurate diagnosis and histological evaluation of surgical margins.⁹ Imiquimod may be useful for treating patients with these conditions in cases where surgical excision is not possible or acceptable to the patient. For the treatment of actinic keratosis, interventions are usually aimed at either treating a single lesion or 'field-directed' treatments applied to a skin area with a number of keratoses. Most field-directed treatments involve the application of a topical treatment, such as imiquimod. A 2012 Cochrane review found that imiquimod treatment had comparable efficacy to other topical treatment options.¹⁰

Currently, imiquimod is subsidised with Special Authority approval for the treatment of genital and perianal warts following the failure of podophyllotoxin. The removal of Special Authority status in February 2015 will mean a choice of first-line treatment options is available. There is no evidence that any specific treatment for genital warts is superior.¹¹ The use of the self-applied topical treatments imiquimod or podophyllotoxin during pregnancy is not recommended, and in this scenario a clinician-administered treatment such as cryotherapy, electrocautery, surgery, laser therapy, or trichloroacetic acid may be considered.¹² Imiquimod should be applied by rubbing it into the skin with the fingertip (the hand should then be washed). Patients should leave the treatment on the skin for six to ten hours and then wash the application site.¹³ A common recommendation is for the patient to apply imiquimod overnight. Patients should be reviewed after four to six weeks to ensure appropriate clinical response. Non-response should be followed-up; actinic keratosis, for example, can give rise to squamous cell carcinoma.

Imiquimod is regarded as a 'high risk' medicine, in that adverse effects can occur even with proper usage.^{13,14} Given its function as an immune modifier, adverse effects involve immune or inflammatory reactions, such as redness, flaking and scaling, or skin pigmentation changes at the application site,¹⁴ but can also include systemic effects such as flu-like symptoms, nausea and malaise.¹³ Since different application regimens are used for the treatment of anogenital warts, superficial basal cell carcinoma and actinic keratosis,¹³ the potential for harm can be reduced by ensuring patients are taking the correct dose and not applying imiquimod more frequently than directed.¹⁵

 For further information, see: "Managing non-melanoma skin cancer in primary care: a focus on topical treatments", BPJ 57 (Dec, 2013).

References:

1. New Zealand Formulary (NZF). NZF v28. 2014. Available from: www.nzf.org.nz (Accessed Oct, 2014).
2. Pharmacy Retailing (NZ) Limited Trading as Healthcare Logistics. Pexsig Tablet. New Zealand Data Sheet. 2009. Available from: www.medsafe.govt.nz/profs/datasheet/p/pexsigtab.pdf (Accessed Oct, 2014).
3. Gardiner SJ, Begg EJ. Pharmacogenetics, drug-metabolizing enzymes, and clinical practice. *Pharmacol Rev* 2006;58:521–90.
4. New Zealand Guidelines Group (NZGG). New Zealand Primary Care Handbook 2012. Wellington: NZGG, 2012. Available from: www.health.govt.nz/publication/new-zealand-primary-care-handbook-2012 (Accessed Oct, 2014).
5. Douglas Pharmaceuticals Limited. Consumer Medicine Information sheet. Myaccord. 2012. Available from: www.medsafe.govt.nz/Consumers/cmi/m/MyaccordCapTab.pdf (Accessed Oct, 2014).
6. Mottet N, Bastian PJ, Bellmunt J, et al. Guidelines on prostate cancer. European Association of Urology, 2014. Available from: www.uroweb.org/gls/pdf/1607%20Prostate%20Cancer_LRV3.pdf (Accessed Oct, 2014).
7. Cancer Council of Australia and Australian Cancer Network. Clinical Practice Guide. Basal cell carcinoma, squamous cell carcinoma (and related lesions) – a guide to clinical management in Australia. Sydney: 2008. Available from: www.cancer.org.au/content/pdf/HealthProfessionals/ClinicalGuidelines/Basal_cell_carcinoma_Squamous_cell_carcinoma_Guide_Nov_2008-Final_with_Corrigendums.pdf (Accessed Oct, 2014).
8. Telfer NR, Colver GB, Morton CA. Guidelines for the management of basal cell carcinoma. *Br J Dermatol* 2008;159:35–48.
9. Scottish Intercollegiate Guidelines Network (SIGN). Management of primary cutaneous squamous cell carcinoma. Edinburgh: 2014. Available from: www.sign.ac.uk/guidelines/fulltext/140/index.html (Accessed Oct, 2014).
10. Gupta AK, Paquet M, Villanueva E, et al. Interventions for actinic keratoses. *Cochrane Database Syst Rev* 2012;12:CD004415.
11. Workowski KA, Berman S, Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. *Recomm Rep Cent Dis Control* 2010;59:1–110.
12. Professional Advisory Board of the New Zealand HPV Project. Guidelines for the management of genital HPV infection in New Zealand. Sexually Transmitted Infection Education Foundation, 2013. Available from: www.herpes.org.nz/files/8514/0010/9217/HPV_Guidelines_2013_web.pdf (Accessed Oct, 2014).
13. Quality Use of Medicines Team, Waitemata District Health Board. Imiquimod (Aldara) - Safe prescribing - a burning issue. Waitemata District Health Board, 2009. Available from: www.saferx.co.nz/full/Imiquimod.pdf (Accessed Oct, 2014).
14. Medsafe. Imiquimod cream - skin pigmentation changes and flu-like symptoms. *Prescr Update* 2008;29:3.
15. NPS Medicinewise. Imiquimod cream (Aldara) for superficial basal cell carcinoma. *NPS Radar* 2013;April:9–18.

Paracetamol and acute liver failure in children in New Zealand and Australia

Recent research from the New Zealand Liver Transplant Unit at Starship Children's Hospital (Auckland), and the Queensland Liver Transplant Service at the Royal Children's Hospital (Brisbane) examined cases of paediatric acute liver failure attributable to paracetamol overdose.¹ This research highlights the possibility of hepatic toxicity from paracetamol use and the need for vigilance from parents, carers and prescribers to avoid paracetamol overdosing in children.

Across these two centres, over an 11 year period, 14 children were identified as exhibiting acute liver failure where paracetamol was determined to be the cause. These cases were almost all in preschool-aged children (12 out of the 14 were aged under five years). Twelve of these 14 children survived, two of whom had liver transplants, and two children died (one following a liver transplant).¹

Most of the children (12 out of 14) received liquid paracetamol. The average dose of paracetamol was 135 mg/kg/day (range 62–250 mg/kg/day). Half of the children had doses above 120 mg/kg/day – twice the recommended amount.¹

The median dosing interval in these children was four hours, which is the recommended dosing interval. However, half of the children had doses in shorter time spans; dosing intervals

ranged from 30 minutes to six hours. The duration of dosing mostly ranged from three to seven days of use. However, one child had an intake of paracetamol within acceptable daily dose amounts, but with dosing continued over 24 days; the child subsequently died.¹

The researchers also provided data on the number of phone calls to New Zealand and Queensland Poisons Information Centres regarding suspected paracetamol poisoning in children for three years from 2009 to 2012. The New Zealand centre received an average of 804 calls per year; which is an average of two to three calls per day.¹ The New Zealand National Poisons Centre reported in 2011 that unintentional overdoses of paracetamol in children were increasing, particularly among children aged under two years.²

This research is a timely reminder that this widely available and widely used medicine can also be highly toxic. Guidance to parents for safe paracetamol use should emphasise: weight-based dosing, appropriate dosing intervals (which could have reduced the cumulative dose taken in half of these cases) and avoiding the prolonged use of paracetamol. Current New Zealand labelling requirements for paracetamol recommend seeking medical advice for use beyond 48 hours.³

Preparations containing paracetamol in New Zealand include:

Liquids	Paracetamol Paracare	Panadol Parapaed	Pamol
Tablets/Capsules	Paracetamol Panadol Parafast Disprol Rexidol Paralgin Dimetapp	Coldrex Nuromol Maxigesic Day & Night Cold and Flu 'Your Pharmacy' Sinus Pain Relief Sudafed	Sinutab Panadeine Mersyndol 'Your Pharmacy' Pain Relief Plus Fiorinal Paramax
From Powder	Lemsip Coldrex	Panadol Cold & Flu 'Your Pharmacy' Cold & Flu	


N.B. This list is not exhaustive, but can help to identify the most common paracetamol-containing medicines available in New Zealand.

Key advice for parents and carers about paracetamol:

- Ensure the correct dose is given, based on the child's weight
- Measure this dose carefully using an appropriate measuring device, e.g. a marked medicine cup or syringe
- Ensure the correct dose intervals are followed: at least four hours between doses and no more than four doses in one day
- Do not give paracetamol to a child for more than 48 hours without seeking advice from your general practice
- If two different strengths of liquid paracetamol are in the household, make sure the correct strength is used for each child
- Be aware of other medicines that contain paracetamol (see above): overdosing can occur when another medicine containing paracetamol is inadvertently given at the same time

Safe paracetamol dosing in children

Although there is debate over how paracetamol doses should be calculated,⁴ we recommend that weight-based dosing is used. Weight-based dose calculations can result in under or over-dosing in very underweight or overweight children. Therefore, clinical judgement should be applied if a calculated dose falls outside of the usual paracetamol dose range. Paracetamol should be used with caution in children who are dehydrated, e.g. following vomiting or diarrhoea, as this can increase the risk of hepatotoxicity.⁵

 The recommended dose of oral paracetamol for children aged one month to 18 years is 15 mg/kg, every four hours, up to four times per day, maximum 1 g per dose and 4 g per day.⁶

A guide for parents, including recommended weight-based doses in mLs for liquid preparations, is available from:
www.saferx.co.nz/paracetamol-for-children_leaflet.pdf

References:

1. Rajanayagam J, Bishop JR, Lewindon PJ, et al. Paracetamol-associated acute liver failure in Australian and New Zealand children: high rate of medication errors. *Arch Dis Child* 2014;[Epub ahead of print].
2. Paracetamol toxicity in children - let's reduce the risk. *Prescr Update* 2011;32:11.
3. Medsafe. Label Statements Database. Edition 1.14. Medsafe, 2014. Available from: www.medsafe.govt.nz/regulatory/labelling.asp (Accessed Oct, 2014).
4. Lenney W. Paracetamol prescription by age or by weight? *Arch Dis Child* 2012;97:277-8.
5. Quay K, Shepherd M. Paracetamol poisoning. *Starship Children's Health clinical guideline*, 2010. Available from: www.adhb.govt.nz/starshipclinicalguidelines/_Documents/Paracetamol%20Poisoning.pdf (Accessed Oct, 2014).
6. New Zealand Formulary (NZF). NZF v28. NZF, 2014. Available from: www.nzf.org.nz (Accessed Oct, 2014).

Extended use of copper and levonorgestrel intrauterine contraceptive devices (IUDs)

Some IUDs appear to be safe and effective to use for a longer time than the manufacturer's approved recommendation. A comprehensive review published in 2014 considered both safety and likely contraceptive effectiveness, based on published and unpublished literature. There are several brands of IUD that are in use in New Zealand that may be left in place for longer than originally recommended, as the benefits are thought to outweigh any risks. However, **this advice only applies to women who were aged at least 25 years and had given birth**, prior to insertion of the device.

IUD contraception

An IUD is a long-acting, reversible contraceptive that may be used in women who have had a pregnancy and those who have not. Around the world, in both developed and developing countries, IUDs have proven to be an effective and cost-effective form of contraception. In some areas, lack of access to a service that can replace an IUD has prompted research about women who have had their device in place for longer than the manufacturer's recommended time. This has led to the conclusion that in some circumstances, IUDs are still effective if they remain in place for an extended period of time.¹

There are two types of IUD – copper and levonorgestrel. The copper IUD works by releasing copper ions, which results in a spermicidal, sterile inflammatory response in the endometrium and copper-rich cervical mucus, which reduces sperm motility.¹ The copper ions are initially released in a burst, and then slowly released over time, at a rate depending on various individual factors. IUDs with greater surface areas of copper have superior contraceptive efficacy.¹ Levonorgestrel IUDs work by releasing approximately 20 mcg/day of levonorgestrel, with a slowly declining rate of release over the lifetime of the IUD. Levonorgestrel acts as a contraceptive via anti-proliferative effects on the endometrium and thickening of cervical mucus.¹

Overall, IUDs have a 99% success rate, i.e. one woman in one hundred will become pregnant each year while using an IUD.² IUD contraception does not affect sexual intercourse or breastfeeding, and there is no evidence of increased risk of breast cancer.² For the copper IUD, heavier or prolonged periods are common in the first three to six months of use; this usually improves with time.² The levonorgestrel-secreting IUD is often used for women who experience heavy menstruation, in whom copper IUDs should not be used.² The presence of sexually transmitted infection (STI) may need to be excluded

before an IUD is inserted; this is not usually necessary for women at low risk of STI. The device should be checked for correct positioning six weeks after insertion.²

The decision to extend duration of IUD use

The review considered the evidence for extended use of both copper- and levonorgestrel-secreting IUDs by looking into several questions:

1. What is the risk of pregnancy associated with extended IUD use? Taking into consideration that the fertility of women, and their chance of pregnancy, will naturally decline with age.
2. How do the pharmacokinetic properties of the devices contribute to an understanding of their potential extended life? Pharmacokinetic understanding should support the conclusions that can be drawn from the evidence.
3. What recommendations can be made from the current evidence? It should be remembered that there are individual variations in fertility of women desiring effective contraception.

The following practice points were recommended:

Women who have given birth and have had an IUD inserted after age 25 years can be reassured that there is consistent, good quality, evidence of the safety of extended duration of use of an IUD (Table 1, over page). Extended use of an IUD, beyond the manufacturer's recommendations, is an off-label use of a medicine, which must be discussed with the woman and her consent obtained.

The decision to leave the IUD in place should be considered using a shared decision-making approach. Discussion should cover pregnancy risk and the woman's feelings about an unintended pregnancy, expected adverse effects if the IUD remains in place and the risk of removing and replacing the IUD.¹ Every time an IUD is inserted or changed, there is a small risk of infection, perforation and expulsion.

Women who have no barriers to accessing medical care for removal/insertion of an IUD and are unable to accept the small potential risk of pregnancy with the IUD remaining in place for an extended duration, should have their IUD replaced at the usual recommended time.¹

Although based on limited and less consistent evidence, off-label extended use of a copper- or levonorgestrel-secreting IUD, is also likely to be effective in overweight and obese women and can be recommended.¹

Table 1. Duration of effectiveness of Intrauterine Contraceptive Devices (IUDs) available in New Zealand compared with manufacturer's recommendations for parous women, aged over 25 years.¹

IUD product	IUD type	Extended duration of effectiveness and safety for parous women aged over 25 years	Manufacturer's recommended duration of use ^{3,4}
Multiload Cu-375 Standard or Short [ⓐ]	Copper wire 375 mm ² surface area	10 years	5 years
Choice TT380 Standard	Copper wire 380 mm ² surface area	12 years	10 years
Choice TT380 Short [ⓐ]	Copper wire 380 mm ² surface area	Do not extend use	5 years
Slimline TT380 Standard [ⓐ]	Copper wire 380 mm ² surface area	12 years	10 years
Slimline TT380 Mini ^{ⓐⓑ}	Copper wire 380 mm ² surface area	Do not extend use	5 years
CuT380A (Paragard) ^{ⓐⓑ}	Copper wire 380 mm ² surface area	12 years	10 years
Mirena	Levonorgestrel 52 mg	7 years	5 years
Skyla [ⓐ]	Levonorgestrel 13.5 mg	Do not extend use	3 years

- ⓐ The copper surface area of the 'Short' or 'Mini' IUDs is the same as for the 'Standard' version; the dimensions of the frames (usually plastic) differ
- ⓑ The mini/short Choice or Slimline devices contain the same surface area of copper as the standard devices, but thinner sheets are wrapped around the sleeves to fit onto the smaller frame, therefore these devices have a shorter recommended duration
- ⓒ Slimline TT380 Standard and MiniTT380 IUDs have been temporarily available and subsidised; these will become unsubsidised on 1 April 2015
- ⓓ Women who were aged 35 years or over at the time of CuT380A IUD insertion may continue with the original device in place until menopause, with only a small theoretical risk of pregnancy occurring. This is also likely for the other copper IUDs of 375 mm² and 380 mm² surface area of copper.
- ⓔ Not routinely available in New Zealand, but may have been inserted overseas

Extended, off-label use of an IUD beyond the manufacturer's recommendation should not be considered for women who are aged under 25 years at the time of insertion of either a copper- or levonorgestrel-secreting IUD. The review did not locate any evidence about extended use of IUDs in younger women, who are likely to have a higher chance of becoming pregnant, resulting in an IUD being less effective with extended use.

Future research

The studies that were reviewed excluded women who were aged under 25 years and had not had a pregnancy, therefore conclusions were not able to be drawn about extended use of IUDs in this patient group. Research into adolescents and nulliparous women who have chosen to extend the use of their IUD is currently occurring. Research is also underway on IUDs that will secrete copper for up to 25 years; these may offer an alternative to surgical sterilisation for some women.

ACKNOWLEDGEMENT: Thank you to **Dr Christine Roke**, National Medical Advisor, Family Planning for expert review of this article.

References

1. Wu J, Pickle S. Extended use of the intrauterine device: a literature review and recommendation for clinical practice. *Contraception* 2014;89:495–503.
2. New Zealand Family Planning (NZFP). Intra uterine device (IUD). NZFP, 2014. Available from: www.familyplanning.org.nz/advice/contraception/intra-uterine-device-iud (Accessed Oct, 2014).
3. Lowth M. Intrauterine contraceptive device (IUCD). Patient.co.uk, 2014. Available from: www.patient.co.uk/doctor/intrauterine-contraceptive-device-iucd-pro (Accessed Oct, 2014).
4. Royal Pharmaceutical Society. BNF. 62nd ed.