



**TIMELY,
INDEPENDENT
INFORMATION
ABOUT NEW
DRUGS**



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**for schizophrenia or bipolar I disorder
(acute mania or maintenance)**

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Cover image: opium poppies

No more effective, but more suitable for some?

More often than not, a new drug has no greater efficacy than existing therapies. So the next step in assessing it is to look for other advantages, such as adverse-effect profile or patient acceptability.

Assessing these factors is usually the first step when choosing an antipsychotic for people with schizophrenia. This is because evidence suggests that there are only minor differences in effectiveness between antipsychotics, apart from the special role of clozapine in treatment-resistant schizophrenia.¹

This issue of *NPS RADAR* includes an in-depth review of asenapine (Saphris), a new antipsychotic for schizophrenia or bipolar I disorder. Like most newer antipsychotics, asenapine does not have an efficacy advantage. Nonetheless, it may be preferred for some individuals. This review will help you assess what is known about asenapine's safety profile, which patients may find it an acceptable alternative, and those patients for whom it is clearly unsuitable.

Prescribers will need to consider the special dosing requirements of asenapine. Asenapine is available only as a sublingual wafer, which is incompletely absorbed if swallowed or if food or drink is consumed within 10 minutes after taking it. Because the consequences of poor adherence are great, prescribers will need to evaluate each patient's ability and willingness to follow these instructions before prescribing.

So far, asenapine's adverse-effect profile looks typical for a newer antipsychotic, although it has a slightly different combination of relative advantages and disadvantages. Asenapine could be a better fit for a patient with unacceptable weight gain or hyperprolactinaemia from other antipsychotics. But prescribers will need to take into account the incidence of extrapyramidal side effects with asenapine, which is higher than that with olanzapine.

As for most new drugs, there is a relative lack of experience with asenapine, meaning that there is uncertainty about its effectiveness among the types of patients who are excluded from clinical trials, and not much knowledge about possible rare adverse effects.

Of course, assessing if a new drug like asenapine is suitable for an individual should also include review of current management. When a patient is responding poorly to their current therapy, assess adherence before considering a switch. Investigating the reasons for poor adherence can help guide choice of a replacement drug and confirm if a switch is required. If adverse effects are intolerable, review other management options such as dose reduction.²

If you'd like to know more about tailoring antipsychotic treatment for people with schizophrenia, see *NPS NEWS 74: Balancing benefits and harms of antipsychotic therapy*.

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Asenapine (Saphris)

for schizophrenia or bipolar I disorder (acute mania or maintenance)

(a-SEN-a-peen)

Sublingual wafer must be taken correctly

KEY POINTS

Asenapine has a similar spectrum of benefits and harms to that of other antipsychotics

As with most newer antipsychotics, asenapine is a potent inhibitor at dopamine D₂ and serotonin 5-HT_{2A} receptors.

Trial data demonstrate efficacy up to 52 weeks in schizophrenia and 12 weeks in bipolar mania or mixed episodes

There are limited efficacy and safety data beyond one year.

Asenapine wafers are ineffective if swallowed

The wafers must be taken sublingually twice daily, with no food or drink for 10 minutes afterwards.

Warn patients to expect tingling or numbing of the tongue and mouth

Asenapine wafers often have a local anaesthetic effect. Symptoms usually resolve within an hour.

Less efficacious than olanzapine in a 52-week trial for schizophrenia and schizoaffective disorder

Of those completing the trial, 52% were rated as much or very much improved with asenapine, and 66% with olanzapine.

Appears to cause a higher incidence of extrapyramidal symptoms (EPS) than olanzapine but a lower incidence of weight gain

In a 52-week trial, 14% of patients receiving asenapine and 7% of patients receiving olanzapine experienced treatment-related EPS; rates of weight gain (≥ 7% of baseline) were 12% and 29%.

PBS listing

Authority required (Streamlined)

Schizophrenia.


Authority required (Streamlined)

Treating an acute episode of mania or mixed episodes associated with bipolar I disorder for up to 6 months.

Maintenance therapy of bipolar I disorder as monotherapy.

May be prescribed by nurse practitioners (shared care model)

Authorised nurse practitioners may prescribe this medicine as part of a formal care plan with

a medical practitioner. See the PBS website  for more information on nurse practitioner PBS prescribing.

What is it?

Asenapine is an antipsychotic with similarities to clozapine, olanzapine and quetiapine, and like these drugs is a potent antagonist at dopamine D₂ and serotonin 5-HT_{2A} receptors.^{1,2} Asenapine also inhibits activity at a range of other receptors. Relevant to its adverse-effect profile, it binds at alpha₁ adrenergic receptors and histamine H₁ receptors, but has little affinity for muscarinic acetylcholine receptors.¹



ADDITIONAL INFORMATION

www.pbs.gov.au/info/healthpro/explanatory-notes/section1/nurse-practitioner

Asenapine is formulated as sublingual wafers that are round and white to off-white in colour. The wafer is placed under the tongue, where the drug is absorbed through the oral mucosa with an absolute bioavailability of about 35% for asenapine 5 mg wafers.³

Asenapine is ineffective if swallowed (bioavailability as a tablet formulation was < 2%).³

Who is it for?

Schizophrenia

Asenapine is indicated for schizophrenia in adults. Most participants in trials had previously received antipsychotic treatment, but treatment-resistant individuals were excluded. People with a history of recent alcohol or illicit drug misuse, symptoms of tardive dyskinesia, a seizure disorder or concomitant treatment with another psychotropic drug were also excluded.^{3,4}

Bipolar I disorder

Asenapine is indicated for manic or mixed episodes associated with bipolar I disorder, and for preventing relapse of manic or mixed episodes. Efficacy has not been adequately assessed beyond 12 weeks. There are no efficacy data in bipolar depression. Exclusion criteria for the bipolar I disorder clinical trials included first moderate to severe mood episode, comorbid psychotic disorder, a history of recent alcohol or illicit drug misuse, seizure disorder, or a history of rapid cycling. Unlike the schizophrenia trials, participants could have a history of unsuccessful antipsychotic treatment.^{3,5}

Where does it fit?

The therapeutic and adverse effects of asenapine are broadly consistent with those of other antipsychotics. Asenapine's particular adverse-effect profile may make it a suitable choice for certain patients (see How does it compare?). However, data suggest it is less efficacious than olanzapine in schizophrenia.

Uncertainty about asenapine's efficacy compared with other antipsychotics and its long-term safety mean that established antipsychotics may be a better first choice for people with schizophrenia

or, if an antipsychotic is indicated, in bipolar I disorder. Consider clozapine for people with treatment-resistant schizophrenia — asenapine is untested in this population.

Asenapine wafers may be unsuitable for some people because they are taken sublingually twice daily and must not be swallowed.

Consider established antipsychotics first in schizophrenia

There are many existing first-line choices for treating schizophrenia. Consider these before asenapine wafers, given the relative lack of comparative data and experience. Efficacy and safety data for asenapine beyond 52 weeks are limited, and rare adverse effects have not been well characterised. At the time of TGA evaluation 779 people had been exposed to asenapine for at least 12 months in clinical studies.⁵ Asenapine was less efficacious and had a higher incidence of treatment-related serious adverse effects than olanzapine in a 52-week trial (see How does it compare?).

No data in treatment-resistant schizophrenia

Consider clozapine for all adults with schizophrenia who have not responded to two or more antipsychotic drugs.⁶ Asenapine has not been tested in people with treatment-resistant schizophrenia. In asenapine clinical trials, participants must have responded previously to an antipsychotic other than clozapine, or be treatment naive.⁴

Efficacy not adequately assessed beyond 12 weeks in bipolar disorder

Antipsychotics, lithium, antidepressants and anticonvulsants all have a place in treating bipolar disorder.⁶⁻⁸ Asenapine is efficacious in acute mania and mixed episodes of bipolar I disorder, but has not been adequately assessed beyond 12 weeks.³ While guidelines recommend several antipsychotics as first-line options for acute mania, olanzapine, quetiapine or risperidone depot injection are the only ones with data showing effectiveness at preventing relapse of mania or depression over 1 year.⁶⁻⁸ Asenapine has not been evaluated in bipolar depression. Bipolar disorder indications and PBS listings for newer antipsychotics are listed in Table 1.



EVIDENCE SNAPSHOT

WHAT IS KNOWN ABOUT THIS DRUG

Asenapine has a similar spectrum of benefits and harms to that of other antipsychotics. Trial data demonstrate efficacy up to 52 weeks in schizophrenia and 12 weeks in bipolar mania and mixed episodes.

In one 52-week schizophrenia and schizoaffective disorder trial, olanzapine reduced PANSS symptom scores slightly more than asenapine (-27.5 vs -21.0, $p < 0.0001$). More people who received asenapine had treatment-related extrapyramidal symptoms (14% vs 7%), but fewer had treatment-related weight gain of $\geq 7\%$ of baseline (12% vs 29%).

AREAS OF UNCERTAINTY

Asenapine has not been adequately assessed for efficacy in bipolar disorder beyond 12 weeks, and has not been evaluated for bipolar depression or treatment-resistant schizophrenia. There are limited data comparing asenapine with other antipsychotics in either bipolar disorder or schizophrenia.

Knowledge about dose response is limited in both schizophrenia and bipolar disorder. There are limited safety data beyond one year, and rare adverse effects have not been well characterised.

WHAT DOES NPS SAY?

Asenapine wafers may be useful in schizophrenia or bipolar disorder when established antipsychotics are relatively contraindicated. Asenapine may cause less QTc prolongation, antimuscarinic effects, hyperprolactinaemia, and weight gain than some other antipsychotics, but more sedation and extrapyramidal symptoms.

Consider antipsychotics with more extensive clinical data before asenapine in schizophrenia; in bipolar disorder, olanzapine, quetiapine and risperidone depot injection have more extensive evidence for relapse prevention. Clozapine is the first choice for treatment-resistant schizophrenia.

Table 1.
Indications and PBS listings for atypical antipsychotic drugs in bipolar I disorder

Drug	PBS listing [†]	
	Acute mania (up to 6 months)	Maintenance
Aripiprazole (Abilify)	No (P)	No (P)
Asenapine (Saphris)	Yes*	Yes (monotherapy only)
Olanzapine (Zyprexa, Zyprexa Zydis)	No (P)	Yes
Olanzapine injection (Zyprexa IM)	No (P)	No
Quetiapine (Seroquel) and Quetiapine extended release (Seroquel XR)	Yes (monotherapy only)	Yes
Risperidone (Ozidal, Resdone, Rispa, Risperdal, Risperdal Quicklet, Rixadone)	Yes (adjunct only)	No
Risperidone depot injection (Risperdal Consta)	No	Yes (adjunct only; treatment-refractory cases)
Ziprasidone (Zeldox)	Yes* (monotherapy only)	No

* Acute mania and mixed episodes

[†] (P) – TGA approved indication available on private prescription only

Asenapine may be useful when other antipsychotics are relatively contraindicated

The choice of antipsychotic should be guided by patient risk factors, history and preferences. As with any antipsychotic, asenapine's specific adverse-effect profile may suit particular patients [see More extrapyramidal symptoms (EPS) than olanzapine but less weight gain]. However, there are limited data to inform these decisions — there have been direct comparisons of asenapine with olanzapine, risperidone or haloperidol, but none with aripiprazole, amisulpride, quetiapine, or ziprasidone.^{1,5}

How does it compare?

Less efficacious than olanzapine in a 52-week trial for schizophrenia and schizoaffective disorder

At 52 weeks, olanzapine reduced the Positive and Negative Syndrome Scale (PANSS) total score* more than asenapine (-27.5 vs -21.0, $p < 0.0001$). A difference of 6 points on the PANSS scale would not be clinically significant for an individual; however, among participants who completed the trial, 66% of those taking olanzapine were rated as much or very much improved, compared with 52% of those taking asenapine. Furthermore, 14% (45/312) of participants receiving olanzapine and 25% (228/913) receiving asenapine discontinued treatment because of a lack of response.⁹

People with a history of non-response or intolerable side effects with olanzapine were excluded from this trial, and this group may do relatively better with asenapine. People with schizoaffective disorder made up 13% of the trial participants. Asenapine may be less effective in schizoaffective disorder and is not registered for this indication.⁹

Efficacy relative to olanzapine in bipolar mania and mixed episodes is uncertain

Asenapine was efficacious and significantly reduced mania symptoms in a 12-week trial.^{† 1,11} At week 12, the difference in Young Mania Rating Scale (YMRS) score‡ between asenapine and olanzapine was not statistically significant in a post hoc analysis

(mixed model for repeated measures estimated difference in YMRS score 0.6, 95% confidence interval -1.3 to 2.5).^{1,11-13} According to European regulators, non-inferiority to olanzapine could not be concluded.¹

Asenapine was efficacious as an adjunct to lithium or valproate in a 12-week trial involving participants with an acute manic or mixed episode that had not completely responded to lithium or valproate alone. At 12 weeks, asenapine reduced the YMRS more than placebo (-12.7 vs -9.3, $p = 0.0073$). Response rates were 25% (39/155) for asenapine and 20% (33/163) for placebo (intention-to-treat population).^{1,5}

More extrapyramidal symptoms (EPS) than olanzapine but less weight gain

In the 52-week schizophrenia and schizoaffective disorder trial, rates of treatment-related adverse events were similar for asenapine (548/908, 60%) and olanzapine (190/311, 61%), as were the rates of discontinuation because of adverse events not related to worsening of disease or inadequate response to treatment (6% vs 7%). However, rates of treatment-related serious adverse events were higher for asenapine (6% vs 2%).⁹

Rates of treatment-related extrapyramidal symptoms (mostly akathisia) were higher with asenapine (14% vs 7%), while rates of weight gain ($\geq 7\%$ of baseline) were lower (12% vs 29%), and rates of sedation were similar (8% vs 10%). Rates of discontinuation due to extrapyramidal symptoms were similar (1% vs 1%). Adverse event rates were not compared statistically, with the exception of a post hoc analysis that found that weight gain was less with asenapine than with olanzapine ($p < 0.0001$).⁹

In pooled short- and long-term safety data, asenapine increased prolactin levels less often than olanzapine or risperidone. Asenapine caused a higher incidence of extrapyramidal symptoms than olanzapine or risperidone, but a lower incidence than haloperidol. The incidence of weight increase by $\geq 7\%$ was less than that of olanzapine and similar to that of haloperidol. The statistical significance of these comparisons was not reported.⁵

* A commonly used schizophrenia symptom rating scale in clinical trials. PANSS scores range from 30 to 210, with higher scores for worse symptoms.¹⁰

† The trial was conducted as two identical 3-week trials and a single 9-week continuation trial.

‡ A commonly used rating scale for mania symptoms in bipolar disorder clinical trials. Scores range from 0 to 60, with higher scores for worse symptoms.¹⁴

Safety issues

Asenapine causes the typical range of antipsychotic adverse effects, including sedation and dose-dependent extrapyramidal symptoms (see More extrapyramidal symptoms (EPS) than olanzapine but less weight gain).³ It caused small increases in QTc interval in a dedicated QT study, but not increased rates of clinically relevant QT prolongation in clinical trials. It may cause orthostatic hypotension in some people, particularly early in treatment, and there have been cases of neuroleptic malignant syndrome.³

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online (www.ebs.tga.gov.au) or by using the 'Blue Card' distributed three times a year with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

Not recommended in pregnancy or during breastfeeding

Asenapine is an Australian pregnancy category C drug. It should be used in pregnancy only if the anticipated benefits outweigh the risks. As a class, antipsychotics are associated with neurological disturbances or withdrawal symptoms in neonates exposed during the third trimester of pregnancy.³

Women receiving asenapine should avoid breastfeeding, as it is not known whether the drug or its metabolites are excreted in human milk.³

Effects on the cardiovascular system

Consider the risk of QT prolongation for people with known cardiovascular disease, a family history of QT prolongation or who are also using other medicines that prolong the QT interval. In a dedicated QT study, asenapine caused a small increase in QTc interval that was considered unlikely to be of clinical relevance under ordinary circumstances.^{4,15} Clinically relevant QT prolongation (i.e. ≥ 500 milliseconds) has not been observed at increased rates in clinical trials.³ The European regulator concluded that asenapine seemed to be benign in terms of QT prolongation, which is an advantage over sertindole and ziprasidone.¹

Asenapine may cause orthostatic hypotension, dizziness and fainting, especially early in treatment. People at particular risk include elderly patients and people with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions that contribute to hypotension (dehydration, hypovolaemia or use of antihypertensives).³

Monitor effect on weight and metabolic parameters

Monitor weight at the start of treatment, regularly for the first 3 months and once to twice yearly thereafter. Consider a change in antipsychotic for people whose weight increases in the first 3 months of treatment.⁶ In trials, the incidence of weight increase by $\geq 7\%$ with asenapine was less than that for olanzapine and appeared similar to that for haloperidol [see More extrapyramidal symptoms (EPS) than olanzapine but less weight gain].

Test fasting blood glucose at the start of treatment and annually thereafter.⁶ There have been cases of hyperglycaemia or exacerbated pre-existing diabetes among people receiving asenapine. In addition, people taking asenapine in trials experienced a small increase in fasting insulin levels.³

Interacts with some SSRI antidepressants

Asenapine interacts with fluvoxamine, paroxetine and possibly fluoxetine. Consider an alternative antidepressant or coadminister these with caution. Fluvoxamine (a strong CYP1A2 inhibitor) can increase blood concentrations of asenapine, while asenapine can increase blood concentrations of paroxetine (a strong inhibitor of CYP2D6 and also a CYP2D6 substrate).³ As fluoxetine is also a strong inhibitor of CYP2D6 and a CYP2D6 substrate, an effect of asenapine on fluoxetine blood concentrations is theoretically possible.¹⁶

Hypersensitivity reactions have been reported

Counsel patients who are receiving asenapine about how to recognise the signs and symptoms of a serious allergic reaction (see Information for patients). Asenapine is contraindicated for people with a known hypersensitivity to the drug.³

* Review the product information for a complete list of known adverse effects and precautions.

Between the US approval of asenapine in August 2009 and September 2010, there were 52 cases that reported type I hypersensitivity reactions associated with asenapine. Eight cases involved hypersensitivity on initial exposure to asenapine. Reported signs and symptoms included anaphylaxis, angioedema, hypotension, tachycardia, swollen tongue, dyspnoea, wheezing, and rash.¹⁷

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing asenapine for schizophrenia on the basis of similar cost and efficacy to that of risperidone (i.e. cost minimisation). The PBAC recommended listing asenapine for bipolar I disorder on a cost-minimisation basis with quetiapine.¹⁸

The PBAC was also concerned that health professionals should be informed about the correct use of the sublingual formulation, in light of the low bioavailability if asenapine is not taken correctly.¹⁸

Dosing issues

Asenapine wafers must be taken sublingually. For schizophrenia the starting dose is asenapine 5 mg twice daily. For monotherapy in bipolar disorder, the starting dose is asenapine 10 mg twice daily, and for combination therapy with lithium or valproate the starting dose is asenapine 5 mg twice daily. The dose can be adjusted in the range 5 mg to 10 mg twice daily after clinical assessment. The safety and efficacy of doses above 10 mg twice daily have not been evaluated.³

Asenapine wafers must not be chewed or swallowed

Asenapine has low bioavailability when swallowed (it was < 2% as a tablet formulation), while the recommended sublingual route has an absolute bioavailability of about 35% for asenapine 5 mg wafers. People taking asenapine must also avoid eating or drinking for at least 10 minutes afterwards because this can reduce the amount absorbed by 10% or more. Wafers can be taken after a meal.³

Give detailed instructions about the sublingual dosing technique

Evaluate each patient's ability to follow the instructions for sublingual dosing (see Information for patients). It may be necessary to review dosing technique regularly. Inform patients that the wafers often have an anaesthetic effect on the mouth and tongue and that these symptoms usually resolve within an hour.³ In one trial, 76% of participants experienced oral paraesthesia.¹⁹

Knowledge about dose response is limited

There is no evidence that asenapine 10 mg twice daily is more effective than asenapine 5 mg twice daily for schizophrenia, but the higher dose increases the likelihood of certain adverse reactions (notably akathisia).³

Dose response in bipolar disorder is unknown because all clinical trials allowed dose adjustment. However, most participants in monotherapy trials for bipolar I disorder continued on asenapine 10 mg twice daily.¹

The safety and efficacy of doses above 10 mg twice daily has not been evaluated, and the efficacy of doses below 5 mg twice daily was not demonstrated for either condition.^{3,5}

Not recommended for people with severe liver impairment

No dose adjustment is required for people who have mild to moderate hepatic impairment (Child-Pugh A or B).⁶ On the other hand, people with severe liver impairment (Child-Pugh C) experienced a large increase in the proportion of asenapine reaching the systemic circulation. Asenapine is extensively metabolised by liver enzymes CYP1A2 and UGT1A4 (glucuronidation).³

No dose adjustment for renal impairment

Asenapine is highly bound to plasma protein, and a study in healthy volunteers found no detectable renal elimination of unmetabolised asenapine.^{3,20} The single-dose pharmacokinetics of asenapine 5 mg were similar in people with different degrees of renal impairment.³



ADDITIONAL INFORMATION

Refer to this review at www.nps.org.au for information about the Child-Pugh classification of liver disease.

Information for patients

Advise patients that:

- ▶ asenapine must be taken twice a day, once in the morning and once in the evening, e.g. after breakfast and dinner
- ▶ asenapine must be taken after all other medicines that are taken by mouth
- ▶ asenapine can cause tingling or numbing of the tongue and mouth for up to an hour after each dose.

Explain the correct way to take asenapine:

- ▶ Make sure you have dry hands.
- ▶ Peel back the coloured tab and gently remove the wafer.
- ▶ Place the wafer under your tongue and it will disintegrate by itself in a few seconds.
- ▶ Do not chew or swallow the wafer, and do not eat or drink for 10 minutes after taking the wafer — otherwise the medicine will not be absorbed completely and may not work properly.

Advise patients and carers of common adverse effects (see Safety issues) and also rare but serious adverse effects. Ask them to seek medical help if they experience:

- ▶ uncontrolled movements of the tongue, face, mouth or jaw
- ▶ a significant rise in body temperature
- ▶ stiff muscles, fast breathing, abnormal sweating or decreased mental alertness
- ▶ sudden signs of allergy such as skin rash, itching or hives, swelling of the face, lips, tongue or difficulty breathing.

Discuss the Saphris consumer medicine information (CMI) leaflet with the patient or carer. It contains detailed, illustrated instructions for taking asenapine wafers.



MEDICINE UPDATE

NPS *Medicine Update* articles on asenapine for schizophrenia and asenapine for bipolar disorder are available for consumers. *Medicine Update* helps consumers to ask the right questions about new medicines, and helps them compare the potential benefits and harms of a new medicine with those of other medicines.

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The information contained in *NPS RADAR* is derived from a critical analysis of a wide range of authoritative evidence and is current at the time of publication. Any treatment decisions based on the information provided in *NPS RADAR* should be made in the context of the clinical circumstances of each patient.

NPS RADAR articles may be updated when there is new evidence about safety or efficacy, or in case of regulatory or PBS listing changes.

Please refer to www.npsradar.org.au for the most recent version as well as any supplementary information.

Oxycodone-with-naloxone controlled-release tablets (Targin)

for chronic severe pain

(OCK-see-CODE-own with na-LOCKS-own)

An option for people with opioid-induced constipation

KEY POINTS

Provides equivalent analgesia to that of oxycodone controlled-release (CR) tablets
Clinical data are largely from people with chronic musculoskeletal pain.

The naloxone component reduces, but does not eliminate, opioid-induced constipation

In key trials, the prevalence of constipation with oxycodone-with-naloxone CR compared with oxycodone CR was about 25% lower among people with a history of constipation, and 7% lower in an unselected group.

Long-term effect on constipation is uncertain

Average constipation symptoms at 52 weeks in uncontrolled extension trials were no worse than at 12 weeks. There are no trial data beyond 52 weeks.

Can initially provoke withdrawal symptoms or diarrhoea in people who are opioid tolerant

However, in key trials the incidence of withdrawal symptoms was low and similar to that for oxycodone CR tablets.

Contraindicated in moderate or severe hepatic impairment

Reduce the dose for people with mild hepatic impairment or creatinine clearance < 60 mL/min.

No evidence regarding potential for problematic or illicit use

The naloxone component may deter injected or intranasal use, but this has not been tested.

PBS listing


Restricted benefit

Chronic, severe disabling pain not responding to non-opioid analgesics.

Authorities for increased maximum quantities will be available for patients meeting the criteria listed in the note in the Schedule of Pharmaceutical Benefits.¹

Oxycodone is a Controlled Drug (Schedule 8) and so must be prescribed in accordance with State or Territory regulations (see www.tga.gov.au/industry/scheduling-st-contacts.htm).

May be prescribed by nurse practitioners (shared care model)

Authorised nurse practitioners may prescribe this medicine as part of a formal care plan with a medical practitioner. See the PBS website  for more information on nurse practitioner PBS prescribing.



ADDITIONAL INFORMATION

www.pbs.gov.au/info/healthpro/explanatory-notes/section1/nurse-practitioner

What is it?

Oxycodone-with-naloxone controlled-release (CR) tablets (Targin) contain a combination of a strong opioid and an opioid antagonist in a controlled-release formulation. The tablets are bioequivalent to oxycodone CR (OxyContin) with regard to their oxycodone content and provide the same duration of action (i.e. approximately 12 hours). The available strengths are oxycodone/naloxone: 5 mg/2.5 mg, 10 mg/5 mg, 20 mg/10 mg and 40 mg/20 mg.

Injected naloxone has long been used to reverse systemic opioid effects, whereas oral naloxone is unsuited for this purpose because it undergoes extensive first-pass metabolism and has low systemic bioavailability. The controlled-release tablets deliver a naloxone dose that blocks opioid receptors in the gut, but not elsewhere (e.g. central nervous system), and therefore reduces gastrointestinal effects with a minimal effect on analgesia.²

Who is it for?

Oxycodone-with-naloxone CR tablets are indicated for severe chronic cancer or non-cancer pain unresponsive to non-opioid analgesia.* The naloxone component reduces opioid-induced constipation.^{1,2} Oxycodone, as with all strong opioids, should be offered to people with chronic non-cancer pain only when:

- ▶ non-opioid methods of analgesia have been tried and failed
- ▶ pain has a significant effect on the patient's quality of life
- ▶ there is no psychological contraindication, drug-seeking behaviour or history of drug or alcohol misuse
- ▶ prescribing is part of an agreed pain management plan that includes non-drug measures.^{2,3}

See *NPS Prescribing Practice Review 51* for information about developing a pain management plan.

Oxycodone-with-naloxone CR tablets are not indicated for acute pain.

Where does it fit?

An option for people with opioid-induced constipation

Oxycodone-with-naloxone CR tablets cause less constipation than conventional oxycodone CR tablets, but not all patients will benefit (see Less constipation than with oxycodone CR tablets). Switching from low-to-medium doses of oxycodone CR tablets to the fixed-dose combination tablets appears useful for people who suffer from constipation despite an adequate laxative regimen.

For palliative care patients experiencing opioid-induced constipation, adding methylnaltrexone (Relistor) to the existing opioid regimen is an option if laxatives fail (see the March 2010 *NPS RADAR* review 'Methylnaltrexone injection (Relistor) for opioid-induced constipation in palliative care').

Among people *without* established opioid-induced constipation, a smaller proportion benefit (see Small benefit among people who do not already have opioid-induced constipation).

Laxatives may be required

As for oxycodone alone, advise people starting oxycodone-with-naloxone CR tablets to increase their fluid and fibre intake and exercise levels to reduce the risk of constipation. Recommend or prescribe regular laxatives as necessary (i.e. combined stool softener with stimulant laxative, such as docusate with senna [Coloxyl with Senna; Soflax], or an osmotic laxative, namely, sorbitol or lactulose).^{4,5}

In trials, people taking oxycodone-with-naloxone CR tablets used laxatives only on demand, and 27–49% experienced some degree of constipation (see Less constipation than with oxycodone CR tablets).

Limited usefulness for people who need high doses of opioids

The maximum recommended daily dose of oxycodone-with-naloxone CR tablets is oxycodone 80 mg/naloxone 40 mg; higher doses have not been evaluated. People requiring a daily dose totalling more than oxycodone 80 mg can take additional oxycodone CR tablets 12 hourly, but a beneficial effect on constipation may be lessened.²

* The tablets are also indicated but not PBS listed for moderate pain unresponsive to non-opioid analgesia.



ADDITIONAL INFORMATION

Refer to this review at www.nps.org.au for an assessment of oxycodone-with-naloxone CR tablets using a checklist of questions about fixed-dose combination preparations.



EVIDENCE SNAPSHOT

WHAT IS KNOWN ABOUT THIS DRUG

Oxycodone-with-naloxone controlled-release (CR) tablets provide equivalent analgesia to that of oxycodone CR tablets of the same oxycodone dose, with a similar adverse-effect profile.

Adding the naloxone component reduces, but does not eliminate, the prevalence of constipation. Compared with oxycodone CR, the number needed to treat (NNT) (for one person using opioids continuously to avoid constipation) was about 4 for people with existing opioid-induced constipation (after 4 weeks), and about 14 for people not selected for constipation symptoms (after 12 weeks).

AREAS OF UNCERTAINTY

Efficacy data regarding analgesia and constipation are from 12-week randomised controlled trials. Longer-term data (up to 52 weeks) are from uncontrolled trials. The tablets have not been compared with a regimen of oxycodone and prophylactic laxatives.

There are insufficient data from randomised controlled trials to characterise rare adverse events.

WHAT DOES NPS SAY?

Switching to the fixed-dose combination tablets may benefit people who experience constipation while taking low to medium doses of oxycodone long term. Everyone taking regular opioids should increase their fluid and fibre intake and exercise levels to reduce the risk of opioid-induced constipation.

Among people without existing constipation, a small proportion will experience a benefit over oxycodone alone.

Long-term efficacy data regarding effect on constipation are lacking

There are no comparative data to demonstrate that oxycodone-with-naloxone CR tablets continue to prevent constipation for longer than 12 weeks, the length of the three key randomised controlled trials. However, average patient-reported constipation symptoms did not worsen over 52 weeks in open-label uncontrolled extension trials.⁶

Naloxone may deter intranasal or injected use

Oxycodone-with-naloxone CR tablets contain a dose of naloxone that will antagonise the acute central nervous system effect of oxycodone if used intranasally or injected. In theory, this will reduce the pleasurable effects and provoke unpleasant withdrawal symptoms for people who are opioid tolerant. The tablets may therefore be less appealing for unsanctioned (problematic or illicit) administration, but there is currently no direct evidence to confirm this. The tablets do not deter unsanctioned oral use.

As with other oxycodone preparations, oxycodone-with-naloxone CR tablets are not recommended for treating opioid withdrawal, and should be prescribed with caution and under close supervision for people who are known or suspected to misuse prescription medicines, alcohol or other substances.²

How does it compare?

Similar analgesia to that of oxycodone CR tablets

A pooled analysis of two 12-week randomised controlled trials found that oxycodone-with-naloxone CR tablets provided analgesia that was no worse than that of conventional oxycodone CR tablets. Participants in the trials had chronic, non-cancer pain, mostly of musculoskeletal origin (e.g. osteoarthritis), and the average age was 58 years. The average difference in pain intensity score at 12 weeks was -0.01 (95% CI -0.15 to 0.13) on a pain scale from 0 to 10. There was no statistically significant difference in the amount of supplemental oxycodone used, and average daily oxycodone doses were similar in the two groups.^{7,8}

Efficacy compared with prophylactic laxatives is not known

None of the clinical trials of oxycodone-with-naloxone CR tablets compared them with the combination of oxycodone or another strong opioid and a prophylactic laxative. Prophylactic laxative use is the standard of care when strong opioids are used regularly in chronic pain.^{4,9}

Less constipation than with oxycodone CR tablets

In three comparative trials, oxycodone-with-naloxone CR tablets caused less constipation than oxycodone CR tablets, after 4 weeks and 12 weeks of therapy.¹⁰⁻¹² Constipation was measured using the Bowel Function Index (BFI).*

As a secondary outcome, all three trials reported the number of participants with fewer than three complete spontaneous bowel movements per week, a common definition for constipation (see Table 1). Using these results it is possible to estimate for each trial the proportion of patients who avoided constipation by using oxycodone-with-naloxone CR tablets rather than oxycodone CR tablets (responder data are not available for BFI).

Small benefit among people who do not already have opioid-induced constipation

One of the three key trials of oxycodone-with-naloxone CR tablets did not actively select participants with pre-existing opioid-induced constipation. In this trial, 80% of participants

had no or mild constipation at randomisation (i.e. a BFI < 50), despite using an opioid analgesic for 2 or more weeks before enrolling in the study.¹²

In this population, there was a 7-percentage-point difference in constipation rates after 12 weeks of treatment between participants receiving oxycodone-with-naloxone CR tablets and participants receiving oxycodone CR tablets (see Table 1). People receiving oxycodone-with-naloxone CR tablets used laxatives on 7.9% of days, while people receiving oxycodone CR tablets used them on 10.4% of days (statistical significance of comparison not reported).^{7,12}

There are few reliable data regarding the typical incidence of opioid-induced constipation, but the median rate of constipation was 30% in a meta-analysis of opioids for chronic non-cancer pain in older adults.¹³

No comparison with methylnaltrexone in palliative care population

Methylnaltrexone is an option for treating opioid-induced constipation in people receiving palliative care who have not responded to adequately titrated laxatives [see the NPS RADAR review 'Methylnaltrexone injection (Relistor) for opioid-induced constipation in palliative care']. A reduction in constipation with oxycodone-with-naloxone CR tablets has been demonstrated with a mean daily oxycodone dose of up to about 70 mg^{7,10-12}; patients with cancer pain or in palliative care may require higher oxycodone doses.

* The Bowel Function Index (BFI) is a patient-assessed score on a scale of 0 to 100 (0 = no symptoms). As well as frequency of bowel movements, the BFI incorporates other constipation-related symptoms such as straining and bloating. It was accepted by regulators as an outcome measure in oxycodone-with-naloxone trials but has not been used by other investigators.

Table 1. Proportion of trial participants with fewer than three complete spontaneous bowel movements per week

Trial	Oxycodone-with-naloxone CR	Oxycodone CR
Patients with existing opioid-induced constipation (OIC)*		
OXN3001 ^{† 11}	35% (50/144)	61% (83/137)
OXN3006 ^{† 10}	49% (64/130)	74% (100/135)
Patients not selected for existing OIC		
OXN3401 ^{‡ 7,12}	27% (41/154)	34% (51/151)

* All trial participants had fewer than three complete spontaneous bowel movements per week at recruitment.

† After 4 weeks of double-blind therapy

‡ After 12 weeks of double-blind therapy. Bowel function variables were secondary outcomes in this study.

Safety issues

Oxycodone-with-naloxone CR tablets appear to have a similar safety profile to that of oxycodone CR tablets; however, there are insufficient data from randomised controlled trials to characterise rare adverse events.

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online (www.ebs.tga.gov.au) or by using the 'Blue Card' distributed three times a year with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

Diarrhoea may occur

In the three key trials, the incidence of diarrhoea was about 5% with either oxycodone-with-naloxone CR tablets or with oxycodone CR tablets. When switching from long-term higher-dose opioid treatment to oxycodone-with-naloxone CR tablets, people may initially experience diarrhoea.²

Contraindicated in moderate or severe hepatic impairment

People with hepatic impairment experience higher systemic exposure to naloxone, which can antagonise the central nervous system effects of oxycodone.² This could result in reduced analgesia, and opioid withdrawal symptoms in people who are opioid tolerant.

If prescribing to people with renal impairment or mild hepatic impairment, titrate the dose cautiously and monitor carefully. As with conventional oxycodone CR tablets, renal or hepatic impairment may increase oxycodone plasma concentrations (see Reduce the dose for people with mild hepatic impairment or creatinine clearance < 60 mL/min). Do not prescribe in moderate or severe hepatic impairment.²

Low incidence of withdrawal symptoms in trials

People receiving long-term higher-dose opioid treatment can initially experience opioid withdrawal symptoms when switching to oxycodone-with-naloxone CR tablets.² In key trials the incidence of withdrawal symptoms was low and similar for oxycodone-with-naloxone CR tablets and oxycodone CR tablets.⁷

Few data about rare adverse events

Naloxone has been used as a parenteral opioid antagonist for several decades, and appears to cause few adverse effects except for those associated with acute opioid withdrawal.⁴

There is less experience with long-term oral use of naloxone and insufficient data from randomised controlled trials to characterise rare adverse events with oxycodone-with-naloxone CR tablets. However, oxycodone-with-naloxone CR tablets were first registered in Germany in 2006, and the Australian TGA-approved product information lists adverse events from European postmarketing data.⁷

Reason for PBS listing

In July 2010, the Pharmaceutical Benefits Advisory Committee (PBAC) rejected a submission requesting the PBS listing of oxycodone-with-naloxone CR tablets because of uncertain cost-effectiveness. The PBAC observed that the benefits appeared modest, especially in the population of patients who were not constipated before starting oxycodone with naloxone.¹⁴

A subsequent submission in November 2010 amended the price and also addressed uncertainties identified by the PBAC, including efficacy in the non-constipated population, the use of prophylactic laxatives, and the likely average daily dose of oxycodone. The PBAC recommended listing on the basis that the revised cost-effectiveness estimates were acceptable, relative to oxycodone CR tablets without prophylactic laxatives.

The PBAC accepted that oxycodone-with-naloxone CR tablets are efficacious in both constipated and non-constipated patients. They considered that availability of the tablets would improve the management of opioid-induced constipation, and may reduce diversion. They noted data indicating that GPs co-prescribed laxatives at a low rate for people receiving opioids, but also noted that many people purchase over-the-counter laxatives.¹⁵

Dosing issues

Initiate and dose oxycodone-with-naloxone CR tablets as for oxycodone CR tablets. People already receiving single-ingredient oral oxycodone preparations (immediate or controlled release) may switch to the combination tablets at the same total daily oxycodone dosage, equally divided into two 12-hourly doses.²

If switching from oral morphine, the Targin product information states that oxycodone 10 mg is equivalent to oral morphine 20 mg. Note that guidelines recommend starting with a lower dose than that calculated (e.g. 50% to 75% of the equianalgesic dose) then titrating to response. This is recommended to cater for differences in how people tolerate different opioids.^{2,4,9}

The tablets are registered for use by children and adolescents from 12 years of age², but oral opioids generally have a very limited role in treating chronic non-cancer pain in children.

Maximum strength is oxycodone 40 mg/ naloxone 20 mg

There is no tablet strength corresponding to existing oxycodone CR 80 mg tablets. The maximum recommended dose is one oxycodone 40 mg/naloxone 20 mg tablet 12 hourly, but supplementary oxycodone CR tablets can be added (see Limited usefulness for people who need high doses of opioids).²

Reduce the dose for people with mild hepatic impairment or creatinine clearance < 60 mL/min

For people with mild hepatic impairment or renal impairment and creatinine clearance < 60 mL/min, reduce the dose to one-third to one-half of the usual. Titrate cautiously with careful monitoring. The tablets are contraindicated in moderate or severe hepatic impairment.²

Advise people to take the tablets whole

Breaking, dissolving, chewing or crushing the tablets can lead to the rapid release of oxycodone and naloxone, and a potential overdose of oxycodone. The tablets are for oral use only.²

Information for patients

Advise patients as follows.

- ▶ Swallow the tablets whole with a full glass of water; do not chew, crush, break or dissolve the tablets.
- ▶ Take every 12 hours, with or without food.
- ▶ Do not take any other pain reliever or opioid, sleeping tablets or muscle relaxants without speaking with a doctor or pharmacist.
- ▶ Avoid drinking alcohol.
- ▶ The tablets can cause constipation, diarrhoea, nausea, vomiting, dizziness, drowsiness, headache, itching and other side effects.
- ▶ Laxatives may still be required — follow the course recommended by your doctor.
- ▶ Note carefully which of your existing medicines are being replaced by the combination tablets and return the unneeded medicines to a pharmacy.

Discuss the Targin consumer medicine information (CMI) leaflet with the patient.

Advise patients to reduce the chance of constipation by drinking water regularly throughout the day, increasing their fibre intake and keeping as mobile as they can. Consider recommending or prescribing regular laxatives (e.g. combined stool softener with stimulant laxative, such as docusate with senna [Coloxyl with Senna; Soflax]).^{4,5}

Patients switching from another opioid preparation may need to reduce their laxative intake.

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The information contained in *NPS RADAR* is derived from a critical analysis of a wide range of authoritative evidence and is current at the time of publication. Any treatment decisions based on the information provided in *NPS RADAR* should be made in the context of the clinical circumstances of each patient.

NPS RADAR articles may be updated when there is new evidence about safety or efficacy, or in case of regulatory or PBS listing changes.

Please refer to www.npsradar.org.au for the most recent version as well as any supplementary information.

A once-daily beta₂-agonist for chronic obstructive pulmonary disease

Indacaterol (Onbrez)

for chronic obstructive pulmonary disease

(IN-da-CAT-er-ol)

KEY POINTS

Once-daily dosing provides symptomatic relief in COPD

Indacaterol (Onbrez Breezhaler) once daily provides rapid-onset bronchodilation in chronic obstructive pulmonary disease (COPD) lasting over 24 hours

Indacaterol has safety and symptom relief similar to that of twice-daily long-acting beta₂-agonist bronchodilators

Indacaterol provides similar symptomatic improvement and greater improvement in lung function compared with salmeterol and eformoterol in COPD.

Indacaterol is no worse than tiotropium in safety and efficacy

Indacaterol has been demonstrated to be non-inferior in safety and efficacy (forced expiratory volume in 1 second [FEV₁] and symptom reduction) to once-daily tiotropium.

Avoid indacaterol in people with asthma

As with other inhaled long-acting beta₂-agonists, indacaterol may result in paradoxical bronchospasm; do not use to treat acute episodes of bronchospasm, acutely deteriorating COPD, or asthma.

Use with caution in people with cardiovascular disease

Use with caution in people with cardiovascular disorders and in people who are unusually responsive to beta₂-agonists.

* Definition according to The COPD-X Plan: Australian and New Zealand Guidelines for the Management of Chronic Obstructive Pulmonary Disease 2010.³

PBS listing

Restricted benefit

Indacaterol (Onbrez) is PBS listed as a Restricted Benefit for treatment of chronic obstructive pulmonary disease.¹

May be prescribed by nurse practitioners

Authorised nurse practitioners may prescribe this medicine on the PBS. See the PBS website for more information on nurse practitioner PBS prescribing.

What is it?

Indacaterol (Onbrez) is a long-acting beta₂-agonist (LABA) producing bronchodilation by stimulation of intracellular adenylyl cyclase. It has an onset of action within 5 minutes after inhalation and duration of effect consistent with once-daily dosing.²

Who is it for?

Indacaterol is for maintenance bronchodilator treatment of airflow limitation in patients with mild to severe COPD (FEV₁ between 30% and 80% of predicted).^{*} It is not indicated for people with acute exacerbations of COPD (i.e. as a rescue therapy), or in patients with acutely deteriorating COPD. Do not use in people with asthma.

Do not use indacaterol in people with asthma or acute deterioration of COPD

Beta₂-agonists, particularly at high doses, are associated with excess mortality in people with asthma. Indacaterol may cause acute exacerbation. Do not use it to treat acute episodes of bronchospasm, people with acutely deteriorating COPD or in people with mixed airways disease.



ADDITIONAL INFORMATION

www.pbs.gov.au/info/healthpro/explanatory-notes/section1/nurse-practitioner



EVIDENCE SNAPSHOT

WHAT IS KNOWN ABOUT THIS DRUG

Indacaterol is a long-acting beta₂-agonist (LABA) providing similar levels of symptom relief for people with COPD, with a similar adverse-effect profile, to that of other inhaled LABA bronchodilators.

AREAS OF UNCERTAINTY

The long-term clinical benefit of indacaterol is unknown, as there are no data beyond 52 weeks. There are no trials investigating inhaled corticosteroids as add-on therapy in people using indacaterol in COPD. The safety of indacaterol in people with asthma and mixed airways disease has not been established.

WHAT DOES NPS SAY?

Indacaterol is a LABA for once-daily use as maintenance treatment for symptomatic relief in people with mild to severe COPD (FEV₁ between 30% and 80% of predicted). It provides similar symptomatic relief of COPD to that of twice-daily LABAs or once-daily tiotropium and appears to cause a similar rate of adverse effects. It is not indicated for the initial treatment of acute exacerbations of COPD, i.e. as a rescue therapy. When starting indacaterol, continue inhaled corticosteroids if taken for COPD but do not use indacaterol with other LABAs. Indacaterol must not be used to treat asthma.

Use cautiously in cardiovascular disease

Beta₂-agonists may cause clinically important cardiovascular effects in some people. Caution is required in people with cardiovascular disease (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension)⁴ (see Safety issues).

Where does it fit?

Maintenance treatment for symptomatic relief in COPD

Current clinical management algorithms support regular use of an inhaled long-acting bronchodilator, in conjunction with short-acting 'rescue' bronchodilators (such as salbutamol, terbutaline and ipratropium) in patients with mild to severe COPD (FEV₁ between 30%

and 80% of predicted). They may also be used in combination with inhaled corticosteroids in severe COPD (FEV₁ < 50% of predicted) if repeated exacerbations occur.^{3,5}

Indacaterol is PBS listed as a long-acting bronchodilator treatment option in COPD. Other long-acting inhaled bronchodilators for COPD include salmeterol, eformoterol and tiotropium, and fixed-dose combinations of fluticasone with salmeterol and budesonide with eformoterol (Table 1).

Do not use indacaterol for relief of acute symptoms; concomitant short-acting beta₂-agonists can be used as needed for acute relief. If repeated exacerbations occur with indacaterol, consider introducing an inhaled corticosteroid but do not use indacaterol in combination with other LABAs.⁴

Table 1.
TGA-registered
treatment options
for long-term
maintenance
in COPD

Name	Class	Dosing Interval	PBS listed for COPD
salmeterol (Serevent)	Long-acting beta ₂ -agonist	Twice daily	—
eformoterol (Foradile, Oxis)	Long-acting beta ₂ -agonist	Twice daily	—
tiotropium (Spiriva)	Long-acting muscarinic antagonist	Once daily	✓
indacaterol (Onbrez)	Long-acting beta ₂ -agonist	Once daily	✓
fluticasone–salmeterol (Seretide)	Corticosteroid + long-acting beta ₂ -agonist	Twice daily	✓*†
budesonide–eformoterol (Symbicort)	Corticosteroid + long-acting beta ₂ -agonist	Twice daily	✓**†

* 500/50 microgram strength only

** 250/25 and 400/12 microgram strengths only

† Restricted benefit if FEV₁ is < 50% predicted and repeated exacerbations despite regular beta₂-agonist bronchodilator

How does it compare?

Indacaterol has similar symptom relief to that of other LABAs

In a 26-week, double-blind randomised study, people with mild to severe COPD (n = 1002) were randomised to three treatment groups (indacaterol 150 micrograms once daily, salmeterol 50 micrograms twice daily or placebo). Spirometry was improved with indacaterol, relative to both placebo and salmeterol (both p < 0.001). Symptom relief with indacaterol was:

- ▶ improved compared with placebo (reduced St George’s Respiratory Questionnaire (SGRQ) score and improved transition dyspnoea index (TDI) at weeks 4, 8, 12 and 26, p < 0.001)
- ▶ equivalent to that with salmeterol, although the clinically relevant reduction in SGRQ (> 4 units from baseline) was greater with indacaterol than salmeterol at week 12 (p < 0.05).⁶

In a 52-week, randomised, double-blind parallel-group study, people with mild to severe COPD were randomised to receive indacaterol 300 or 600 micrograms once daily or eformoterol twice daily. Indacaterol groups had improved symptomatic outcomes compared with placebo (p < 0.001 for both dose levels). Although this

study was not primarily powered to detect significant differences between the two active treatments, indacaterol reduced use of as-needed salbutamol and enhanced peak expiratory flow (PEF) and TDI scores compared with eformoterol.⁷

Indacaterol is no worse than tiotropium

In a 26-week study, 1683 people with moderate to severe COPD were randomised to open-label tiotropium 18 micrograms or double-blind indacaterol 150 micrograms or 300 micrograms or placebo, all once daily.⁸ Symptoms, assessed by the self-reporting measures of TDI and SGRQ, were improved relative to placebo for both active treatments over 26 weeks, although the effect on exacerbations was not consistently demonstrated; time to first exacerbation was only significantly reduced for indacaterol 150 mg (hazard ratio 0.69, 95% CI 0.51 to 0.94) but not significantly reduced for indacaterol 300 mg or tiotropium.⁸

In a randomised study of 169 patients in a double-blinded, crossover clinical comparison of the effects of indacaterol 150 micrograms and 300 micrograms once daily versus tiotropium 18 micrograms once daily or matching placebo, indacaterol at both doses satisfied the statistical criterion for non-inferiority compared with tiotropium in regard to trough FEV₁ after 14 days of treatment.⁹

No head-to-head trials of indacaterol against the combination of salmeterol with fluticasone

In a meta-analysis that compared randomised controlled studies of indacaterol versus placebo (four studies) to randomised controlled studies of salmeterol-fluticasone versus placebo (five studies), comparable efficacy outcomes were reported.¹⁰ It is important to note that, in the absence of a head-to-head comparison of indacaterol and salmeterol-fluticasone in randomised controlled studies, no conclusions can be drawn about their relative efficacy.

Safety issues

The most commonly reported adverse effects in a 26-week safety population were generally events that would be expected in people with COPD, and effects that would be anticipated with a beta₂-agonist.¹¹

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online (www.ebs.tga.gov.au) or by using the 'Blue Card' distributed three times a year with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

Similar adverse effects to those of other LABAs

The most frequent treatment-related systemic adverse effects included atrial fibrillation, ventricular tachycardia, and muscle spasms, although the incidence of atrial fibrillation and cardiac arrhythmias was uncommon with no dose response seen.¹¹

In a randomised placebo-controlled study over 1 year, class-related adverse effects of beta₂-agonists (hyperglycaemia, hypokalaemia, prolonged QTc interval) occurred no more frequently with indacaterol than in placebo control or eformoterol twice-daily comparator groups.⁷

In a post hoc analysis of pooled data from three randomised controlled studies of indacaterol 150 micrograms and 300 micrograms over 6 months, there was no increase in cardiovascular

or cerebrovascular events or QT interval changes, and no relevant effect of indacaterol on development of arrhythmias.¹²

Caution is required in people with cardiovascular disease

Beta₂-agonist bronchodilators can cause cardiovascular effects such as increases in pulse rate, blood pressure, and cardiovascular symptoms (such as chest pain).^{4,13} Caution is required in people with cardiovascular disease (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension) and if such adverse effects occur the medicine should be discontinued⁴ and alternative therapy chosen, as described in current clinical management algorithms.^{3,5}

Be aware of possibility of paradoxical bronchospasm

Paradoxical bronchospasm occurs rarely with any inhaled beta₂-agonist and may occur with indacaterol.¹⁴ If paradoxical bronchospasm occurs, stop indacaterol and choose an alternative therapy⁴, as described in current clinical management algorithms.^{3,5}

Do not use in people with asthma

LABAs, particularly at high doses, have been associated with severe asthma exacerbations and deaths in people who use these drugs to treat asthma.¹⁵ The safety and efficacy of indacaterol in asthma has not been established; exclude asthma or mixed airways disease before initiating indacaterol treatment.⁴ Do not use indacaterol in people with acutely deteriorating COPD, or to relieve acute symptoms of COPD.⁴

Interactions with other medicines

As with other beta₂-agonists, indacaterol may potentiate the effects of drugs known to prolong the QT interval. Concomitant administration of other sympathomimetic agents may potentiate the systemic beta₂-adrenergic effects of indacaterol. Avoid using methylxanthine derivatives (such as theophylline), steroids or non-potassium-sparing diuretics with indacaterol; they may potentiate the possible hypokalaemic effect.⁴ Do not use indacaterol in people who are using beta₂-adrenergic-blocking medicines (including eye drops).⁴

Do not use in combination with other LABAs

Do not use indacaterol in conjunction with other LABAs such as salmeterol or eformoterol or with combination products that contain LABAs.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) considered that indacaterol would be used as an alternative to both tiotropium and LABAs with corticosteroid combination therapies in COPD. The PBAC also noted safety concerns if LABAs are used for asthma and recommended the addition of a note to the restriction that indacaterol is not PBS subsidised in asthma, to minimise its use for this indication.^{1,16} Indacaterol (Onbrez) is PBS listed as a Restricted Benefit for the treatment of chronic obstructive pulmonary disease on a cost-minimisation basis compared with fluticasone in combination with salmeterol. The equi-effective doses were considered to be indacaterol 150 micrograms daily, fluticasone with salmeterol 250/25 micrograms, two puffs twice daily and tiotropium 18 micrograms daily.¹

Dosing issues

The recommended adult dosage of indacaterol is one 150 microgram capsule inhaled once daily. In some people one 300 microgram capsule inhaled once daily may provide additional clinical benefit. The maximum dose is 300 micrograms once daily. People who are being treated with long-term inhaled corticosteroid therapy should continue this therapy when starting indacaterol but should not use indacaterol in combination with other LABAs.⁴

Do not use indacaterol in people under 18 years of age or in people with asthma, mixed airways disease or with rapidly deteriorating COPD.⁴

Instruct patients in the proper use of the inhaler device.

For more information on managing chronic obstructive pulmonary disease, refer to *NPS Case study 63 report*.

No dose adjustment required in renal impairment or in mild to moderate hepatic impairment

Due to its low renal excretion, no dose adjustment is required in people with renal impairment.⁴ No dose adjustments are required in people with mild to moderate hepatic insufficiency.⁴ There are no data on people with severe hepatic impairment.

Information for patients

Provide patients and carers with the following information about indacaterol.

- ▶ You may cough immediately after using the indacaterol inhaler; this should only last for a short time.
- ▶ Do not swallow the capsules, use the inhalation device.
- ▶ Do not use this medicine more than once each day.
- ▶ Use this medicine every day even if you feel well.
- ▶ Talk to your healthcare professional if you think or feel that indacaterol is not working as well as it should.
- ▶ Tell your healthcare professional about any other medicines you are currently using before taking this medicine.
- ▶ If you start on any new medicine, remind your healthcare professional that you are using this medicine.
- ▶ Tell your healthcare professional as soon as possible if you do not feel well while you are using indacaterol.

Discuss the Onbrez consumer medicine information (CMI) leaflet with the patient.

Search for CMI at www.nps.org.au/search_by_medicine_name



MEDICINE UPDATE

An NPS *Medicine Update* article on indacaterol is available for consumers. *Medicine Update* helps consumers to ask the right questions about new medicines, and helps them compare the potential benefits and harms of a new medicine with those of other medicines.

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Please refer to www.npsradar.org.au for the most recent version as well as any supplementary information.

Another oral
antiplatelet

Ticagrelor (Brilinta)

for acute coronary syndrome

(*tie-CAG-re-lor*)

KEY POINTS

Ticagrelor is an oral antiplatelet drug

It binds to the P2Y₁₂ adenosine diphosphate receptor to reduce platelet activation and aggregation.

Ticagrelor must be prescribed with aspirin

Prescribe aspirin at a dose between 75 and 150 mg/day. At higher aspirin doses ticagrelor may not be more effective than clopidogrel.

Ticagrelor and aspirin reduces the incidence of vascular deaths and myocardial infarctions more than clopidogrel and aspirin

However, there was a non-significantly greater number of strokes and intracranial bleeds among people taking ticagrelor and aspirin compared with those taking clopidogrel and aspirin.

Some adverse events are more common than with clopidogrel

Discontinuations, minor bleeding requiring medical intervention, non-coronary artery bypass graft (CABG) bleeding, dyspnoea and ventricular pauses are significantly higher among people taking ticagrelor and aspirin rather than clopidogrel and aspirin.

Safety and efficacy after 12 months has not been studied

The optimal duration of therapy is unknown. The median exposure to ticagrelor in the PLATO study was 276 days.

Ticagrelor must be taken twice daily

Unlike clopidogrel and prasugrel which are taken once daily.

PBS listing

Ticagrelor is approved by the Therapeutic Goods Administration (TGA) for the treatment of acute coronary syndrome (myocardial infarction [MI] or unstable angina) in combination with aspirin. In July 2011 the Pharmaceutical Benefits Advisory Committee (PBAC) gave a positive recommendation for the PBS listing of ticagrelor for the treatment of acute coronary syndrome (MI or unstable angina) in combination with aspirin.^{1,2}



EVIDENCE SNAPSHOT

WHAT IS KNOWN ABOUT THIS DRUG

In acute coronary syndrome, the combination of ticagrelor and aspirin reduced the incidence of vascular deaths and myocardial infarctions more than clopidogrel and aspirin. It did not lower the risk of stroke compared with clopidogrel and aspirin.

Some adverse events appear to be more common among people taking ticagrelor and aspirin rather than clopidogrel and aspirin. Bleeding (non-CABG bleeding, minor bleeding requiring medical intervention and fatal intracranial bleeds), dyspnoea, ventricular pauses and raised serum uric acid and serum creatinine are all significantly more common among people taking ticagrelor and aspirin. Discontinuations due to adverse effects were significantly higher among people taking ticagrelor and aspirin instead of clopidogrel and aspirin.

AREAS OF UNCERTAINTY

The safety and efficacy of ticagrelor and aspirin after 12 months have not been studied. There have been no head-to-head trials against prasugrel.

WHAT DOES NPS SAY?

The combination of ticagrelor and aspirin reduces the incidence of vascular deaths and myocardial infarctions more than clopidogrel and aspirin. This must be weighed against an increased risk of adverse events. Clopidogrel and aspirin may be a better option for people at high risk of bleeding or at increased risk of dyspnoea or bradycardia.

What is it?

Ticagrelor is another oral antiplatelet drug. Like clopidogrel and prasugrel it inhibits platelet aggregation by blocking the platelet P2Y₁₂ adenosine diphosphate receptor. But unlike prasugrel and clopidogrel, ticagrelor binds reversibly, so its inhibitory effect on platelet aggregation is more quickly reversed. The inhibitory effects of ticagrelor 3 days after discontinuation are similar to those seen 5 days after stopping clopidogrel.^{3,4}

Clopidogrel and prasugrel are prodrugs, whereas ticagrelor does not need to be metabolised to become biologically active.

Who is it for?

Ticagrelor — in combination with aspirin — is for the treatment of acute coronary syndrome (MI or unstable angina).

It should not be used in people with a history of intracranial haemorrhage, moderate to severe hepatic impairment or in people using strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin).⁵

Use with caution in people with:

- ▶ an increased risk of bleeding
- ▶ a history of dyspnoea or bradycardia
- ▶ asthma, chronic obstructive pulmonary disease or heart failure (see Safety issues).

* The combination of prasugrel and aspirin is only PBS listed for treatment of an acute coronary syndrome managed by percutaneous coronary intervention.

† Includes people who have chest pain at rest or repetitive or prolonged pain in addition to changes on their electrocardiogram or elevated troponin levels.

‡ In the PLATO study, individual endpoints were organised hierarchically then tested sequentially until the first non-significant endpoint difference was observed. At this point formal statistical testing stopped and any further tests were only exploratory. The endpoint of stroke was tested before all-cause mortality. Because stroke was non-significant the all-cause mortality result is only exploratory.

Where does it fit?

Ticagrelor in combination with aspirin is an alternative to clopidogrel and aspirin or prasugrel and aspirin* in people with an acute coronary syndrome (MI or unstable angina).

ST-segment-elevation myocardial infarction (STEMI)

Current Australian guidelines recommend treatment with aspirin and clopidogrel for up to 12 months after an ST-segment-elevation MI. The newer antiplatelet therapies, ticagrelor and prasugrel, can be considered if the patient is undergoing percutaneous coronary intervention (PCI) and is at high risk of another ischaemic event (e.g. people with diabetes, stent thrombosis) although the risk of bleeding needs to be carefully assessed.⁶

Non-ST-segment-elevation acute coronary syndromes (NSTEMACS)

Current Australian guidelines recommend people with high-risk NSTEMACS[†] and at low risk of bleeding be treated with prasugrel or ticagrelor. People with high-risk NSTEMACS[†] who are also at high risk of bleeding should be treated with clopidogrel.⁶

How does it compare?

The pivotal study on ticagrelor (the PLATO study; n = 18,624) enrolled people hospitalised for an acute coronary syndrome (STEMI or NSTEMACS) whose symptoms had begun within the previous 24 hours.

At 12 months, ticagrelor in combination with aspirin lowered the incidence of a composite outcome of death from vascular causes, MI or stroke compared with the combination of clopidogrel and aspirin (Table 1). Ticagrelor and aspirin reduced the incidence of vascular deaths and MI more than clopidogrel and aspirin. However, there was a non-significant increase in the number of strokes among the group taking ticagrelor rather than clopidogrel.⁷

All-cause mortality was lower in the ticagrelor and aspirin arm than in the clopidogrel and aspirin arm of the PLATO study (4.5% vs. 5.9%, respectively).⁷ However, this can only be considered an exploratory finding.[‡]

Optimal duration of therapy is unknown

Although the product information recommends that ticagrelor therapy be continued for at least 12 months, its safety and efficacy after 12 months has not been studied. The median exposure to ticagrelor in the PLATO study was 276 days, and 34% (n = 3138) of participants in the ticagrelor arm took the drug for longer than 360 days.^{4,7} About half of the participants in the ticagrelor arm took the drug for less than 9 months.⁴ Reassess the risks and benefits of treatment if considering continuing ticagrelor after 12 months.

At high aspirin doses clopidogrel may be more effective than ticagrelor

The PLATO protocol specified an aspirin dose of 75–100 mg daily. However, if a patient received a stent the dose could be increased up to 325 mg daily for 6 months or less.^{8,9}

Table 1. PLATO efficacy study results at 12 months as a percentage of all randomised participants⁷

Outcome	Ticagrelor and aspirin (n = 9333)	Clopidogrel and aspirin (n = 9291)	Hazard ratio (95% CI)	Difference: ticagrelor and aspirin compared with clopidogrel and aspirin
Death from vascular causes*, MI or stroke	9.8%	11.7%	0.84 (0.77 to 0.92)	19 fewer events per 1000 people
MI	5.8%	6.9%	0.84 (0.75 to 0.95)	11 fewer events per 1000 people
Death from vascular causes*	4.0%	5.1%	0.79 (0.69 to 0.91)	11 fewer events per 1000 people
Stroke	1.5%	1.3%	1.17 (0.91 to 1.52)	Two more events per 1000 people

* Death from cardiovascular causes or cerebrovascular causes and any death without another known cause

§ Making multiple comparisons increases the likelihood of finding something by chance. As this result was one of a large number of PLATO subgroup analyses it may be a chance finding.

// Identified by platelet function testing.

In a subgroup analysis ticagrelor and aspirin was not as effective as clopidogrel and aspirin in North American participants.⁹ Most of these participants took ≥ 300 mg aspirin throughout the study.¹⁰ Post-hoc analyses suggest that clopidogrel is superior to ticagrelor when the aspirin dose is > 150 mg daily.⁴

No head-to-head trials with prasugrel

There have been no studies directly comparing ticagrelor with prasugrel.

Ticagrelor is effective in clopidogrel non-responders

In one small trial, 41 people identified as being non-responders^{||} to clopidogrel were randomised to clopidogrel or ticagrelor for 14 days. They were then immediately switched to the other medication for another 14 days of treatment. Inhibition of platelet aggregation was significantly improved when people were taking ticagrelor rather than clopidogrel.³

The effect of ticagrelor did not appear to be affected by the presence or absence of the CYP2C19 or ARCB1 polymorphisms.¹¹ These polymorphisms account for some but not all of the variability in response to clopidogrel.¹²

There is no evidence that switching people already on long-term clopidogrel therapy to ticagrelor in the absence of a new coronary event improves outcomes. Nor is there randomised evidence that altering antiplatelet therapy based on genetic tests improves clinical outcomes.^{12,13}

Safety issues

Some adverse events are more common among people taking ticagrelor and aspirin rather than clopidogrel and aspirin. Major bleeding unrelated to a CABG, minor bleeding that required medical intervention, dyspnoea, ventricular pauses and raised serum uric acid and serum creatinine levels were all significantly more common among people taking ticagrelor and aspirin. There was a small but non-significant increase in the number of intracranial bleeds among people taking ticagrelor and aspirin. However, significantly more of these intracranial bleeds were fatal in people taking ticagrelor and aspirin. Significantly more people taking ticagrelor and aspirin discontinued treatment because of adverse events or because they were no longer willing to continue treatment.⁷

The safety of ticagrelor beyond 12 months is yet to be established.

Table 2. Bleeding events at 12 months in the PLATO safety population as a percentage of all participants who received at least one dose of study drug^{4,7}

Outcome	Ticagrelor and aspirin (n = 9235)	Clopidogrel and aspirin (n = 9186)	Hazard ratio (95% CI) or p-value	Difference: ticagrelor and aspirin compared with clopidogrel and aspirin
Major* or minor bleeding [†]	16.1%	14.6%	1.11 (1.03 to 1.20)	15 more events per 1000 people
Major bleeding (primary endpoint)*	11.6%	11.2%	1.04 (0.95 to 1.13)	Four more events per 1000 people
Major bleeding unrelated to CABG	4.5%	3.8%	1.19 (1.02 to 1.38)	Seven more events per 1000 people
Minor bleeding [†]	4.8%	3.8%	p < 0.05	10 more events per 1000 people
Life-threatening or fatal bleeding	5.8%	5.8%	1.03 (0.90 to 1.16)	n/a

* Defined as fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolaemic shock or severe hypotension due to bleeding and requiring pressors or surgery, significantly disabling bleeding, a drop in haemoglobin levels ≥ 30 g/L, or transfusion of ≥ 2 units of red blood cells

† Any bleeding requiring medical intervention but not meeting the criteria for major bleeding

Report suspected adverse reactions to the TGA online (www.ebs.tga.gov.au) or by using the 'Blue Card' distributed three times a year with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

Increased risk of bleeding

While the overall rate of major bleeding and life-threatening or fatal bleeding (Table 2) did not differ between ticagrelor and clopidogrel in the PLATO study, more people taking ticagrelor and aspirin experienced major bleeding that was unrelated to CABG, intracranial bleeding and minor bleeding requiring medical intervention.^{4,7}

Avoid ticagrelor in certain patients at higher risk of bleeding

People at risk of bleeding were excluded from the PLATO study. Avoid using ticagrelor in these people. They include people:

- ▶ with active bleeding
- ▶ with a history of bleeds (e.g. intracranial or gastrointestinal)
- ▶ who have had major surgery in the last 30 days
- ▶ who required treatment with anticoagulants or thrombolytics
- ▶ with thrombocytopenia.^{4,5,8}

Small increase in intracranial bleeding

There were 26 cases (0.3%) of intracranial bleeding in the ticagrelor group compared with 14 cases (0.2%) in the clopidogrel group (hazard ratio [HR] 1.87, 95% confidence interval [CI] 0.98 to 3.58). In 11 of the ticagrelor patients (0.1%) this bleed was fatal compared with one fatal intracranial bleed (0.01%) in the clopidogrel group (p = 0.02).⁷

Do not use ticagrelor in people with a history of intracranial haemorrhage⁵ or in those at increased risk of intracranial haemorrhage.

There were fewer non-intracranial fatal bleeds in the ticagrelor group (0.1% vs 0.3%).⁷

Discontinuations were more common among people taking ticagrelor

In the PLATO study, significantly more people stopped taking ticagrelor than clopidogrel (23.4% vs 21.5%, respectively). Significantly more people

stopped taking ticagrelor because of adverse events (7.4% vs 6.0%) or because they were no longer willing to continue treatment (10.1% vs 9.2%).⁷

Higher rates of dyspnoea

Dyspnoea, including that leading to treatment discontinuation, is more common among people taking ticagrelor rather than clopidogrel.^{3,7,14} At 12 months in the PLATO study, 13.8% of people taking ticagrelor experienced dyspnoea compared with 7.8% of people taking clopidogrel (HR 1.84, 95% CI 1.68 to 2.02). Significantly more people taking ticagrelor discontinued treatment because of dyspnoea although absolute numbers were small (0.9% vs 0.1%, HR 6.12, 95% CI 3.41 to 11.01).⁷ Older people, people with asthma, chronic pulmonary obstructive disease or heart failure and people with a history of dyspnoea appear to be more likely to experience dyspnoea.⁴ Use ticagrelor with caution in these people.

Dyspnoea is usually mild or moderate^{5,9} and often begins within 7 days of starting treatment with ticagrelor.¹⁵ Most episodes of dyspnoea resolved during the PLATO study, but usually lasted for more than 20 days.¹⁶ Dyspnoea may persist for the duration of ticagrelor therapy.¹⁴ Significantly more people in the ticagrelor and aspirin group still had ongoing dyspnoea 30 days after the PLATO study was completed — and study medication had been discontinued — than in the clopidogrel and aspirin group (5.0% vs 3.1%; p < 0.0001).¹⁵

Increased occurrence of ventricular pauses

Ambulatory electrocardiographic monitoring was performed in a subset of participants (n = 2908) in the PLATO study. Significantly more people taking ticagrelor experienced ventricular pauses of 3 seconds or more in the first week of treatment (5.8% vs 3.6%, respectively; p = 0.01). While there was no significant difference in the incidence of ventricular pauses at 1 month, almost one-third of people had dropped out of the substudy by this time. There was no difference in the rates of symptomatic bradycardia in the ticagrelor or the clopidogrel group.^{7,17}

Avoid using ticagrelor in people who are at risk of bradycardia. People at increased risk of bradycardia were excluded from the PLATO trial.⁸

§§ In the PLATO study mild dyspnoea was defined as dyspnoea that was recognised as being present but was easily tolerated. Moderate dyspnoea was defined as that which caused discomfort sufficient to cause interference with normal activities.¹⁵

Reason for PBS recommendation

In July 2011 the PBAC gave a positive recommendation for the PBS listing of ticagrelor on the basis of acceptable cost-effectiveness compared with clopidogrel in combination with aspirin. While the PBAC considered it reasonable to describe ticagrelor in combination with aspirin as superior in effectiveness compared with clopidogrel and aspirin, it stated that the claim of comparative safety may not be reasonable.²

Dosing issues

In people who are started on ticagrelor therapy, a single loading dose of 180 mg (two tablets of 90 mg) is recommended. After that, dosing is one 90 mg tablet twice daily.⁵

Ticagrelor must be used in combination with low-dose aspirin.¹ The product information recommends aspirin 100 mg daily although this can be varied according to clinical need.⁵ Australian guidelines recommend an aspirin dose of 75–150 mg daily after an acute coronary event.⁹ At higher aspirin doses ticagrelor may not be more effective than clopidogrel.

While the antiplatelet effects of ticagrelor are more rapidly reversible, the extent of platelet aggregation 24 hours after the last dose is similar in people taking clopidogrel or ticagrelor.³ Therefore, a single missed dose may not adversely affect patient outcomes.

Ticagrelor should not be used in people with a history of intracranial haemorrhage, moderate to severe hepatic impairment or in people using strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin).⁵ Do not use it in people at increased risk of intracranial haemorrhage.

It may be necessary to reduce the antiplatelet effect before surgery. Stop ticagrelor 5 days before elective surgery.⁵

Drug interactions

CYP3A4 inhibitors may increase the risk of bleeding in patients taking ticagrelor. Do not use ticagrelor and strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin) concomitantly. Moderate CYP3A4 inhibitors (e.g. verapamil, erythromycin, fluconazole) should be used cautiously.⁵

Avoid use in people taking doses of simvastatin > 40 mg/day, as this may increase the risk of myopathy and rhabdomyolysis.⁵

Information for patients

Advise patients and carers:

- ▶ that ticagrelor must be taken twice daily
- ▶ if they miss a dose, they should take their next dose (90 mg) at the usual time. They should not take a double dose
- ▶ to take low-dose aspirin as prescribed
- ▶ to see a doctor immediately if they have any prolonged or excessive bleeding or signs of internal bleeding, such as unexplained bruising, blood in the urine or black stools
- ▶ that ticagrelor may cause shortness of breath and that they should see a doctor if they experience prolonged or worsening shortness of breath or if it prevents them from carrying out their usual activities
- ▶ not to take non-prescription medicines containing aspirin or NSAIDs, as this increases the risk of bleeds; paracetamol can be used for minor ailments
- ▶ to tell all their health professionals that they are taking ticagrelor
- ▶ that they must not stop taking ticagrelor without speaking with their doctor.

Discuss the Brilinta consumer medicine information (CMI) leaflet with the patient.

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Please refer to www.npsradar.org.au for the most recent version as well as any supplementary information.



Question answers



Answer questions

FINDING EVIDENCE — RECOGNISING HYPE

A free **online learning program** for prescribers to improve skills in assessing new medicines.

What you will learn

This case-based program, developed by *NPS: Better choices, Better health*, focuses on the key skills needed to make informed decisions about new medicines.

Finding Evidence — Recognising Hype provides access to tools and resources to quickly locate evidence-based information to respond to patients' questions about new medicines.

What the program offers

- ▶ interactive learning with case-based activities you complete in your own time
- ▶ an introduction to high quality resources and tools for evidence-based prescribing
- ▶ understanding about the limitations of new medicines
- ▶ effective ways to communicate risks and benefits to patients
- ▶ short-cuts in appraising clinical trials and understanding the evidence
- ▶ a critical look at the role of promotional materials

This activity is approved by

- ▶ RACGP QI & CPD program, 40 points (Category 1)
- ▶ ACRRM Professional Development program, 6 PDP Core points
- ▶ Pharmaceutical Society of Australia, Group 2 activity, 12 credit points (available to all registered pharmacists)
- ▶ APEC on behalf of the Royal College of Nursing, Australia, 12 x Continuing Nurse Education points



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IN BRIEF

A digest of news items about *NPS RADAR*, new drugs and changes to PBS listings

Buprenorphine with naloxone (Suboxone Sublingual Film) for opiate dependence

Buprenorphine-with-naloxone sublingual film can be prescribed on the Pharmaceutical Benefits Scheme (PBS) for opiate dependence from 1 September 2011. Its listing means that there are now three buprenorphine products subsidised for this indication (Table 1).

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing buprenorphine-with-naloxone sublingual film on a cost-minimisation basis — that is, similar efficacy and cost — compared with buprenorphine-with-naloxone sublingual tablets.¹ Treatment must be in conjunction with medical, psychological and social counselling as part of a comprehensive addiction program, and must be in accordance with State or Territory law. For contact details of State or Territory approval bodies, see Appendix 2 of the National clinical guidelines and procedure for use of buprenorphine.[†] Where State or Territory laws permit, authorised nurse practitioners may prescribe this medicine as part of a formal care plan with a medical practitioner (shared care model). See the PBS website for more information on nurse practitioner PBS prescribing.[‡]

Less potential for abuse in supervised dosing settings

The sublingual film formulation of buprenorphine with naloxone is intended to make dosing of buprenorphine easier to supervise and so deter misuse of the drug.² Effective supervision reduces the opportunity for patients to remove the dose from their mouth, which can be later misused by the patient (e.g. injected, snorted) or diverted to others (e.g. given to friends or sold on the illicit drug market).³ Buprenorphine-containing sublingual tablets take 2-10 minutes to dissolve⁴, which can make supervision of dosing difficult, particularly in pharmacies.⁵

Buprenorphine-with-naloxone sublingual films dissolve faster under the tongue than buprenorphine-with-naloxone sublingual tablets (on average 6 minutes faster for the 8 mg / 2 mg dose²). More importantly, the film rapidly adheres to the oral mucosa, making it difficult to remove.² While these characteristics should deter removal of the product, it remains to be seen whether the sublingual film has a lower rate of abuse than the combination sublingual tablet (administered whole, broken or crushed) or than methadone syrup.

[†] www.health.gov.au/internet/drugstrategy/publishing.nsf/Content/buprenorphine-guide

[‡] www.pbs.gov.au/info/healthpro/explanatory-notes/section1/nurse-practitioner

Table 1. Sublingual buprenorphine products PBS listed for opiate dependence*

	Formulation	Strengths available
Single-ingredient		
buprenorphine (Subutex)	tablet	400 micrograms 2 mg 8 mg
Combination		
buprenorphine-naloxone (Suboxone)	tablet	2 mg / 0.5 mg 8 mg / 2 mg
buprenorphine-naloxone (Suboxone Sublingual Film)	film	2 mg / 0.5 mg 8mg / 2 mg

* Listed under Section 100 (Opiate Dependence Treatment Program) with supply only through clinics and pharmacies approved by State and Territory governments.

History of buprenorphine use for opiate dependence

Buprenorphine is a partial opioid agonist with a high affinity for the μ -receptor. It reduces craving and diminishes the effects of heroin or other full opioid agonists by blocking them from binding to the μ -receptor.³

Buprenorphine is less effective than methadone syrup for retaining people on treatment, but is equally effective — in flexible doses — at suppressing heroin use.⁶

Its partial agonist activity means it has a lower overdose risk than methadone, although it can cause fatal overdose if combined with other sedatives.³

Given differences between individuals and programs, factors such as individual preference, variation in absorption, response to treatment, adverse effects and logistics of dosing should determine treatment selection.³

Buprenorphine is poorly absorbed if swallowed (10% bioavailability) and so must be administered sublingually (30–55% bioavailability) to be effective.³

Naloxone is used to discourage injection of buprenorphine.³ Naloxone is poorly absorbed sublingually and orally but if injected can reduce the agonist effects of buprenorphine and may precipitate unpleasant withdrawal symptoms in people who are opioid dependent.³

Buprenorphine sublingual tablets (Subutex) were PBS listed in 2001 but have been associated with high rates of diversion and abuse.^{7,8} Buprenorphine-with-naloxone sublingual tablets (Suboxone) were PBS listed in 2006⁹, postmarketing surveillance indicates that they are less abused than the single-ingredient tablet (see right).¹⁰⁻¹²

* Adjusted for availability of the opioid substitution therapy

An alternative to buprenorphine-with-naloxone tablets for unsupervised dosing

There are no data to suggest that the sublingual film is less likely to be abused than the combination tablets when dosing is unsupervised.

Naloxone has reduced but not eliminated buprenorphine abuse.¹⁰ Australian postmarketing surveillance from 2006 to 2009 found that a minority of people who inject drugs (either on or off treatment with opioid substitution) had recently injected buprenorphine-with-naloxone sublingual tablets.^{11,12} However, fewer had injected them than had injected buprenorphine single-ingredient tablets or methadone syrup. Overall, levels of injection for the combination tablets were lower than for the single-ingredient tablets but were about the same as for methadone syrup.^{11,12} *

Be vigilant for intravenous misuse

It is not known whether the risk of post-injection thrombosis differs between buprenorphine-with-naloxone film and buprenorphine-containing tablets.

Serious local reactions, such as tissue necrosis, thrombosis, nerve damage and limb ischaemia as well as potentially serious acute hepatitis have been reported with injection of sublingual buprenorphine tablets.^{10,13}

Possible film-specific adverse reactions

Like buprenorphine-with-naloxone tablets, the sublingual film, particularly if not dosed carefully, commonly causes withdrawal symptoms, including insomnia, abdominal pain, diarrhoea, muscle aches, anxiety, and/or sweating.¹³

Oral mucosal erythema, glossodynia, oral hypo-aesthesia, stomatitis, toothache and a coated tongue were reported in small numbers of people in an uncontrolled safety study of buprenorphine-with-naloxone film, but it is uncertain if they are related to the film formulation specifically.²

Dose adjustment may be required when switching between tablets and film

Monitor closely and assess if dosage adjustment is required when switching between the sublingual film and buprenorphine-containing tablets because some individuals may experience a difference in clinical effect.¹³ The bioavailability (C_{max} or AUC) of buprenorphine is about 20% greater for buprenorphine-with-naloxone 8 mg / 2 mg sublingual film than for the corresponding tablets; but this may not be clinically important for many patients.²

A starting dose of 6–8 mg of buprenorphine on day 1 is recommended.³ This can be given as a single dose if the patient is in moderate to severe opiate withdrawal. For patients who are in mild to moderate opiate withdrawal or transferring from methadone, the dose should be divided (e.g. 4 mg + 4 mg) with an observation period of at least 1 hour after the first dose.³

Doses should be titrated on subsequent days by increments of 2–8 mg/day until a therapeutic dose is achieved (usually between 12–24 mg/day for most patients).^{14,15} The maximum daily dose of buprenorphine is 32 mg.¹³

Starting buprenorphine-with-naloxone sublingual film

To help plan dosing, assess the following before starting buprenorphine^{3,13}:

- ▶ opioid dependency (quantity, frequency, duration)
- ▶ the time when the person last administered an opioid
- ▶ the type of opioid dependence (that is, long- or short-acting opiates)
- ▶ the likelihood of concurrent opiate use
- ▶ concurrent medical conditions
- ▶ use of other drugs, particularly benzodiazepines and alcohol.

To avoid precipitating opioid withdrawal, delay the first buprenorphine dose until early signs of withdrawal appear.

Start buprenorphine³:

- ▶ at least 6 hours, and preferably 12 hours, after last heroin use.
- ▶ at least 24 hours after last methadone dose – reduce methadone dose to lowest tolerable level before transfer (generally aim for methadone doses of < 40 mg).

If the patient has recently used methadone, treat initially with buprenorphine monotherapy rather than the naloxone-containing tablet or film, and switch to buprenorphine-with-naloxone film or tablet on the third day.³

Advice for patients

Provide patients with the following information.^{13,16}

- ▶ Place buprenorphine-with-naloxone sublingual film under the tongue and keep it there until completely dissolved (4–8 minutes on average).
- ▶ Do not swallow, chew or move the film after it is placed under the tongue, as doing any of these makes the medicine less effective.
- ▶ Do not eat or drink anything until the film is completely dissolved.
- ▶ Do not inject buprenorphine-with-naloxone sublingual film. People are likely to experience strong opioid withdrawal symptoms from naloxone if they inject the medicine while still receiving other opioids. Also, people have developed blood clots, liver problems, and infections from injecting buprenorphine-with-naloxone tablets.^{13,17}
- ▶ For people on a dose that requires more than one film:
 - place no more than two films at a time under the tongue, taking care not to overlap them.
 - wait until the first two films are completely dissolved before placing any additional ones.

- ▶ Do not use any benzodiazepines (medicines used to treat anxiety or sleeping problems) unless prescribed. People have died from respiratory failure when using benzodiazepines at the same time as buprenorphine.
- ▶ Do not take buprenorphine-with-naloxone sublingual film too close to other opioids, as it can cause withdrawal symptoms. Wait 6 hours or more after short-acting opioids (e.g. heroin, morphine, oxycodone) and wait 24 hours or more after methadone before taking buprenorphine with naloxone.
- ▶ Buprenorphine-with-naloxone sublingual film can cause drowsiness, which is made worse by drinking alcohol or taking sedatives or anti-anxiety medicines.
- ▶ Tell your doctor about all other medicines you are taking. Several medicines can change the effect of buprenorphine with naloxone, making it either less effective (e.g. some medicines for HIV) or increasing the risk of side effects (e.g. benzodiazepines, sedative antihistamines, antidepressants, antipsychotics).

What does the sublingual film look like?

Buprenorphine-with-naloxone sublingual film is a paper-thin, orange-coloured rectangular strip. The two strengths (buprenorphine with naloxone 2 mg / 0.5 mg and 8 mg / 2 mg) are identical in length and width (approximately 22 × 13 mm) but are distinguishable by a white ink imprint of the product strength on each film: 'N2' and 'N8', respectively. Each film is enclosed in a sachet, with 28 films per carton.^{2,13}

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Drugs for Alzheimer’s disease: PBS criteria no longer include referral to a specialist

As of 1 November 2011, Authority listings for the following drugs for Alzheimer’s disease have changed:

- ▶ donepezil (Aricept)
- ▶ galantamine (Reminyl, Galantyl)
- ▶ rivastigmine (Exelon, Exelon Patch)
- ▶ memantine (Ebixa, APO-Memantine, Memanxa).

Under the revised listings, diagnosis can be made either by a general practitioner in consultation with a specialist (e.g. geriatrician, psychiatrist, neurologist) or by a specialist as previously.

Authorised nurse practitioners cannot initiate donepezil, galantamine, rivastigmine, or memantine, but can continue them as part of a formal care plan with a medical practitioner (continuing therapy only model). See the PBS website for more information on nurse practitioner PBS prescribing.

The PBAC recommended this change to improve access to drug treatment for people with Alzheimer’s disease living in remote areas.¹

Drug treatments have modest effects

Drug treatments do not alter the pathology of Alzheimer’s disease.² At best, cholinesterase inhibitors (donepezil, galantamine and rivastigmine) or the *N*-methyl-*D*-aspartate antagonist (memantine) may result in a temporary and modest improvement in symptoms or delay decline in cognitive function.³

Evidence does not support prescribing these drugs for everyone with Alzheimer’s disease — none of the drug treatments is PBS listed for severe dementia, and stabilisation or slowing decline may not be an appropriate goal for people with poor quality of life.⁴

There is insufficient evidence to show that any one drug is more effective than another.⁵ Base choice of drug on⁴:

- ▶ patient comorbidities (contraindications to use)
- ▶ tolerance
- ▶ adverse-effect profile
- ▶ ease of use.

Discontinuation due to adverse events (e.g. gastrointestinal symptoms with the cholinesterase inhibitors) is common with these medicines.²

Regardless of drug treatment, individualised management involving family and carers and non-drug treatments, particularly social support, remain important for people with Alzheimer’s disease.^{2,5}

Assessing patients for drug treatment of Alzheimer’s disease

Use either the MMSE or the Standardised Mini-Mental State Examination (SMMSE) to assess a patient’s eligibility for PBS subsidy of a cholinesterase inhibitor or memantine. These 30-point scales assess cognitive function, with lower scores indicating poorer function.

The cholinesterase inhibitors are PBS listed for mild to moderate Alzheimer’s disease and can only be prescribed for people with an MMSE score of 10 or more (see Table 1).



ADDITIONAL INFORMATION

www.pbs.gov.au/info/healthpro/explanatory-notes/section1/nurse-practitioner

Table 1. PBS eligibility criteria for initiating and continuing drug treatment

Drug	MMSE score for treatment initiation*	Increase in MMSE score at 6 months for treatment continuation
Cholinesterase inhibitors (donepezil, galantamine, rivastigmine)	10–24 (inclusive)	≥ 2
	≥ 25	≥ 2 (and/or decrease in ADAS-Cog score of ≤ 4)
Memantine	10–14 (inclusive)	≥ 2

* Can also be prescribed for people who cannot register a score of ≥ 10 for reasons other than Alzheimer’s disease (e.g. learning or sensory disability). See www.pbs.gov.au for full list of these criteria.

ADAS-Cog: Alzheimer’s Disease Assessment Scale – Cognitive subscale

If a patient's MMSE score is ≥ 25 points at baseline, also assess their score using the Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog), and include both results in the authority application. For people with this mild level of cognitive impairment at baseline, improvement on either scale is sufficient to merit continued treatment at 6 months.

Memantine is PBS listed for moderately severe Alzheimer's disease and can only be prescribed for people with a MMSE score of 10–14, inclusive (see Table 1).

Assessing effectiveness of drug treatment

Not everyone with Alzheimer's disease responds to drug treatment and it is not possible to predict those who will (see *NPS News 59: Drugs used in dementia in the elderly*). Review treatment at 3–6 months, when a beneficial effect is expected.^{4,6} Consider stopping treatment in the event of poor adherence, significant adverse effects or a lack of stabilisation or improvement in symptoms.^{4–6} At 6 months, patients need to demonstrate cognitive improvement to qualify for continuing treatment (Table 1).

Effectiveness beyond one year unknown

The optimal duration of therapy for a cholinesterase inhibitor or memantine has not been established; there is limited evidence of effectiveness with any of the drugs beyond one year.⁴

Review patients regularly to determine if the benefit of treatment outweighs any adverse effects; assess cognitive function (e.g. using the MMSE or General Practitioner Assessment of Cognition test) as well as day-to-day functioning and behaviour.⁵

When should people with dementia be referred to a specialist?

Refer patients to a specialist when⁷:

- ▶ diagnosis is in doubt
- ▶ the patient is young
- ▶ the presentation is unusual
- ▶ the patient or family requests it.

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Generic losartan (Cozavan) PBS listed for hypertension

Losartan (Cozavan) 25 mg and 50 mg tablets — the first generic angiotensin II-receptor antagonist in Australia — were PBS listed on 1 December 2011 for the treatment of hypertension. The PBAC recommended listing generic losartan on a cost-minimisation basis — that is, similar efficacy and cost — compared with irbesartan.¹

In a meta-analysis of short-term trials against placebo all angiotensin II-receptor antagonists, including losartan, reduced trough blood pressure to a similar extent.² However, meta-analyses of head-to-head trials found that losartan reduced systolic blood pressure by slightly less (around 3 mmHg) than candesartan³ and telmisartan.⁴

The branded formulation of losartan (Cozaar) is only available as a 50 mg tablet on private prescription. If switching to the generic formulation ensure that the patient takes only the generic tablets and returns any remaining branded tablets to their pharmacist for safe disposal.

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Budesonide with eformoterol (Symbicort Turbuhaler) for asthma and chronic obstructive pulmonary disease

From 1 December 2011 the PBS listing of the fixed-dose combination of budesonide 400 micrograms with eformoterol 12 micrograms (400/12; Symbicort Turbuhaler) for asthma will be extended to include symptomatic treatment of moderate to severe chronic obstructive pulmonary disease (COPD).¹

Under the new listing, budesonide with eformoterol (400/12) cannot be prescribed to initiate bronchodilator therapy for COPD.

The extended listing applies to adults with forced expiratory volume in 1 second (FEV₁) ≤ 50% of predicted normal, with frequent symptoms despite long-acting bronchodilator use and/or a history of recurrent exacerbations.¹

The listing does not apply to the fixed-dose combination of budesonide-with-eformoterol 100/6 or 200/6 inhalers.

The PBAC recommended the listing on a cost minimisation basis — that is, similar efficacy and cost — compared with fluticasone 250 micrograms with salmeterol 25 micrograms. The equi-effective doses are fluticasone 500 micrograms with salmeterol 50 micrograms twice daily, and budesonide 400 micrograms with eformoterol 12 micrograms twice daily.

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Long-acting intramuscular injectable form of paliperidone (Invega Sustenna) for schizophrenia

A long-acting intramuscular injectable or depot form of paliperidone was listed on the PBS as Authority required (streamlined) on 1 December 2011^{1,2}. It is an alternative to existing long-acting antipsychotics for people with schizophrenia. A maintenance dose is given once a month.³ Paliperidone is the main active metabolite of risperidone²; refer to the product information for information about switching people from oral paliperidone, or oral or injectable risperidone, to injectable paliperidone.³

* *Paliperidone tablets have been PBS listed (Authority required [streamlined]) for schizophrenia since 1 April 2008.*

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Dabigatran (Pradaxa) safety update: assess and monitor kidney function

After evaluating international reports of bleeding, the Therapeutic Goods Administration published a Safety Advisory on 3 November 2011 regarding the risk of bleeding in people using dabigatran (Pradaxa).¹ This advisory summarises new recommendations now in place for assessing kidney function before starting this medicine and during its use.

The TGA advises that kidney function should be assessed:

- ▶ for all patients before starting dabigatran therapy
- ▶ during treatment when a decline in kidney function is suspected, for example, low blood volume, dehydration and when certain medicines which may affect kidney function are taken at the same time
- ▶ at least once a year in elderly patients (> 75 years) or in patients with moderate kidney impairment (creatinine clearance < 50 mL/min).

Patients with severe kidney impairment (creatinine clearance < 30 mL/min) should not take dabigatran.

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ERRATUM:

Note that in the August 2011 *NPS RADAR* article 'Dabigatran (Pradaxa) for stroke prevention in patients with non-valvular atrial fibrillation', a typographical error appeared in the margin note on page 6 relating to the age range criteria of who is at risk: '≤ 75' should have read '≥ 75'.



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**NPS RADAR reviews are also available in GP prescribing software
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