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Naratriptan 2.5 mg (Naramig), sumatriptan 50 mg (Imigran, Suvalan) and zolmitriptan 2.5 mg (Zomig) tablets for migraine

Summary

PBS listing	The maximum quantity has been increased from 2 to 4 tablets. The PBS listing for the triptans (naratriptan, sumatripan and zolmitriptan) is otherwise unchanged.
Reason for listing	The PBAC recommended an increase in the maximum quantity to cater more adequately for patients who have more than one migraine each month.
Place in therapy	Triptans should be reserved for patients who have had an adequate trial of a prophylactic agent and in whom other agents have failed to relieve previous attacks.
Safety issues	There has been no change in the safety considerations for triptans. Serious cardiovascular events have been associated with the triptans; it is therefore particularly important to adhere to the dosing recommendations for this class. Ensure that patients are aware of the appropriate dosing of triptans.
Dosing issues	There has been no change to the dosing recommendations for triptans.

PBS listing

The maximum quantity has been increased from 2 to 4 tablets.[1] The PBS listing for the triptans (naratriptan, sumatriptan and zolmitriptan) is otherwise unchanged:

Authority required

Migraine attacks in patients receiving, or who have failed a reasonable trial of, prophylactic medication and where attacks in the past have usually failed to respond to oral therapy with ergotamine and other appropriate agents, or in whom these agents are contraindicated.

No applications for increased maximum quantities and/or repeats will be authorised.

Reason for listing

The PBAC recommended an increase in the maximum quantity to cater more adequately for patients who have more than one migraine each month.

The previous listing of a maximum quantity of 2 tablets with 5 repeats (that is, 12 tablets in total) provided 6 months' supply for patients who treated one migraine each month with two tablets. The new listing provides a maximum quantity of 4 tablets with 5 repeats (that is, 24 tablets in total).

GlaxoSmithKline Australia Pty Ltd, who market sumatriptan (Imigran) and naratriptan (Naramig), presented evidence that a significant proportion of patients likely to receive triptans on the PBS have 4 or more attacks per month and treat each attack with 1.6 sumatriptan tablets. This information came from data collected about patients entering the sumatriptan Special Access Scheme conducted between 1991 and 1993.[2] Other supporting evidence for a higher average frequency of migraine came from a random telephone survey of 1022 people to estimate migraine prevalence in the general community and a survey of 16 neurologists in Sydney, Melbourne and Brisbane. [2]

The PBAC applied the increased maximum quantity to all triptans available on the PBS.[1]

Place in therapy

Non-drug treatment for acute migraine consists of rest in a quiet, dark room.[3,4]

First-line agents include simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). If these do not control attacks, substitute ergotamine or a triptan. [3,4] Patients who do not usually respond to ergotamine and other agents, and who have failed a trial of prophylactic therapy, are eligible to receive a triptan on the PBS.[5]

For further information about management of migraine, refer to the *Australian Medicines Handbook, Therapeutic Guidelines: Neurology* or the New South Wales Therapeutic Advisory Group Migraine Guidelines for GPs (http://www.clininfo.health.nsw.gov.au/nswtag/publications/guidelines/Migraine4=12=02.pdf).[3,4]

Safety issues

There has been no change in the safety considerations for triptans.

Note that the increased availability of doses to patients may prompt some to use more tablets to treat each migraine. Some patients may consequently exceed the recommended maximum daily dose. Ensure that patients are aware of the appropriate dosing of triptans (see *Information for patients*).

The possibility of serious cardiovascular events in some patients, including angina and acute myocardial infarction, highlights the importance of adhering to the recommended dosing and precautions for use of this class.[6]

Although the PBS maximum quantity has increased to 4 tablets, it is possible to prescribe a smaller number of tablets.

Dosing Issues

Recommended doses for the triptans have not changed. Refer to the product information for dosage recommendations.

Ensure that patients are aware of the appropriate dosing of triptans (see *Information for patients*).

Information for patients

Inform patients that although they may have a larger quantity of medicine on hand, there have been no changes to the dosing recommendations for triptans. Patients must receive clear instructions on the correct initial dose, the minimum interval between doses and the maximum daily dose. The Consumer Medicine Information (CMI) contains information about dosing.

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Medicines used in palliative care

Summary

PBS listing	A new and separate section—the Palliative Care Section—has been introduced into the Schedule of Pharmaceutical Benefits as of 1 February 2004 for palliative care medicines. **Authority required** for all palliative care listings.
Reason for listing	Many drugs used in palliative care were not listed on the PBS for palliative care indications. This created inconsistency between patients being treated in institutions versus the community in accessing some palliative care medicines. The Pharmaceutical Benefits Advisory Committee (PBAC) has responded to this demonstrated need and accepted the proposal to subsidise certain palliative care medicines for patients in the community.
Place in therapy	The Palliative Care Section adds to the medicines that are currently available on the PBS (such as opioid analgesics) for use in patients typically with malignant neoplasia. Medicines in this first phase of listings in this Section include clonazepam, hyoscine butylbromide, paracetamol suppositories, promethazine, a saliva substitute, and a range of laxative preparations.
Safety issues	There are no specific safety issues of concern.
Dosing issues	There are no specific dosing issues of concern.

PBS listing

A new and separate section has been introduced in the Schedule of Pharmaceutical Benefits for palliative care medications. For the purposes of prescribing under the Palliative Care Section of the PBS, a palliative care patient is defined as:

a patient with an active, progressive, far-advanced disease for whom the prognosis is limited and the focus of care is the quality of life.[1]

Authority required for all palliative care listings.

Prescribers can request an initial authority to provide for a maximum of 4-months' therapy for palliative care patients. Where continued therapy is required, authority approvals for subsequent prescriptions will be for a maximum of one month's supply only, unless the prescriber consults with a palliative care specialist or palliative care service in which case up to 4-months' supply may be requested.

Reason for listing

It is often difficult for patients to access medicines for palliative care use, at a reasonable cost, as many have not been available on the PBS.[2] This can result in people having to choose inpatient hospital care over community-based care in order to gain access to some palliative care medicines.

The PBAC accepted the proposal to subsidise certain palliative care medicines for patients in the community.

In this first phase of listing it is recognised that a limited group of medicines have been made available for palliative care patients. However, it is anticipated this list will be added to over time as evidence is provided that using individual medicines in the palliative care population is cost-effective—a requirement for any item listed on the PBS.

Place in therapy

The Palliative Care Section adds to the medicines that are currently available on the PBS (such as opioid analgesics) for use in patients typically with malignant neoplasia.

The following medicines are new listings in the Palliative Care Section:

- Carmellose mouth spray (Aquae) as a saliva substitute
- Clonazepam 500 micrograms and 2 mg tablets (Paxam, Rivotril); 2.5 mg/mL oral liquid (Rivotril) for preventing epilepsy
- Hyoscine butylbromide 20 mg/mL injection (Buscopan) for colicky pain
- Paracetamol 500 mg suppositories (Panadol) for analgesia
- Promethazine hydrochloride 10 mg and 25 mg tablets; 5 mg/5 mL elixir (Phenergan) for nausea and vomiting.

A number of laxative products currently listed for palliative care in the Schedule of Pharmaceutical Benefits will be included in the new Palliative Care Section. These include:

- Bisacodyl 5 mg tablets and 10 mg in 5 mL enemas (Bisalax); 10 mg suppositories (Durolax, Fleet Laxative Suppositories, Petrus Bisacodyl Suppositories)
- Docusate sodium with bisacodyl 100 mg/10 mg suppositories (Coloxyl)
- Glycerol suppositories 700 mg (for infants), 1.4 g (for children), 2.8 g (for adults) (Petrus)
- Sorbitol, sodium citrate and sodium lauryl sulfoacetate enemas (Microlax)
- Sterculia with frangula bark granules (Granocol, Normacol Plus).

The PBAC noted that these laxative products are already listed for palliative care in the Schedule. Consequently, the PBAC considered it appropriate that these palliative care listings be transferred to the new Palliative Care Section of the PBS Schedule, effective from 1 February 2004. The PBAC recommended deleting the palliative care indication that applies to these preparations on 1 May 2004, allowing prescribers a 3-month transition period to become familiar with the listings under the new Palliative Care Section of the Schedule.

Safety issues

There are no specific safety issues of concern.

Dosing issues

There are no specific dosing issues of concern.

Information for patients

Therapeutic Guidelines: Palliative care[3] contains a list of potentially useful palliative care resources and organisations that may provide support to patients, their families, and carers.

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Escitalopram (Lexapro) for major depressive disorder

Summary

PBS listing

Restricted benefit: Major depressive disorders.

Reason for listing

Escitalopram was listed on the basis of cost-minimisation compared to citalopram. Escitalopram was considered to have similar — not superior — efficacy to citalopram.

Place in therapy

Escitalopram is not a new concept; it is merely the active isomer of the antidepressant, citalopram. On existing evidence, little difference to citalopram is expected.

For patients whose depression is well-managed on citalopram or another selective serotonin re-uptake inhibitor (SSRI) there is no reason to change to escitalopram. Similarly, patients who have a poor response or adverse effects with citalopram are unlikely to do any better with escitalopram.

Safety issues

The safety profile of escitalopram appears to be similar to that of citalopram. No unexpected adverse events have occurred in the short-term studies of escitalopram conducted to date.

Escitalopram is an SSRI, and has similar drug interactions. In particular, do not prescribe with: other serotonergic agents, including tramadol and sumatriptan; or MAO inhibitors. Using other antidepressants concurrently is not recommended and a washout period may be required. This includes complementary medicines used for depression such as St John's Wort.

Dosing issues

- Escitalopram 10 mg is the usual effective dose, and is equivalent to citalopram 20 mg.
- Escitalopram doses should not exceed 20 mg. As with any SSRI, trial at the minimum effective dose for at least 4 to 6 weeks before changing treatment.
- Adverse effects are dose-related.

PBS Listing

Restricted benefit Major depressive disorders.

Reason for PBS Listing

Efficacy of escitalopram and citalopram were similar — superiority was not demonstrated. Therefore, the PBAC recommended listing escitalopram on the basis of cost-minimisation compared with citalopram. At the proposed pricing, escitalopram would cost the PBS slightly less than citalopram. However if prescribing of higher doses increases with escitalopram, the cost to the PBS will increase compared to citalopram.

Place in therapy

Escitalopram is listed for the treatment of major depressive disorder only.

Evidence for the effectiveness of antidepressant medication in less severe depression is lacking. (See *Therapeutic Guidelines: Psychotropic* for diagnostic criteria for major depression.)

Escitalopram does not have a novel mechanism of action, but is merely the active isomer of the SSRI antidepressant, citalopram (*See Isomer drugs below*). To date, no significant advantage over citalopram has been shown.[1]

Compared to existing therapy

For patients well managed on citalopram or another SSRI, there is no reason to change to escitalopram. Similarly, patients with a poor response or adverse effects on citalopram are unlikely to benefit from escitalopram.

There is no evidence to suggest greater efficacy of escitalopram compared with equipotent doses of citalopram. Evidence of superiority was not presented to PBAC and was not the basis of PBS listing.

All SSRIs have similar efficacy,[2,3] and there is no reason to expect escitalopram to be any different. Like citalopram, escitalopram does not affect uptake of noradrenaline, dopamine or GABA — hence it is a highly selective serotonin inhibitor.[4] However, this has not resulted in a therapeutic advantage over other SSRIs and as stated in the Cipramil product information, the clinical relevance of this *in vitro* finding has not been established.

Role of non-drug therapy

Cognitive behavioural therapy or supportive psychotherapy can be considered for patients with mild-to-moderate major depression and medication may not be required.

However in severe or melancholic major depression, psychological treatment alone is not recommended as first-line treatment.[3]

Isomer drugs

What is an active isomer?

Some drug molecules are made up of pairs of isomers or stereoisomers. Like left and right hands, stereoisomers are mirror images of identical structures and are referred to as the 'S' (left) and 'R' (right) isomers. Hence ***es***citalopram is the ***S***-isomer of citalopram. S and R isomers can have different properties — in citalopram, the S-isomer is responsible for most of the serotonergic activity.[4]

How to assess the value of an 'isomer' drug

Creating medicines from single isomers of known drugs is an expanding area of pharmaceutical development — e.g. esomeprazole and omeprazole. The relationship between the parent drug and its isomers differs from drug to drug. Frequently one of the isomers has most of the activity. In theory, isolating the active isomer may potentially improve a drug by reducing adverse effects or interactions. However isomer derivatives can also cause more adverse effects.[5]

Commercial advantages include the ability to create a new product with lower than usual development costs,[5] and to protect market share when a medicine nears patent expiry, by patenting a "new" drug.[6]

Evaluating 'isomer' drugs[5,6]

Question	**Answer for escitalopram**
Does selecting one isomer	
• Eliminate any adverse effects?	No adverse effects eliminated.
• Remove important drug interactions?	No drug interactions eliminated.
• Enhance the clinical effect?	Not better than citalopram.
Have **equipotent doses** been used in comparison trials?	Yes.[1,7]
Is there good evidence that the isomer drug has any therapeutic advantage over equipotent doses of the parent drug?	Comparisons of escitalopram and citalopram show similar efficacy.[1,7] There is no good evidence of a therapeutic advantage.
Does the isomer drug cost more, and is the cost justified by projected benefits?	Escitalopram is similarly priced to generic citalopram, which is reasonable since there is no proven advantage.

Potency and the dose in milligrams — 10 is not less than 20

Escitalopram 10 mg is equivalent to citalopram 20 mg. There is no advantage in prescribing a smaller escitalopram dose, because the dose of the active isomer is the same as with citalopram 20 mg.

Within the citalopram molecule, the S-isomer is more active and therefore more 'potent' than the R-isomer, but this bears no relation to the clinical comparison of escitalopram and citalopram. One comparative trial found no difference in effectiveness between escitalopram 20 mg and the equipotent dose of citalopram.[1]

As with any SSRI, the likelihood of adverse events increases with higher doses. (See Adverse Drug Reactions)

Safety issues

Assumptions about long-term safety for escitalopram are based on experience with citalopram. The safety profiles of escitalopram and citalopram appear to be similar.

Adverse Drug Reactions

Adverse effects can be expected to be similar for escitalopram and citalopram at equipotent doses. No unexpected adverse events have occurred in the short-term 8-week trials conducted to date, [1,7,8] but there are no long-term safety data for escitalopram.

The most common adverse events in patients taking escitalopram included nausea, increased sweating, insomnia, ejaculatory disorder, diarrhoea, dry mouth and somnolence.[1,7]

Higher doses of most SSRIs increase the likelihood of adverse effects. The increase in adverse events with higher doses is shown in Table 2.

Table 2: Adverse events with citalopram and escitalopram[1]

	Placebo	**Escitalopram 10 mg/day***	**Escitalopram 20 mg/day***	**Citalopram 40 mg/day***
Discontinued due to adverse events:	3%	4%	10%	9%
		No different to placebo	Significantly higher than placebo ($p \leq 0.05$)	
Rate of adverse events	71%	79%	86%	86%
		No different to placebo	Significantly higher than placebo ($p \leq 0.01$)	

* Note: 20 mg citalopram was not tested in this trial

Drug interactions

Serotonergic drugs such as tramadol, sumatriptan, and other SSRIs can increase serotonergic effects and should be avoided while using escitalopram. St John's Wort (*Hypericum perforatum*) interacts with a number of prescription medicines including antidepressants. SAMe (S-adenosylmethionine), a complementary medicine for depression and arthritis, is also thought to interact with tricyclic antidepressants and may have serotonergic properties.[9]

As with any SSRI, monoamine oxidase inhibitors are contraindicated and a washout period is required when changing between these drugs and escitalopram. See the Australian Medicines Handbook,[2] or the Lexapro product information for more information on interactions.

Dosing issues

Dose-equivalence for escitalopram and citalopram

Escitalopram		Citalopram
10 mg	equivalent to	20 mg
20 mg	equivalent to	40 mg*

*Note that higher doses of SSRIs are not necessarily more effective and carry an increased risk of adverse events.

Based on experience with citalopram, escitalopram 10 mg should be sufficient to manage most depression. A small proportion of patients with particularly severe depression may require the higher dose (20 mg). However, as with any SSRI, trial at the minimum effective dose for at least 4–6 weeks before changing treatment. Allow 2–4 weeks between dose increases and taper doses gradually when reducing doses or discontinuing.[3]

Remember that most adverse effects are dose-related. Doses of escitalopram should not exceed 20 mg, or 10 mg for the elderly.

Information for patients

For more detailed information, suggest or provide the Lexapro Consumer Medicine Information (CMI).

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Deferiprone (Ferriprox) for thalassaemia major

Summary

PBS listing	**Section 100 Private hospital authority required** For treatment of iron overload in patients with thalassaemia major who are unable to take desferrioxamine therapy or in whom desferrioxamine therapy has proven ineffective.
Reason for listing	Acceptable cost-effectiveness compared with no treatment or severe under-dosing with desferrioxamine. Thalassaemia major patients inadequately treated with desferrioxamine are at greatest risk of early death and clinical complications from iron overload.
Place in therapy	Deferiprone is an iron-chelator. Although it offers the advantage of oral administration it is associated with significant toxicity and there are questions about its long-term safety and efficacy. It should only be used in patients who are unable to use desferrioxamine because of adverse effects, allergy or lack of effectiveness.
Safety issues	Serious safety issues include genotoxicity, neutropenia and agranulocytosis. Weekly monitoring of neutrophils is recommended. Gastrointestinal and joint problems can occur and liver toxicity has been reported.

PBS listing

Section 100 Private hospital authority required
For treatment of iron overload in patients with thalassaemia major who are unable to take desferrioxamine therapy or in whom desferrioxamine therapy has proven ineffective.

Deferiprone is available under the Highly Specialised Drugs Program and supplied only through hospitals with access to appropriate specialist facilities.

Reason for listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing on the basis of acceptable cost-effectiveness compared with no treatment or severe under-dosing with desferrioxamine.[1] Patients with thalassaemia major inadequately treated with desferrioxamine are at greatest risk of early death and clinical complications from iron overload.[2]

The PBAC expressed concern about toxicities associated with the product (see under *Safety Issues*) and prescribers and patients should be well informed of these. The PBAC noted that there would be occasions where patients may use deferiprone and desferrioxamine in combination and advised that this is clinically acceptable.[1]

Place in therapy

The thalassaemias are a common group of genetic blood diseases, prevalent particularly in the Mediterranean basin, Middle East, Indian subcontinent and SE Asia. They are characterised by decreased synthesis of one of the two types of polypeptide chains (α or β) which form the normal adult human haemoglobin molecule, resulting in decreased haemoglobin production and anaemia. Depending on the involved genes, the defect is identified as α-thalassaemia or β-thalassaemia. Homozygous (2 defective genes) β-thalassaemia carriers who are transfusion dependent are classified as having thalassaemia major.[3] In Australia it is estimated that there are about 300–400 patients with this condition.

If left untreated patients with thalassaemia major will usually die from anaemia in childhood. Treatment involves regular blood transfusions to maintain the haemoglobin level above 90–105 g/L.[3] Without chelation therapy, accumulation of iron from these transfusions causes serious problems. Death, usually from cardiac failure, occurs typically around the age of twenty.[3,4] Other complications of iron overload include pituitary damage, diabetes, hypothyroidism and hypoparathyroidism. Liver fibrosis and cirrhosis can also occur.[3]

Desferrioxamine remains first-line

Desferrioxamine is an effective iron-chelator. If used as recommended, it improves survival and reduces the complications of iron overload[2,4] but must be administered parenterally, usually as a continuous subcutaneous infusion over a 12-hour period, from three to seven times a week.[5] Treatment is time consuming and can be painful. As a result compliance is often poor. Side-effects include local skin reactions, hearing loss, nephrotoxicity, pulmonary toxicity, growth retardation and infection.[5,6]

Although deferiprone offers the advantage of oral administration it is associated with significant toxicity and there are questions about its long-term safety and efficacy.[3,6-8] It should therefore be reserved for patients:

- unable to tolerate desferrioxamine because of adverse effects or allergy,or
- for whom desferrioxamine treatment has not been effective.

The effectiveness of desferrioxamine depends on compliance and every effort should be made to address psychosocial or administration-related barriers to compliance before considering deferiprone as an alternative.[3]

Efficacy questions

The efficacy of deferiprone in patients intolerant of, or poorly compliant with, desferrioxamine has been investigated in a number of small, open-label studies, ranging from 1 to 4 years.[8-11] Most studies contain significant design flaws, making interpretation of results difficult. Some[9-11] but not all[8] studies were able to demonstrate a decline in mean serum ferritin levels (an indirect indicator of body iron load) over the study period, with patients with higher baseline ferritin levels consistently more responsive to treatment.

A significant proportion of patients may not respond to deferiprone in the longer term.[8-9,12] In a 4-year study of 187 patients, 47 patients discontinued deferiprone because of concerns regarding effectiveness.[8]

Safety issues

Serious safety issues identified with deferiprone include genotoxicity, neutropenia and agranulocytosis, and liver toxicity.[6-9,11-13]

Long-term safety not established

Deferiprone displayed genotoxic characteristics in pre-clinical studies, inducing chromosomal breakage in some animal models.[11] Carcinogenicity studies have not been conducted but in view of the genotoxicity results a potential for carcinogenic effects in humans cannot be ruled out.[7,11]

The effects of deferiprone on growth and fertility have not been studied.[7]

Iron chelation therapy in thalassaemia typically commences in childhood and continues for life so the above are potential issues of concern that should be clearly communicated to patients. Experience in children aged less than ten years is limited.[7]

Deferiprone is teratogenic in two animal species and women of childbearing potential should avoid pregnancy.[7]

Adverse Drug Reactions

Deferiprone has been shown to cause neutropenia and agranulocytosis at an incidence of 6% and 0.8%, respectively.[7] Both conditions appear reversible if deferiprone is withdrawn. Patients with an intact spleen may be at increased risk.[8,9] Rechallenge is generally not recommended and is contra-indicated in agranulocytosis.[7,9]

Patient neutrophil counts should be monitored on a weekly basis.[7] Studies suggest that this may reduce the incidence of agranulocytosis[8,9] but this requirement will add to the cost of treatment and cause inconvenience for patients.

Other common side-effects include:

- a reddish-brown discolouration of urine
- nausea, vomiting and abdominal pain
- arthralgia, arthritis
- increased appetite and
- zinc deficiency—supplements may be necessary.[7]

Deferiprone can cause raised alanine aminotransferase (ALT) levels. Most rises are asymptomatic and transient but treatment may need to be interrupted in patients with persistent increases.[7,8]

Iron overload in the liver can lead to the development of fibrosis, which may progress to cirrhosis.[13] Patients with hepatitis C appear at greatest risk and should be carefully monitored.[7,13] In 1998 concerns were raised that deferiprone may worsen hepatic fibrosis[12] but subsequent studies have cast doubt on these findings.[7,13]

Potential for over-the-counter drug interactions

High-dose ascorbic acid is suspected of aggravating cardiac failure in desferrioxamine-treated patients so the product information recommends caution when deferiprone is administered with vitamin C.[6,7,11]

Due to its chelating properties, deferiprone should not be administered at the same time as aluminium-based antacids.[7]

Dosing issues

The recommended dose is 25 mg/kg, orally, three times daily.[7] Therapy should be interrupted if serum ferritin levels drop below 500 micrograms/L.[7,9]

For complete dosing information as well as a list of all deferiprone contra-indications, precautions, drug interactions and side-effects please consult the Ferriprox product information.

Information for patients

Refer patients to the Ferriprox Consumer Medicine Information (CMI).
Advise patients:

- to immediately report any symptoms of infection e.g. fever, sore throat or flu-like symptoms.[7]
- that deferiprone can cause a reddish-brown discolouration of urine. This is not cause for alarm.[7]
- to avoid self-treatment with vitamin C or aluminium antacids.[7]

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