

5.34 POSACONAZOLE
100mg modified release tablet;
Noxafil®; Merck Sharp & Dohme (Australia) Pty Ltd.

1 Purpose of Application

1.1 The minor submission sought an Authority Required listing of a new dose presentation of posaconazole for the same indications that currently apply to the oral liquid presentation.

2 Requested listing

2.1 The requested new listing does not meet current electronic media requirements and has been remodelled by the Secretariat below. Any changes proposed should also be updated for listing of the liquid formulation. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
POSACONAZOLE 100mg modified release tablets, 24	1	0	\$ [REDACTED]	Noxafil® MSD

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	-
Condition:	Invasive aspergillosis
PBS Indication:	Invasive aspergillosis
Treatment phase:	Treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	<i>Patient must be intolerant to alternative therapy;</i> <i>OR</i> <i>The condition must be refractory to alternative therapy.</i>
Population criteria:	-
Foreword	-

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Definitions	-
Prescriber Instructions	-
Administrative Advice	<p><i>Application for an increased maximum quantity to allow for up to 1 month's treatment and repeats sufficient for up to 6 months' treatment may be authorised.</i></p> <p>Shared Care Model: <i>For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.</i></p>
Cautions	-

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	-
Condition:	Fusariosis, zygomycosis, coccidioidomycosis, chromoblastomycosis and mycetoma
PBS Indication:	Fusariosis, zygomycosis, coccidioidomycosis, chromoblastomycosis and mycetoma
Treatment phase:	Treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	<p><i>Patient must be intolerant to alternative therapy;</i></p> <p><i>OR</i></p> <p><i>The condition must be refractory to alternative therapy.</i></p>
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions	-
Administrative Advice	<p><i>Application for an increased maximum quantity to allow for up to 1 month's treatment and repeats sufficient for up to 6 months' treatment may be authorised.</i></p> <p>Shared Care Model: <i>For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.</i></p>

Cautions	-
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Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	-
Condition:	Prophylaxis of invasive fungal infections including both yeasts and moulds
PBS Indication:	Prophylaxis of invasive fungal infections including both yeasts and moulds
Treatment phase:	
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	<i>Patient must be considered at high risk of developing an invasive fungal infection due to anticipated neutropenia (an absolute neutrophil count less than 500 cells per cubic millimetre) for at least 10 days whilst receiving chemotherapy for acute myeloid leukaemia or myelodysplastic syndrome;</i> <i>OR</i> <i>Patient must be considered at high risk of developing an invasive fungal infection due to having acute graft versus host disease (GVHD) grade II, III or IV, or, extensive chronic GVHD whilst receiving intensive immunosuppressive therapy after allogeneic haematopoietic stem cell transplant.</i>
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions	-
Administrative Advice	Shared Care Model: <i>For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.</i> <i>For patients with graft versus host disease, acute myeloid leukaemia or myelodysplastic syndrome, applications for an increased maximum quantity to allow for up to 1 month's treatment and repeats sufficient for up to 6 month' treatment may be authorised.</i>
Cautions	-

For more detail on PBAC's view, see section 6 "PBAC outcome"

3 Background

- 3.1 Posaconazole tablets are TGA registered for the treatment of the following invasive fungal infections in patients 13 years of age or older:
- Invasive aspergillosis in patients intolerant of, or with disease that is refractory to, alternative therapy
 - Fusariosis, zygomycosis, coccidioidomycosis, chromoblastomycosis, and mycetoma in patients intolerant of, or with disease that is refractory to, alternative therapy.
 - Prophylaxis of invasive fungal infections, in patients who are at high risk of developing these infections, such as patients with prolonged neutropenia or haematopoietic stem cell transplant (HSCT) recipients.
- 3.2 Posaconazole tablets have not previously been considered by PBAC.

4 Clinical place for the proposed therapy

- 4.1 Posaconazole liquid has poor bioavailability if taken on an empty stomach (2-3 fold decrease in bioavailability). The submission claimed that people unable to take posaconazole liquid with a large meal may have a sub-optimal treatment response.
- 4.2 Posaconazole tablets have been formulated to remove the need for administration with food, claiming to result in more predictable plasma levels and less monitoring, as well as improving patient convenience. The submission claimed that posaconazole tablets will be used in preference to liquid due to these factors.
- 4.3 The TGA approved Product Information for posaconazole tablets lists the recommended dose as 3 tablets twice daily on day 1 as a loading dose, followed by 3 tablets daily thereafter. This regimen is the same for both prophylaxis and treatment. In contrast, the recommended dose for the liquid formulation is 200mg three times daily for prophylaxis and 400mg twice daily for treatment.
- 4.4 The TGA considered the two dosage forms of posaconazole were not interchangeable due to differences in dosing regimen.

For more detail on PBAC's view, see section 6 "PBAC outcome"

5 Consideration of evidence

Sponsor hearing

- 5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 5.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 5.3 As a minor submission, no clinical trials were presented in the submission.

Economic analysis

- 5.4 Due to the differing treatment regimens between the liquid and tablet preparations, it is not possible to calculate equi-effective doses or a simple comparative price per milligram.
- 5.5 The minor submission instead presented an economic evaluation based on a 10% sample of Medicare data to evaluate the proportion of use of posaconazole in prophylaxis compared to treatment, estimating a proportion of patients requiring a loading dose and calculating patient co-payments to estimate the average days of therapy per pack and price per day. As a minor submission, the appropriateness of this approach could not be evaluated prior to consideration by the PBAC.
- 5.6 The submission proposed a DPMQ of \$[REDACTED] as it is claimed that this represents the price that is equivalent per day to the price of posaconazole oral suspension, with a \$[REDACTED] offset for each pack of tablets to account for the reduction in patient co-payment. The submission based the proposed price on factors including whether the treatment is for refractory disease or prophylaxis, the number of patient days of therapy and daily dose. The submission used an ad hoc analysis based on a 10% sample of Medicare Australia data, combined with PBS Authorities data to determine the price per day of the tablets. Duration of therapy was based on severity of disease and clinical response.

For more detail on PBAC's view, see section 6 "PBAC outcome"

Estimated PBS usage & financial implications

- 5.7 The submission used a market-share approach to estimate the extent of use and financial implications of listing posaconazole tablets. It was claimed that posaconazole tablets will replace a large proportion of the current use of posaconazole liquid due to ease of use. The submission proposed that the listing of posaconazole tablets will be cost neutral.
- 5.8 The price to pharmacy was used in the financial estimates. This was incorrect and should be calculated at an ex-manufacturer level. The calculations have been updated in the table below. Differences in patient co-payment were not included but may impact upon overall net cost to the PBS, particularly as prescribers are able to obtain authority to prescribed increased quantities.
- 5.9 The PBAC recalled its March 2008 recommendation regarding posaconazole liquid that the Government enter into a risk share agreement (RSA) with the sponsor to manage the possibility of usage beyond the restriction. The PBAC noted that utilisation of posaconazole liquid had subsequently been lower than projected, and considered that this may be attributed to the requirement to take the liquid with a large meal. The PBAC considered that posaconazole tablets may be easier to administer than the liquid formulation and that this may result in utilisation of the tablet formulation being greater than the utilisation observed with the liquid. The PBAC therefore reaffirmed its concerns about utilisation beyond the restriction, and recommended that the financial risks to the Commonwealth should be managed through an RSA; or through a reduction in price of the tablet formulation.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of tablet packs	█	█	█	█	█
Cost to PBS of tablets	\$ █	\$ █	\$ █	\$ █	\$ █
Number of liquid packs replaced	█	█	█	█	█
Cost of liquid replaced	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to PBS	\$ █	\$ █	\$ █	\$ █	\$ █

For more detail on PBAC’s view, see section 6 “PBAC outcome”

5.10 The redacted table above shows the estimated number of packs supplied is less than 10,000 in Year 1, increasing to 10,000 – 50,000 in Year 5. The overall estimated total saving to the PBS will increase in each year over the first five years.

6 PBAC Outcome

6.1 The PBAC recommended the listing of posaconazole tablets, on the basis that it should be available as an Authority Required item on the General Schedule for both prophylaxis and treatment of invasive fungal infections.

6.2 The PBAC is satisfied that posaconazole tablets provide the same benefits as seen with posaconazole liquid but with the potential for greater ease of administration as the tablet formulation does not need to be taken with food.

6.3 The PBAC considered it appropriate for the tablet formulation of posaconazole to have the same restriction as the liquid formulation.

6.4 The PBAC noted that due to the differing treatment regimens between the tablet and liquid preparations, it was not possible to calculate equi-effective doses or a simple comparative price per milligram.

6.5 The PBAC noted the TGA recommendation that the tablet and liquid forms of posaconazole are not considered interchangeable due to the differing treatment regimens and considered that the two formulations should not be able to be substituted on the PBS.

6.6 The PBAC considered that the price per treatment course should be equivalent for the two formulations of posaconazole.

6.7 The PBAC considered that duration of therapy is a significant source of uncertainty. As there are no conclusive data to inform a clinical decision to discontinue treatment or discontinue prophylaxis in chronic graft-versus-host disease, the PBAC considered that there is a risk that patients will persist on treatment in the absence of clear additional clinical benefit.

6.8 The PBAC considered that utilisation of posaconazole tablets should be reviewed by DUSC after listing, noting that usage is likely to increase due to ease of use of tablets over liquid. The Committee considered that it is uncertain whether any additional patient benefit from such increased use will accrue. In the context of a DUSC

analysis, the PBAC considered it appropriate to consult experts responsible for the current antifungal treatment guidelines to ascertain the most appropriate duration of therapy for both prophylaxis and treatment in order to form a basis for accurately analysing usage.

- 6.9 The PBAC considered that there may be uptake from the current voriconazole market, and that the market share of posaconazole may increase with listing of the tablet formulation.
- 6.10 The PBAC recommended that posaconazole should not be treated as interchangeable on an individual patient basis with voriconazole or any other drug.
- 6.11 The PBAC advised that posaconazole is suitable for prescribing by nurse practitioners under a shared care model.
- 6.12 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

Outcome:

Recommended

7 Recommended listing

7.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
POSACONAZOLE 100mg modified release tablets, 24	1	0	Noxafil	MSD

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	-
Condition:	Invasive aspergillosis
PBS Indication:	Invasive aspergillosis
Treatment phase:	Treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	-

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Clinical criteria:	Patient must be unable to tolerate alternative therapy; OR Patient must have disease refractory to alternative therapy.
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions	-
Administrative Advice	Application for an increased maximum quantity to allow for up to 1 month's treatment and repeats sufficient for up to 6 months' treatment may be authorised. Shared Care Model: For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.
Cautions	-

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
POSACONAZOLE 100mg modified release tablets, 24	1	0	Noxafil	MSD

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	-
Condition:	Fungal disease
PBS Indication:	Fungal disease
Treatment phase:	Treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	-

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Clinical criteria:	<p>The condition must be fusariosis; OR The condition must be zygomycosis; OR The condition must be coccidioidomycosis; OR The condition must be chromoblastomycosis; OR The condition must be mycetoma</p> <p>AND</p> <p>Patient must be unable to tolerate alternative therapy; OR Patient must have disease refractory to alternative therapy.</p>
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions	-
Administrative Advice	<p>Application for an increased maximum quantity to allow for up to 1 month's treatment and repeats sufficient for up to 6 months' treatment may be authorised.</p> <p>Shared Care Model: For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.</p>
Cautions	-

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
POSACONAZOLE 100mg modified release tablets, 24	1	0	Noxafil	MSD

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	-
Condition:	Prophylaxis of invasive fungal infections including both yeasts and moulds
PBS Indication:	Prophylaxis of invasive fungal infections including both yeasts and moulds
Treatment phase:	
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

Treatment criteria:	-
Clinical criteria:	<p>Patient must be considered at high risk of developing an invasive fungal infection due to anticipated neutropenia (an absolute neutrophil count less than 500 cells per cubic millimetre) for at least 10 days whilst receiving chemotherapy for acute myeloid leukaemia or myelodysplastic syndrome;</p> <p>OR</p> <p>Patient must be considered at high risk of developing an invasive fungal infection due to having acute graft versus host disease (GVHD) grade II, III or IV, or, extensive chronic GVHD and receiving intensive immunosuppressive therapy after allogeneic haematopoietic stem cell transplant.</p> <p>Treatment of neutropenia should continue until recovery of the neutrophil count to at least 500 cells per cubic millimetre.</p> <p>Patients who have had a previous invasive fungal infection should have secondary prophylaxis during subsequent episodes of neutropenia.</p>
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions	-
Administrative Advice	<p>Shared Care Model:</p> <p>For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.</p> <p>For patients with graft versus host disease, acute myeloid leukaemia or myelodysplastic syndrome, applications for an increased maximum quantity to allow for up to 1 month's treatment and repeats sufficient for up to 6 month' treatment may be authorised.</p>
Cautions	-

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor had no comment.