

NOVEMBER 2017 PBAC OUTCOMES – SUBSEQUENT DECISIONS NOT TO RECOMMEND

DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR / PURPOSE OF SUBMISSION	PBAC OUTCOME
<p>CLADRIBINE</p> <p>Tablet 10 mg</p> <p>Mavenclad®</p> <p>Merck Serono Australia Pty Ltd</p> <p>New listing (Major Submission)</p>	<p>At time of PBAC consideration:</p> <p>Indication is for treatment of relapsing-remitting multiple sclerosis for a maximum duration of two years.</p> <p>At time of publication:</p> <p>Indication is for the treatment of relapsing-remitting multiple sclerosis (RRMS) to reduce the frequency of clinical relapses and to delay the progression of physical disability. Following completion of the 2 treatment courses, no further cladribine treatment is required in years 3 and 4. Re-initiation of therapy after year 4 has not been studied.</p>	<p>CLADRIBINE (tablet) is not currently PBS listed.</p>	<p>Resubmission to request an Authority Required listing for the treatment of Relapsing-remitting multiple sclerosis (RRMS).</p> <p>Comparator: The resubmission nominated fingolimod as the main comparator</p> <p>Clinical claim: Cladribine is non-inferior in terms of effectiveness and safety compared with fingolimod.</p> <p>Economic claim: cost minimisation analysis based on a claim of non-inferiority to fingolimod</p>	<p>The PBAC did not recommend the listing of cladribine for the treatment of relapsing remitting multiple sclerosis (RRMS), on the basis of uncertainty in the non-inferior efficacy claim of cladribine versus fingolimod over two and four years. The PBAC considered there was insufficient clinical evidence to support the time horizon of four years for estimating the equi-effective doses of cladribine and fingolimod. The PBAC also considered that it was unrealistic to assume that patients who receive cladribine and experience disease relapse would not be prescribed another medicine for RRMS before the four-year period or that patients would be 100% persistent to fingolimod. Therefore, the PBAC did not accept two years of cladribine treatment versus four years of fingolimod treatment as the basis for the cost-minimisation analysis proposed by the resubmission. The PBAC noted that there were significant uncertainties in the financial analysis, including the persistence rates assumed by the resubmission. The PBAC further noted that the financial analysis estimated a significant net cost to the PBS, which undermines the first principles of a cost-minimisation analysis.</p> <p>The PBAC accepted fingolimod as the appropriate main comparator, however considered that cladribine may replace or displace all PBS listed RRMS treatments.</p> <p>The PBAC considered that there was insufficient data to accurately assess the claim of non-inferior efficacy and safety of cladribine versus fingolimod.</p> <p>The PBAC considered that it was inappropriate to conduct the cost-minimisation analysis based on two years of cladribine treatment versus four years of fingolimod treatment. As the PBAC did not accept the claim of non-inferiority of two years of cladribine treatment versus four years of fingolimod treatment, the Committee did not accept this</p>

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				as the basis for estimating the equi-effective doses of cladribine and fingolimod.
<p>IBRUTINIB</p> <p>Capsule 140 mg</p> <p>Imbruvica®</p> <p>Janssen-Cilag Pty Ltd</p> <p>Change to recommended listing (Major Submission)</p>	<p>Indicated for the treatment of:</p> <ul style="list-style-type: none"> •patients with mantle cell lymphoma who have received at least one prior therapy. •adult patients with CLL/SLL who have received at least one prior therapy or adult patients with previously untreated CLL/SLL •Patients with CLL/SLL with deletion 17p; and •adult patients with Waldenstrom's macroglobulinaemia who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy. 	<p>Chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL)</p>	Sponsor's comments:	The Sponsor had no comment.
			Resubmission to request an Authority Required listing for treatment of patients with relapsed or refractory mantle cell lymphoma.	The PBAC did not recommend the listing of ibrutinib for mantle cell lymphoma on the basis of an unacceptably high incremental cost effectiveness ratio (ICER). Further, the PBAC considered that the financial impact was high and likely overestimated.
			Comparator: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP).	Accepted.
			Clinical claim: Superior comparative efficacy compared with R-CHOP; superior comparative safety compared with patients on active R-CHOP treatment; and inferior comparative safety compared with patients who have completed or discontinued R-CHOP treatment but remained progression free.	<p>The PBAC considered that ibrutinib had superior efficacy compared with R-CHOP, however the magnitude of the benefit remained uncertain due to the limitations of the comparison presented in the submission. Despite the low quality of the evidence, the PBAC considered that ibrutinib was likely to offer benefit in an area of high clinical need.</p> <p>The PBAC considered that the safety claim was reasonable.</p>
			Economic claim: cost-utility analysis compared with R-CHOP.	<p>The PBAC noted that the resubmission presented scenario analyses to generate four measures of cost-effectiveness. The PBAC considered that Scenarios 1 and 3 were overly optimistic as the overall survival curves projected results unlikely to be observed in clinical practice. Scenario 2 was considered uncertain, and likely optimistic, given it was based on adjusted trial results. The PBAC noted that the incremental cost-effectiveness ratio (ICER) resulting from Scenario 4 was in the range of \$105,000 to \$200,000/QALY gained, and considered that this was unacceptably high. However, overall, the PBAC considered that Scenario 4 had addressed many of its previous concerns.</p>
Sponsor's comments:	Janssen will continue to work with the PBAC to make ibrutinib available to patients as soon as practical.			

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<p>MIGALASTAT</p> <p>Capsule containing migalastat hydrochloride 150 mg</p> <p>Galafold®</p> <p>Amicus Therapeutics</p> <p>New listing (Minor Submission)</p>	<p>Indicated for long-term treatment of adult and adolescent patients 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation.</p>	<p>MIGALASTAT is not currently PBS listed.</p>	<p>Resubmission to request a Section 100 (Highly Specialised Drug) Authority Required listing for the treatment of Fabry disease.</p>	<p>The PBAC did not recommend the Section 100 (Highly Specialised Drug Program) Authority Required listing of migalastat for the treatment of Fabry disease. In making this decision, the PBAC considered that the submission's clinical claim of non-inferior comparative effectiveness compared with enzyme replacement therapy (ERT) was uncertain and could not be supported. The PBAC considered that migalastat does provide a clinical benefit in stabilising renal function in patients with Fabry disease. The PBAC noted and welcomed the input from individuals and Fabry Australia via the Consumer Comments facility on the PBS website. The comments described the benefits of treatment with migalastat (a tablet) compared to the current ERTs in avoiding the burden of fortnightly intravenous infusion, which would improve people's quality of life.</p>
			<p>Comparator: agalsidase alfa and agalsidase beta (used in ERT)</p>	<p>Accepted. However, these two treatments are not listed on the PBS and have not been considered to be cost-effective for listing on the PBS.</p>
			<p>Clinical claim:</p> <ul style="list-style-type: none"> • Non-inferior comparative effectiveness of migalastat compared to ERT. • Non-inferior comparative safety of migalastat compared to ERT. 	<p>The PBAC did not accept the clinical claim of non-inferior effectiveness compared with the primary comparator of ERT, in either treatment naïve patients or in treatment experienced or switch patients. The PBAC previously considered that it was reasonable to accept the claim of non-inferior comparative safety of migalastat compared to ERT.</p>
			<p>Economic claim: cost-minimisation analysis compared with ERT.</p>	<p>Not Accepted. The PBAC did not accept the submission's clinical claim of non-inferiority versus ERT and therefore the basis for determining the equi-effective doses and the cost-minimisation approach were not accepted.</p> <p>As the submission's comparators are not listed on the PBS, the sponsor did not present a cost-effectiveness argument for the listing of migalastat on the PBS itself.</p>

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			Sponsor's comments:	Amicus thanks the PBAC for its consideration of migalastat to treat Fabry disease. Based on the Committee's recognition that migalastat is clinically effective in stabilising renal function in patients with Fabry disease, we look forward to liaising with the Life Saving Drugs Program to ensure that this novel oral therapy is made available to eligible Australian Fabry disease patients.
<p>PALBOCICLIB</p> <p>Capsule 75 mg Capsule 100 mg Capsule 125 mg</p> <p>Ibrance®</p> <p>Pfizer Australia Pty Ltd</p> <p>New listing (Major Submission)</p>	<p>Indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:</p> <ul style="list-style-type: none"> • an aromatase inhibitor as initial endocrine-based therapy; • fulvestrant in patients who have received prior therapy. 	<p>PALBOCICLIB is not currently PBS listed.</p>	<p>Resubmission to request an Authority Required listing as initial endocrine-based therapy in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor-2 negative (HER2-) locally advanced, inoperable or metastatic breast cancer in combination with a non-steroidal aromatase inhibitor.</p>	<p>The PBAC did not recommend the listing of palbociclib on the PBS as initial endocrine-based therapy for hormone receptor positive (HR+), HER2-negative (HER2-) advanced breast cancer on the basis that:</p> <ul style="list-style-type: none"> • palbociclib had a high and uncertain cost-effectiveness at the price proposed by the sponsor • single agent endocrine therapy as first-line therapy is associated with significant clinical benefits in most patients and the addition of palbociclib increases the toxicity of treatment with an uncertain effect on overall survival • the likely net cost of listing palbociclib on the PBS would be more than \$100 million over the first five years, and as such, there would be a significant opportunity cost to the Commonwealth. <p>The PBAC noted that breast cancer is the most common cancer in females and that the majority of patients with advanced breast cancer patients have the HR+ / HER2 negative type. The PBAC welcomed the comments received via the Consumer Comments facility on the PBS website. The PBAC noted the significant public interest in the listing of CDK4/6 inhibitors, such as palbociclib. The consumer comments that were considered by the Committee included the benefits that palbociclib improved quality of life, delayed disease progression and time to chemotherapy but had a very high financial cost to patients.</p>

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			Comparator: NSAID (letrozole or anastrozole) alone	The PBAC recalled it previously accepted non-steroidal aromatase inhibitor (NSAI) (letrozole or anastrozole) alone as the main comparator. The major re-submission did not change the comparator. The PBAC considered ribociclib, which was also considered by the Committee for a similar indication at its November 2017 meeting, should have been considered as a near market comparator.
			Clinical claim: Superior efficacy and inferior safety over NSAID alone	<p>The PBAC considered that the clinical benefit of adding palbociclib to letrozole was uncertain because although the results of the clinical trials (called PALOMA-1 and PALOMA-2, including updated clinical data) presented in the re-submission showed a progression-free survival (PFS) benefit associated with the use of palbociclib, there were no improvements in overall survival nor any improvement in patient's overall quality of life score. In addition, the PBAC noted that many women with advanced breast cancer are managed effectively on hormone therapy only, and the next line chemotherapies include well-tolerated oral therapies. Therefore the benefit of palbociclib in delaying time to chemotherapy is uncertain, particularly given that palbociclib itself is associated with significant toxicities.</p> <p>The PBAC accepted the re-submission's comparative safety claim that palbociclib was inferior over NSAID alone. The PBAC noted that there appears to be significant toxicity associated with the use of palbociclib, as patients who received palbociclib in the trials reported increased numbers of adverse events compared to those treated with letrozole alone, and that this was particularly important for a therapy that may be taken for a prolonged period.</p> <p>On the basis of direct evidence presented by the re-submission, for every 100 patients treated with</p>

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				<p>palbociclib plus letrozole in comparison with letrozole alone there would be:</p> <ul style="list-style-type: none"> • Approximately 8 more patients progression-free at 12 months based on PALOMA 1. • Approximately 10 more patients at 12 months and 14 more patients at 24 months progression-free based on PALOMA-2. • No improvement in OS, based on PALOMA-1. • Approximately 54 additional patients would experience a grade ≥ 3 adverse event. • Approximately 54 additional patients would experience grade 3 neutropenia (low count of one type of white blood cell, neutrophils, which carries an increased risk of infection) and 8 additional patients would experience grade 4 neutropenia. • Approximately 2 additional patients would experience febrile neutropenia (development of fever in a patient with neutropenia). • Approximately 42 additional patients would experience leukopenia (low white blood cell count). • Approximately 15 additional patients would experience fatigue. • The increased risk of pulmonary embolism (where an artery in the lungs becomes blocked by a blood clot) was small but observed in both clinical trials.
			Economic claim: Cost-effectiveness and cost-utility analysis	<p>The PBAC considered the economic model in the re-submission to be unreliable for decision making, because the cost of palbociclib had been underestimated and the claimed outcomes were likely to have been overestimated based on the evidence available in the clinical trials. The PBAC were still of the view that increased cost to the health care system for the potential patient benefit of palbociclib over the treatments currently available in Australia would be substantially greater than the sponsor claimed, and would have an opportunity cost to the funding of other</p>

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			Sponsor's comments:	therapies through the PBS. The Sponsor is committed to working with the PBAC and the Department of Health to make palbociclib available for the treatment of locally advanced and metastatic HR-positive, HER2-negative breast cancer.
<p>RIBOCICLIB</p> <p>Tablet 200 mg</p> <p>Kisqali®</p> <p>Novartis Pharmaceuticals Australia Pty Ltd</p> <p>New listing (Major Submission)</p>	<p>Indicated in combination with an aromatase inhibitor for the treatment of men and postmenopausal women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer, as an initial endocrine-based therapy.</p>	<p>RIBOCICLIB is not currently PBS listed.</p>	<p>Resubmission to request an Authority Required listing as initial endocrine-based therapy in patients with Hormone receptor-positive (HR+), human epidermal growth factor receptor-2 negative (HER2-) locally advanced, inoperable or metastatic breast cancer in combination with a non-steroidal aromatase inhibitor, who are not premenopausal.</p>	<p>The PBAC did not recommend the listing of ribociclib on the PBS in combination with a non-steroidal aromatase inhibitor (NSAI) for first-line endocrine based treatment of patients with non-premenopausal, hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer on the basis that:</p> <ul style="list-style-type: none"> • ribociclib had a high and uncertain cost-effectiveness at the price proposed by the sponsor. • single agent endocrine therapy as first-line therapy is associated with significant clinical benefits in most patients and the addition of ribociclib increases the toxicity of treatment with an uncertain effect on overall survival. • the likely net cost of listing ribociclib to the PBS would be more than \$100 million over the first five years, and as such, there would be a significant opportunity cost to the Commonwealth. <p>The PBAC noted that breast cancer is the most common cancer in females and that the majority of patients with advanced breast cancer patients have the HR+ / HER2 negative type. The PBAC welcomed the comments received via the Consumer Comments facility on the PBS website. The PBAC noted the significant public interest in the listing of CDK4/6 inhibitors, such as ribociclib. The consumer comments that were considered by the Committee included the benefits that ribociclib improved quality of life, delayed disease progression and time to chemotherapy but had a very</p>

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				high financial cost to patients.
			Comparator: NSAID (letrozole or anastrozole)	The PBAC recalled it previously accepted NSAID (letrozole or anastrozole) alone as the main comparator. The PBAC considered that palbociclib was an appropriate near market comparator which was also considered by the Committee for a similar indication at its November 2017 meeting.
			Clinical claim: Superior efficacy and inferior safety over NSAID alone	<p>The PBAC considered that the clinical benefit of adding ribociclib to letrozole was uncertain because although the results of the clinical trial (called MONALEESA-2) presented in the re-submission showed a progression-free survival (PFS) benefit associated with the use of ribociclib, there were no improvements in overall survival and not any improvement in patient's overall quality of life score. In addition, the PBAC noted that many women with advanced breast cancer are managed effectively on hormone therapy only, and the next line chemotherapies include well-tolerated oral therapies. Therefore the benefit of ribociclib in delaying time to chemotherapy is uncertain, particularly given that ribociclib itself is associated with significant toxicities.</p> <p>The PBAC accepted the re-submission's comparative safety claim that ribociclib was inferior over NSAID alone. The PBAC noted that there appears to be significant toxicity associated with the use of ribociclib, as patients who received ribociclib in the trials reported increased numbers of adverse events compared to those treated with letrozole alone, and that this was particularly important for a therapy that may be taken for a prolonged period.</p> <p>On the basis of direct evidence presented by the re-submission, for every 100 patients treated with ribociclib plus letrozole in comparison to letrozole alone there</p>

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				<p>would be:</p> <ul style="list-style-type: none"> • Approximately 12 more patients progression-free at 12 months, and 19 more patients at 24 months. • No improvement in OS. • Approximately 48 additional patients would experience a grade 3 adverse event and 14 would experience a grade 4 adverse event. • Approximately 59 additional patients would experience neutropenia (low count of one type of white blood cell, neutrophils, which carries an increased risk of infection), of which 41 would experience grade 3 neutropenia and 9 would experience grade 4 neutropenia. • Approximately 23 additional patients would experience nausea. • Approximately 9 additional patients would experience fatigue. • Approximately 1 additional patient would experience febrile neutropenia (development of fever in a patient with neutropenia). • The increased risk of pulmonary embolism (where an artery in the lungs becomes blocked by a blood clot) was small but observed in the clinical trial. • The increased risk of occurrence of QTc interval prolongation (changes in the heart's rhythm) was small but observed in the clinical trial.
			Economic claim: Cost-effectiveness and cost-utility analysis	<p>The PBAC considered the economic model in the re-submission to be unreliable for decision making, because the claimed outcomes were likely to have been overestimated based on the evidence available in the clinical trials. The PBAC were still of the view that increased cost to the health care system for the potential patient benefit of ribociclib over the treatments currently available in Australia may be greater than the sponsor claimed, and would have an opportunity cost to the funding of other therapies through the PBS.</p>

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<p>TRIFLURIDINE WITH TIPIRACIL</p> <p>Tablet containing 15 mg trifluridine with 6.14 mg tipiracil (as hydrochloride) Tablet containing 20 mg trifluridine with 8.19 mg tipiracil (as hydrochloride)</p> <p>Lonsurf®</p> <p>Servier Laboratories (Australia) Pty Ltd</p> <p>New listing (Minor Submission)</p>	<p>Indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.</p>	<p>TRIFLURIDINE WITH TIPIRACIL is not currently PBS listed.</p>	<p>Sponsor's comments:</p>	<p>The sponsor had no comment.</p>
			<p>Resubmission to request an Authority Required (STREAMLINED) listing for the treatment of metastatic colorectal cancer (mCRC).</p>	<p>The PBAC did not recommend the listing of trifluridine with tipiracil on the PBS for treatment of patients with metastatic colorectal cancer (mCRC) who have been treated previously or are not considered suitable for current available therapies. The PBAC based its decision on the modest clinical benefit and moderate toxicity, noting that the clinical benefit observed in the trial may not be realised in clinical practice. The PBAC was concerned that the financial impact of listing was substantial, with a total net cost to the PBS of \$30 -\$60 million over the first 6 years of listing. The PBAC considered that this represented a significant opportunity cost for the Commonwealth for funding of other therapies through the PBS.</p>
			<p>Comparator: Best supportive care (BSC)</p>	<p>Accepted</p>
			<p>Clinical claim: Superior efficacy and inferior safety of trifluridine/tipiracil compared with BSC.</p>	<p>There was no change to the clinical claim from March 2017 resubmission. The PBAC previously accepted the claim of superior comparative effectiveness and inferior safety. However the PBAC considered the magnitude of benefit to be modest.</p>
			<p>Economic claim: Cost-utility analysis of trifluridine/tipiracil Cost-utility analysis of trifluridine/tipiracil</p>	<p>The PBAC noted that incorporating the proposed reduced price for trifluridine/tipiracil resulted in an incremental cost-effectiveness ratio (ICER) lower than that presented in the previous July 2017 submission. The PBAC considered that the analysis did not adequately account for PBS patients being likely to have additional and/or more extensive comorbidities compared with the trial patients.</p>
<p>Sponsor's comments:</p>	<p>The Sponsor had no comment.</p>			