

March 2007 PBAC Outcomes – Subsequent Decisions not to Recommend

Drug and Form	TGA Indication	Current PBS Listing	Listing Requested by Sponsor	PBAC Outcome and Comments
<p>Adefovir dipivoxil tablet 10 mg (Hepsera[®]) Gilead Sciences Pty Ltd</p> <p>Major submission</p>	<p>Treatment of chronic hepatitis B in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease. This indication is based on histological, virological, biochemical, and serological responses in adult patients with HBeAg+ and HBeAg-/HBV DNA+ chronic hepatitis B with compensated liver function, and in adult patients with clinical evidence of lamivudine-resistant hepatitis B virus with either compensated or decompensated liver function</p>	<p>Section 100 Highly Specialised Drug listing for: Chronic hepatitis B in a patient who has failed antihepadnaviral therapy and who satisfy all of the following criteria (1) Repeatedly elevated (greater than 1.2 times the upper limit of normal) serum ALT levels while on concurrent antihepadnaviral therapy of greater than or equal to 6 months duration in conjunction with documented chronic hepatitis B infection (HBe antigen positive and/or serum HBV DNA positive); (2) Female patients of child-bearing age are not pregnant, not breast-feeding, and are using an effective form of contraception. Persons with Child's class B or C cirrhosis (ascites, variceal bleeding, encephalopathy, albumin</p>		<p>PBAC rejected the application because of uncertain clinical effect and uncertain cost-effectiveness in the population for whom listing was requested.</p>
			<p>Section 100 Highly Specialised Drug listing for: Patients with chronic hepatitis B who satisfy the following criteria: (1) Active chronic hepatitis B (HBe antigen positive and/or serum HBV DNA positive) with advanced liver disease (either evidence of cirrhosis on liver biopsy or a Child Pugh Turcotte score greater than 5), adefovir may be used in combination with lamivudine. (2) Active chronic hepatitis B (HBe antigen positive and/or serum HBV DNA positive) in patients who are failing antihepadnaviral therapy as demonstrated by repeatedly elevated (greater than 1.2 times the upper limit of normal) serum ALT levels. Patients must have received concurrent antihepadnaviral therapy of greater than or equal to 6 months. Patients may receive PBS subsidised treatment of</p>	<p>Accepted</p>

		<p>less than 30 g per L, bilirubin greater than 30 micromoles per L) should have their treatment discussed with a transplant unit prior to initiating therapy.</p> <p>NOTE: Patients should have undergone a liver biopsy at some point since initial diagnosis to obtain histological evidence of chronic hepatitis.</p> <p>Patients may receive treatment in combination with lamivudine for the initial 3 months only of PBS-subsidised adefovir dipivoxil therapy. Patients who are immunocompromised may receive treatment in combination with lamivudine for the initial 12 months of PBS-subsidised adefovir dipivoxil therapy. Thereafter, PBS-subsidised adefovir dipivoxil must be used as monotherapy.</p>	<p>lamivudine in combination with adefovir for the initial 3 months only of PBS subsidised adefovir, unless patients have advanced liver disease (evidence of cirrhosis on liver biopsy or a Child Pugh Turcotte score greater than 5), in which case adefovir may be used in combination with lamivudine.</p> <p>(3) Patients with a prior history of liver transplant for CHB. Adefovir may be used in combination with lamivudine.</p> <p>(4) Female patients of childbearing age are not pregnant, not breastfeeding, and are using an effective form of contraception.</p> <p>NOTE Patients should have undergone a liver biopsy at some point since initial diagnosis to obtain histological evidence of chronic hepatitis.</p>	
			<p>Comparator: lamivudine monotherapy followed by adefovir dipivoxil monotherapy as the main comparator for patients with lamivudine-sensitive HBV (treatment-naive, treatment-experienced/lamivudine-sensitive, post-transplant/lamivudine sensitive) and adefovir dipivoxil monotherapy for patients with lamivudine-resistant HBV (treatment-experienced/lamivudine-resistant, post-transplant/lamivudine resistant)</p>	<p>PBAC agreed that entecavir is a potentially competing drug with the adefovir and lamivudine combination.</p>

			<p>Clinical claim: adefovir dipivoxil plus lamivudine combination therapy has significant advantages in effectiveness over the main comparator and is associated with similar or less toxicity.</p>	<p>Partially accepted. The PBAC noted that new information had been provided to: (i) support the claim that the development of resistance in CHB patients with cirrhosis or post-liver transplant leads to clinically meaningful outcomes; (ii) the resistance rates reported for adefovir given sequentially in lamivudine resistant patients are higher than for treatment naïve patients given adefovir; and (iii) lower rates of resistance develop to lamivudine and adefovir when given concomitantly compared with sequential lamivudine and adefovir treatment. A conclusion that the onset of resistance was delayed by 12 months, rather than for an extended period could be drawn from the new information.</p>
			<p>Economic claim: cost-effectiveness</p>	<p>Partially accepted. The new data presented did not assist the PBAC in forming a view about the cost effectiveness of combination therapy. The results were difficult to critically appraise given the lack of control, lack of blinding, possible confounding variables and selection bias inherent in the study designs.</p>
			<p>Sponsor's comments:</p>	<p>The sponsor looks forward to working with the PBAC to resolve the issues that have been identified.</p>

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<p>Memantine hydrochloride tablets 10 mg and 10 mg/mL drops (Ebixa®) Lundbeck Australia Pty Ltd</p> <p>Major submission</p>	<p>Treatment of the symptoms of moderately severe to severe Alzheimer's disease.</p>	<p>Not PBS listed.</p>		<p>PBAC considered that it could not be concluded that memantine is no worse than donepezil in terms of effectiveness and therefore rejected the submission for listing.</p>
			<p><u>Authority required</u> Initial treatment of moderately severe Alzheimer's disease. Confirmation of this diagnosis must be made by a specialist/consultant physician (including a psychiatrist). The authority application must include the result of the baseline Mini-Mental State Examination (MMSE) or Standardised Mini-Mental State Examination (SMMSE). This baseline (S)MMSE must be a score of 10 - 14. This application must be made in writing, but initial supply may be sought by telephone. For telephone applications, up to a maximum of 2 months' initial therapy will be authorised. This telephone application must be followed by a written authority application for no more than 1 month's therapy and sufficient repeats to complete a maximum of up to 6 months' initial treatment. For written applications where no prior telephone approval has been issued, up to a maximum of 1 month's therapy plus 5 repeats</p>	<p>PBAC noted that listing was sought for the treatment of moderately severe Alzheimer's disease in patients who have a baseline Mini-Mental State Examination (MMSE) or SMMSE (standardised MMSE) of 10-14 and considered the submission did not provide sufficiently comprehensive Mini-Mental State Examination (MMSE) data for memantine.</p>

			<p>will be authorised</p> <p>Continuing treatment, following initial PBS-subsidised therapy, of moderately severe Alzheimer's disease in patients with demonstrated improvement in cognitive function as measured by an increase of at least 2 points from baseline on the Mini-Mental State Examination (MMSE) or Standardised Mini-Mental State Examination (SMMSE).</p> <p>The initial authority application for continuing treatment must include the relevant result from the (S)MMSE and must be in writing. Subsequent applications for continuing treatment can be made by telephone.</p> <p><u>Authority required</u></p> <p>Initial treatment of moderately severe Alzheimer's disease of patients with a baseline Mini-Mental State Examination (MMSE) or Standardised Mini-Mental State Examination (SMMSE) score of 9 or less, who are unable to register a score of 10-14 for reasons other than their Alzheimer's disease, as specified below. Confirmation of this diagnosis must be made by a specialist/consultant physician (including a psychiatrist). Such patients will need to be assessed using the Clinicians Interview Based Impression of Severity (CIBIS) scale. The authority application must include the result of the baseline (S)MMSE and specify to which</p>	
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			<p>group(s) (see below) the patient belongs.</p> <p>This application must be made in writing, but initial supply may be sought by telephone.</p> <p>For telephone applications, up to a maximum of 2 months' initial therapy will be authorised. This telephone application must be followed by a written authority application for no more than 1 month's therapy and sufficient repeats to complete a maximum of up to 6 months' initial treatment.</p> <p>For written applications where no prior telephone approval has been issued, up to a maximum of 1 month's therapy plus 5 repeats will be authorised.</p> <p>Patients who qualify under this criterion are from 1 or more of the following groups:</p> <ul style="list-style-type: none">(1) Unable to communicate adequately because of lack of competence in English, in people of non-English speaking background;(2) Limited education, as defined by less than 6 years of education, or who are illiterate or innumerate;(3) Aboriginal or Torres Strait Islanders who, by virtue of cultural factors, are unable to complete an (S)MMSE test;(4) Intellectual (developmental or acquired) disability, eg Down's syndrome;(5) Significant sensory impairment despite best correction, which precludes completion of an	
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			<p>(S)MMSE test; (6) Prominent dysphasia, out of proportion to other cognitive and functional impairment Continuing treatment, following initial PBS-subsidised therapy, of moderately severe Alzheimer's disease in patients with demonstrated improvement in function, based on a rating of "very much improved" or "much improved" on the Clinicians Interview Based Impression of Change (CIBIC) scale, which must be assessed by the same clinician who initiated treatment. The initial authority application for continuing treatment must state the improvement achieved on the CIBIC scale and must be in writing. Subsequent applications for continuing treatment can be made by telephone.</p>	
			<p>Comparator: Donepezil</p>	<p>Accepted.</p>
			<p>Clinical claim: Memantine is as safe and effective as donepezil for the treatment of moderately severe Alzheimer's disease.</p>	<p>Notwithstanding the statistical results indicating that there is no statistically significant difference between memantine and donepezil (indirect comparison vs. placebo), the mean data suggested that memantine may have a numerically smaller effect overall. Further, no evidence was provided to demonstrate that memantine can increase the MMSE score by 2 points. PBAC also noted that in general, the trial results presented for donepezil vs. placebo were consistently larger in most of the</p>

				measures (except Severe Impairment Battery). In addition, the trial results for Neuropsychiatric Inventory (NPI) were close to reaching a statistically significant difference favouring donepezil.
			Economic claim: Cost minimisation	Rejected. PBAC considered that it could not be concluded that memantine is no worse than donepezil in terms of effectiveness.
			Sponsor's comments:	The sponsor looks forward to working with the PBAC to resolve the issues that have been identified.

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<p>Nicotinic acid tablets prolonged release 500 mg, 750 mg and 1000 mg. (Niaspan[®]) Alphapharm Pty Limited</p> <p>Major submission</p>	<p>“Treatment of mixed dyslipidaemia, and primary hypercholesterolaemia, as adjunctive therapy to diet. Prior to initiating therapy with nicotinic acid, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.”</p>	<p>Not PBS listed.</p>		<p>PBAC rejected the application on clinical grounds because in the key trial submitted there was no statistically significant benefit demonstrated for prolonged release nicotinic acid plus statin over placebo plus statin, uncertainty that the key trial outcome (change in CIMT) was a validate surrogate for improved cardiovascular outcomes, and uncertainty associated with the impact of raising HDL-C on cardiovascular outcomes.</p>
			<p><u>Restricted benefit</u> Niaspan is indicated for use in combination with a HMG CoA reductase inhibitor (statin) in patients with dyslipidaemia with adequately controlled LDL-C and whose HDL-C levels are inadequately controlled despite monotherapy with a statin. Inadequate control is defined as HDL-C<1 mmol/L after at least 3 month's treatment with a statin.</p>	<p>Accepted, subject to minor changes.</p>
			<p>Comparator: placebo in combination with ongoing statin therapy.</p>	<p>Accepted</p>
			<p>Clinical claim: Nicotinic acid has significant advantages in effectiveness over the main comparator and is associated with similar or less toxicity.</p>	<p>Not accepted. PBAC noted there was no statistically significant difference in mean change from baseline to endpoint CIMT (carotid intima-media thickness) for patients treated with prolonged release nicotinic acid plus a statin, however, there was a significant increase in CIMT in patients treated</p>

				<p>with placebo plus a statin. The difference between the two treatment groups did not reach statistical significance (p=0.08). There was a statistically significant increase in HDL-C during the 12-month trial duration for patients treated with prolonged release nicotinic acid plus a statin, and there was no evidence of a change in HDL-C for patients treated with placebo plus a statin. However, the use of changes in CIMT as a surrogate outcome was not considered by the PBAC to be adequately validated at this time.</p>
			Economic claim: Cost-effectiveness	Not accepted given the PBAC's conclusion about the clinical data.
			Sponsor's comments:	The sponsor is considering its position regarding any future submission.