National Centre for Pharmacoeconomics
NCPE Ireland

Beneluxa
Initiative on Pharmaceutical Policy

Beneluxa Joint Assessment

Summary

September 2022

Atidarsagene autotemcel (Libmeldy™) for the treatment of metachromatic leukodystrophy characterized by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity:

- in children with late infantile or early juvenile forms, without clinical manifestations of the disease
- in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline

The Beneluxa Joint Assessment was conducted as part of the Beneluxa Initiative on Pharmaceutical Policy. The cost-effectiveness component of the Joint Assessment was conducted by the National Centre for Pharmacoeconomics, Ireland, with input from the ZIN, Netherlands. The pharmacotherapeutic component of the Joint Assessment was conducted by RIZIV-INAMI, Belgium. Please see https://beneluxa.org/ for further information.

Key Points for the Decision Maker

- Metachromatic leukodystrophy (MLD) is a rare inherited lysosomal storage disease caused by deficiency of arylsulfatase A (ARSA).
- The intervention assessed in this dossier is atidarsagene autotemcel (Libmeldy™) licensed by the EMA in December 2020. It a one-time gene therapy consisting of genetically modified autologous CD34+ haematopoietic stem and progenitor cells which contain the functional human arylsulfatase A *(*ARSA*)* gene.
- Clinical efficacy is derived from single-armed, open-label studies. Comparative effectiveness is informed by a comparison with a symptomatic cohort of MLD patients from the natural history OSR-TIGET NHx study.
- Clinical benefit is marginally greater in pre-symptomatic late infantile patients although there remains considerable uncertainty about the quantity of benefit.
- A cost utility model examines the cost effectiveness in three patient subgroups: pre-symptomatic late infantile (PS-LI); pre-symptomatic early juvenile (PS-EJ); and early symptomatic early juvenile (ES-EJ). The groups are modelled separately and combined for the full population using a weighted average of each subgroup per country.
- The model structure adequately maps the disease and treatment pathway; however, choices around how patients progress through the model are overly optimistic for atidarsagene autotemcel.
- Best supportive care (BSC) is considered as comparator for all three countries.
- The data used to inform treatment effectiveness in the model for the BSC arm comes from the OSR-TIGET NHx. Treatment effect for the intervention is informed by a subset of patients from the single-arm clinical study (Study 201222) and data from expanded access programmes.
- Assumptions in relation to treatment effects have a significant impact on the model; in particular, the classification of response and the assumption of cure.
- As quality-of-life data was not gathered in the clinical trials, a study was commissioned by the Applicant to inform the cost utility model. This study and the subsequent analysis are not considered to be robust by the Review Group.

- The estimates of cost effectiveness lie above all explicit country specific thresholds and therefore atidarsagene autotemcel is not considered to be cost effective at the proposed price.
- The Review Group has presented a proposal for an alternative base case where a treatment waning effect is considered after 10 years in a proportion of patients. This has a substantial impact on the ICERs, increasing them across all patients' groups.
- The budget impact is appropriately estimated to include incident patients only. The cumulative net drug budget impact for Ireland for five years is €9.8m.

Summary

The National Centre for Pharmacoeconomics (NCPE) completed a joint assessment as part of the Beneluxa collaboration for atidarsagene autotemcel (Libmeldy™) for the treatment of patients with metachromic leukodystrophy (MLD). The assessment was undertaken between the Netherlands, Belgium and Ireland. Below is a summary of the two reports completed on relative effectiveness and the pharmacoeconomic assessment.

Table 1 Description of atidarsagene autotemcel

International non-proprietary name	Atidarsagene autotemcel
Proprietary Name	Libmeldy™
Pharmacotherapeutic Group	Other haematological agents
ATC code	A16AB21
Licensed indication	For the treatment of metachromatic leukodystrophy characterized by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity: • in children with late infantile (LI) or early juvenile (EJ) forms, without clinical manifestations of the disease • in children with the EJ form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.
Mechanism of action	Atidarsagene autotemcel is a gene therapy containing an autologous CD34+ cell enriched population that contains haematopoietic stem and progenitor cells transduced *ex vivo* using a lentiviral vector encoding the human ARSA gene. When administered to a patient following administration of a myeloablative conditioning regimen, the genetically modified cells engraft and can produce and secrete the functional ARSA enzyme. This can then be used to break down, or prevent the build-up of, harmful sulfatides. Following successful and stable engraftment in the patient, the effects of the product are expected to be persistent.
Formulation	Dispersion for infusion. The medicinal product is composed of one or more infusion bags containing a dispersion of 2-10 x 10^6 cells/mL suspended in a cryopreservative solution. Each infusion bag contains 10 to 20 mL of AA. The total number of cells and concentration of CD34+ cells can vary between individual patient batches.
Dose	The dose of Atidarsagene autotemcel to be administered is defined based on the patient's weight at the time of infusion. The minimum dose of AA is 3 x 10^6 CD34+ cells/kg.
Administration	Single-dose intravenous infusion preceded by myeloablative conditioning.
Duration of treatment	Once only administration
Other aspects	Atidarsagene autotemcel is a hospital-only treatment which must be administered in a qualified treatment centre with experience in haematopoietic stem cell transplantation (HSCT). Atidarsagene autotemcel is intended solely for autologous use and should under no circumstances be administered to other patients. It is administered via a central venous catheter. Treatment should be performed before the disease enters its rapidly progressive phase.

Description and Epidemiology of the disease

MLD is an autosomal recessively inherited lysosomal storage disorder caused by mutations in the ARSA gene, resulting in deficiency of its corresponding ARSA enzyme. The ARSA enzyme breaks down sulfatides in the nervous system; ARSA deficiency results in accumulation of harmful sulfatides in the nervous system tissues and other organs. Over time, accumulation of sulfatides leads to neurodegeneration, loss of motor and cognitive function, and early death.

The clinical classification of MLD depends on age of onset. The forms of MLD relevant to this submission include the late infantile form (LI; onset before 30 months) and the early juvenile form (EJ; onset 30 months to ≤7 years). Atidarsagene autotemcel is not licensed for use in late juvenile and adult forms. The clinical course of MLD can be divided into a 'pre-symptomatic' (PS) stage with normal development, followed by onset of first symptoms ('early symptomatic' [ES]) and a period of developmental stagnation. Following this plateau, rapid disease progression occurs, characterised by neurodegeneration which leads to a severely disabled state with loss of all motor and cognitive function. Death occurs within 1 to 7 years of onset in patients with the LI form, and 3 to 15 years of onset in patients with the EJ form.

The estimated incidence of MLD ranges from 1.4-1.8/100,000 live births, with a prevalence rate of 1 in 40,000-160,000. Using Irish population data, prevalence is expected to range from 31 to 125 individuals, with an incidence of approximately one patient (0.8 to 1.1) per year.

Clinical and comparative effectiveness

Clinical effectiveness

Two studies (Study 201222 [n=20] and Study 205756 [n=4]) were included in the clinical study program. Clinical data were also available from three expanded access programs (EAPs) (CUP 207394, CUP 206258 and HE 205029 [n=9]). Of the 33 participants enrolled, 18 had the LI form of MLD and 15 had the EJ form. Of the LI patients, all but one participant had PS-LI MLD (one participant developed symptoms of progression immediately prior to treatment with atidarsagene autotemcel). Of the participants with the EJ form, eight were

pre-symptomatic (PS-EJ) and seven were early symptomatic (ES-EJ). Participants in Study 201222 and the EAPs were treated with the fresh formulation of atidarsagene autotemcel. Participants in Study 205756 received the intended commercial cryopreserved formulation, to evaluate the efficacy and safety of the cryopreserved formulation vs. the fresh formulation. Due to the very limited data and short follow-up period, a valid comparison with the fresh formulation was not feasible. The primary efficacy outcome parameters measured in the clinical studies included mortality, motor function (Gross Motor Function Measure-88 [GMFM-88] and Gross Motor Function Classification in MLD [GMFC-MLD]) and cognitive development (IQ). Clinical data from the initial data cut-off (March 2018) was provided, with additional data from a later data cut-off (December 2019) provided for a subset of participants.

Table 2 Clinical efficacy outcomes

	Study 201222			Study 205756		EAP*	
Form of MLD	**PS-LI**	**PS-EJ**	**ES-EJ**	**PS-LI**	**PS-EJ**	**PS-LI**	**PS-EJ**
Number of patients	9	4	7	3	1	7	1
Survival, n (%)	9/9 (100%)	4/4 (100%)	5/7 (71.4%)	3/3 (100%)	1/1	6/7 (85.7%)	1/1
GMFM-88 score							
At baseline	59.1%	92.4%	84.6%	45.8%	94.9%	41.5%	56.1%
Follow-up (at 2 years)	72.5%	96.7%	60.7%	76.66%†	NA	NA	NA
GMFM-88 within normal median range, n (%)							
Yes	4/9 (44.4%)	3/4 (75%)	0/7 (0%)	3/3 (100%)	1/1	7/7 (100%)	1/1
No	5/9 (55.6%)	1/4 (25%)	7/7 (100%)	0/3 (0%)	0/1	0/7 (0%)	0/1
Median IQ (verbal), points							
At 3 years	94	100	89‡	NA	NA	NA	
Median IQ (performance), points							
At 3 years	102	119	95‡	NA	NA	NA	

EAP: expanded access program; **GMFM-88**: Gross Motor Function Measure 88; **IQ**: intelligence quotient; **NA**: not available

*Data for HE 205029 and CUP 206258 included; data from CUP 207394 (n=1; ES-EJ) not included

†Follow-up at one year

‡Follow-up at one year; n=1

To date, only open-label, single-arm studies are available. The numbers of participants recruited to the clinical study program are low. For many participants the available follow-up period is limited.

Comparative effectiveness

Efficacy data from participants who received atidarsagene autotemcel were compared to a natural history cohort (Telethon Institute for Gene therapy, Natural History Study 204949 [OSR-TIGET NHx]), who were considered representative of patients treated with BSC. All of the 19 LI MLD patients and all of the 12 EJ MLD patients in the comparative OSR-TIGET NHX study were symptomatic at enrolment in the study, which introduces a timing bias for the comparison on MLD progression and therefore comparisons with pre-symptomatic patients is challenging.

When comparing patients who received atidarsagene autotemcel to the OSR-TIGET NHx cohort, in the pre-symptomatic cohorts some benefit was observed for gross motor function and IQ; however, given the limited patient numbers this benefit is considered to be associated with uncertainty. For the ES-EJ cohort, the clinical effectiveness of atidarsagene autotemcel appears less pronounced. The adjusted least squares mean GMFM-88 total score at year two post-treatment was 60.7%, compared to a non-statistically significant difference from the OSR-TIGET NHx group of 28.7% (95% CI -14.1 to 71.5, p=0.35). At year three, the difference remained not statistically significant, with a treatment effect difference of 43.9% (59.8% vs. 15.9%; p=0.054). In some of these patients, the baseline GMFM-88 scores were initially below the normal range, and these patients experienced either a rapid or a slower decline in GMFM-88 after atidarsagene autotemcel.

The results of the comparisons between outcomes in patients on atidarsagene autotemcel and in the OSR-TIGET NHx cohort are likely to be subject to bias and are highly uncertain. As highlighted, no pre-symptomatic patients were included in the OSR-TIGET NHx cohort, meaning it is likely a comparison versus this dataset will be biased in favour of atidarsagene autotemcel due to the slightly more advanced stage of patients in the OSR-TIGET NHx study (symptomatic). Given the limitations of the data, it is difficult to conclude on the added clinical benefit in terms of mortality. In addition, the follow-up period for the majority of patients at this time is too short.

Safety

Treatment with atidarsagene autotemcel is preceded by medical interventions (either haematopoietic stem cell collection or peripheral blood mobilisation, and myeloablative conditioning [preferably with busulfan]), which are associated with considerable risk of toxicity. The majority of adverse events reported by participants in the clinical study program occurred in the three-month post-treatment and short-term follow-up phases. No adverse events deemed to be associated with atidarsagene autotemcel were reported. To date, three deaths have occurred in subjects treated with atidarsagene autotemcel (two were related to disease progression, one was from a cerebral infarction).

Cost effectiveness

The Applicant submitted a cost-utility analysis to assess the cost effectiveness of atidarsagene autotemcel compared to best supportive care (BSC).

Model structure

A cohort state-transition model was submitted, consisting of eight health states: seven motor function health states defined mainly by GMFC-MLD score, and a death state. Only forward transitions to worse health states were considered, and mortality related to MLD only occurred from the worst motor function health state. Within each motor function health state, cognitive substates were also modelled for EJ populations.

Table 3 Decision problem and model structure

Population	The modelled population is a combination of three patient subgroups: • pre-symptomatic late infantile (PS-LI): children with a confirmed diagnosis of late infantile (LI) metachromatic leukodystrophy (MLD) without clinical manifestations of the disease. • pre-symptomatic early juvenile (PS-EJ): children with a confirmed diagnosis early juvenile (EJ) MLD without clinical manifestations of the disease. • early symptomatic early juvenile (ES-EJ): children with EJ MLD who have early clinical manifestations of the disease with the ability to walk independently and before the onset of cognitive decline (defined as gross motor function classification in MLD (GMFC-MLD) ≤1 and intelligence quotient (IQ) ≥85). Results are presented separately for each subgroup, and combined for the full population (as a weighted average across the subgroups)
Intervention	Atidarsagene autotemcel
Comparators	Best Supportive Care (BSC)
Outcomes	Quality adjusted life years (QALYs) and costs
Time horizon	Lifetime
Discount rate	Ireland: 4% for costs and benefits Belgium: 3% for costs and 1.5% for benefits. Netherlands: 4% for costs and 1.5% for benefits.
Perspective	Ireland: Payer Belgium: Payer Netherlands: Societal

Treatment effects for the cost-effectiveness model

For atidarsagene autotemcel, pooled data from a subset of patients from Study 201222 and the EAPs (CUP 206258 and HE 205029) who met the definition of the modelled population were used to inform the analysis (n=25). Study 205756 of the cryopreserved formulation of atidarsagene autotemcel was not used, as the Applicant considered the available length of follow-up too short. Data from the OSR-TIGET NHx study were used to inform BSC.

Treatment effects for atidarsagene autotemcel versus BSC were informed by a naïve ITC. The Applicant classified patients in the pooled atidarsagene autotemcel clinical data as either full or partial responders, with partial responders additionally separated into stable and unstable partial responders. The Review Group considers the classification methodology

used in the analysis to be highly subjective, and lacks both rigour and transparency. In the Applicant's base case, it was assumed that the treatment effect of atidarsagene autotemcel would be maintained throughout the lifetime, implying a curative effect. The Review Group considered this assumption to be subject to considerable uncertainty, with very limited supportive clinical evidence.

Health-related quality of life

No health-related quality of life endpoints were collected during the clinical study program. Health state utilities are primarily informed by a UK study commissioned by the Applicant using vignettes and the time trade off approach to utility calculation. The Review Group had concerns regarding the plausibility of the utility values applied in the model. A number of issues arose including poor correlation of the valuations with gross motor function states, inconsistency in some of the valuations where worse states are valued higher than better health states and, as advised by clinical opinion, the plausibility of the severe worse than death health states. Furthermore, there are large differences in the utilities experienced by patients with LI and EJ subtypes for the same motor function health state, which does not seem plausible. No alternative plausible values were identified through literature review. While the Review Group conducted various scenario analyses, alternative approaches did not have substantial impact on the cost-effectiveness estimates.

Health care resource use and costs

The Price to Wholesaler of atidarsagene autotemcel is €2,875,000 per dose. Costs for administration of atidarsagene autotemcel and BSC were also included, as well as the cost components of long-term provision of BSC. The estimation of the anticipated cost of administering atidarsagene autotemcel and follow-up of these patients is complicated by the fact that patients in Belgium and Ireland will receive treatment in other jurisdictions. While the cost inputs, outside of the cost of atidarsagene autotemcel, applied in the model are associated with uncertainties, they have limited impact on the cost-effectiveness estimates.

Results

Results of the cost utility analysis

The Applicant estimated ICERs for atidarsagene autotemcel versus BSC for three subgroups (PS-LI, PS-EJ and ES-EJ) and the combined cohort (Table 4). The Review Group highlighted that the combined cohort ICER has limited usefulness given the considerable differences in treatment benefit (and therefore cost effectiveness) and associated uncertainty between disease subgroups.

Table 4 Results of Applicant's base case cost-effectiveness analysis (discounted)

	Intervention	Total Costs (€)	Total Lys	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)
Population: combined cohort							
Belgium							
	AA	3,187,424	39.90	25.40	3,011,290	25.47	118,234
	BSC	176,135	11.30	0.00	-	-	
The Netherlands (societal)							
	AA	3,648,703	39.51	24.48	2,649,787	24.59	107,777
	BSC	998,916	11.58	-0.11	-	-	-
Ireland							
	AA	2,991,128	22.74	14.49	2,269,761	15.48	146,642
	BSC	721,367	8.92	-0.99	-	-	-
Population: PS-LI subgroup							
Belgium							
	AA	3,165,215	43.82	26.77	2,997,291	26.60	112,676
	BSC	167,924	9.40	0.17	-	-	
The Netherlands (societal)							
	AA	3,607,596	44.14	26.82	2,639,667	26.65	99,035
	BSC	967,929	9.40	0.17	-	-	-
Ireland							
	AA	2,957,293	23.39	14.53	2,224,505	15.44	144,078
	BSC	732,788	8.20	-0.91	-	-	-
Population: PS-EJ subgroup							
Belgium							
	AA	3,138,381	38.51	32.12	2,958,946	32.03	92,374
	BSC	179,435	12.36	0.09	-	-	
The Netherlands (societal)							
	AA	3,256,280	38.77	31.80	2,229,654	31.72	70,299
	BSC	1,026,625	12.36	0.08	-	-	-
Ireland							
	AA	2,934,128	21.48	17.69	2,238,988	18.63	120,207
	BSC	695,140	10.43	-0.94	-	-	-
Population: ES-EJ subgroup							
Belgium							
	AA	3,257,757	37.61	17.44	3,077,053	17.82	172,671
	BSC	180,704	11.95	-0.38	-	-	
The Netherlands (societal)							
	AA	3,981,147	37.99	17.56	2,990,215	17.94	166,671
	BSC	990,931	11.95	-0.39	-	-	-
Ireland							
	AA	3,214,112	21.47	10.16	2,509,341	11.59	216,567
	BSC	704,772	10.11	-1.43	-	-	-

AA: atidarsagene autotemcel; **BSC**: best supportive care; **ICER**: incremental cost-effectiveness ratio; **LY**: life adjusted life years, **QALY**: Quality Adjusted Life Year

The Review Group considered the quantity of overly optimistic assumptions and the lack of transparency around how data were used to inform key parameters to be problematic. The Review Group highlighted that the assumption of cure associated with atidarsagene autotemcel is subject to considerable uncertainty given the limited data availability. In order to consider the impact of these uncertainties on the cost effectiveness, the Review Group implemented an alternative base case where after ten years all full and stable partial responders experienced a decline in motor function health state, in line with the transition probabilities for unstable partial responders (
Table 5). While the implementation of this alternative base case results in higher ICERs than the Applicant's base case there remain uncertainties around these estimates. In particular, the structural uncertainties associated with the modelling choices for response criteria and the limited amount of patient data informing some subgroups mean that the ICERs are not equally sensitive to variations around the assumption of cure.

Table 5 Results of the Review Group's alternative base case (discounted)

	Intervention	Total Costs (€)	Total Lys	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)
Population: combined cohort							
Belgium							
	AA	3,246,072	19.62	8.39	3,069,938	8.43	364,048
	BSC	176,135	11.26	-0.04	-	-	-
The Netherlands (societal)							
	AA	3,815,220	19.73	8.49	2,816,304	8.60	327,423
	BSC	998,916	11.58	-0.11	-	-	-
Ireland							
	AA	3,307,102	14.88	5.78	2,585,735	6.77	382,069
	BSC	721,367	8.92	-0.99	-	-	-
Population: PS-LI subgroup							
Belgium							
	AA	3,238,154	18.54	6.51	3,070,230	6.33	484,711
	BSC	167,924	9.40	0.17	-	-	-
The Netherlands (societal)							
	AA	3,884,761	18.54	6.47	2,916,832	6.30	462,632
	BSC	967,929	9.40	0.17	-	-	-
Ireland							
	AA	3,309,802	14.57	4.97	2,577,014	5.88	438,495
	BSC	732,788	8.20	-0.91	-	-	-
Population: PS-EJ subgroup							
Belgium							
	AA	3,232,047	21.25	11.41	3,052,612	11.32	269,672
	BSC	179,435	12.36	0.09	-	-	-
The Netherlands (societal)							

	AA	3,555,048	21.26	11.30	2,528,422	11.22	225,400
	BSC	1,026,625	12.36	0.08	-	-	-
Ireland							
	AA	3,247,812	16.01	8.86	2,552,672	9.80	260,467
	BSC	695,140	10.43	-0.94	-	-	-
Population: ES-EJ subgroup							
Belgium							
	AA	3,267,688	19.03	7.18	3,086,984	7.56	408,461
	BSC	180,704	11.95	-0.38	-	-	-
The Netherlands (societal)							
	AA	3,991,388	19.04	7.17	3,000,457	7.56	396,882
	BSC	990,931	11.95	-0.39	-	-	-
Ireland							
	AA	3,371,687	14.80	5.36	2,666,915	6.79	392,864
	BSC	704,772	10.11	-1.43	-	-	-

AA: atidarsagene autotemcel**; BSC**: best supportive care; **ICER**: incremental cost-effectiveness ratio; **LY**: life adjusted life years, **QALY**: Quality Adjusted Life Year

Uncertainty

The modelling of treatment effectiveness was the key driver in the cost-effectiveness analysis. Given the limited data informing the cost-effectiveness model, sensitivity analysis based on arbitrary +/- 20% variation is limited in its ability to meaningfully capture uncertainty in the model inputs and their impact on cost effectiveness. It was not possible to vary all parameters according to the variance of the observed data, meaning it is likely that uncertainty is underestimated.

Budget Impact

The budget impact of atidarsagene autotemcel across all three countries is presented in Table 6. In Ireland, it is assumed that three patients will be treated over the five-year period. The five-year cumulative gross drug budget impact is €9,940,314. The net drug budget impact is similar as there are no appreciable cost offsets from comparator therapies. When additional non-drug, health-related costs and cost offsets are considered, the five-year cumulative net health budget impact is €9,763,011.

Table 6 Budget impact for atidarsagene autotemcel

	Year 1	Year 2	Year 3	Year 4	Year 5	Cumulative
Gross drug						
Belgium*	€3.05m	€0	€3.05m			€6.10m (3 year)
Netherlands*†	€5.75m	€2.88m	€575.m			€14.38m (3 year)
Ireland	€3.33m	€0	€3.33m	€0	€3.33m	€9.94m (5 year)
Net health^						

Belgium*	€3.08m	€0	€3.07m			€6.15m
Ireland	€3.40m	-€0.05m	€3.32m	-€0.14m	€3.25m	€9.76m

Figures are rounded and therefore calculations may not be reproducible. For all countries, the gross drug budget impact equals the net drug budget impact.
^Net health budget impact not required for Netherlands
*Three year budget impact only required for Belgium and The Netherlands.
†This scenario uses clinical opinion to estimate the number of eligible patients. Using the epidemiological model, two patients were estimated to be eligible for treatment over five years, at a gross drugs budget impact of €5,750,000

Patient Submission

A patient organisation submission, from Rare Diseases Ireland, was received during the course of this assessment and this forms part of the documentation submitted to the HSE for consideration in the decision making process.

Conclusion

The benefit of atidarsagene autotemcel (versus BSC) appears to be marginally greater in patients who have not yet developed symptoms and in those with the LI subtype. While longer-term data in some patients up to eight years indicates that there is disease stabilisation, it is not clear how this fully compares with a robustly matched cohort of patients. The main driver of cost effectiveness is the classification and duration of response; the amount of data available to robustly inform this was limited. For these reasons, the Review Group consider the uncertainty associated with both the added clinical benefit and cost effectiveness of atidarsagene autotemcel relative to BSC to be considerable. For all countries, a significant price reduction would be required to reduce the uncertainty with regard to cost effectiveness.

Recommendation for Ireland

The NCPE recommends that atidarsagene autotemcel not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatment*.

**This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.*