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Market Projections

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Introductory remarks

- This market assessment is based on published literature, subscription databases and Alacrita analysis as stated in the report.
- Market estimations represent potential theoretical maximum figures. A number of factors may constrain actual outcomes in practice, including:
 - Restrictions due to regulatory factors (which were not assessed by Alacrita); certain regions, e.g. MENA have stringent restrictions on cannabis products which can significantly restrict the number of accessible patients;
 - The clinical profile of MGC's products has yet to be established; clearly, these will play a key role in determining the ultimate market potential. The magnitude of responses, the proportion of responding patients, the side effect profile and the durability of responses have yet to be demonstrated;
 - Requirements for clinical data and health economic data which may be required by relevant authorities in different territories. These may exceed the data that MGC currently plans to generate in its clinical trials programme;
 - Attitudes of insurance companies and reimbursement agencies which may limit the pricing and/or the number of eligible patients for the therapy
- The above risk factors apply to all estimations expressed throughout this report.

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Drug-refractory epilepsy

Item	Assessment
Disease presentation	Epilepsy is a disorder of the brain characterized by recurrent, unprovoked seizures, and is the oldest recognized and most common chronic neurological disorder. People with epilepsy respond to treatment with anti-epileptic drugs approximately 70% of the time. Although some causes of epilepsy are known, the majority of epilepsy cases are idiopathic and are often presumed to be genetic, with onset during childhood.
Epidemiology	In 2017, there were 4.6m diagnosed prevalent cases of active epilepsy in the US, Japan, and EU5. By 2037, the number of diagnosed prevalent cases in these territories is predicted to increase to 5m.
Standard of care	<p>Surgery is currently the last resort for patients resistant to AEDs, of which several options exist:</p> <ul style="list-style-type: none">▪ Resective surgery▪ Palliative surgery▪ Neurostimulation▪ Stereotactic radiosurgery and laser ablation <p>However, surgery is not readily available in all countries and in all cases, after surgery the patient will need to remain on an AED.</p>

Datamonitor – May 2019

Sheng et al (2018) Curr. Neuropharmacol. 16(1): 17-28

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Estimated epilepsy patient population in the EU5

Territory	Current total epilepsy population	Population aged <=19	% generalized seizures (GS)	% drug-treated GS	% drug-refractory	Total (=/<19)	Total (all ages)
UK	480,596	46,713	48%	92%	25%	5,158	53,058
France	311,703	35,164	49%	90%	22%	3,412	30,242
Spain	308,968	59,125	38%	91%	20%	4,090	21,369
Germany	406,431	33,353	44%	91%	24%	3,206	39,057
Italy	401,621	71,013	44%	90%	25%	7,031	39,761
<i>Average</i>		13%	45%	91%	23%		
Total	1,909,319	245,368				22,897	183,487

All data in this table is taken from Datamonitor, who surveyed 260 physicians in 2017 and extrapolated values countrywide – Accessed May 2019

Estimated epilepsy patient population in Australia, MENA and Thailand

Territory	Current total epilepsy population	Population aged <=19	% generalized seizures (GS)	% drug-treated GS	% drug-refractory	Total (=/ \leq 19)	Total (all ages)
Australia	225,000	13%	45%	91%	25%	2,995	23,035
MENA	724,500		45%	91%	25%	9,643	74,171
Thailand	501,548		39%	36%	25%	2,288	17,605
Total						14,926	114,811

- Data extrapolated from Datamonitor together with publications listed in the assumption slides.
- Refractory or drug-resistant epilepsy is known to develop in 20–30% (epilepsysociety.org.uk) of patients, therefore a value of 25% was applied to Australia, MENA and Thailand.
- **Note:** access to medicinal cannabis products in certain regions (particularly MENA) is highly restricted, therefore the number of accessible patients could be lower than assumed above.

Patient population at launch

- The CAGR for epilepsy to 2025 is estimated at 0.9%*, therefore assuming a launch of CannEpiL in 2024, the following will be the expected patient populations in each region.

Region	Pediatric population Aged <=19	Total population
EU5	23,946	191,894
Australia	3,133	24,091
MENA	10,085	77,570
Thailand	2,392	18,411
Total	39,574	311,966

- Note: access to medicinal cannabis products in certain regions (particularly MENA) is highly restricted, therefore the number of accessible patients could be lower than assumed above.

*Datamonitor – Accessed September 2019

Pricing in each region

Item	Assessment
Pricing	<p>At the date of this report, the price of Epidiolex is US\$32,500 (£26,000) per patient, per year, however, this drug is indicated to treat rare and potentially fatal conditions. Given CannEpiL will be treating patients who have no other options we could assume slightly lower pricing compared to Epidiolex, if marketed in the US.</p> <p>However, given the EU market is the initial target for CannEpiL, we have assumed a price for CannEpiL at £6,000 (\$10,800 AUD) per patient per year in Europe based on Alacrita's assessment of possible pricing points relative to Epidiolex pricing and also for novel CNS drugs (note that this will depend critically on the performance of the drug). Pricing in other regions has been calculated as a factor of the EU price as presented in the assumptions slides (based on Alacrita's analysis of relative pricing in the relevant regions for other epilepsy medications).</p>

Region	Price per patient per year (£/\$AUD)
EU5	£6,000-8,000 (A\$10,800-A\$14,400)
Australia	£3,700-£4,900 (A\$6,700-A\$8,900)
MENA	£6,000-£8,000 (A\$10,800-A\$14,400)
Thailand	£4,700-£6,200 (A\$8,500-A\$11,300)

Market penetration

Item	Assessment
Market penetration	<p>Epidiolex may well be on the market in the US for broader indications than Dravet and LGS by the time CannEpi is approved - not necessarily in Europe, but uptake of CannEpi could be impacted in regions outside of the US by off-label use. We might expect a potential peak market penetration to be 80% or more until/unless direct competition emerges in all regions.</p>
Access to medicinal cannabis	<p>Given there are no other therapy options as at the date of this report, CannEpi could theoretically access 100% of the available drug-refractory patient population. However, there are diverse regulatory and healthcare systems in place in the various regions in which CannEpi expects to launch which could limit the accessibility of treatment for patients, including but not limited to regulations around cannabis-derived products, the clinical performance of the drug to be established in clinical trials, the requirements for clinical and/or health economic assessment data to be provided to relevant authorities, attitudes or insurers or reimbursement agencies, etc.</p> <p>MENA includes countries with diverse economic status and health care systems and the application of health economic methods for health policy decisions, is much less advanced compared to other geographical areas. The less efficient regulation of medicinal cannabis in this region would also hinder access. Although Thailand has a progressive attitude towards medicinal cannabis, Alacrita believes it is likely that CannEpi would be limited to those in private hospital settings initially.</p> <p>Our projected sales do not take these potential limitations into account and assume 100% of drug-refractory patients could be made accessible to CannEpi. We have also assumed all patients will respond which is highly likely to be an overestimate.</p>

Peak sales estimations for CannEpiL

Item	Assessment
Peak sales	<p>We assume that peak sales do not account for any off-label revenue. The initial available patient population for CannEpiL will be small until/if the label is extended to adult patients.</p> <p>As below, peak sales in pediatric patients could reach £181m (A\$326m) with total adult and pediatric peak sales reaching £1.4b (A\$2.6b). Time to reach peak sales is unpredictable for reasons stated above.</p> <p>All of the uncertainties listed above apply to these figures which should be treated as theoretical maximum estimates. Actual sales will depend critically on clinical performance (level of efficacy, proportion of responding patients, durability of responses, etc.) which is as yet unknown.</p>

Region	Price per patient per year (£)	Accessible population	Peak penetration	Pediatric peak sales (£)	Total peak sales (£)
EU5	6,000-8,000	100%	80%	115-153m	921-1,228m
Australia	3,700-4,900			9-12m	71-95m
MENA	6,000-8,000			48-64m	372-496m
Thailand	4,700-6,200			9-12m	69-92m
Total				£181-241m	£1,433-1,911m

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Dementia in Alzheimer's disease

Item	Assessment
Disease presentation	Alzheimer's disease is an irreversible, progressive, neurodegenerative, and fatal disease that slowly affects memory, cognition, and function. Alzheimer's disease is the most common cause of dementia among older people. Dementia is the loss of cognitive functioning – thinking, remembering, and reasoning – and behavioral abilities, to such an extent that it interferes with a person's daily life and activities. Dementia ranges in severity from mild to the most severe stage, when the person must depend completely on others for basic activities of daily living.
Epidemiology	AD is the most common form of dementia, and accounts for an estimated 60–80% of dementia cases. In 2018, there were 9.8m prevalent cases of AD in the US, Japan, and EU5 markets. By 2038, the number is forecast to increase to 16m. Increasing aging populations, particularly of those aged 65 years and older, will contribute to the increasing prevalence.
Standard of care	All approved treatments for AD possess a symptomatic mode of action, in that they target the cognitive and functional deficits in patients. The underlying neurodegeneration continues to progress and generally any symptomatic improvements are lost within a few years. Cholinesterase inhibitors are generally prescribed for mild to moderate Alzheimer's disease, and memantine add-on for more severe cases.

Datamonitor – May 2019

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Estimated dementia patient populations in the EU5 (2015 data)

Territory	AD population	% diagnosed mild	% mild receiving drug treatment	% diagnosed moderate	% moderate receiving drug treatment	Total mild-AD	Total mild and moderate-AD
UK	776,950	44%	67%	40%	81%	229,045	480,777
France	386,546	43%	77%	39%	85%	127,986	256,126
Spain	275,553	35%	90%	46%	94%	86,800	205,950
Germany	537,512	37%	76%	40%	82%	151,149	327,453
Italy	317,043	37%	82%	40%	87%	96,191	206,522
<i>Average</i>		39%	78%	41%	86%		
Total	2,293,604					691,171	1,476,828

Data taken from Datamonitor who surveyed 223 physicians in 2015 and extrapolated values countrywide – Accessed May 2019

Estimated dementia patient populations in Australia, MENA and Thailand

Territory	AD population	% diagnosed mild	% mild receiving drug treatment	% diagnosed moderate	% moderate receiving drug treatment	Total mild AD	Total mild and moderate AD
Australia	447,115	39%	78%	41%	86%	136,013	293,666
MENA	5,600,000					1,703,520	3,678,080
Thailand	600,000	39%	88%	37%	92%	205,920	410,160
Total	6,647,115					2,045,453	4,381,906

- Data extrapolated from Datamonitor in Europe for Australia/MENA and in Japan for Thailand.
- Access to medicinal cannabis products in certain regions (particularly MENA) is highly restricted, therefore the number of accessible patients could be lower than assumed above.

Patient population at launch (ca. 2024)

- In Europe, the number of cases of Dementia is expected to grow by 15% by 2024*, from 2019. We have assumed the same value for all regions.

Region	Mild AD population	Mild and Moderate population
EU5	794,847	1,698,353
Australia	156,415	337,716
MENA	1,959,048	4,229,792
Thailand	236,808	471,684
Total	3,147,118	6,737,545

*Datamonitor – Accessed September 2019

Pricing and uptake

Item	Assessment
Pricing	<p>Without any clinical data it is difficult to predict how CogniCann might be priced next to current therapies in the area. A drug that provided cognitive benefits could potentially meet MGC's suggested price of £4,400 (A\$7,900) per patient per year will be achievable once approved.</p> <p>However, initial clinical trials will be limited to demonstrating a QoL benefit only. Depending on the magnitude and clinical significance of such benefits, Alacrita estimates potential pricing to be ca. £400-£800 per patient per year* and have made the peak sales calculations with this value across all regions.</p>
Market penetration	<p>100% of the population could theoretically be available at some point in the AD treatment cycle for mild (initially) AD patients. However, given CogniCann is initially being used to improve QoL only, we would suggest a maximum penetration rate of only 5-10% given the significant competition in the area; this is dependent on CogniCann showing a significant improvement in QoL, without it, peak penetration might be closer to 3-5%.</p>
Access to medicinal cannabis	<p>As discussed above for CannEpil, there will likely be significant regulatory and market access limitations for access to CogniCann in certain regions, particularly if highly priced. We have not factored these uncertainties into the calculations.</p>

*Alacrita analysis based on pricing of current generic AD drugs. This is a very rough estimation only and carries very high uncertainty as to date there is no clinical profile for the product

Peak sales estimations for CogniCann

Item	Assessment
Peak sales	<p>We assume that peak sales do not account for the off-label revenue. If CogniCann could go onto show benefit in moderate AD patients, in addition to mild, there is potential for its value to double.</p> <p>All of these projections are speculative in the absence of clinical data.</p> <p>As below, peak sales in mild AD patients could reach £62m-£125m (A\$112m-A\$225m) with total mild and moderate AD peak sales reaching £134m-£269m (A\$241m-A\$484m). Time to reach peak sales is unpredictable for reasons stated above.</p> <p>If CogniCann could ultimately show significant benefits in cognition, these peak sales estimates could rise by a factor of >5 through a combination of higher price and increased sales penetration. Again, these numbers are speculative in the absence of clinical data.</p>

Region	Price per patient per year (£)	Accessible population	Peak penetration	Mild AD peak sales (£)	Total peak sales (£)
EU5	£400-800	100%	5%	16m – 32m	34m – 68m
Australia				3m – 6m	7m – 14m
MENA				39m – 78m	84m – 169m
Thailand				4m – 9m	9m – 18m
Total				£62m – 125m	£134m – 269m

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Epilepsy patient population assumptions (1)

Parameter	Region	Total population	Pediatric population	Source
Total patient populations	EU5	1,909,319	245,368	Datamonitor values – accessed September 2019
	Australia	225,000	29,250	Epilepsy Action Australia https://www.epilepsy.org.au/ Assumed the same ratio of adults/pediatrics as seen in Europe (av. 13%) as taken from Datamonitor
	MENA	724,500	94,185	Epilepsy in the WHO Eastern Mediterranean Region http://applications.emro.who.int/dsaf/dsa1039.pdf Assumed the same ratio of adults/pediatrics as seen in Europe (av. 13%) as taken from Datamonitor
	Thailand	501,548	65,202	Trinka E, et al (2019) Epilepsia. 60, 7-21 https://www.ncbi.nlm.nih.gov/pubmed/29953579 Assumed the same ratio of adults/pediatrics as seen in Europe (av. 13%) as taken from Datamonitor

Epilepsy patient population assumptions (2)

Parameter	Region	%	Source
% generalised seizures	EU5	45%	Datamonitor values – accessed September 2019 (av. 45% across Europe) Epilepsy Society also suggests that 45% of patients in developed countries have generalised (compared to partial) seizures. https://www.epilepsysociety.org.uk/sites/default/files/attachments/Chapter01Neligan-2015.pdf
	Australia	45%	Have applied the European average as above.
	MENA	45%	
	Thailand	39%	Have used the value for Japan provided by Datamonitor (39% epilepsy patients have generalised seizures)
% drug-treated	EU5	91%	Datamonitor values used - accessed September 2019 (av. 91% across Europe)
	Australia	91%	Assumed to be the same as Europe above.
	MENA	91%	
	Thailand	36%	The treatment gap for epilepsy in Asia is 64% https://www.epilepsysociety.org.uk/sites/default/files/attachments/Chapter01Neligan-2015.pdf

Epilepsy pricing assumptions (1)

		Example AED medication				
		Price per patient per year (€)				
Region	Lamotrigine	Levetiracetam				
US	680	-				
UK	260	102				
Germany	135	51				
Italy	374	137				
Spain	434	210				
France	230	154				
Av. EU5	287	131	Factor of EU5 pricing			
			Lamotrigine	Levetiracetam	Average	
South Africa	170	99	0.59	0.76	0.68	
Turkey	259	126	0.90	0.96	0.93	
Australia	181	80	0.63	0.61	0.62	
Saudi Arabia	760	237	2.65	1.81	2.23	
UAE	896	267	3.12	2.04	2.58	

- Assumes 200mg (lamotrigine) or 250mg (levetiracetam) oral tablet with BD dosing
- Average taken across all manufacturers, excludes branded prices
- Ex factory prices used

- We have proposed £6,000 (A\$10,800) per patient per year to be the pricing of CannEpil in Europe.
- For Australian pricing, we have applied a factor of 0.62 to the estimated EU price (£3,720, A\$6,700)

Data taken from Pharma14 pricing database

Epilepsy pricing assumptions (2)

MENA

Pricing

- Saudi Arabia and the UAE have significantly higher priced epileptic medications compared to Europe.
- However, other countries in the area are expected to have lower pricing. This, for example was shown with a study of Remicade pricing in the region, where countries like Algeria, Tunisia and Iraq having lower pricing than UAE and Saudi Arabia.
- Therefore, on balance, for MENA we assume an equal pricing to Europe (£6,000 per patient per year).

Access

- There may be a potentially lower penetration rate given the higher uncertainty in regulation of cannabis and poorer access to medication in certain regions.

Thailand

Pricing

- The monthly cost of 200mg (BD) epilepsy generic carbamazepine costs €3.5, compared with €4.5 in the UK.
- We have therefore proposed a price of CannEpil in Thailand to be 78% of that proposed for the EU5 (£4,700)

Access

- Access to an expensive innovative product in Thailand may only be reserved for those in the private sector (50% of hospitals), even though Thailand has a progressive approach to medicinal cannabis.
- We might therefore expect access to CannEpil to be restricted in the initial launch.

Almaaytah A (2019) International Journal of Pharmaceutical Investigation. 9(1)
Pharma 14 database – Accessed September 2019

<https://haiweb.org/wp-content/uploads/2015/07/Thailand-Report-Pricing-Surveys.pdf>
Pharmaceutical pricing and reimbursement in the Middle East and North Africa region (2018) LSE

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Dementia patient population assumptions (1)

AD population				
Region		Mild	Moderate	Source
EU5	2,293,604	39%	41%	Datamonitor values used for EU5 values. Dementia Australia estimates there are ca. 447,115 current cases of dementia in AD: https://www.dementia.org.au/statistics <i>Supporting literature:</i> 91% of total assumed AD were officially diagnosed as AD (Spain) https://www.ncbi.nlm.nih.gov/pubmed/30881138 40% of AD patients in high-income countries are only given social care, and therefore assumed to be mild patients https://www.who.int/mental_health/neurology/dementia/dementia_thematicbrief_epidemiology.pdf
Australia	447,115			
MENA	5,600,000			
				1.15 million in 2010 expected to increase to 2.59m (Middle East) and 6.19m (North Africa) by 2030. http://www.emro.who.int/health-topics/dementia/index.html Alacrita have estimated the 2019 prevalence at 1.9 million in ME and 3.7 million in NA; current total of 5.6 million patients. Have applied EU values for % mild v moderate.
Thailand	600,000	39%	37%	Estimated 600,000 people with Dementia in Thailand. https://www.alz.co.uk/adi/pdf/Dementia-Asia-Pacific-2014.pdf A study in China estimated mild (46%) and moderate (27%) AD classification. https://www.nature.com/articles/s41598-017-13951-7 Data presented for Japan (Datamonitor) proposed 32% were diagnosed mild and 46% diagnosed moderate. An average of the two sources was used for Thailand.

Dementia patient population assumptions (2)

Region	% mild AD receiving treatment	% moderate AD receiving treatment	Source
EU5	78%	86%	Datamonitor data values used for the EU – Accessed September 2019
Australia	78%	86%	
MENA	78%	86%	
Thailand	88%	92%	Datamonitor data values used for Japan – Accessed September 2019

Dementia pricing assumptions

Example AD medication	
Price per patient per year (€)	
Region	Rivastigmine
UK	217
Germany	386
Italy	314
Spain	178
France	188
Av. EU5	257
Turkey	178
Australia	528
Saudi Arabia	593
UAE	907

- Assumes 5mg (donepezil, OD) or 1.5mg (Rivastigmine, BD) oral tablet dosing
- Average taken across manufacturers, excludes branded prices
- Ex factory prices used

- We have proposed a pricing range of £400-800 across all regions

Data taken from Pharma14 pricing database

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