Report by the Domain Taskforce Horizon Scanning,
Taskforce of the Beneluxa Initiative

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Pharmaceutical Developments

on

Alzheimer's Disease

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Executive Summary

This report, by the Taskforce Horizon Scanning of the Beneluxa Initiative, describes the current situation of Alzheimer's disease and provides an overview of new pharmaceutical developments regarding this disease.

The current treatment options are listed, as well as the available guidelines and an estimation of the current pharmaceutical costs for this disease in the Beneluxa countries.

The main focus of the report is on the new pharmaceuticals to enter the market between 2022 and 2027. The setup of the clinical trials, including the used biomarkers, are summarised. Also, the possible challenges, both on HTA level as on Health care level, are described.

With this report, Beneluxa aims to timely inform policy makers, healthcare organizations, payers and the general public on upcoming new pharmaceuticals and possible challenges.

The authors declare that there is no conflict of interest

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PHARMACEUTICAL DEVELOPMENTS - ALZHEIMER'S DISEASE

Report by the taskforce Horizon Scanning of the Beneluxa Initiative

Introduction

Developments on new drugs often come in bursts. As soon as a new working mechanism or disease pathway is discovered, pharmaceutical companies seize the opportunity to develop new treatments for the relevant patients. The Horizon Scanning task force of Beneluxa is trying to capture these developments and boils it down to a short report. It describes the background of the respective indication, current treatment options and most importantly, new pharmaceuticals that are expected to enter the market in the coming years. This report is focusing on Alzheimer's Disease.

Pharmacological treatment of Alzheimer's Disease has not changed in the past years and is mainly focused on symptom reduction. Recently, several new pharmaceuticals reached the clinical phase of development. This might be exciting news for a currently incurable disease.

The report is based on information from clinical trials, published on clinicaltrials.gov and assembled between Q2 and Q4 of 2021.

With this report, the authors aim to timely inform policy makers, healthcare organizations, payers and the general public on upcoming new pharmaceuticals and possible challenges.

Background on indication

Alzheimer's disease (AD) is a neurodegenerative disorder, which mainly affects older adults and is estimated to account for 60 – 80% of cases of dementia [1-3]. The characteristic pathologies of AD are the accumulation of beta-amyloid protein fragments (plaques) outside neurons in the brain, and twisted strands of tau protein (tangles) inside neurons. The pathological processes associated with AD begin decades before the onset of clinical symptoms. There are three phases which comprise the AD continuum: Preclinical AD, Mild Cognitive Impairment (MCI) due to AD (or Prodromal AD) and Dementia due to AD [3,4].

- Preclinical AD: Biomarker evidence of AD in the brain but no symptoms present
- MCI due to AD/Prodromal AD: Biomarker evidence of AD in addition to subtle symptoms
- AD Dementia:
  - Mild: Symptoms interfere with ability to carry out some daily activities
  - Moderate: Symptoms interfere with many daily activities
  - Severe: Symptoms interefere with most daily activities

Incidence and Prevalence of AD and other dementias

The incidence of dementia increases exponentially from age 65 years [5]. Studies in Europe and North America have reported a decline in incidence of dementia in recent decades [6]. Population growth combined with ageing demographics however indicate that the overall numbers of people living with dementia in many European countries are likely to increase significantly [7]. A recent analysis by Alzheimer Europe estimated that the numbers of people with dementia in Europe are likely to double between 2018 and 2050.

Estimated prevalence of dementia

	2018		2050	
	Patient numbers	**% of population**	**Patient numbers**	**% of population**
Austria	146 801	1.66	290 499	3.18
Belgium	192 926	1.69	360 766	2.95
Ireland	52 736	1.09	141 200	2.49
Luxembourg	7 539	1.25	19 284	2.44
Netherlands	256 532	1.49	540 221	3.15

Source: Alzheimer Europe. Dementia in Europe Yearbook 2019 [7]

Economic burden of AD

There is a very high economic burden associated with AD [8]. Social care and informal care costs are key drivers of total costs as direct medical costs represent a relatively small proportion of total costs. The costs associated with AD increase according to disease severity.

Expected positioning of new therapies

The drug pipeline for AD contains agents that are aimed at disease-modification or symptom reduction. Recent years have seen trends for increased target diversity, clinical trials in earlier stages of the AD continuum, and increasing use of biomarkers [9]. Research is ongoing to develop therapies that could prevent or significantly delay the progression of AD. Combination therapies may be recommended in the future, with different therapies aimed at different targets.

Current treatment options

Currently, only symptom-reducing drugs are used for the management for AD. There are two classes of drugs that are used: cholinesterase inhibitors (ChEIs) (donepezil, rivastigmine and galantamine) and an N-methyl-D-aspartate receptor (NMDA) antagonist (memantine). All three ChEIs are indicated for mild to moderately severe Alzheimer's dementia, and rivastigmine is also indicated for mild to moderately severe dementia in patients with idiopathic Parkinson's disease [10-12]. Memantine is indicated for moderate to severe AD [13]. Some treatment guidelines recommend consideration of a combination of a ChEI plus memantine in patients with moderate to severe AD.

International Guidelines

Guidelines on the use of current treatments for AD include:

- **National Institute for Health and Care Excellence (NICE).** *Dementia: assessment, management and support for people living with dementia and their carers. June 2018*
- **European Federation of Neurological Societies (EFNS)-European Neurological Society (ENS)/European Academy of Neurology (EAN).** *EFNS-ENS/EAN Guideline on concomitant use of cholinesterase inhibitors and memantine in moderate to severe Alzheimer's disease. March 2015*
- **European Federation of the Neurological Societies (EFNS).** *EFNS guidelines for the diagnosis and management of Alzheimer's disease. October 2010*
- **American Psychiatric Association (APA).** *Practice guideline for the treatment of patients with Alzheimer's disease and other dementias. October 2007*

Current treatment costs

Country	Active Ingredient	Reimbursement	Estimated Current Annual Treatment Costs Per Patient[a]	Annual Treatment Costs[b]
Beneluxa	Donepezil	Y	€ 205	€ 9,1 million
	Galantamine	Y	€ 246	€ 2,6 million
	Rivastigmine	Y	€ 347	€ 14,1 million
	Memantine	Y	€ 267	€ 6,8 million

[a] Estimated current average price payed per patient for all Beneluxa countries, based on 2019 and 2020 data. [b] Total treatment costs of the respective pharmaceutical products, for all Beneluxa countries combined. Prices for the individual countries are reserved for the Beneluxa members.

New pharmaceuticals to enter the market between 2022 and 2027

INN	Mf.	Label	MoA	Trial / EMA numbers	PEs	PCD	Filed at EMA?	MA (est.)[1]	Chance of MA[2]	Cost pp/py (est.)[3]	Other studies?
Aducanumab	Biogen	Early AD	Aβ antibody	NCT04241068 Phase 3: ENGAGE EMERGE	Safety endpoints	Oct '23	Yes, Oct 2020	N/A	Unlikely – negative opinion from EMA in Dec 2021	€ 46k[4] ICER: $ 2.5-8.3 k[5]	F/up open label: EMBARK.
Donanemab	Eli Lilly	Early AD & Presymptomatic	Aβ antibody	NCT04437511 TRAILBLAZER-ALZ 1 & 2	Change from baseline on iADRS	Feb '23 & '24	No	2024	Uncertain – breakthrough therapy designation by FDA in Jun 2021[6]	€€€	None
				NCT05026866 TRAILBLAZER-ALZ 3	Time to clinical progression CDR-GS	Sep '27					
				NCT05108922 TRAILBLAZER-ALZ 4	Amyloid plaque clearance compared with aducanumab in early AD	Jun '22					
Gantenerumab	Roche	Early AD	Aβ antibody	NCT01760005 DIAN-TU001	Assess cognitive efficacy measured by the DIAN-MCE	Jul '22	No	2022	Uncertain – breakthrough therapy designation by FDA in Oct 2021[7]	€€€	None
				NCT01224106 Scarlet RoAD	Change from baseline in CDR-S	Sep '20 Nov '23 May '22					

[1] Based on an average lead time 13 months for EMA evaluation, ChMP opinion and market authorisation by the European Commission. If multiple phase 3 studies are conducted, MA is estimated based in filing after the earliest trial end date.
[2] Market approval is a rough estimate consisting of 3 options: Unlikely: if only studies exists with unmet endpoints; uncertain: when studies have not yet reached endpoints OR are done in non-Caucasian countries OR if studies exists that did not reach their endpoint; Likely: if only studies exists that reached their endpoints AND are Phase 3 clinical trials AND are done in European/Caucasian countries.
[3] Costs are rough estimates meant for comparison between new upcoming pharmaceuticals; € < 1k euro's pp/py, e.g. for new combinations of existing off-patent pharmaceuticals; €€ >1k <25k euro's pp/py e.g. for new small molecules; €€€ >25 k <100k pp/py e.g. for new biologicals; €€€€ >100k e.g. for new ATMP's such as gene therapies.
[4] https://www.reuters.com/business/healthcare-pharmaceuticals/us-fda-set-rule-controversial-biogen-alzheimers-drug-2021-06-07/
[5] https://alzheimersnewstoday.com/2021/05/10/insufficient-evidence-aducanumab-efficacy-alzheimers-disease-icer-draft-report-finds/
[6] https://alzheimersnewstoday.com/2021/07/01/lillys-donanemab-alzheimers-granted-fda-breakthrough-therapy-status/
[7] https://alzheimersnewstoday.com/2021/10/12/gantenerumab-alzheimers-named-fda-breakthrough-therapy/

INN	Mf.	Label	MoA	Trial / EMA numbers	PEs	PCD	Filed at EMA?	MA (est.)[1]	Chance of MA[2]	Cost pp/py (est.)[3]	Other studies?
				NCT03443973 GRADUATE 2 NCT03444870 GRADUATE 1							
				NCT02051608 Marguerite RoAD	Change from baseline in ADAS-Cog13	Apr '21					
				NCT04339413 NCT04374253 Open RoAD	Change in C-SSRS Score	Apr '23 Dec '24					
Lecanemab	Eiasi/ Biogen	Early AD	Aβ antibody	NCT03887455 Clarity AD	Change from baseline in CDR-SB	Sep '22	No	2023	Uncertain – rolling submission at FDA started in Oct 2021[8]	€€€	None
				NCT04468659 AHEAD 3-45	Change from baseline in PACC5 score Change from baseline in amyloid PET SUVr	Oct '27					
Solanezumab	Eli Lilly	Early AD in dominantly inherited AD (DIAD)	Aβ antibody	NCT01760005 DIAN-TU001	Change from baseline in the DIAN-MCE	July '22	No	2023	Unlikely – results failed to show clinical efficacy	€€€	None
				NCT02008357 A4 Study	Change from baseline of the PACC	Dec '22					
ALZT-OP1a/OP1B; (combination of cromolyn and ibuprofen)	AZ Therapies Inc.	Early AD	Cytokine Inhibitor and NSAID	NCT02547818 Cognite	CDR-S	Nov '20	No	2022	Uncertain – no clinical results known	€	None
ANAVEX 2-73; blarcamesine	Anavex Life Science Corp.	AD	Sigma 1 & Muscarine receptor agonist	NCT04314934 Anavex 2-73-AD-004	ADAS-Cog; ADCS-ADL	May '24	No	2025	Uncertain – no clinical results known	€€	Parkinson Disease Dementia ph. 2); Rett
				NCT03790709	ADAS-Cog; ADCS-ADL	May '22					

[8] https://alzheimersnewstoday.com/2021/10/04/eisai-starting-fda-submission-alzheimers-therapy-lecanemab/

INN	Mf.	Label	MoA	Trial / EMA numbers	PEs	PCD	Filed at EMA?	MA (est.)[1]	Chance of MA[2]	Cost pp/py (est.)[3]	Other studies?
											syndrome (ph. 2/3)
BHV4157; troriluzole	Biohaven Pharmaceuticals	AD	Glutamate uptake enhancer	NCT03605667	ADAS-Cog 11 from baseline to week 48 The change in CDR-SB	Nov '20	No	2022	Unlikely - results failed to show clinical efficacy	€€	OCD (ph. 2/3), Spinocerebellar ataxia (ph. 3), generalized anxiety disorder (ph. 3), several lymphoma's (ph. 1).
COR388; Atuzaginstat	Cortexyme Inc.	AD	Gingipains inhibitor (inhibition of enzymes released by P. gingivalis, known to be linked with AD development)	NCT03823404 GAIN trial	ADAS-Cog 11; ADCS-ADL	Dec '21	No	2024	Uncertain – first results show decreased cognitive impairment in AD patients with severe GUM disease[9]	€€	None
Tricaprilin (CER-0001)	Cerecin	Mild-to-Moderate AD	Improvement of mitochondrial metabolism	NCT04187547	ADAS-Cog11. Total Score up to 20-weeks	Dec '23	No	2025	Uncertain – no clinical results known	€	Spasms (ph. 1), Migraine (ph. 2),
LMTM (TRx0237)	TauRx Therapeutics Ltd	AD	Tau aggregation inhibtor	NCT03446001	ADAS-cog11, 52 weeks ADCS-ADL23	Jun '22	No	2023	Uncertain – Conflicting results in earlier studies[10]	€€	COVID-19 (ph. 1)
NE3107	BioVie	Mild-to-Moderate AD	NFkB & TNF inhibitor	NCT04669028 NM101	ADAS Cog12, 30 weeks; ADCS CGIC	Dec '22	No	2024	Uncertain – no clinical results known	€€€	None

[9] https://alzheimersnewstoday.com/2021/11/02/cortexyme-gain-trial-atuzaginstat-potential-benefit-alzheimers-patients-severe-gum-disease/
[10] https://www.alzforum.org/therapeutics/lmtm

INN	Mf.	Label	MoA	Trial / EMA numbers	PEs	PCD	Filed at EMA?	MA (est.)[1]	Chance of MA[2]	Cost pp/py (est.)[3]	Other studies?
Oligomannate (GV-971)	Shanghai Green Valley Pharmaceuticals	Mild-to-Moderate AD	Inflammation modulation	NCT04520412 GREEN MEMORY	ADAS-cog/11 score ADCS-CGIC score 48 weeks	Dec '25	No	2027	Uncertain – no clinical results known	€€	None
ALZ-801	Alzheon Inc.	Early AD in APOE 4/4 genotype patients	Tau aggregation inhibtor	NCT04770220 APOLLOE4	ADAS-cog 13 Primary fluid biomarker endpoint Primary imaging biomarker endpoint 78 weeks	Apr '24	No	2025	Uncertain – no clinical results known	€€	Down Syndrome dementia; dry age-related macular degeneration
Dextro-methorphan and quinidine (AVP-786)	Avanir Pharmaceuticals	Agitation in patients with AD	NMDA antagonist & sigma 1 agonist	NCT03393520 NCT04408755 NCT04464564	Change from Baseline to Week 12 in the CMAI scores	Jul '22 Dec '24 Dec '24	No	2023	Uncertain – Conflicting results in earlier studies[11]	€	Negative symptoms of schizophrenia (phase 2)
Dextromethorphan bupropion (AXS-05)	Axsome Therapeutics	Agitation in patients with AD	NMDA antagonist & sigma 1 agonist	NCT04797715 ACCORD	Time from randomization to relapse of agitation symptoms.	Dec '22	No	2024	Uncertain - breakthrough therapy designation by FDA in Jun 2020[12]	€	Major Depressive Disorder (phase 3)
Donepezil/ memantine (BPDO-1603)	Hyundai Pharmaceutical	Moderate-to Severe AD	ACE inhibitor/ NMDA antagonist	NCT04229927	Change in SIB total scores CIBIC+ total score	Feb '22	No	2023	Uncertain – no clinical results known	€	None
Octohydroamino-acridine succinate	Changchun Huayang High-Tech	Mild-to-Moderate AD	Acetylcholinesterase inhibtor	NCT03283059	ADAS-Cog; CIBIC+; ADL; NPI	Sep '20	No	2022	Uncertain – no clinical results known	€€	None

[11] https://www.alzforum.org/therapeutics/avp-786
[12] https://alzheimersnewstoday.com/2021/01/18/axsome-launches-phase-3-accord-trial-testing-axs-05-among-patients-with-alzheimers-associated-agitation/

INN	Mf.	Label	MoA	Trial / EMA numbers	PEs	PCD	Filed at EMA?	MA (est.)[1]	Chance of MA[2]	Cost pp/py (est.)[3]	Other studies?
Simufilam (PTI-125)	Cassava Sciences	Mild-to-Moderate AD	Binds filamin, a stabilizer of Aβ	NCT04994483 RETHINK-ALZ NCT05026177 REFOCUS-ALZ	ADAS-Cog ADCS-ADL	Oct '23 Jun '24	No	2025	Uncertain – no clinical results known	€€	None
Semaglutide	Novo Nordisk	Early AD	GLP-1 antagonist	NCT04777396 EVOKE NCT04777409 EVOKE plus	CDR-SB score toe week 104	Aug '24 Aug '24	No	2026	Uncertain – no clinical results known	€€	Type 2 diabetes (already on the market)

Aβ=beta amyloid; AD=Alzheimer's disease; ADAS-Cog13= Alzheimer's Disease Activity Scale-Cognitive subscale 13; ADCS-ADL= Alzheimer's Disease Cooperative Study-Activities of Daily Living; CDR-S=Clinical Dementia Rating Scale; CDR-GS=Clinical Dementia Rating-Global Score; CDR-SB=Clinical Dementia Rating-Sum of Boxes; CGIS = Clinical Global Impression – Severity; CIBIC+ = Clinician's Interview Based Impression of Change – plus; CMAI = Cohen-Mansfield Agitation Inventory; C-SSRS= Columbia-Suicide Severity Rating Scale; DIAN-MCE= DIAN-Multivariate Cognitive Endpoint; EMA=European Medicines Agency; iADRs= integrated Alzheimer's disease rating scale; INN=International Non-proprietary Name; MA=marketing authorisation; Mf=manufacturer; MoA=Mechanism of Action; NPI = Neuropsychiatric Inventory; PACC5= preclinical Alzheimer cognitive composite 5; PCD=Primary Completion Date; Pes=Primary Endpoints; PET= positron emission tomography; SIB = Severe Impairment Battery; SUVr= standard uptake value ratio; TBC=to be confirmed

€	<€1,000 per patient per annum
€€	€1,000 to < €25,000 per patient per annum
€€€	€25,000 to <€100,000 per patient per annum
€€€€	≥ €100,000 per patient per annum

General characteristics of new studies/pharmaceuticals

Setup of clinical trials [4,9,14]

- Patient characteristics: New diagnostic criteria for AD facilitate clinical trials in preclinical and prodromal populations
- Biomarkers: Increasing use of biomarkers in clinical trials (e.g. for disease staging and as outcome measures)
- Novel outcome measures: Currently no gold standard for assessing treatment effect in preclinical AD
- Prevention trials require large samples and long follow-up (typically at least 3 years)

Biomarkers used in clinical trials [4,9]

- Cerebrospinal fluid (CSF) amyloid
- CSF tau
- Volumetric magnetic resonance imaging (MRI)
- Amyloid positron emission tomography (PET)
- Tau PET
- Research on new biomarkers is ongoing (e.g. biomarkers for neuroinflammation, blood or metabolic signatures)

Possible challenges [15-17]

- HTA challenges
    - Gap between regulatory and HTA data requirements
    - Real world evidence will be needed to characterise the impact of new drugs on long-term outcomes, care givers and health systems
- Health system challenges
    - New treatments for AD are anticipated to have higher costs per patient compared to currently used medicines
    - Infusion capacity to meet potential demand: Some new treatments for AD are expected to be administered by intravenous infusion
    - Imaging capacity: Some new treatments for AD are expected to need imaging before and throughout treatment. This capacity might not be readily available.
    - Testing for biomarkers: Biomarker testing for AD is not routinely done in clinical practice currently

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