Drug Approval Process for the Treatment of Dementia

This information sheet includes the following topics:

I. How drugs are approved in Canada
II. Drugs approved for dementia in Canada
III. Clinical trials and research studies recruiting people living with dementia in Canada
IV. Some things to consider before getting involved in clinical trials

I. How drugs are approved in Canada

The Pharmaceutical Drug Directorate of the Health Products and Food Branch at Health Canada is responsible for ensuring that all drugs are safe, effective and of high quality for specific conditions. The directorate must also ensure that drug manufacturers have tested the drugs they wish to market and that the public is protected during each stage of the drug's development.

Before the drug enters Health Canada's approval process, the manufacturer must test that drug according to strict procedures. Even if Health Canada approves a drug, the monitoring of its effectiveness and side effects continues. For example, some side effects can be uncommon and do not show up during clinical trials; but they are found once the drug is in use and given to a greater number of people. Here is an outline of key steps involved in developing a drug:

Pre-clinical development
The manufacturer completes laboratory tests in a variety of cells, tissue samples and/or animals to determine the effects of the drug in different amounts and time periods. Pre-clinical studies, including chemical and biological research, often take two to three years to complete.

If the drug causes no serious or unexpected harm at the doses required to be effective on the condition it's treating, the manufacturer will apply to Health Canada's Health Products and Food Branch to begin clinical trials. If the testing will take place in Canada, the manufacturer must prepare a Clinical Trial Application including the results of the pre-clinical trials and a proposal for testing in humans.

A Health Canada research ethics board must review and accept the application before clinical trials can begin.

Clinical trials – Phase 1
Phase 1 clinical trials usually involve fewer than 100 healthy humans.

During this phase, the drug is tested for safety, dosage range, side effects and more. (Other factors to consider may include pharmacokinetic studies. Pharmacokinetic studies examine how a drug is absorbed, distributed, metabolized and eliminated from the body.) These trials typically consist of single doses given at one time under carefully monitored conditions.

Phase 1 trials generally take at least one year to complete. If the results are successful, Phase 2 clinical trials can begin.

Clinical trials – Phase 2
Phase 2 clinical trials give the drug to a larger group of people - usually 100 or more.

During this phase, researchers gather information about how well the drug works to treat a specific condition, confirm the drug's safety in a wider population and determine the best dose to give.

Usually, it takes at least two years to gather enough information to allow the drug to be tested in Phase 3 clinical trials. If the results from Phase 2 are successful – that is, if the drug is found to be safe in the doses required – a Phase 3 trial will occur next.

Clinical trials – Phase 3
Phase 3 clinical trials involve a larger number of participants, usually between 1,000 and 3,000 people. This means that potentially hundreds or thousands of people living with dementia around the world will be involved. Depending on the drug and/or trial, people who have other medical conditions and those who are taking other medications may also be involved.

During this phase, most often one group receives the treatment being researched, and a matching group receives a placebo (that is, a treatment with no effect). Usually, both the participants and the researchers will not know who receives the drug and who receives the placebo. This can help to make sure that the results reported are fair and not biased. However, sometimes this is not possible, depending on the type of drug. Researchers will continue to monitor the safety of the drug during Phase 3 to ensure that if any severe side effects are reported, it will not be a cause for concern for the general population. This stage also ensures that all serious side effects of the drug, if they exist, are well recognized before moving any further into the drug approval process.

If a drug is successful in treating a condition right through to the end of the Phase 3 trials, a New Drug Submission is sent to Health Canada for approval. Phase 3 trials usually take anywhere from 1 to 3 years to complete, but this can vary.

New drug submission
If the results from Phase 3 continue to be successful, the manufacturer can create a New Drug Submission for the Pharmaceutical Drug Directorate at Health Canada. A drug manufacturer can create a submission regardless of whether the clinical trials were carried out in Canada or not.

The directorate reviews all the information gathered during the development of the drug and assesses the risks and benefits of the drug.

If it is decided that, for a specific group of people and condition, the benefits of the drug are higher than the known risks, the Health Canada Health Products and Food Branch will approve the drug by issuing a Notice of Compliance (also known as a NOC). That branch will also review and edit the Product Monograph submitted by the manufacturer. This monograph briefly describes the composition of, effects from, and conditions of use of the drug, so that medical professionals understand how to use the drug properly.

For conditions that are life-threatening or cause severe impairment (such as dementia), the Health Products and Food Branch can authorize a manufacturer to sell a drug with the requirement that the manufacturer undertake additional studies to verify the drug's benefit. The branch does this by issuing what is called a Notice of Compliance with conditions (also known as a NOC/c). The NOC/c is applied to drugs for life-threatening conditions when there is either no other existing drug that is similar and available in Canada, or when a new drug submission demonstrates that it may significantly benefit the intended population, outweighing the risks, more so than the existing drugs available.

A Notice of Compliance with condition can be given to an eligible drug which has demonstrated clinical effectiveness in clinical trials. The product must be of high quality and have an acceptable benefit. The conditions include a requirement to closely monitor the drug for adverse reactions and to provide branch with regular updates. Once the conditions are met, the designation is removed.

If the drug is approved and released to the public, Phase 4 clinical trials may begin.

Clinical trials - Phase 4
Phase 4 clinical trials take place after a drug has been approved and is available to the public. These trials are not always required, but are often conducted to learn about potential side effects of the drug over a long period of time with greater numbers of people using it. For example, people with other medical conditions or in different age or gender categories may be researched.

During Phase 4 trials, information is obtained about the long-term risks and benefits of the drug. Phase 4 trials are not always completed but may be required by regulatory authorities for various reasons (e.g., testing how the drug interacts with other drugs).

This phase may take another two to four years to complete.

Overall, the drug may be approved for administration by doctors approximately 15 years after human studies first began.

How to obtain a drug before it is approved
The Health Products and Food Branch of Health Canada can also approve the early release of a drug under its **Special Access Program**.

Health-care providers can request a drug to be released early when treating a person with a serious or life-threatening condition. The request can only be made if all other traditional treatments have either failed, are unsuitable or are not available in Canada.

Some drugs being investigated for the treatment of dementia may be obtained through this program. A person's physician can contact the Health Products and Food Branch or the drug's manufacturer to obtain information about access.

II. Drugs approved for dementia in Canada

There are a few different drugs approved for treating different types of dementia in Canada. Each type of dementia has specific recommended medications. So the medications on this list may not be able to treat the symptoms of all types of dementia. Each drug listed below may go by other names, depending on the drug company it is offered through. To learn more about which drugs are right for you, consult with your doctor or health-care provider.

PLEASE NOTE: Always check with your health-care provider to learn about all possible side effects.

1. CHOLINESTERASE INHIBITORS

Acetylcholine, which is involved in memory function, is available in lower levels in the brains of people with Alzheimer's disease. This drug inhibits the action of acetylcholinesterase, a substance that breaks down acetylcholine. In this way, the drug is intended to increase the level of acetylcholine in the brain. This is also why it belongs to a class of drugs called acetylcholinesterase inhibitors.

Aricept™ (brand name) or Donepezil (generic name)
Drug manufacturer: Pfizer Canada Inc.
Approved for: Mild, moderate and advanced Alzheimer's disease and for Lewy body dementia.

Exelon™ (brand name) or Rivastigmine (generic name)
Drug manufacturer: Lundbeck Canada Inc.
Approved for: Mild to moderate Alzheimer's disease, as well as for Parkinson's disease dementia and Lewy body dementia.

Reminyl ER™ (brand name) or Galantamine (generic name)
Drug manufacturer: Janssen Inc.
Approved for: Mild to moderate Alzheimer's disease and for Lewy body dementia.

PLEASE NOTE: *There is not enough evidence supporting use of cholinesterase inhibitors for people with vascular dementia or frontotemporal dementia.*

2. NMDA RECEPTOR ANTAGONISTS

The brain chemical, glutamate helps send messages between brain cells. However, when a person has Alzheimer's disease, too much glutamate is released, which becomes toxic to brain cells. Memantine prevents that excess glutamate from overstimulating the brain's N-methyl-D-aspartate (NMDA) receptors. These receptors play an important role in memory formation and other nerve functions.

Ebixa® (brand name) or Memantine (generic name)
Drug manufacturer: Lundbeck Canada Inc.
Approved for: Moderate to advanced Alzheimer's disease and for Lewy body dementia.

PLEASE NOTE: *There is not enough evidence supporting use of Memantine for people with vascular dementia or frontotemporal dementia.*

III. Clinical trials and research studies recruiting people living with dementia in Canada

For information about clinical trials and research studies now recruiting people living with dementia in your community, please visit alzheimer.ca/Find-Studies. On this website, you will find research studies available both online and in-person across Canada for people living with dementia and their caregivers. There are sometimes also opportunities for other family members and health-care workers.

To access all the trials being conducted around the world, please visit clinicaltrials.gov (to find Canadian clinical trials, you can filter your search by selecting Canada).

For more information, you can also email info@alz.to or call 416-322-6560.

IV. Some things to consider before getting involved in clinical trials

There are potential risks and benefits to participating in any kind of research. So, it is important to consider both when making the decision to get involved in a research study.

Visit alz.to/resourcelibrary to read our checklist of questions to ask, learn about the importance of research ethics boards, and more.

This resource is informed by research and the experiences of people living with dementia. We thank Mario Gregorio, a person living with dementia, and Dr. Tejal Patel, Clinical Associate Professor, University of Waterloo, for their generous contributions to the development of this resource.

Alzheimer Society of Toronto
20 Eglinton Avenue West, 16th Floor, Toronto, Ontario, M4R 1K8
Tel: 416-322-6560 • E-mail: info@alz.to • Website: www.alz.to

Charitable registration number: 10670 5262 RR0001

R300-14E 2023