

## DRUG APPROVAL PROCESS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

There are certain principles that should be followed when involving people with Alzheimer's disease in research. For more information, see the Alzheimer Society's *Tough Issues, Participation in Research*, found on our website, [www.alzheimer.ca](http://www.alzheimer.ca), or contact your local Alzheimer Society.

This information sheet includes the following topics:

- I. How drugs are approved in Canada
- II. Drugs approved for Alzheimer's disease
- III. Clinical trials and research studies recruiting in Canada

### I. How drugs are approved in Canada

It is the responsibility of the Therapeutic Products Directorate (TPD) of the Health Products and Food Branch (HPFB), Health Canada, to ensure that all drugs used by the public are safe and effective for specific conditions, and of high quality. This responsibility includes ensuring 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 being approved, a drug for the treatment of Alzheimer's disease must be tested by the manufacturer according to strict procedures. Even if a drug receives approval for use in Canada, 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 are found once the drug is marketed and given to a greater number of people. The following outlines the various steps involved in developing a drug:

#### ***Chemical and biological research***

Laboratory tests are carried out in tissue cultures and with a variety of small animals to determine the effects of the drug. If the results are promising, the manufacturer will proceed to the next step of development.

#### ***Pre-clinical development***

The drug is given to animals in various amounts and over different periods of time. If it can be shown that the drug causes no serious or unexpected harm at the doses required to have an effect which is relevant to the disorder in question, the manufacturer will proceed to clinical trials. These preclinical studies often take two to three years.

#### ***Clinical trials – Phase 1***

The objective of Phase 1, the first administration in humans, is to test if people can tolerate the drug. If this testing is to take place in Canada, the manufacturer must prepare a Clinical Trial Application for the TPD. This includes the results of the first two steps and a proposal for the testing in humans. If the information is sufficient, the HPFB grants permission to start testing the drug, generally first on healthy

volunteers. These trials typically consist of single doses given at one time, under carefully monitored conditions. This testing starts the process of identifying common side effects, as well as finding out how high the dosages can be before adverse side effects occur. Phase 1 studies generally take at least one year to complete. If they look promising, they go into Phase 2 trials.

### ***Clinical trials – Phase 2***

Phase 2 trials are carried out on people with Alzheimer's disease, who are usually otherwise healthy, with no other medical condition. Trials carried out in Canada must be approved by the TPD. In Phase 2, the objective of the trials is to continue to gather information on the safety of the drug and begin to determine its effectiveness. Trials are designed and carried out by highly qualified investigators with expertise in Alzheimer's disease. The drug is given for sufficient time to determine if it makes a difference, compared to people who are given another type of treatment. Side effects are identified and effective drug doses are determined. Usually it takes at least two years to obtain enough positive information to justify the much larger and more extensive Phase 3 trials.

### ***Clinical trials – Phase 3***

If the results from Phase 2 show promise, the drug manufacturer provides an updated Clinical Trial Application to the TPD for any Phase 3 trials, which will include Canadian sites. Hundreds or even thousands of people with Alzheimer's disease around the world will be involved, including those who have other medical conditions and those who are taking other medications. One group of patients receives the prospective treatment and a matching group receives a "placebo," a harmless inactive substance. It can take up to at least three years to find out if the treated group does better than the untreated one, and to confirm drug dosages which work without causing adverse side effects. If a drug successfully maintains its original promise right through to the end of the Phase 3 trial, it is submitted to the appropriate government agencies for their approval. Usually drugs are sent back for yet more study in Phase 4 trials on people with other medical conditions, in different age or sex categories. This phase may take another two to four years.

In summary, the treatment may be approved for administration by doctors approximately eight to ten years after human studies first began.

### ***New drug submission***

If the results from Phase 3 continue to be favourable, the drug manufacturer can submit a New Drug Submission (NDS) to the TPD. A drug manufacturer can submit a NDS regardless of whether the clinical trials were carried out in Canada. The TPD reviews all the information gathered during the development of the drug and assesses the risks and benefits of the drug. If it is judged that, for a specific patient population and specific conditions of use, the benefits of the drug outweigh the known risks, the HPFB will approve the drug by issuing a Notice of Compliance. The HPFB will also review and edit the Product Monograph submitted by the manufacturer. This document helps to ensure that the drug is used properly by providing physicians with the information they need.

For conditions that are life-threatening or cause severe impairment (such as Alzheimer's disease), the HPFB can authorize a drug manufacturer to market a drug with the condition that the drug manufacturer undertake additional studies to verify the drug's benefit. This authorization is a Notice of Compliance with condition (NOC/c). A NOC/c is given to an eligible drug which has demonstrated promising clinical effectiveness in clinical trials. The product must be of high quality and possess an acceptable benefit. The conditions include a requirement to closely monitor the drug for adverse reactions and to provide HPFB with regular updates. Once the conditions are met, the designation is removed.

### ***How to obtain a drug before it is approved***

The HPFB can approve the release of a drug under the Special Access Program. Some drugs being investigated for the treatment of Alzheimer's disease may be obtained through this program. The individual's physician should contact the HPFB or the drug manufacturer directly to obtain information about access.

## II. Drugs approved for Alzheimer's disease

**Drug name:** Donepezil hydrochloride (also known as Aricept™, Co Donepezil, Sandoz Donepezil, Apo-Donepezil, Auro-Donepezil, Bio-Donepezil, Jamp-Donepezil, Mar-Donepezil, Mylan-Donepezil, Nat-Donepezil, PMS-Donepezil, Ran-Donepezil, Teva-Donepezil or Van-Donepezil)

**Drug manufacturer:** Eisai Co. Ltd. Co-developed and marketed by Pfizer Canada Inc.

**Proposed action:** Inhibits acetylcholinesterase action which will increase the level of acetylcholine in the brain. There is a decrease of acetylcholine in the brains of people with Alzheimer's disease.

**Phase of development:** Approved for use in mild, moderate and advanced Alzheimer's disease.

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**Drug name:** Memantine hydrochloride (also known as Ebixa®, Apo-Memantine, Co Memantine, Med-Memantine, Mylan-Memantine, PMS-Memantine, Ran-Memantine, Ratio-Memantine or Sandoz Memantine )

**Proposed action:** Acts on the brain's N-methyl-D-aspartate (NMDA) receptors, which respond to glutamate, one of the brain's chemical messengers involved in the formation of memories and other nerve functions. In Alzheimer's disease, glutamate leaks out of sick nerve cells and reaches levels outside the cells which are actually toxic to the cells. Memantine prevents that excess glutamate from over-stimulating the NMDA receptors.

**Phase of development:** Conditional approval for use in moderate to severe Alzheimer's disease.

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**Drug name:** Rivastigmine (also known as Exelon™, Apo-Rivastigmine, Med-Rivastigmine, Mint-Rivastigmine, PMS-Rivastigmine, Sandoz Rivastigmine or Mylan-Rivastigmine)

**Drug manufacturer:** The Exelon Patch is produced by Novartis Canada Inc.

**Proposed action:** Inhibits acetylcholinesterase action which will increase the level of acetylcholine in the brain. There is a decrease of acetylcholine in the brains of people with Alzheimer's disease. Rivastigmine is available as a capsule or patch. The patch may be of particular benefit to people who are susceptible to gastrointestinal problems.

**Phase of development:** Approved for use in mild to moderate Alzheimer's disease and for Parkinson's Disease Dementia.

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**Drug name:** Galantamine hydrobromide (also known as Reminyl™, Auro-Galantamine, Mar-Galantamine, Mylan-Galantamine, PMS-Galantamine or Pat-Galantamine)

**Drug manufacturer:** Janssen-Ortho Inc.

**Proposed action:** Inhibits acetylcholinesterase action which will increase the level of acetylcholine in the brain. There is a decrease of acetylcholine in the brains of people with Alzheimer's disease.

**Phase of development:** Approved for use in mild to moderate Alzheimer's disease.

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## III. Clinical trials and research studies recruiting in Canada

Please visit [www.alzheimer.ca/researchportal](http://www.alzheimer.ca/researchportal) for information about clinical trials and research studies currently recruiting participants in your province or community. For more information about clinical trials taking place in Canada please contact your local Alzheimer Society. To find the office nearest you, please visit [www.alzheimer.ca](http://www.alzheimer.ca) or call 1-800-616-8816.

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