

GLOSSARY

Acute Administration: "Acute" is a measure of the time scale of a treatment and is in contrast to "subacute" and "chronic". Acute generally means a period of treatment of less than a week. "Subacute" indicates a longer duration of treatment, whilst "Chronic" indicates indefinite duration or treatment.

Acute Injury: The sudden onset of disease or symptoms; for example the onset of a stroke.

Agonist: A drug that mimics the action of a naturally occurring substance.

Alzheimer's Disease: A progressive neurodegenerative disease characterized by loss of function and death of nerve cells in several areas of the brain leading to loss of cognitive function such as memory and language. The cause of nerve cell death is unknown. Alzheimer's disease is the most common cause of dementia.

Antagonist: A drug or compound that partially or completely blocks the effect of another drug or naturally occurring compound such as a hormone.

Anti-apoptotic agent: A compound that blocks apoptosis.

Anti-coagulant: A chemical which prevents blood from clotting.

Anti-inflammatory agent: A substance which directly reduces the inflammatory response of tissue.

Anti-oxidant: A chemical which prevents the abnormal oxidization of compounds by free radicals released from cells in the body. The anti-oxidant, by reacting with the oxidant, protects cells from being damaged.

Apoptosis: A type of regulated cell death in which the cell uses specialized cellular machinery to kill itself. The cell suicide mechanism enables the body to control cell number and eliminate cells that threaten an individual's survival. Also called *programmed cell death*.

Apoptotic Cascade: A normal regulated series of sequential events in a cell that leads to its death by apoptosis.

Astrocytes: A type of glial cell in the brain that helps support the neurons.

Axons: Processes of nerve cells (neurons) along which the electrical signal flows to the next nerve cell.

Bioavailability: The degree to which a drug or other substance becomes available to the target tissue after administration.

Bioinformatics: The organization and use of biological information, particularly computer-driven processing and analysis of data and databases in the fields of molecular biology and genetics.

Biopharmaceutical: A drug derived by a genetic engineering process or by any other biotechnological means.

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Blood Brain Barrier: The barrier system separating the blood from the tissue of the central nervous system. Its anatomical component consists of the cells lining blood vessels having especially tight junctions, which limits the movement of substances in the bloodstream into the brain.

Central Nervous System (CNS): The brain and spinal cord.

Chemoattractive: Any substance that promotes the migration of brain cells, including neurons, in the brain during development or after damage.

Choline Acetyl Transferase (ChAT): An enzyme involved in the production of acetylcholine, which is important in the processing of memory. Reduced activity of ChAT is associated with mild cognitive impairment and Alzheimer's disease.

Chronic Disease: A disease lasting for a long period of time.

Clinical Trial: Research conducted with volunteer patients, usually to evaluate a new treatment, under strictly controlled conditions. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease.

Cognitive Impairment: A deficiency in the ability to think, perceive, reason or remember resulting in loss of the ability to take care of one's daily living needs.

Contusion: An injury to a part of the body without a break in the skin and leading to a subcutaneous haemorrhage.

Coronary Artery Bypass Graft (CABG) surgery: A surgical procedure which involves replacing diseased (narrowed) coronary arteries with veins obtained from the patient's lower extremities. During this procedure the patient is placed on a heart bypass machine (heart-lung machine) to allow the surgeon adequate time to perform surgery on the resting (non-beating) heart.

Current Good Manufacturing Practice (cGMP): The regulated manufacturing procedures required to ensure quality and purity of a drug compound during production.

Cytokines: Proteins secreted by cells of the immune system that affect other cells in the immune system.

Devic's Disease: A disease causing demyelination of the optic nerve and sometimes the spinal cord. Also called *optic neuroencephalomyelopathy*.

Diketopiperazines (DKPs): A family of small cyclic neuroprotective compounds being developed by Neuren.

Efficacy: To produce the desired effect.

Encephalomyelitis: Inflammation of the brain and spinal cord.

Endarterectomy: Surgical removal of the inner lining of an artery that is clogged with atherosclerosis.

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Endocrinology: The branch of medicine dealing with the endocrine glands and their hormone secretions.

FDA: Food and Drug Administration, the regulatory body in the USA that approves the marketing of new drugs.

Formulation: The drug substance comprising the active drug product and inert inactive ingredients.

Glial cells: The cells in the brain which do not generate electrical signals. There are three main types of glial cell; the oligodendrocyte, microglia and astrocyte. Oligodendrocytes are the source of myelin, the substance surrounding axons that makes electrical conduction efficient. Astrocytes provide the support to the neurons. Microglia are the brains resident immune cells.

Glutamic Acid Decarboxylase (GAD): An enzyme involved in the synthesis of gamma amino butyric acid (GABA).

Glypromate: Neuren's lead drug candidate derived from the three amino acids Glycine-Proline-Glutamate.

Good Clinical Practice (GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Good Laboratory Practice (GLP): A set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived. GLP helps assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments.

GPE: Original abbreviation used for Glypromate derived from the standard single letter abbreviation for the amino acids Glycine (G), Proline (P) and Glutamate (E).

Grey Matter: Regions of the brain tissue with many nerve cell bodies and few myelinated axons.

Growth Factors: A protein that is involved in promoting cell differentiation and growth.

Growth Hormone: A hormone produced by the anterior pituitary gland that promotes growth and regulates metabolism in the body.

Huntington's Disease: An inherited neurodegenerative condition characterized by abnormal body movements, dementia and psychiatric problems.

Hyperphagia: Increased food intake due to excessive unsuppressible appetite

Hypoxic-Ischemic Injury: An injury caused by lack of oxygen and/or blood supply to an organ.

Immunomodulation: Regulation of the immune response.

GLOSSARY

In Vitro: Within a test tube or outside a living organism or cell.

In Vivo: Within a living organism or cell.

IND: Investigational New Drug. Before beginning tests (clinical trials) of a new drug on humans, a drug sponsor must submit an IND application to the FDA. The IND contains the plan for the study and must give a complete picture of the drug, including its structural formula, animal test results, and manufacturing information.

Insulin Resistance Syndrome: Failure of insulin to function normally, a condition that often leads to non-insulin-dependent diabetes in which normal levels of insulin in the blood do not produce the normal biological response because of defects in the ability of the tissues to respond.

Insulin-like Growth Factor-1 (IGF1): A 71 amino acid peptide growth factor that is produced in many tissues, especially the liver. It mediates some of the actions of growth hormone.

Intellectual Property: Promoting the progress of science and useful arts by securing for limited times to authors and inventors, the exclusive rights to their respective writings and discoveries.

Interferons: Natural proteins produced by the cells of the immune systems of most animals in response to a challenge by foreign agents such as viruses, bacteria, parasites and tumour cells. Interferons belong to the large class of glycoproteins known as cytokines.

Leukodystrophies: A disorder of the white matter of the brain.

Leukoencephalopathy: Any group of diseases affecting the white matter of the brain.

Lipid Disorders: Condition resulting in abnormal levels of the body's fats, including cholesterol and triglycerides.

Macrocyclics (MCs): A family of highly stable larger cyclic neuroprotective compounds being developed by Neuren.

Metabolic Syndrome: A combination of health conditions that place a person at high risk for heart disease. These conditions are type-2 diabetes, hypertension (high blood pressure), hyperlipidemia (high levels of fat in the blood), and obesity. All of these conditions are associated with high blood insulin levels.

Metabolism: The way cells chemically change food so that it can be used to keep the body alive. It is a two-part process. One part is called catabolism - when the body uses food for energy. The other is called anabolism - when the body uses food to build or mend cells. Insulin is necessary for the metabolism of food.

Microemboli: A small abnormal particle such as an air bubble or part of a clot circulating in the blood.

Microglia: The resident immune cells of the brain which are only activated after disease, injury or infection.

Mode of Action: The cellular mechanism of how a drug produces its effect in the body.

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Motor Neuron Disease: A degenerative disease that affects predominantly motor neurons of the spinal cord, cranial nerve and motor cortex.

Multiple Sclerosis: A chronic progressive nervous disorder involving loss of myelin sheath around certain nerve fibres, which can present with a variety of neurological symptoms. The disease occurs in attacks or slowly progresses over time. It has no cure yet and the exact cause remains unknown. Due to its effects of the nervous system, it can lead to long-term impaired mobility and disability in severe cases.

Muscular Dystrophy: Any of several hereditary diseases of the muscular system characterized by weakness and wasting of skeletal muscles.

Necrosis: The name given to unprogrammed death of cells and living tissue (compare with *apoptosis - programmed cell death*).

Neural Regeneration Peptides (NRPs): A family of over 20 peptides discovered by Neuren scientists with unique cell survival, differentiation and migrational properties.

Neurodegenerative Diseases: A varied assortment of central nervous disorders characterized by gradual and progressive loss of neural tissue.

Neurons: The cells of the nervous system that generate electrical activity. A typical neuron consists of a cell body, containing the nucleus and the surrounding cytoplasm (perikaryon); several short radiating processes (dendrites); and one long process (the axon), which terminates in twiglike branches (telodendrons) and may have branches (collaterals) projecting along its course.

Neuroprotection: Treatments being developed to protect against neurotoxicity and the death of brain cells.

NNZ-2566: Neuren's second lead drug candidate. An analogue of Glypromate developed using the backbone structure of Glypromate.

Nitric Oxide Synthase (NOS): An enzyme involved in the synthesis of nitric oxide. In the brain, nitric oxide acts as a neuromodulator to control behavioural activity, influence memory formation, and intensify responses to painful stimuli.

Oligodendrocytes: A form of glial cell which secretes the myelin that coats axons to make conduction more efficient. They are found in the white matter of the brain and spinal cord.

Optic Neuritis: The inflammation of the optic nerve that may cause a complete or partial loss of vision.

Parkinson's Disease: A slowly progressive neurologic disease characterized by a fixed inexpressive face, a tremor at rest, slowing of voluntary movements, a gait with short accelerating steps, peculiar posture and muscle weakness, caused by degeneration of an area of the brain called the substantia nigra and by low production of the neurotransmitter dopamine.

Peptidomimetics: Compounds containing non-peptidic structural elements that are capable of mimicking the biological action(s) of a natural parent peptide.

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Peripheral Neuropathy: A functional disturbance or pathological change in the peripheral nervous system; the aetiology may be known or unknown. Known aetiologies include complications of other diseases, such as diabetes.

Peripheral Vascular Disease: Arteriosclerosis of the blood vessels of the extremities characterized by narrowing and hardening of the arteries that supply the legs and feet. This causes a decrease in blood flow that can injure nerves and other tissues.

Pharmacodynamics: The study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of actions and effects of drugs with their chemical structure.

Pharmacokinetics: The activity or fate of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation and excretion.

Phase 1 Clinical Trial: A clinical trial in normal healthy volunteers to assess drug safety, tolerability and pharmacokinetics.

Phase 2 Clinical Trial: A clinical trial in the patient population to assess drug safety, tolerability, pharmacokinetics and preliminary efficacy data.

Phase 3 Clinical Trial: Large clinical trials across multiple centres to assess the efficacy of a drug in treating a specific disease.

Pontine Myelinolysis: A neurologic disease caused by severe damage of the myelin sheath of nerve cells in the brainstem, more precisely in the pons.

Post-asphyxial Seizures: A seizure caused by lack of oxygen to the brain, resulting in hypoxia.

Pre-clinical Development: Drug development studies in animals and in vitro to assess dose, efficacy, pharmacokinetics and safety before clinical trials.

Pre-clinical Toxicology: The testing of new drug candidates for toxic effects in animals undertaken prior to human clinical trials.

Programmed Cell Death: The body's normal method of disposing of damaged, unwanted, or unneeded cells. Also called *apoptosis*.

Prophylactic: A treatment to ward off or prevent a particular disease.

Secondary Necrosis: A second phase of necrosis of brain cells delayed for some time from the injury.

Somatosensory: The system of brain cells that sense pain and other sensations from the skin or deep tissues.

Stroke: An acute clinical event that leads to impairment of blood flow to the brain; it can either be due to a blockage of a blood vessel or to rupture of a blood vessel within the brain.

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Syndrome X: An alternative name for Metabolic Syndrome.

Therapeutic Intervention: A treatment aimed at curing or restoring a person's health.

Transverse Myelitis: A neurologic disorder caused by a loss of the myelin encasing the spinal cord, also known as demyelination. It may occur alone or together with multiple sclerosis.

Traumatic Brain Injury (TBI): Brain damage from trauma or injury. It may be penetrating or non-penetrating depending on whether the skull is fractured.

Tyrosine Hydroxylase (TH): An enzyme that causes the hydroxylation of tyrosine to dopa. Dopa is the precursor of the neurotransmitter dopamine. Deficiency of dopamine in the brain results in Parkinson's disease.

Valvuloplasty: Repair of a cardiac or venous valve.

White Matter: Brain tissue composed of nerve cells processes (axons and dendrites) that connect various parts of the brain to each other and carry nerve impulses to or from the bodies of nerve cells (neurons). It is rich in myelin.