Summary of Risk Assessment Conducted Pursuant to subsection 83(1) of the *Canadian Environmental Protection Act, 1999*

Ministerial Condition No: EAU-740: Androsta-5, 16-dien-3-ol, 17-(3-pyridinyl)-, acetate (ester), (3β)-; Chemical Abstracts Service Registry No. 154229-18-2

Regulatory Decisions

Under the provisions for Substances and Activities New to Canada in Part 5 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), and pursuant to section 83 of that Act, the Minister of the Environment and the Minister of Health have assessed information in respect of the substance, and determined that the substance is anticipated to enter the environment in a quantity or concentration or under conditions that have or may have an immediate or long term harmful effect on the environment or its biological diversity.

In order to ensure that the substance does not cause harm to the environment in Canada, its import and formulation are authorized subject to conditions on its use, handling and disposal as described in Ministerial Condition No. EAU-740, published in the *Canada Gazette* Part I, Vol. 148, No. 28, July 12, 2014.

Substance Identity

The substance is a chemical that can be classified as a cycloalkane acetate.

Notified Activities

The substance is proposed to be imported into Canada in quantities greater than 100 kg/year for the purpose of formulation into final end-use products for use as a pharmaceutical ingredient in the treatment of cancer. The metabolite of the substance is the active pharmaceutical ingredient. Thus, the notified substance is a prodrug.

Environmental Fate and Behaviour

Based on its physical and chemical properties, if released to the environment, the substance will tend to partition to suspended particulate matter, sediment and soil. The substance and its metabolite are not expected to be persistent in these compartments based on degradation in aerobic aquatic sediment systems. The substance and its metabolite are not expected to be bioaccumulative based on low experimental bioconcentration values.

Ecological Assessment

Based on the available hazard information on the substance, the substance has high acute toxicity in fish (96-h LC50 < 1 mg/L) and daphnia (EC50 < 1 mg/L) and high subchronic toxicity in fish (NOEC < 30 ng/L) and daphnia (NOEC < 1 µg/L). The predicted no effect concentration (PNEC) was calculated to be less than 30 ng/L for reproduction in the most sensitive organism, fish, which was used to estimate the ecological risk.

The notified and other potential activities in Canada were assessed to estimate the environmental exposure potential of the substance throughout its life cycle. Environmental exposure from the notified activity is expected to be mainly from releases to surface water following use by the intended patient population in Canada. The predicted environmental concentration (PEC) for notified activities is estimated to be at levels of 10^{-9} to 10^{-6} mg/L. However, if use of the substance is expanded, if it is formulated in a manner that results in less rigorous waste management practices prior to environmental release, and/or if the substance is manufactured in Canada in the future, an increased exposure potential may exist from industrial releases to surface water.

Based on the potential for increased exposure in surface water from industrial release in conjunction with high aquatic toxicity, the substance is anticipated to cause ecological harm in Canada. Risks have been identified with release of the substance to water when use is expanded or less rigorous methods of disposal are employed during manufacture or blending/formulation.

Human Health Assessment

Based on the available hazard information on the substance by the oral route of exposure, the substance has potential for moderate acute toxicity (LD50 = 50–1,000 mg/kg bw) and potential for high subchronic toxicity, including reproductive and liver toxicity, following repeat oral doses in mammalian test animals (LOAEL < 500 mg/kg/day). The substance has potential for liver, reproductive and cardio toxicity in humans. The substance is not genotoxic *in vitro* in multiple assays nor *in vivo* in the rat. Thus, the substance is considered unlikely to cause genetic damage.

When used as a pharmacologically active ingredient, direct exposure to the general non-patient population is not expected. Indirect exposure of the general population from environmental media such as ingestion of drinking water is expected to be very low. However, if the substance is used in other therapeutic applications, or if the industrial release is increased through manufacture or less rigorous disposal methods, an increased indirect exposure potential (ingestion or frequent, sustained, dermal contact to the skin) may exist, but is still expected to be low.

Although the substance shows high repeated oral dose toxicity, with low expected exposure the substance is not likely to pose a significant health risk to the general population, and is therefore unlikely to be harmful to human health.

Assessment Conclusion

The substance is suspected to be harmful to the environment according to the criteria under paragraph 64(*a*) of CEPA 1999.
When used as notified, with appropriate measures to prevent environmental release, the substance is not suspected to be harmful to human health or the environment according to the criteria under section 64 of CEPA 1999. However, due to the potential risk to the environment related to the high aquatic toxicity if the substance is manufactured or imported for

blending/formulating with less rigorous waste management practices, a Ministerial Condition No. EAU 740 was published in *Canada Gazette* Part I, Vol. 148, No. 28, July 12, 2014 to restrict the manner in which the notifier may import and manufacture the substance with conditions on its use, handling and disposal in order to mitigate these potential risks.