



ADVICE SUMMARY

APPLICATION FOR REGISTRATION OF A CHEMICAL PRODUCT

Product name: LIFETIDE SW 5 INJECTABLE PLASMID ENCODING PORCINE GHRH
Applicant: VGX ANIMAL HEALTH, INC.
Product number: 59865
Application number: 36936

Purpose of Application and Description of Use: Registration of an injectable 2.5mg per mL synthetic porcine GHRH-encoding plasmid, including approval of the new active constituent (HAG659865) for administration by electroporation following anaesthesia to breeding age sows and gilts to increase the number of piglets weaned.

Active Constituent(s): SYNTHETIC PORCINE GROWTH HORMONE RELEASING HORMONE (GHRH) – ENCODING PLASMID

Regulatory Decision:

To grant the application subject to the following conditions:

For full conditions, refer to http://www.apvma.gov.au/advice_summaries/adv_summaries.shtml.

ADVICE

Australian Government Department Of Health And Ageing, Office Of Chemical Safety

The applicant. submitted a data package seeking approval of a Synthetic Porcine growth hormone-releasing hormone (GHRH)-encoding plasmid, and an injectable product containing this new active, namely Lifetide SW 5 Injectable Plasmid Encoding Porcine GHRH which contains the cassette at a concentration of 2.5 mg/mL. The product is intended for administration by injection to breeding sows to increase the number of piglets weaned.

No ADI or ARfD has been established for the synthetic DNA expression cassette encoding for porcine growth hormone releasing hormone.

As well as consideration of potential hazards from dietary exposure, OCS assessment addressed possible hazards from self-injection of the product. The applicant has submitted a range of studies, including single and multiple dose (injection) studies on a similar product conducted with dogs and some published papers on the effects of plasmid-mediated GHRH supplementation in mice and dogs. They have also provided some reference papers. Published literature was also reviewed in order to identify and assess potential hazards posed by use of the product.

No Safety Directions were proposed since the product is a veterinary injectable. The proposed use of “Lifetide SW 5 Injectable Plasmid Encoding Porcine GHRH” would not be an undue health hazard to humans according to the criteria stipulated in Section 14 (5)(e) of the Ag/Vet Code Act of 1994. At its 48th meeting, in October 2006, the NDPSC agreed to foreshadow that GHRH Injectable Plasmid be included in Schedule 4 of the SUSDP noting the need for veterinary supervision. The scheduling of GHRH would therefore again be considered at the February 2007 NDPSC meeting. The NDPSC at its 49th meeting on 20-22 February 2007 confirmed the schedule 4 prescription animal remedy status noting the need for veterinary supervision of the use of the product.

Data relied on to provide the advice

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
9236	S	Pollard H et al	Ca ²⁺ -sensitive cytosolic nucleases prevent efficient delivery to the nucleus of injected plasmids	2001	Toxicology	Other Information	Public	
9220	S	Aihara H et al	Gene transfer into muscle by electroporation in vivo.	1998	Toxicology	Other Information	Public	
9237	S	Haworth R & Pilling A	The PCR assay in the preclinical safety evaluation of nucleic acid medicines.	2000	Toxicology	Other Information	Public	
9222	S	Hartikka J et al	Electroporation-facilitated delivery of plasmid DNA in skeletal muscle: plasmid dependence of muscle damage and effect of poloxamer 188.	2001	Toxicology	Other Information	Public	
9238	S	Anon	Statement of Policy: Foods Derived from New Plant Varieties: Notice.	1992	Toxicology	Other Information	Public	
9224	S	Rizzuto G et al	Gene electrotransfer results in a high-level transduction of rat skeletal muscle and corrects anemia of renal failure.	2000	Toxicology	Other Information	Public	
9239	S	Roy K et al	Oral gene delivery with chitosan--DNA nanoparticles generates immunologic protection in a murine model of peanut allergy.	1999	Toxicology	Other Information	Public	
9226	S	Fattori E et al	Gene electro-transfer of an improved	2005	Toxicology	Other Information	Public	

			erythropoietin plasmid in mice and non-human primates.					
9240	S	Levine M et al	Recombinant DNA risk assessment studies in humans: efficacy of poorly mobilizable plasmids in biologic containment.	1983	Toxicology	Other Information	Public	
9228	S	Gehl J et al	In vivo electroporation of skeletal muscle: threshold, efficacy and relation to electric field distribution.	1999	Toxicology	Other Information	Public	
9241	S	Faglia G et al	Ectopic acromegaly	1992	Toxicology	Other Information	Public	
9230	S	Imai E & Isaka Y	Gene electrotransfer: Potential for gene therapy of renal diseases.	2002	Toxicology	Other Information	Public	
9242	S	Melmed S	Extrapituitary Acromegaly	1991	Toxicology	Other Information	Public	
9232	S	Wolff J et al	Conditions affecting direct gene transfer into rodent muscle in vivo.	1991	Toxicology	Other Information	Public	
9243	S	Esch F et al	Characterization of a 40 residue peptide from a human pancreatic tumor with growth hormone releasing activity	1982	Toxicology	Other Information	Public	
9234	S	Barry M et al	Role of endogenous endonucleases and tissue site in transfection and CpG-mediated immune activation after naked DNA injection.	1999	Toxicology	Other Information	Public	
9244	S	Thorner M et al	Extrahypothalamic growth-hormone-releasing factor (GRF) secretion is a rare cause of acromegaly: plasma GRF levels in 177 acromegalic patients.	1984	Toxicology	Other Information	Public	
9221	S	Kreiss P et al	Erythropoietin secretion and physiological effect in mouse after intramuscular plasmid DNA electrotransfer	1999	Toxicology	Other Information	Public	
9219	S	Mir L et al	High-efficiency gene transfer into skeletal muscle mediated by electric pulses.	1999	Toxicology	Other Information	Public	
9225	S	Schakman O et al	Insulin-like growth factor-I gene transfer by electroporation prevents skeletal muscle atrophy in glucocorticoid-treated rats.	2005	Toxicology	Other Information	Public	
9218	S	Dean D	Nonviral gene transfer to skeletal, smooth, and cardiac muscle in living animals.	2005	Toxicology	Other Information	Public	
9229	S	Hanna E et al	Intramuscular electroporation delivery of IL-12 gene for treatment of squamous cell carcinoma located at distant site.	2001	Toxicology	Other Information	Public	
9217	S	Ratanamart J & Shaw J	Plasmid-mediated muscle-targeted gene therapy for circulating therapeutic protein replacement: a	2006	Toxicology	Other Information	Public	

			tale of the tortoise and the hare?					
9233	S	Cappelletti M et al	Gene electro-transfer improves transduction by modifying the fate of intramuscular DNA.	2003	Toxicology	Other Information	Public	
9216	S	Wolff J et al	Direct gene transfer into mouse muscle in vivo.	1990	Toxicology	Other Information	Public	
9223	S	Thanaketpaisarn O et al	Tissue-specific characteristics of in vivo electric gene: transfer by tissue and intravenous injection of plasmid DNA.	2005	Toxicology	Other Information	Public	
9215	S	Wolff J et al	Long-term persistence of plasmid DNA and foreign gene expression in mouse muscle.	1992	Toxicology	Other Information	Public	
9235	S	Lechardeur D et al	Metabolic instability of plasmid DNA in the cytosol: a potential barrier to gene transfer.	1999	Toxicology	Other Information	Public	
9227	S	Babiuk S et al	Electroporation improves the efficacy of DNA vaccines in large animals.	2002	Toxicology	Other Information	Public	
9231	S	Lesbordes J et al	In vivo electrotransfer of the cardiotrophin-1 gene into skeletal muscle slows down progression of motor neuron degeneration in pmn mice.	2002	Toxicology	Other Information	Public	
9214	S	Khan A et al	Highly efficient constant-current electroporation increases in vivo plasmid expression	2005	Toxicology	Other Information	Public	
9213	S	Draghia-Akli R	Discussion on the safety of LifeTide SW 5 following inadvertent administration to humans	09/06	Toxicology	Other Information	Applicant	
1524	S	Perez A	Single dose tolerance and safety study of ADViSYS, Inc HV plasmid in beagle dogs	11/02	Toxicology	Acute Oral Studies, Active	Applicant	
1525	S	Perez A	Multiple dose tolerance and safety study of ADViSYS, Inc plasmid Lot #paV0125.98158 in beagle dogs	1/03	Toxicology	Short-term studies	Applicant	
1563	S	Li et al	Synthetic muscle promoters: activities exceeding naturally occurring regulatory sequences.	1999	Metabolism and Kinetics	Other Information	Public	
1562	S	Frohman et al	Dipeptidylpeptidase IV and trypsin-like enzymatic degradation of human growth hormone-releasing hormone in plasma.	1989	Metabolism and Kinetics	Other Information	Public	
1561	S	Dubreuil et al	The use of pigs as an animal model to evaluate the efficacy, potency and specificity of two growth hormone releasing factor analogues.	2001	Metabolism and Kinetics	Other Information	Public	
1560	S	Bureau et al	Intramuscular plasmid DNA electrotransfer biodistribution and degradation.	2004	Metabolism and Kinetics	Other Information	Public	
1564	S	Maeda et al	Expression of LacZ gene in canine muscle by intramuscular inoculation of a plasmid DNA.	2004	Metabolism and Kinetics	Other Information	Public	

Australian Government Department Of Environment And Heritage

In completing the assessment, the Department convened a workshop to consult with relevant industry, regulatory and scientific experts on the environmental risks posed generally by plasmid DNA therapies. This was necessary as no environmental fate and ecotoxicity data was submitted with the application.

The Department has recommended that an MSDS should be provided for the product, the label should include disposal instructions, and that Kanamycin C or related antibiotics for which the kanamycin resistance gene confers resistance should not be administered to animals treated with Life Tide within 7 days of treatment. The Department concludes that providing these conditions are included, the proposal is acceptable and recommended that the APVMA be satisfied that the proposed release will not lead to an unintended effect that is harmful to animals, plants or things, or to the environment.

APVMA Chemistry And Residues Program, Residues Section

The application was assessed by the APVMA's veterinary residues (VRS). VRS advised that the active is a naturally occurring compound found in pigs and porcine growth hormone releasing hormone would not be detectable as a residue in tissues. VRS confirmed that there would be a MRL Standard Table 5 entry. Appropriate withhold and ESI statements have been placed on the label.

State/External Efficacy Reviewer

The application was referred to an external expert for assessment and the final technical report (FTR) was completed in consultation with the States and Territories. The applicant addressed issues raised in the FTR which led to the supplementary FTR. The FTR concluded that the data supported the safety of the product. The APVMA reviewed the FTR following agreement by the applicant to change the claim to "For use in sows to increase the number of piglets weaned" and concluded that the data supported the claim in the context of the proposed pattern of use. The intramuscular injection of the product requires electroporation under short sedation or anaesthesia and will therefore be administered by or under the direction of a registered veterinarian. Any animal welfare concerns regarding possible pain on administration of the product are thus addressed by the pattern of use. Appropriate label amendments have been made.

Data relied on to provide the advice

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
1555	S	Khan et al	Optimization of electroporation parameters for the intramuscular delivery of plasmids in pigs.	2003	Efficacy and Safety	Efficacy	Public	
5764	S	Davis R	Correspondence containing additional efficacy data for Lifetide SW 5	2006	Efficacy and Safety	Efficacy	Applicant	
1559	S	Draghia-Akli et al	Electrical enhancement of formulated plasmid	2002	Efficacy and Safety	Efficacy	Public	

			delivery in animals.					
1554	S	Khan et al	Maternal GHRH plasmid administration changes pituitary cell lineage and improves progeny growth of pigs.	1/04/2003	Efficacy and Safety	Efficacy	Public	
1551	S	RC Person	Effects of GHRH plasmid treatment in sows.	14/04/2005	Efficacy and Safety	Efficacy	Applicant	
1553	S	Khan et al	Nonhereditary enhancement of progeny growth.	2002	Efficacy and Safety	Efficacy	Public	
1556	S	Draghia-Akli R and Fiorotto ML	A new plasmid-mediated approach to supplement somatotropin production in pigs.	2004	Efficacy and Safety	Efficacy	Public	
8123	S	Anon	Supplemental Analysis to Study 1551 Large Scale Efficacy Study (applicant reference 03PO79C)	1/8/06	Efficacy and Safety	Efficacy	Applicant	
1557	S	Draghia-Akli et al	Myogenic expression of an injectable protease-resistant growth hormone-releasing hormone augments long-term growth in pigs.	1999	Efficacy and Safety	Efficacy	Public	
1558	S	Draghia-Akli et al	High-efficiency growth hormone releasing hormone plasmid vector administration into skeletal muscle mediated by electroporation in pigs.	2003	Efficacy and Safety	Efficacy	Public	
1550	S	RC Person	Effects of ADViSYS GHRH plasmid treatment of sows and progeny	14/04/2005	Efficacy and Safety	Efficacy	Applicant	
7509	S	Brown P et al	Immune enhancing effects of growth hormone releasing hormone delivered by plasmid injection and electroporation.	2004	Efficacy and Safety	Efficacy	Public	
6210	S	Kimoto H & Taketo A	Studies on electrotransfer of DNA into Escherichia coli: effect of molecular form of DNA	1996	Efficacy and Safety	Efficacy	Public	
7519	S	Frohman L et al	Regulation of Growth Hormone Secretion	1992	Efficacy and Safety	Other Information	Public	
6211	S	Labhasetwar V et al	A DNA controlled-release coating for gene transfer: transfection in skeletal and cardiac muscle	1998	Efficacy and Safety	Other Information	Public	
7520	S	Alt J et al	Influenza virus-induced glucocorticoid and hypothalamic and lung cytokine mRNA responses in dwarf lit/lit mice.	2005	Efficacy and Safety	Other Information	Public	
7510	S	Campbell R et al	Enhanced stability and potency of novel growth hormone-releasing factor (GRF) analogues derived from rodent and human GRF sequences.	1994	Efficacy and Safety	Other Information	Public	
6208	S	Draghia-Akli R & Smith L	Electrokinetic enhancement of plasmid delivery in vivo	2003	Efficacy and Safety	Other Information	Public	

7512	S	Nuoffer J et al	Regulation of human GH receptor gene transcription by 20 and 22 kDa GH in a human hepatoma cell	2000	Efficacy and Safety	Other Information	Public	
6207	S	Bergan D et al	Gene transfer In Vitro and In Vivo by cationic lipids is not significantly affects by levels of supercoiling of a reporter plasmid	2000	Efficacy and Safety	Other Information	Public	
7514	S	Sarradell J et al	A morphologic and immunohistochemical study of the bronchus-associated lymphoid tissue of pigs naturally infected with Mycoplasma hyopneumoniae.	2003	Efficacy and Safety	Other Information	Public	
6206	S	Gammon R	Sample assay for bacteriophages/prophage	2003	Efficacy and Safety	Other Information	Applicant	
7516	S	Takahashi S & Satozawa N	The 20-kD human growth hormone reduces body fat by increasing lipolysis and decreasing lipoprotein lipase activity.	2001	Efficacy and Safety	Other Information	Public	
7513	S	Prud'homme G et al	Electroporation-enhanced nonviral gene transfer for the prevention or treatment of immunological, endocrine and neoplastic diseases.	2006	Efficacy and Safety	Other Information	Public	
7515	S	Siejka A et al	Effect of growth hormone-releasing hormone (GHRH) and GHRH antagonist (MZ-4-71) on interferon-gamma secretion from human peripheral blood mononuclear cells in vitro.	2004	Efficacy and Safety	Other Information	Public	
7511	S	Draghia-Akli R et al	Enhanced growth by ectopic expression of growth hormone releasing hormone using an injectable myogenic vector	1997	Efficacy and Safety	Other Information	Public	
7518	S	Berghe G	Endocrine evaluation of patients with critical illness.	2003	Efficacy and Safety	Other Information	Public	
6209	S	Hodges B et al	Long term transgene expression from plasmid DNA gene therapy vectors is negatively affected by CpG dinucleotides	2004	Efficacy and Safety	Other Information	Public	
7517	S	Thacker E et al	Plasmid-mediated growth hormone-releasing hormone efficacy in reducing disease associated with Mycoplasma hyopneumoniae and porcine reproductive and respiratory syndrome virus infection.	2006	Efficacy and Safety	Other Information	Public	
1552	S	Holtkamp D	Summary of reported adverse reactions related to anaesthesia and plasmid treatment of swine.	12-Mar	Efficacy and Safety	Target Animal Safety Studies	Applicant	

Office of the Gene Technology Regulator

The application was passed to the Office of the Gene Technology Regulator (OGTR) for advice. Following the passing of the Gene Technology Amendment Regulations 2006 (no 1), the OGTR confirmed that this product and the animals treated with this product do not fall within the provisions of the Act and Regulations and that no further assessment by the OGTR would be required.

External Chemistry Reviewer

The application for the active and product was assessed by an external reviewer whose Final Technical Report (FTR) incorporated comments from State Coordinators. The applicant responded by presenting experimental data and scientific argument at a meeting on 7th July 2006 to the APVMA and its advisers including representatives from the Office of Chemical Safety (OCS), and the OGTR. The response to the chemistry issues of batch release efficacy, safety and stability testing were passed to the reviewer. The reviewer's supplementary comments supported the changes proposed to ensure a biological test was used to ensure the potency of the active. The external reviewer supported registration and considered that the active and the product are safe and effective with the proposed in vivo biological batch release testing protocols as confirmed by the applicant. The Good Manufacturing Practice (GMP) status of the formulator was confirmed by the APVMA's Quality Assurance Team for the facility at Suite 180, 2700 Research Forest Drive, The Woodlands TX 77381 USA.

In the light of the recommendation of the external reviewer for the chemistry and manufacturing aspects of the active, and the GMP acceptability of the facility, the APVMA approved the active under section 14A at the time of product registration. The active and product are manufactured to a standard which satisfies the chemistry and manufacturing provisions of the Agvet Chemicals Code Act.

Data relied on to provide the advice

Data No	Data Source*	Author(s)	Title	Date	Data Type	Data Sub-type	Authorising Party	Inherited Application No.
12029	S	Anon	Batch release Mouse In vivo Efficacy Testing	March 2007	Chemistry and Manufacture	Product, Batch Analysis	Applicant	
12030	S	Anon	Batch release Mouse In vivo Efficacy Testing Form	March 2007	Chemistry and Manufacture	Product, Batch Analysis	Applicant	
12033	S	Anon	Out of specification Investigation procedure	Nov 2006	Chemistry and Manufacture	Product, Batch Analysis	Applicant	
12028	S	Davis R	Correspondence reporting two in vivo mouse batch release optimisation experiments	March 2007	Chemistry and Manufacture	Product, Batch Analysis	Applicant	
12032	S	Anon	Batch in vivo safety testing	March 2007	Chemistry and Manufacture	Product, Batch Analysis	Applicant	
12031	S	Anon	ADP0002 Release Testing - Serial and Subserials	March 2007	Chemistry and Manufacture	Product, Batch Analysis	Applicant	

8142	S	Various	Chemistry data received in conjunction with an application made between 01/01/2005 and 31/08/2005.	Various	Chemistry and Manufacture	Product, Other Information	Applicant	
12034	S	Anon	Investigations	July 2006	Chemistry and Manufacture	Product, Other Information	Applicant	

Other Details About The APVMA's Decision To Grant The Application

Since there were no residues issues to consider, the trade assessment was completed in consultation with the industry. The peak industry body, Australian Pork Limited (APL) advised that there was no trade risk associated with the registration and use of the product as proposed.

* *S = Data submitted with the application*

I = Data inherited (that is, referenced) from another application