



Australian Government
**Australian Pesticides and
Veterinary Medicines Authority**



PUBLIC RELEASE SUMMARY

on the Evaluation of Rabbit Haemorrhagic Disease Virus, 08Q712 strain in the
product RHDV K5

APVMA Product Number 80188

DECEMBER 2015

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PREFACE

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator with responsibility for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia.

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health, Office of Chemical Safety (OCS), Department of Environment (DE), and State Departments of Primary Industries.

The APVMA has a policy of encouraging openness and transparency in its activities and of seeking community involvement in decision making. Part of that process is the publication of Public Release Summaries for products containing new active constituents.

The information and technical data required by the APVMA to assess the safety of new chemical products, and the methods of assessment, must be consistent with accepted scientific principles and processes.

This Public Release Summary is intended as a brief overview of the assessment that has been conducted by the APVMA and of the specialist advice received from its advisory agencies. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience thereby encouraging public comment.

About this document

This is a Public Release Summary.

It indicates that the Australian Pesticides and Veterinary Medicines Authority (APVMA) is considering an application for registration of an agricultural or veterinary chemical. It provides a summary of the APVMA's assessment, which may include details of:

- the toxicology of both the active constituent and product
- the residues and trade assessment
- occupational exposure aspects
- environmental fate, toxicity, potential exposure and hazard
- efficacy and target crop or animal safety.

Comment is sought from interested stakeholders on the information contained within this document.

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of RHDV K5 should be granted. Submissions should relate only to matters that the APVMA is required, by legislation, to take into account in deciding whether to grant the application. These matters include aspects of public health, occupational

health and safety, chemistry and manufacture, residues in food, environmental safety, trade, and efficacy and target crop or animal safety. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on Friday 29 January 2016 and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

Relevant comments will be taken into account by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- contact name
- company or group name (if relevant)
- email or postal address (if available)
- the date you made the submission.

All personal information, and confidential information judged by the APVMA to be *confidential commercial information (CCI)*¹ contained in submissions will be treated confidentially.

Written submissions on the APVMA's proposal to grant the application for registration that relate to the grounds for registration should be addressed in writing to:

Case Management and Administration Unit
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
Kingston ACT 2604

Phone: +61 2 6210 4701

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Further information

Further information can be obtained via the contact details provided above.

Further information on public release summaries can be found on the APVMA website: www.apvma.gov.au

¹ A full definition of 'confidential commercial information' is contained in the Agvet Code.

1 INTRODUCTION

This publication provides a summary of the data reviewed and an outline of the regulatory considerations for the proposed registration of RHDV K5, and approval of the new active constituent, Rabbit Haemorrhagic Disease Virus, 08Q712 strain.

Following an application by NSW Department of Primary Industries, it is proposed to register RHDV K5 containing >30,000 ID₅₀ units of Rabbit haemorrhagic disease virus, 08Q712 strain (RHDV 08Q712) for the infection of wild European rabbits (*Oryctolagus cuniculus*). Further information about RHDV 08Q712 is included in Section 1.1 of this document.

The product is a lyophilised formulation that must be reconstituted in distilled water prior to use. Once reconstituted, it will be used to either inject live rabbits, or prepare a carrot or oat bait and fed to live rabbits, in order to infect them with RHDV 08Q712. Infected rabbits will then spread RHDV 08Q712 to other rabbits by direct contact or indirectly through faeces and other vectors such as insects. This should lead to a local epizootic of rabbit haemorrhagic disease (RHD) which causes mortality and is claimed to reduce overall rabbit numbers across Australia.

The mode of action is the same as a currently registered product (APVMA Product Number 50675) which contains a different strain of the same virus, RHDV v351 (commonly known as the Czech strain, or more generally as rabbit calicivirus). RHD is normally lethal two to three days post infection without noticeable behavioural change. The applicant stated that after consideration of all the evidence it appears that RHD is more humane in its action than most other methods of rabbit control.

A RHDV vaccine, with an existing APVMA registration, is available from veterinarians for the protection of valuable rabbits that are farmed or kept as domestic pets. This vaccine is protective, when used in accordance with its directions for use, against RHDV v351 and RHDV 08Q712.

European rabbits were introduced into Australia with the first fleet in 1788 and a wild population was first observed in Tasmania in 1827. In 1859, 24 rabbits kept for hunting purposes, escaped their enclosures at a property in Victoria and by 1886 they had reached the NSW/Queensland border. By the 1920s it was estimated there were up to 10 billion wild rabbits spread across Australia. Despite the release of the Myxoma virus (the cause of Myxomatosis) in the 1950s and the release of RHDV v351 in 1996, they are still the most economically and environmentally damaging vertebrate pest species in Australia:

- rabbits cause an estimated \$206 million in losses each year to the agricultural industry (Gong *et al.* 2009)
- rabbits are recognised as a potential threat to more than 300 threatened species (15 birds, 20 mammals, 6 reptiles, 1 invertebrate, 1 fish, 1 amphibian and 260 plant species) (DotE 2015)

Whilst RHDV 08Q712 will infect rabbits in all regions of Australia, the greatest effect is expected to be seen in the cool-wet regions of the country. An endemic benign virus, rabbit calicivirus Australia 1 (RCV-A1), is found in the cool-wet regions and partially protects rabbits from RHDV v351. RHDV 08Q712 was selected by the applicant after trials of several different strains showed RHDV 08Q712 can overcome RCV-A1 protection and lead to infection. Refer to Section 1.2 of this document for further information.

A national release (www.pestsmart.org.au/boosting-rabbit-biocontrol-rhdv-k5-national-release/) of RHDV 08Q712 through the use of RHDV K5 will be coordinated by the Invasive Animals Cooperative Research Centre (IACRC) with oversight by the Invasive Plants and Animals Committee. IACRC has 27 members across government and industry with a mix of industry investors, research providers, commercial businesses and extension organisations that cover all key points on the value chain from R&D to adoption (www.invasiveanimals.com/).

RHDV K5 is a Restricted Chemical Product (RCP) under an existing declaration so its supply is restricted in accordance with State or Territory legislation (apvma.gov.au/node/988). Its release requires separate approval under other legislation such as the Biological Control Act 1984.

1.1 Categorisation of RHDV and related lagoviruses

RHDV is a naturally occurring RNA based Lagovirus (Family *Caliciviridae*), and was first reported in domestic rabbits in China in 1984. RHDV then spread rapidly and is now considered endemic in most parts of Europe, Asia, and some parts of Africa. It has also been observed in the Americas. It is endemic in Australia and New Zealand after deliberate releases to control pest European rabbit populations in the 1990s.

Table 1 explains the differences between some lagoviruses. In this table, bold text is used to indicate the categorisation of RHDV 08Q712 (an RHDVa sub-type of RHDV). It is important to note that different naming conventions have been used by different authors. This has led to inconsistencies and potential confusion regarding categorisation, particularly if a single source is relied upon without an understanding of the extensive body of scientific literature.

Table 1: Comparison of different lagoviruses

LAGOVIRUS	LAGOVIRUS SUB-TYPES	PATHOGENICITY	CAPABLE OF INFECTING	RHDV VACCINE
RHDV	'classical' RHDV (genogroups 1-5 (G1-5), Clade 2/C, Clade 3/A or Clade 4/B) RHDVa (genogroup 6 (G6) or Clade 1/D)	Pathogenic	European rabbits (<i>Oryctolagus cuniculus</i>)	<u>Protective</u> when used in accordance with label directions for use
RCV-A1	N/A	Benign	European rabbits (<i>Oryctolagus cuniculus</i>)	N/A
EBHSV	N/A	Pathogenic	European brown hare (<i>Lepus europaeus</i>), Mountain hare (<i>Lepus timidus</i>) and Italian hare (<i>Lepus corsicanus</i>).	<u>Not protective</u> when used in accordance with label directions for use
RHDV2	N/A	Pathogenic	European rabbits (<i>Oryctolagus cuniculus</i>), Sardinian cape hare (<i>Lepus capensis mediterraneus</i>) and Italian hare (<i>Lepus corsicanus</i>).	<u>Not completely protective</u> when used in accordance with label directions for use

RHDV 08Q712 was first isolated in the South Korean province of Incheon in 2008 and was reported as an RHDVa sub-type of RHDV in a scientific publication the following year (Oem *et al.* 2009). It was imported into Australia from the Korean National Veterinary Research and Quarantine Service in 2010 in accordance with the requirements of the Quarantine Act 1908.

During evaluation trials of different RHDV strains conducted by the applicant, RHDV 08Q712 was designated as 'K5' (the fifth strain trialled from a group of Korean isolates) within 'Group II' (Group I consisted of 'classical' RHDV; Group II consisted of RHDVa). It is important to note that these designations could be misinterpreted due to the similarity of 'RHDV Group II' to 'RHDV2'; however, it is clear that RHDV 08Q712 is not an RHDV2 lagovirus. Some authors have also used RHDVb instead of RHDV2 and RHDV1 instead of RHDV.

It should also be noted that a recent publication (Lavazza *et al.* 2015) cited that a single Eastern cottontail (*Sylvilagus floridanus*), which was found dead in an area with hares that died in an EBHSV outbreak, tested positive to EBHSV; this was replicated in laboratory experiments. In another recent publication (Lopes *et al.* 2014), it was cited that two livers, which were collected from two wild Iberian hares (*Lepus granatensis*) which were found dead in the 1990s, tested positive to 'classical' RHDV; this has not been confirmed in laboratory experiments and there has been no other instance observed in almost 20 years. Authors of both publications concluded that these data have no epidemiological relevance for either EBHSV or RHDV, and as neither species is found in Australia, these isolated instances are not relevant to RHDV 08Q712.

1.2 History of RHDV in Australia

RHDV was first trialled in Australia by the CSIRO in the early 1990s. A strain known as v351 (RHDV v351), which was isolated in Czechoslovakia in 1987, was imported to Australia in 1991. It was confirmed to be lethal to the Australian population of wild European rabbits at the Australian Animal Health Laboratory. A field trial was then conducted in 1995 on Wardang Island in Spencer Gulf, South Australia.

An accidental release occurred in late 1995 before widespread release was approved following the registration of a product containing RHDV v351 in 1996. This product was a suspension formulation that was only used to inject live rabbits. In 2006 the use was extended to the preparation of carrot or oat bait, and in 2015 a new lyophilised formulation was registered for both injection and bait use.

In the 13 years following its release, RHDV v351 resulted in close to 6 billion dollars of savings associated with reduced rabbit populations and impacts (Ward *et al.* 2010). However, it was reported that RHDV v351 was less efficient in controlling rabbits in cool-wet regions of Australia (Cooke and Fenner 2002). It has recently been reported that a newly discovered lagovirus endemic to Australia, rabbit calicivirus Australia-1 (RCV-A1), is a cause of an observed reduction of RHDV-induced rabbit mortality in these cool-wet regions of Australia as it may act as a natural vaccine conferring at least partial protection from lethal RHDV infection (Strive *et al.* 2010).

These observations resulted in the Invasive Animals Cooperative Research Centre (IACRC) commissioning a project called RHD BOOST. The objective of this project was to identify, seek approval, release and selectively measure the performance of new naturally occurring overseas RHDV strains found to be superior to the one existing approved RHDV strain in Australia (Cox *et al.* 2013). RHDV K5 containing RHDV 08Q712 is the outcome of this project.

2 CHEMISTRY AND MANUFACTURE

The chemical active constituent Rabbit haemorrhagic disease virus, 08Q712 strain (RHDV 08Q712), and the product RHDV K5 have the following properties:

COMMON NAME (ISO):	Rabbit haemorrhagic disease virus, 08Q712 strain
CHEMICAL NAME:	Rabbit haemorrhagic disease virus, Korean 08Q712 strain (Incheon)
PRODUCT NAME:	RHDV K5
ACTIVE CONSTITUENT CONCENTRATION:	>30,000 ID50 units of Rabbit haemorrhagic disease virus, 08Q712 strain
CAS REGISTRY NUMBER:	N/A
EMPIRICAL FORMULA:	N/A
MOLECULAR WEIGHT:	N/A
PHYSICAL FORM:	RHDV is an RNA virus which has been measured in the range of 28-42 nm in diameter.
FORMULATION TYPE:	Lyophilised (aka freeze dried)
STRUCTURAL FORMULA:	N/A

The APVMA has evaluated the chemistry aspects (manufacturing process, quality control procedures, batch analysis results, stability, analytical methods, physico-chemical properties, formulation process, and packaging) of both active, RHDV 08Q712, and product, RHDV K5, concurrently and found them to be acceptable.

The product will be formulated by the NSW Department of Primary Industries. The manufacturing and quality control procedures, including compliance with the release specifications, are acceptable.

The applicant provided the results of stability testing conducted using samples in 10 mL multi-use glass vials. Testing of all of the important parameters for this lyophilised formulation was conducted. The results indicate that the formulated product is expected to be stable for:

- 24 months when stored under freezing conditions (<-20°C)
- 12 months when stored under refrigerated conditions (4°C), and
- 7 days at room temperature (<27°C).

Based on a review of the data provided by the applicant, the APVMA proposes to be satisfied that the chemistry and manufacturing details of RHDV K5 product are acceptable.

3 TOXICOLOGICAL ASSESSMENT

NSW Department of Primary Industries (NSW DPI) has submitted an application seeking approval of a new biological active constituent, Rabbit haemorrhagic disease virus, 08Q712 strain (RHDV 08Q712) and registration of a new biological product RHDV K5 (containing >30,000 ID50 units of RHDV 08Q712).

RHDV 08Q712 is an antigenic variant of the existing approved Rabbit Calicivirus (RCV) strain, RHDV v351 contained in APVMA Product Number 50675. The product is in a lyophilised formulation that must be reconstituted in distilled water prior to use.

RHDV is a member of the Lagovirus genus (Family *Caliciviridae*). RHDV infects only the European rabbit (*Oryctolagus cuniculus*) and the 08Q712 strain is an antigenic variant of RHDV. The proposed product is intended for the control of the wild rabbit population in Australia.

The ADI for RHDV 08Q712 has not been established. An ARfD has not been established for RHDV 08Q712, and no data were submitted to enable an ARfD to be set. The approved Rabbit Calicivirus (RCV) was considered not to require listing in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) due to no apparent toxicological concerns. As RHDV 08Q712 is an antigenic variant of the existing approved RCV, placement in the poisons schedule is also not recommended.

No new toxicology studies on the active constituent or on the product were submitted. Based on the information provided by the applicant in support of their application, there are no known physicochemical differences between different strains of RHDV. Ninety per cent (90%) nucleotide homology has been observed both within and between genogroups of RHDV. RHDV 08Q712 shares 90% nucleotide homology and 95% amino acid homology (95.5% ORF1, 97.2% ORF2 VP10 and 94.5% capsid amino acid homology) with RHDV v351 (the currently approved RCV strain previously introduced into Australia).

No acute or repeat dose toxicity studies have been submitted with the current application. New information defining the biological origin of RHDV 08Q712 along with previously evaluated information on the toxicology of the already approved RHDV v351 were relied on to establish a hazard profile for the proposed product.

4 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

NSW Department of Primary Industries (NSW DPI) has submitted an application seeking approval of a new biological active constituent, Rabbit haemorrhagic disease virus, 08Q712 strain (RHDV 08Q712) and registration of a new biological product RHDV K5 (containing >30,000 ID50 units of RHDV 08Q712).

RHDV 08Q712 is an antigenic variant of the existing approved Rabbit Calicivirus (RCV) strain, RHDV v351 contained in APVMA Product Number 50675. The product is in a lyophilised formulation that must be reconstituted in distilled water prior to use.

RHDV is a member of the Lagovirus genus (Family *Caliciviridae*). RHDV infects only the European rabbit (*Oryctolagus cuniculus*) and the 08Q712 strain is an antigenic variant of RHDV. The proposed product is intended for the control of the wild rabbit population in Australia.

A quantitative exposure assessment could not be conducted as no NOEL was available for the risk assessment. The hazard profile was used to determine whether the proposed use of the product would be an undue health hazard to humans (refer to Section 3 of this document).

The major concern from a human health perspective is the possibility that RHDV 08Q712 may infect, or mutate with the potential to infect, humans. The existing approved RCV strain, RHDV v351, is structurally and antigenically distinct from most other caliciviruses, including those which can infect humans. This observation makes the possibility of a mutation sufficient to cause "host switching" unlikely. The occasional reports of "host switching" in the *Caliciviridae* family may simply reflect the identification of a greater number of natural hosts. There is evidence of minor mutations occurring in RCV over time; however the virulence or host range does not appear to have altered. Furthermore, other caliciviruses such as the feline calicivirus which are endemic in the environment have not shown any tendency to alter host specificity.

The active constituent RHDV 08Q712 for which approval is sought is an antigenic variant of RHDV v351 and therefore, due to the high conservation of the RNA and amino acid sequences with those of RCV, host switching is considered to be unlikely.

RHDV 08Q712 is considered substantially equivalent to RHDV v351 and will therefore not pose an increased risk to human health. The intended use patterns for RHDV K5, which include injection, carrot or oat bait preparation, loading and laying bait are equivalent to those used for the existing product containing RHDV v351.

Therefore, the First Aid Instructions and Safety Directions that were recommended by NOHSC for the existing approved RHDV v351 product have been considered in establishing First Aid Instructions and Safety Directions for inclusion on the RHDV K5 product label. Based on these considerations, First Aid Instructions and Safety Directions have been recommended.

5 ENVIRONMENTAL ASSESSMENT

NSW Department of Primary Industries (NSW DPI) has submitted an application seeking approval of a new biological active constituent, Rabbit haemorrhagic disease virus, 08Q712 strain (RHDV 08Q712) and registration of a new biological product RHDV K5 (containing >30,000 ID50 units of RHDV 08Q712).

RHDV 08Q712 is an antigenic variant of the existing approved Rabbit Calicivirus (RCV) strain, RHDV v351 contained in APVMA Product Number 50675. The product is in a lyophilised formulation that must be reconstituted in distilled water prior to use.

RHDV is a member of the Lagovirus genus (Family *Caliciviridae*). RHDV infects only the European rabbit (*Oryctolagus cuniculus*) and the 08Q712 strain is an antigenic variant of RHDV. The proposed product is intended for the control of the wild rabbit population in Australia.

It is argued that the RHDV 08Q712 has an equivalent environment risk profile to the existing strain RHDV v351 strain (contained in APVMA Product Number 50675). As such, argument that RHDV 08Q712 has an equivalent environment fate and ecotoxicity profile to RHDV v351 strain was presented.

Despite genetic and antigenic variability, the variants are the same lagovirus type but belong to differing subtypes (RHDV and RHDVa). Importantly, RHDV 08Q712 is not an RHDV2 lagovirus which have been shown to partially overcome RHDV vaccinations and cause mortality in both rabbits and hares.

As such, the product containing RHDV 08Q712 is appropriate to assist in the characterisation of environmental fate, ecotoxicity and risk of the proposed product. However, it is still important to consider the fate in the environment in relation to host resistance and potential for direct and indirect effects on non-target plants and animals.

The exposure to the environment is likely to occur through both administration types (intramuscular injection and prepared carrot or oat baits). Some field and laboratory studies have shown how predatory mammals and birds play a role in the transmission of RHDV. In the wild, rabbit warren environs, soil exposed to rabbit droppings, and possibly predator faeces will be, or are likely to be, contaminated with virus particles.

Studies conducted in Australia suggest that RHDV v351 has become less effective in keeping wild rabbit numbers low. As the currently approved strain is becoming less effective in controlling rabbit populations, resistance management is vitally important. RHDV 08Q712 has been shown to overcome the partial protection offered by the endemic benign calicivirus RCV-A1. 'Classical' RHDV and RHDVa strains have a slightly different specificity for histo-blood group antigens, which may enable RHDVa strains to infect rabbits that are naturally less prone to infection with 'classical' RHDV strains.

There seems to be at least some justification for assuming that some exposure of native animals to 'live' virions is possible through physical contact with contaminated materials, including soil and faeces, and in rabbit warrens where environmental conditions are more stable than the soil surface. This will generally be substantially less than the direct exposure of predators and carrion feeders to RHDV. There are no substantiated reports of epidemiologically relevant infectivity of RHDV in animal species other than rabbit and its type derivatives. The relationship between changes in rabbit abundance and declines in either feral

cats or foxes has not been clearly demonstrated in Australia and little to no information is available that demonstrates that a change in rabbit abundance leads to increased rates of predation on native species.

It was determined that RHDV 08Q712 is considered substantially equivalent to RHDV v351 and will therefore not pose an increased risk to the environment.

6 EFFICACY AND SAFETY ASSESSMENT

NSW Department of Primary Industries (NSW DPI) has submitted an application seeking approval of a new biological active constituent, Rabbit haemorrhagic disease virus, 08Q712 strain (RHDV 08Q712) and registration of a new biological product RHDV K5 (containing >30,000 ID50 units of RHDV 08Q712).

RHDV 08Q712 is an antigenic variant of the existing approved Rabbit Calicivirus (RCV) strain, RHDV v351 contained in APVMA Product Number 50675. The product is in a lyophilised formulation that must be reconstituted in distilled water prior to use.

RHDV is a member of the Lagovirus genus (Family *Caliciviridae*). RHDV infects only the European rabbit (*Oryctolagus cuniculus*) and the 08Q712 strain is an antigenic variant of RHDV. The proposed product is intended for the control of the wild rabbit population in Australia.

European rabbits are the most economically and environmentally important vertebrate pest species in Australia:

- rabbits cause an estimated \$206 million in losses each year to the agricultural industry (Gong *et al.* 2009)
- rabbits are recognised as a potential threat to over 300 threatened species (15 birds, 20 mammals, 6 reptiles, 1 invertebrate, 1 fish, 1 amphibian and 260 plant species) under the *Environment Protection and Biodiversity Conservation Act 1999* (DotE 2015)

A variety of scientific argument, published papers and the results of laboratory trials were presented to support the registration package.

Published papers were presented that:

- document RHDV 08Q712 as a strain of RHDV capable of inducing lethal epizootics of rabbit haemorrhagic disease in overseas populations.
- demonstrate some Australian wild rabbits are likely have some resistance to RHDV v351
- demonstrate the taxonomy of RHD viruses is complex but documented and justifies the selection of RHDV 08Q712
- demonstrate that there is no evidence of replication of RHDV in non-target species.

Several Australian laboratory trials were conducted that:

- demonstrate that RHDV 08Q712 is as lethal to rabbits when injected or orally administered as RHDV v351; additionally, it was observed that RHDV 08Q712 was lethal to rabbits in a simulated field exposure experiment (involving exposure to livers collected from rabbits infected with RHDV 08Q712)
- demonstrate RHDV 08Q712 is more infectious than RHDV v351 to putatively genetically resistant wild rabbits and rabbit calicivirus Australia 1 (RCV-A1) exposed rabbits.

No data was presented to demonstrate that RHDV 08Q712 can control local populations of rabbits. This was due to field trials not being conducted in order to prevent another accidental release (as occurred with RHDV v351). Despite this, the presented data and scientific argument (namely prior registration of products

containing RHDV v351 and published research on RHDV lethal epizootics) indicate that RHDV 08Q712 will be effective at controlling wild populations.

6.1 Protection of valuable rabbits

An RHDV vaccine, with an existing APVMA registration, is available for the protection of valuable (non-pest) rabbits that are farmed or kept as domestic pets. This vaccine is protective, when used in accordance with its directions for use, against RHDV v351 and RHDV 08Q712.

Protection against RHDV 08Q712 was demonstrated through two Australian laboratory trials. In one trial, rabbits were vaccinated according to label instructions and all vaccinated rabbits were protected against RHDV 08Q712 whilst unvaccinated controls became infected; this was demonstrated through two different exposure pathways:

- direct oral administration of RHDV 08Q712
- a simulated field exposure experiment involving exposure of rabbits to livers collected from dead rabbits infected with RHDV 08Q712

In another trial, rabbits were not vaccinated according to label instructions (up to 2 injections of 0.25 mL compared to a single 1 mL injection in accordance with label instructions), but all vaccinated rabbits were still protected against RHDV 08Q712 whilst unvaccinated controls became infected.

7 LABELLING REQUIREMENTS

Label Name:	RHDV K5
Signal Headings:	READ SAFETY DIRECTIONS BEFORE OPENING OR USING
Constituent Statements:	ACTIVE CONSTITUENT: RABBIT HAEMORRHAGIC DISEASE VIRUS, 08Q712 STRAIN >30,000 ID50 UNITS
Statement of Claims:	For the infection of wild European rabbits (<i>Oryctolagus cuniculus</i>) in accordance with directions of the appropriate State or Territory government authority.
Net Contents:	At least 30,000 ID50 units of Lyophilised Rabbit Haemorrhagic Disease Virus (RHDV) 08Q712 strain
Restraints:	<p>DO NOT administer to any animal other than wild European rabbits.</p> <p>DO NOT administer to rabbits visibly affected by myxomatosis. Rabbits affected by active myxoma virus infection may be less likely to die as a result of Rabbit haemorrhagic disease (RHD).</p> <p>DO NOT administer to rabbits younger than 12 weeks. Younger rabbits may be infected with rabbit haemorrhagic disease virus (RHDV) but are less likely to die as a result of RHDV, particularly in the presence of maternal antibodies. RHDV may be administered to susceptible rabbits either by direct injection or by means of infected carrot or oat feed.</p> <p>To prevent resistance and ensure adequate rabbit control, DO NOT administer to rabbits of any age when there is a high proportion of rabbits younger than 12 weeks in the local population. The appropriate State or Territory government authority can provide advice on optimal RHDV release times.</p>
Directions for Use:	<p>Administration by intramuscular injection: Capture at least two wild rabbits from each warren. Using a sterile syringe, reconstitute the RHDV K5 lyophilised virus by adding 10 mL of sterile distilled water and swirl gently for a few minutes. Using a sterile syringe, remove a 0.5 mL dose of virus suspension from the vial. Inject each recipient rabbit at an intramuscular (IM) site in the hind leg with 0.5 mL of reconstituted virus suspension and release the rabbits back into the warren from which they were captured.</p> <p>It is recommended that rabbits be captured and re-released into the same warren to maximise the likelihood of acceptance of the infected rabbit by its cohorts.</p> <p>A minimum of two rabbits should be injected at each release site but preferably up to 20 rabbits should be treated.</p> <p>Administration by medicated feed: RHDV K5 can be administered to susceptible rabbits via the oral route on either oats or chopped carrots. Oats should be standard intact oats with husks attached. Carrots should be freshly diced.</p> <p>RHDV K5 treated oats must be applied in trails but RHDV K5 treated chopped carrot may be applied by trails or broadcast. Free feed the area by broadcast or by</p>

	<p>trail with untreated oats or chopped carrots at a rate appropriate to the local rabbit density. Typically the rate will be in the range of 2-5 kg per km of trail for oats and 5-10 kg per km of trail for carrots. Free feeds should be given on at least two and, for oats, on preferably three occasions to train rabbits to accept the feed.</p> <p>Prepare the RHDV K5 treated oats or carrots by first reconstituting lyophilised virus using 10 mL of distilled water and then diluting a reconstituted vial of virus to a final volume of 100 mL with distilled water (i.e. add the contents of one 10 mL vial to 90 mL of water). Add the diluted suspension to carrots or oats while tumbling in an enclosed mixing device (as per the minimum standard requirement of 1080 or pindone bait mixing), and continue to mix until the suspension is evenly distributed amongst the feed.</p> <p>RATES OF APPLICATION OF RHDV TO FEED The recommended dose rates of RHDV K5 to the feed are as follows:</p> <p>One vial of reconstituted product (10 mL) diluted with an additional 90 mL of water (100 mL total volume) is sufficient to treat 5 kg of oats or 10 kg of chopped carrots.</p> <p>Treated oats or carrots should be offered to rabbits in a number of warrens in the area in which it is desired to induce an outbreak of RHD by adequate deployment of trails or broadcast baiting.</p> <p>The medicated feed should be used as soon as possible after preparation. It should be laid in the evening and bait not consumed by the following morning should be recovered and destroyed by deep burial.</p>
Other Limitations:	NOT TO BE USED FOR ANY PURPOSE, OR IN ANY MANNER, CONTRARY TO THIS LABEL UNLESS AUTHORIZED UNDER APPROPRIATE LEGISLATION.
General Instructions:	Rabbit haemorrhagic disease virus (RHDV) is a highly infectious and usually fatal pathogen that causes acute clinical symptoms resulting in death only to European rabbits (<i>Oryctolagus cuniculus</i>). All breeds of rabbits in Australia are derived from <i>Oryctolagus cuniculus</i> and are therefore potentially susceptible to infection with RHDV. A vaccine to protect pet and farmed rabbits from RHDV is available from your local veterinarian. Once a rabbit is infected, the virus replicates rapidly within the liver. The rabbit usually dies within three days of infection but may survive longer and may recover. While young rabbits (less than 12 weeks old) often fail to succumb to RHDV, older rabbits are highly susceptible. Rabbits that have become resistant to the Czech v351 RHDV strain, due to genetic immunity or exposure to the non-lethal rabbit calicivirus Australia 1 (RCV-A1) virus, may be more susceptible to infection by this strain of RHDV (08Q712).
Precautions:	NOTE: RHDV has the potential to spread rapidly from individual infected rabbits to cohorts within the same warren and to new warrens in the same area or some distance (up to many kilometres) away from the initial site of infection. However, the rate of movement and proportion of warrens affected is highly variable. Since the factors which control the rate of spread are not fully understood, no guarantee can be given that the virus will spread from an infected rabbit to other rabbits.
Protections:	<p>PROTECTION OF NATIVE ANIMALS: Decline of rabbit numbers from any cause can result in increased predation on critical populations of vulnerable or endangered native animals, at least in the short term. If the existence of a critical population is suspected in the area of a deliberate</p>

	<p>release of RHDV K5, advice should be sought from State or Territory conservation agencies so that appropriate predator control measures can be implemented if necessary.</p> <p>PROTECTION OF CROPS AND LIVESTOCK DO NOT apply treated bait to crops or situations where livestock may have access to the bait.</p>
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<p>Storage and Disposal:</p>	<p>Freeze-dried virus is to be kept cool at all times during transport.</p> <p>Freeze-dried virus can be stored at 4-8°C for up to 12 months. Do not re-freeze.</p> <p>Use entire contents of freeze-dried virus vial within 24 hours of initial opening. Store open vial at 4-8°C.</p> <p>Reconstituted virus may be stored at 4°C for no more than 24 hours before use.</p> <p>Lay bait mixed with virus as soon as possible after preparation.</p> <p>Any needles/sharps should immediately be placed in a designated and appropriately labelled 'sharps' container. Open and used vials, and used needles and syringes, should not be left in the open environment, or in other places where unintended contact is possible. Used vials and syringes should be soaked in 0.5% sodium hypochlorite (e.g. a 1 in 20 dilution in water of household bleach solution containing 10% sodium hypochlorite) and buried in a local authority landfill. If a local authority landfill is not available, bury the containers below 500 mm in a disposal pit specifically marked and set up for this purpose clear of waterways, vegetation and roots. Unused baits should also be buried in this manner. Empty containers and products should not be burnt.</p> <p>Equipment used to prepare the medicated feed should be decontaminated and cleaned at the end of each day by rinsing with 0.5% sodium hypochlorite. Following this treatment, wash thoroughly with excess water and allow equipment to dry.</p>
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<p>Safety Directions:</p>	<p>RHDV affects only European rabbits <i>Oryctolagus cuniculus</i>. However, due to the presence of rabbit and viral proteins in the product, it is possible that accidental administration of the product to a user could be accompanied by an adverse allergic reaction.</p> <p>When opening the container, reconstituting the virus, injecting live rabbits, preparing bait, using the prepared bait, collecting any untaken bait and disposing of bait, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing), a face shield and chemical resistant gloves.</p> <p>Wash hands after use. After each day's use wash or dispose of gloves, face shield and contaminated clothing.</p>
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<p>First Aid Instructions:</p>	<p>If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126; New Zealand 0800 764 766.</p>
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ABBREVIATIONS

AAHL	Australian Animal Health Laboratory
ac	active constituent
ADI	Acceptable Daily Intake
aka	also known as
ARfD	Acute Reference Dose
EBHSV	European brown hare syndrome virus
g	gram
h	hour
ha	hectare
ID ₅₀	dose that infects 50% of the target population of organisms
im	intramuscular
IACRC	Invasive Animals Cooperative Research Centre
kg	kilogram
L	Litre
mL	millilitre
SDS	Safety Data Sheet
nm	nanometre
NOEL	No Observable Effect Level
NSW DPI	New South Wales Department of Primary Industries
PPE	Personal Protective Equipment
RCV	rabbit calicivirus
RCV-A1	rabbit calicivirus Australia 1
RHD	Rabbit haemorrhagic disease
RHDV	Rabbit haemorrhagic disease virus
RNA	Ribonucleic acid
RCP	Restricted Chemical Product

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration.
Antigenic	An infectious organism, such as a protozoan bacterium or virus, which has altered its surface proteins in order to evade a host immune response
Benign	Non-pathogenic. Not harmful, not malignant, not recurrent. Favourable for recovery.
Calicivirus	A virus from the family Caliciviridae
Capsid	The outer covering of protein surrounding the nucleic acid of a virus
'Classical' RHDV	Has the same meaning as Rabbit haemorrhagic disease virus (RHDV)
Efficacy	Production of the desired effect
Endemic	a disease (or anything resembling a disease) constantly present to greater or lesser extent in a particular locality
Epizootic	A disease event in an animal population other than humans (in humans the equivalent is an epidemic)
Formulation	A combination of both active and inactive constituents to form the end use product
Genogroup	A group of related viruses within a genus
Lagovirus	A genus of viruses from the family Caliciviridae
Lyophilised	Having been freeze dried
Pathogenic	Producing disease
Rabbit haemorrhagic disease (RHD)	A disease in rabbits caused by infection of RHDV
Rabbit haemorrhagic disease virus (RHDV)	An RNA lagovirus from the Family Caliciviridae
RHDV1	Has the same meaning as Rabbit haemorrhagic disease virus (RHDV)
RHDV2	A different lagovirus that is related to, but not the same as, Rabbit haemorrhagic disease virus (RHDV)
RHDVa	An antigenic variant of Rabbit haemorrhagic disease virus (RHDV)
RHDVb	Has the same meaning as RHDV2
RHDV 08Q712	The 08Q712 strain of RHDV (isolated in the Korean province of Incheon in 2008)
RHDV v351	The v351 strain of RHDV (isolated the Czechoslovakia in 1988)

Toxicokinetics	The study of the movement of toxins through the body
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Toxicology	The study of the nature and effects of poisons
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