Environmental Assessment

to Support an Import Tolerance Request for the

Use of Ampicillin in Perciformes Fish

DATE: **March 25, 2021**

NAME OF APPLICANT/PETITIONER: **ALVIS Inc.**

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ACRONYMS AND ABBREVIATIONS

API	active pharmaceutical ingredient
EA	environmental assessment
EPA	U.S. Environmental Protection Agency
FAO	Food and Agriculture Organization
FDA	U.S. Food and Drug Administration
JECFA	Joint (FAO/WHO) Expert Committee on Food Additives
K_{oc}	adsorption/desorption partition co-efficient normalized to the organic carbon content
MRL	maximum residue limit
WHO	World Health Organization
WWTP	wastewater treatment plant

1. DESCRIPTION OF PROPOSED ACTION(S) AND NEED

Ampicillin (CAS No. 69-53-4) is the active pharmaceutical ingredient (API) in two products in Japan: Ampicillin 10% Powder for Fish and Ampicillin 20% Powder for Fish. It is the subject of this environmental assessment (EA) of a new animal drug used in food-producing animals, which has been prepared in support of an import tolerance request. Ampicillin is indicated for control of mortality in finfish due to the following disease caused by ampicillin-sensitive bacteria: Pseudotuberculosis in Perciformes fish. It is administered in fish feed to provide a dose of 5 to 20 mg of ampicillin/kg body weight/day for five consecutive days, with a 5-day withdrawal period. In Japan, ampicillin has been approved for use in both freshwater and saltwater fish in the order Perciformes; however, all cultivated Perciformes in Japan are marine species. The major approved use is in Amberjacks which includes Japanese amberjack, yellowtail amberjack and greater amberjack In South Korea, ampicillin is approved for use in many fish species (including saltwater and freshwater Perciformes) as well as crustaceans. An MRL of 50 µg/kg (50 ppb) in finfish muscle and in muscle plus skin in natural proportion is established for all finfish in EU countries.

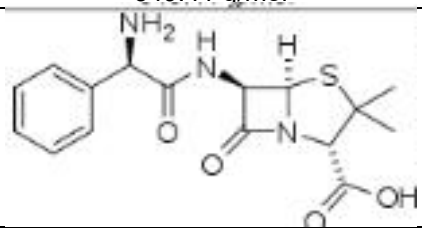
ALVIS, Inc. (DUNS # 718403459) is requesting the establishment of an import tolerance for residues (50 ppb) of ampicillin in edible tissues and skin of Perciformes fish, so that imported food derived from such fish treated with, and containing potential residues of, ampicillin may be legally imported and marketed in the United States for human consumption.

Establishment of an import tolerance is an action by the U.S. Food and Drug Administration (FDA) that requires preparation of an EA unless that action meets the criteria for categorical exclusion under FDA regulations at 21 CFR Part 25, Subpart C. Because the categorical exclusion criteria are not met, this EA has been prepared to address and evaluate the potential direct and indirect environmental impacts in the United States should the FDA establish an import tolerance for residues of ampicillin in edible tissues of Perciformes fish.

2. IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

Ampicillin is classified as an aminopenicillin β-lactam antimicrobial agent effective against both gram-positive and gram-negative bacteria. It works by causing irreversible inhibition of transpeptidase, an enzyme important for building bacterial cell walls. Ampicillin is used as a veterinary drug against bacterial infections in farmed fish, specifically Amberjacks which includes Japanese amberjack, yellowtail amberjack and greater amberjack, and other Perciformes in Japan. Ampicillin is used only for the treatment of pseudotuberculosis in Japan. Ampicillin is also used to treat Perciformes for vibrosis, streptococcosis, and edwardsiellosis in other countries. Further identification of ampicillin and its physico-chemical properties are given in Table 2-1.

Table 2-1. Identification of ampicillin and physico-chemical characteristics

Drug Established (nonproprietary) Name	Ampicillin
Synonyms	Adobacillin, Albipen, Ampicilin A, Aminobenzylpenicillin, Ampicillin acid, Totacillin
Chemical Name	(2S,5R,6R)-6-([(2R)-2-amino-2-phenylacetyl]amino)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid
Chemical Abstracts Service Number	69-53-4
Empirical Formula	$C_{16}H_{19}N_3O_4S$
Molecular Weight	349.41 g/mol
Structure	
Drug Class	Aminopenicillins
Mechanism of Action	Causes irreversible inhibition of transpeptidase
Spectrum of Activity	Effective against both gram-positive and gram-negative bacteria
Existing Tolerances in Food	0.01 ppm cattle, edible tissue 0.01 ppm swine, edible tissue (21 CFR §556.40)
Color and Physical state	White or almost white crystalline powder
pH	3.5-5.5 ampicillin 8.0-10.0 ampicillin sodium 3.5-5.5 ampicillin trihydrate
Melting Point (ºC)	199 – 202 208*
Dissociation Constants (pKa)	2.5; 7.3 (25ºC)
Water Solubility (mg/L)	439.3 (CALC); 10,100 (EXP)*
Log Octanol-Water Partition Coefficient (Log P)	1.45 (CALC); 1.35 (EXP)*
Vapor Pressure (Pa)	3.79×10^{-11}*
References: All information from JECFA (2018) and FDA Guidance for Industry #152 except as noted by *. * Information is from EPISuite™ (U.S. EPA, 2000–2012); CALC indicates calculated values, EXP indicates experimental values.	

In Japan, Ampicillin Powder for Fish (10% or 20%) contains ampicillin hydrate corresponding to 100 or 200 mg ampicillin, respectively. The excipients consist of Food Yellow No. 5 and lactose. It is unlikely the excipients in the formulation will pose an environmental risk or increase any theoretical risk posed by the API. Ampicillin Powder for Fish is either surface-coated on fish feed (typically extruded pellets) with a

carboxymethylcellulose binder or incorporated into the feed before extrusion of the pellets. Dosing is typically 5-20 mg ampicillin/kg body weight (bw)/day for 5 consecutive days, with a 5-day withdrawal period.

The typical size of Perciformes fish at treatment are 50-200 grams (fry) and 700-1000 grams. Treatments are typically done at time of occurrence of the target disease, May through June and September, respectively. The typical size of the fish at harvest is 5 kg or more in Japan. Please note that it takes 2 years or more for the fish to grow from 1.0 kg to 5 kg in size; therefore, the likelihood of ampicillin residues in fish tissues and skin is unlikely.

An English translation of example labels are provided in Appendix A and B.

3. ECOSYSTEM AT THE SITE OF INTRODUCTION

This EA supports an import tolerance request relevant for the import of fish products (i.e., Amberjacks and other Perciformes) from countries using ampicillin but does not support the potential use of ampicillin in the United States. There are two potential pathways for introduction of ampicillin residues to the U.S. environment that could result from establishing this import tolerance: (1) pathways arising from the release of drug residues, if present, from imported food derived from treated fish, and (2) pathways arising from the use of the drug in treated fish from neighboring countries where use could be authorized.

For the first pathway (following the import of food from treated fish), release of ampicillin into the U.S. environment (e.g., soil, surface water, air) could potentially occur through points of introduction to the following ecosystems: (a) ecosystems where the residues of ampicillin from consumed fish products might be introduced into surface water through wastewater from wastewater treatment plants (WWTPs); (b) ecosystems where biosolids from WWTPs are applied to soil; and (c) ecosystems where the residues of ampicillin from unconsumed fish products, waste from fish processing plants, or sludge from WWTPs might be introduced through landfilling.

For the second pathway (following use of the drug in neighboring countries), a potential point of introduction to the U.S. environment could consist of water flow or sediment transport from areas where fish are treated in countries adjoining the U.S. (e.g., Canada). Although ampicillin is not currently licensed for use in fish treatment in any countries adjoining the U.S., it is reasonably foreseeable that it could be approved in Canada in the future because fish farming is a major industry in Canada.

4. EXPOSURE ASSESSMENT

The potential exposures are evaluated based on the pathways previously described and environmental fate data for ampicillin.

4.1 Environmental fate

The environmental fate of ampicillin can be predicted based on its properties. Ampicillin in solution exists mainly in three different forms, cation, zwitterion, and anion, with the minimum solubility occurring at pH 4.9 and increased solubility at lower and higher pH (Hou and Poole 1969). EPISuite™ provides a calculated water solubility of 439.3 mg/L at 25°C and an experimental value of 10,100 mg/L at 21°C. Given its high water solubility and low vapor pressure (3.79×10^{-11} Pa at 25°C), ampicillin is not expected to volatilize from water.

Ampicillin can undergo photolysis and hydrolysis in the environment, although the latter process is slower. An investigation of the photolysis of ampicillin in river water indicated rapid degradation within 48 hours to various transformation products, with a rate constant at 30ºC of 0.1148 h^{-1} (Arsand et al. 2018). Timm et al. (2019) found that ampicillin was photolytically degradable by simulated sunlight with a half-life of 3.89 hours at 19ºC. Mitchell et al. (2014) reported that hydrolysis of ampicillin occurs under ambient conditions and determined the hydrolysis half-life at 25ºC and pH 7 to be 27 days.

EPISuite™ predicts an octanol-water partition coefficient (Log K_{OW} or Log P) of 1.45 and cites an experimental value of 1.35. The estimated K_{OC} (adsorption/desorption partition co-efficient normalized to the organic carbon content) from EPISuite™ is 6.423 L/kg, which may vary with pH. The estimated bioconcentration factors from EPISuite™ are approximately 1.8 to 3.3 L/kg, depending on whether or not biotransformation is included.

Li and Zhang (2010) investigated the removal of ampicillin in the activated sludge process and concluded that removal was mainly by adsorption rather than biodegradation, with approximately 57% adsorbed within 15 minutes in freshwater sewage sludge systems. Shen et al. (2010) investigated the treatment of ampicillin-loaded wastewater in airlift reactors where biofilms were developed on granular activated carbon. During 40 days of operation, ampicillin was not detected in the effluent from the reactors. Using mature biofilm-covered substrate, they concluded that adsorption accounted for about 60% of the observed ampicillin removal while the other 40% could be attributed to biodegradation.

4.2 Introduction from consumed fish products into U.S. ecosystems via wastewater

Ampicillin was evaluated at the 85th meeting of the Food and Agriculture Organization (FAO)/World Health Organization (WHO) Joint Expert Committee on Food Additives (JECFA). The committee recommended maximum residue limits (MRLs) for ampicillin in finfish muscle (and muscle and skin in natural proportions) of 50 µg/kg (JECFA 2018). It can therefore be assumed that all Perciformes fish products imported into the United States that have been treated with ampicillin would have potential residues of the substance ≤50 µg/kg. Human consumption of these products will potentially result in the excretion of residues into wastewater. Based on the environmental fate properties previously discussed, these residues would be expected to be removed in the wastewater treatment process, primarily by sorption onto solids and secondarily by biodegradation. Residues in the solids from wastewater treatment are likely to be disposed of by land application, landfilling, or incineration, as discussed below. A qualitative assessment of the potential environmental impacts related to discharge of wastewater from WWTPs is provided in Section 5.

4.3 Introduction from consumed fish products into U.S. ecosystems via land application of biosolids

An additional potential pathway of exposure related to wastewater treatment is the application of biosolids or residuals from wastewater treatment to agricultural soils as fertilizer. This pathway could introduce low levels of ampicillin to the soil. A qualitative assessment of the potential environmental impacts relating to land application of biosolids is provided in Section 5.

4.4 Introduction from unconsumed fish products, waste from fish processing plants, or sludge from WWTPs into U.S. ecosystems via disposal in landfills

A small possibility exists of imported Perciformes fish products ending up in U.S. landfills due to spoilage, rejection due to violative residues or other compliance parameters, or some other mismanagement of the products. The worst-case scenario (which would be rare) would be if a batch of imported Perciformes fish products exceeding the MRL of 50 µg/kg was seized and disposed of at once in a landfill.

Wastes from processing plants that handle imported Perciformes fish products could be another potential source of ampicillin residues to the environment. If such wastes were not incinerated, they might be landfilled. Sludge from WWTPs is also typically disposed of in landfills. A qualitative assessment of the potential environmental impacts relating to landfills is discussed in Section 5.

5. ASSESSMENT OF ENVIRONMENTAL IMPACT

As stated previously, there are two potential pathways for introduction of ampicillin residues to the U.S. environment that could result from establishing this import

tolerance: (1) pathways arising from the release of drug residues, if present, from imported food derived from treated Perciformes fish, and (2) pathways arising from the use of the drug in treated fish from neighboring countries where use could be authorized.

For the first pathway, three ecosystems are considered in the evaluation of the potential environmental impacts from the release of ampicillin (following the import of treated products) into the U.S. environment: (a) ecosystems where residues from consumed Perciformes fish products might be introduced through wastewater; (b) ecosystems where residues from consumed Perciformes fish products might be introduced through landfilled biosolids; and (c) ecosystems where residues from unconsumed Perciformes fish products might be introduced through landfilling of noncompliant products, waste from fish processing plants, or sludge from WWTPs. These three ecosystems are discussed below under the headings wastewater, biosolids, and landfills.

For the second pathway, ampicillin could potentially enter the U.S. environment via water flow from neighboring countries such as Canada where Perciformes fish are produced. This is discussed under Section 5.4.

5.1 Wastewater

Consumption rates of fish in the United States are low compared to most other types of meats. In addition, the residues will be further reduced (diluted) by the excreta from other consumers who have not consumed ampicillin-treated Perciformes fish. Due to these expected consumption patterns, only very low concentrations of ampicillin are estimated to enter wastewater. In addition, the distribution of residues will likely be spatially and temporally variable. Ampicillin is expected to be removed in wastewater treatment through a combination of sorption to sludge and biodegradation, with minimal release in the aqueous effluent. Further dissipation, degradation, and dilution can be expected in the receiving water. Ampicillin is not expected to bioaccumulate (Log K_{OW} of 1.35-1.45); therefore, uptake through food chains eventually leading to secondary poisoning can be excluded. Taken together, these considerations indicate that potential adverse effects on the aquatic environment from discharged wastewater are unlikely.

5.2 Biosolids

Due to consumption patterns, residues of ampicillin entering wastewater are likely to be very low. Partitioning will take place from the water to the solid phase, with residues in biosolids exceeding those in water (as indicated by the K_{oc} values). Nevertheless, due to the very low concentrations in wastewater, concentrations in soil following application of biosolids as fertilizer are anticipated to be very low as well. In this context, it is worth mentioning that <1% of agricultural lands use WWTP biosolids as a fertilizer (Lu et al. 2012). Although limited, the sorption properties of ampicillin indicate that residues are unlikely to leach into groundwater.

5.3 Landfills

Disposal of spoiled, non-compliant, or mismanaged imported Perciformes fish products into landfills is expected to be sporadic and rare; therefore, only a negligible amount of ampicillin is expected to be available for disposal into landfills through this pathway.

Wastes from processing plants that handle imported Perciformes fish products could be another potential source of ampicillin to the environment. If such wastes were not incinerated, they might be landfilled. Assuming that the imported products contained levels of ampicillin below the established MRL, leachates from these wastes would be at this level or lower and would be unlikely to pose a risk to the environment as discussed for wastewater.

Landfills would also be likely to receive sludge from WWTPs. Due to the low concentrations of ampicillin predicted in wastewater and ultimately in sludge, it is unlikely that significant concentrations of the drug would be available for disposal into landfills. This pathway is also considered very minor.

Fish processing plants and municipal WWTPs can be expected to operate in compliance with applicable regulations regarding landfill disposal. Municipal solid waste landfills are regulated by the U.S. Environmental Protection Agency (EPA) to restrict movement of waste into the environment, including location restrictions, composite liner requirements, leachate collection and removal systems, operating practices, groundwater monitoring requirements, and closure and postclosure care requirements (40 CFR Part 258). Ampicillin will tend to sorb to soil, sediment, and other organic materials found in landfills and, thus, is not likely to extensively migrate to groundwater. Therefore, only a negligible amount of ampicillin is expected to be available to potentially leach into groundwater (and from there to surface water) from landfill disposal. In conclusion, the potential environmental impact from landfill disposal of imported Perciformes fish products, wastes from fish processing plants, or WWTP sludge containing ampicillin is insignificant.

5.4 Water flow and sediment transport from treatment of fish in foreign countries (e.g., Canada) adjoining the U.S.

Ampicillin is currently not approved as an animal drug for use in fish in Canada or any other countries adjoining the U.S. However, it is reasonably foreseeable that it could be approved there in the future because fish farming is a major industry in Canada. Therefore, for this reason and because of Canada's close proximity to the U.S., the possible impact to the U.S. environment due to discharge in a neighboring country is assessed below.

Ampicillin is approved in Japan and South Korea to be administered in fish feed (see Appendix A for a copy of an English translation of the label for the Japanese approval). Assuming the same conditions of use from Japan are approved in the future in countries adjoining the U.S., the administration process will occur to growing fish held in sea surface cages (net pens). There are two production systems employed. In the "natural"

system, wild fish (larvae/fry) are captured and kept in net pens, where the cage sizes are increased as the fish grow to market size. In the “artificial” production system, parent fish production, hatching, and fry stages are all performed in land-based tanks. Once the fish grow to fry stage, they are relocated and housed in net pens, where they continue to grow to market size. Under both production systems, drug administration occurs to the growing fish in net pens through feed. Owing to demanding biosecurity measures in land-based systems, diseases are well-controlled and ampicillin would be only rarely administered in these systems.

When ampicillin enters the aquatic environment due to use in fish farming from net pens (as opposed to consumption of fish by humans, discussed earlier), it enters via uneaten feed or fish excreta. It is expected that most of the feed containing ampicillin will be consumed by fish, and thus, ampicillin residue from the uneaten feed will be low. The predominant fate of ampicillin residues from marine fish farming is deposition (from feed or feces) directly underneath the net pens and to some extent around the vicinity of the farm, with incorporation in sediment over time. In the unlikely event that ampicillin is administered to fish in land-based tanks, ampicillin may enter the marine aquatic environment from effluent water. In either case (treatment in net pens or land-based tanks), residues of ampicillin are expected to be substantially diluted in the marine environment.

In addition, these discharges would be regulated and/or permitted by the country where the drug is approved. For example, the operation of fish farms in Canada is regulated to prevent adverse impacts on the environment around the farms. Given this, it is unlikely that an animal drug being used on a Canadian farm would enter U.S. waters at concentrations that could have adverse environmental impacts to the U.S. environment.

Further, it is expected that other physical and chemical processes (i.e., photolysis, hydrolysis, biodegradation, etc.) would occur concurrently to further limit the exposure of ampicillin to non-target organisms in the U.S. environment. For the above reasons, impacts to the U.S. environment from the use of ampicillin as a fish drug product in foreign countries, including Canada which shares a border with the U.S., are highly unlikely.

6. MITIGATION MEASURES

Because the establishment of an import tolerance for Perciformes fish products treated with ampicillin in accordance with label directions in countries outside the United States would not have a significant effect on the environment in the United States, no mitigation measures will be required.

7. ALTERNATIVES TO THE PROPOSED ACTION

The proposed action is to establish a tolerance for ampicillin in Perciformes fish imported into the United States for human consumption. The only alternative to the proposed action is the “no action” alternative, which would be the failure to establish a tolerance for residues of ampicillin in these fish products. However, based on our

analysis in this EA, we do not believe that significant environmental impacts will occur from this action; therefore, the “no action” alternative was eliminated from consideration.

8. LIST OF PREPARERS

This document was prepared by Exponent, Inc., under the direction of Jane P. Staveley.

9. AGENCIES AND PERSONS CONSULTED

This EA was prepared with input from members of the Environmental Team 1 in the Office of New Animal Drug Evaluation in the U.S. FDA’s Center for Veterinary Medicine.

10. CERTIFICATION

The undersigned official certifies that the information presented in this Environmental Assessment is true, accurate, and complete to the best of his knowledge.

03/25/2021

Eiji (Eddie) Fuku, DVM, PhD
Managing Director
ALVIS Inc.

Date

11. REFERENCES

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APPENDIX A
Label for Ampicillin 10% powder

Last updated: March 2019 (Ver. 2)
First published: December 2016

Storage	Room Temperature

1903-02

Notice of Approval No.	30 NVAL No. 1818

Animal Drug
Oral Penicillin Antibiotic
Controlled Pharmaceutical Drug Subject to Specific Directions

ASKA Ampicillin 10% Powder for Fish

QUALITATIVE AND QUANTITATIVE COMPOSITION

Product Name	ASKA Ampicillin 10% Powder for Fish
Active Ingredient	Ampicillin hydrate
Quantity	Each 1 g contains 100 mg ampicillin hydrate

INDICATIONS

Control of mortality in finfish due to the following disease caused by ampicillin-sensitive bacteria:

Pseudotuberculosis in Perciformes fish (Yellowtail/Amberjack, Japanese red seabream, Japanese jack mackerel, Tilapia, and other Perciformes species)

DOSAGE AND ADMINISTRATION

Administer the following dose per 1 kg fish weight per day:

Five to 20 mg as ampicillin hydrate for Perciformes fish (Yellowtail/Amberjack, Japanese red seabream, Japanese jack mackerel, Tilapia, and other Perciformes species)

PRECAUTIONS FOR USE

PRINCIPLES

1. Warnings
General

- ASKA Ampicillin 10% Powder for Fish is indicated for the treatment of pseudotuberculosis in Perciformes fish (Yellowtail/Amberjack, Japanese red seabream, Japanese jack mackerel, Tilapia, and other Perciformes species). Do not administer to other fish species or animals.
- The product must be administered within the effective dose range to ensure the expected therapeutic efficacy, and an overdose may cause unexpected adverse effects. Administer correctly according to the instructions in **DOSAGE AND ADMINISTRATION**.

- This product must be administered for the shortest period of time needed for the treatment. Discontinue use when the disease is controlled. The product should not be administered for longer than 7 consecutive days or repeatedly, whether or not noticeable effects are observed.
- Use only after consultation with the supervising body (e.g., prefectural livestock hygiene service centers, fish disease control and diagnostic centers, and fisheries experimental stations).
- This product is subject to specific directions defined by the law.

Cautions: This product is an animal drug product regulated under Article 83-4 of the Pharmaceutical Affairs Law (Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices). It must be administered to target species (Perciformes fish) according to the instructions in **DOSAGE AND ADMINISTRATION** above and the following withdrawal period:

Five days before harvesting for human consumption for Perciformes fish (Yellowtail/Amberjack, Japanese red seabream, Japanese jack mackerel, Tilapia, and other Perciformes species)

Handling and Disposal

- Shake well before use.
- If the product is divided over several applications, use as soon as possible.
- Do not use if an abnormal color is noticed.
- Dispose of empty containers in accordance with the local authority regulations.
- Dispose of any unused product in accordance with the local authority regulations to minimize contamination of the environment and water ways.
- Keep out of reach of children.
- Protect from direct sunlight, high temperature and high humidity.
- Do not transfer the content to a different container to avoid misuse and to protect the quality of the product.

2. Precautions

Precautions for Users

- In case of accidental ingestion, seek medical advice immediately.
- In case of accidental eye contact, rinse eyes with water immediately and seek medical advice.
- When mixing the product with feeds, wear a mask or a protective equipment to avoid inhalation of dust.
- Wear protective goggles, mask, gloves and protective clothing when handling.
- Wash hands and exposed skin thoroughly with soap after each use.

PARTICULARS

Important General Precautions

- Ampicillin is not effective against penicillinase-producing bacteria. Select a different agent for these bacteria.

HOW SUPPLIED

ASKA Ampicillin 10% Powder is available in a pack size of 10 kg (1 kg × 10 bags).

CONTACT INFORMATION

ASKA Animal Health Co., Ltd.
2-15-6 Shibaura, Minato-ku, Tokyo 108-0023 Japan
Phone: +81-3-5439-4188

Manufacturer/Distributor

製造販売元
あすかアニマルヘルス株式会社
東京都港区芝浦二丁目15番6号
TEL. 03-5439-4188 FAX. 03-5439-4191

Veterinarians, pharmacists and other healthcare professionals are encouraged to report any adverse event that resulted in disease, pathology or death as well as any outbreak of relevant infectious diseases to the manufacturer in **CONTACT INFORMATION** and the National Veterinary Assay Laboratory (http://www.maff.go.jp/nval/iyakutou/fukusayo/sousa/index.html), if the event is likely associated with the use of the product and requires immediate attention for prevention or control of public health risks.

APPENDIX B
Label for Ampicillin 20% powder

Last updated: September 2018 (Ver. 5)

Storage	At room temperature in airtight container

Notice of Approval No.	16 FSCAB No. 2055

Animal Drug

Oral Penicillin Antibiotic

Controlled Pharmaceutical Drug Subject to Specific Directions

KS Ampicillin 20% Powder for Fish

Ampicillin Powder

DESCRIPTION

KS Ampicillin 20% Powder for Fish contains the active ingredient ampicillin hydrate, which is a semi-synthetic penicillin. It is intended for oral administration in farmed fish.
Ampicillin (aminobenzylpenicillin) is a broad-spectrum antibiotic derived from 6-aminopenicillanic acid (6-APA) with a bactericidal activity against both Gram-positive and Gram-negative bacteria. It is well absorbed after oral administration and reaches tissue concentrations effective for bactericidal action against pseudotuberculosis-causing bacteria.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 g contains:

Active Ingredient	Quantity
Ampicillin hydrate	200 mg (potency)

INDICATIONS

Control of mortality in finfish due to the following disease caused by ampicillin-sensitive bacteria:

Pseudotuberculosis in Perciformes fish

DOSAGE AND ADMINISTRATION

Administer the following dose per 1 kg fish weight per day for 5 days by thoroughly mixing into feeds:

5 to 20 mg as ampicillin hydrate for pseudotuberculosis in Perciformes fish
(equivalent to 0.025 to 0.1 g of the product)

Dosage by fish weight per day

Fish Weight (kg)	Product Weight (g)
10	0.25 – 1.0
100	2.5 – 10.0
200	5.0 – 20.0
300	7.5 – 30.0
400	10.0 – 40.0
500	12.5 – 50.0
1,000	25.0 – 100.0

PRECAUTIONS FOR USE

PRINCIPLES

1. Warnings

General

- KS Ampicillin 20% Powder for Fish is indicated for the treatment of pseudotuberculosis in Perciformes fish. Do not administer to other fish species or animals.
- Overdosing does not improve the efficacy. Administer the correct dose according to the instructions in **DOSAGE AND ADMINISTRATION**.
- Discontinue use at the end of the treatment period defined in **DOSAGE AND ADMINISTRATION** regardless of the efficacy achieved. Treatment should not be repeated.
- This product must be administered for the shortest period of time needed for the treatment. Discontinue use when the disease is controlled.
- Use only after consultation with the supervising body (e.g., prefectural livestock hygiene service centers, fish disease control and diagnostic centers, and fisheries experimental stations).
- This product is subject to specific directions defined by the law.

Cautions: This product is an animal drug product regulated under Article 83-4 of the Pharmaceutical Affairs Law (Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices). It must be administered to target species (Perciformes fish) according to the instructions in **DOSAGE AND ADMINISTRATION** above and the following withdrawal period:

5 days before harvesting for human consumption for Perciformes fish

Precautions for Users

- When mixing the product with feeds, wear protective goggles, mask, gloves and protective clothing to avoid inhalation of dust.

Handling and Disposal

- Do not use after expiration date.
- Do not use if an abnormal color is noticed.
- Keep out of reach of children.
- Protect from direct sunlight, high temperature and high humidity.
- Shake well before use.
- Do not transfer the content to a different container to avoid misuse and to protect the quality of the product.
- Dispose of empty containers in accordance with the local authority regulations. Do not reuse containers for other purposes.
- Dispose of any unused product in accordance with the local authority regulations to minimize contamination of the environment and water systems.

2. Precautions

Precautions for Users
- In case of accidental ingestion, seek medical advice immediately.
- In case of accidental eye contact, rinse eyes with water immediately and seek medical advice.

Handling
- Use immediately after opening.

PHARMACOLOGICAL INFORMATION

Pharmacokinetics
After a single oral administration of 20 mg ampicillin/kg of body weight at a water temperature of about 23°C in yellowtail fish weighing approximately 232 g, the maximum blood concentration was reached in 1 hour (t_{max}). The maximum blood concentration (C_{max}) was 0.80 μg (potency)/mL, and the area under the blood concentration-time curve (AUC_{48}) was 2.78 μg·hr/mL.

PHARMACOLOGY
Ampicillin exerts its bactericidal activity by inhibiting the cross-linking of peptidoglycans in the bacterial cell wall.

HOW SUPPLIED
KS Ampicillin 20% Powder is available in a pack size of 10 kg (1 kg × 10 bags).

CONTACT INFORMATION
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Phone: +81-3-3264-7559

Manufacturer/Distributor
Kyoritsu Seiyaku Corporation
1-5-10 Kudanminami, Chiyoda-ku, Tokyo 102-0074 Japan

製造販売業者
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Veterinarians, pharmacists and other healthcare professionals are encouraged to report any adverse event that resulted in disease, pathology or death as well as any outbreak of relevant infectious diseases to the manufacturer in **CONTACT INFORMATION** and the National Veterinary Assay Laboratory (http://www.maff.go.jp/nval/iyakutou/fukusayo/sousa/index.html), if the event is likely associated with the use of the product and requires immediate attention for prevention or control of public health risks.

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