FULL PRESCRIBING INFORMATION

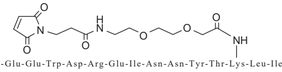
See full prescribing information for AIKENING and use it under the instruction of medical professionals.

AIKENING (Albuvirtide for Injection) for intravenous use

[Product Name]
Generic name: Albuvirtide for Injection
Trade name: AIKENING

[Ingredients]
Active pharmaceutical ingredient (API): albuvirtide
Chemical name:
Acetyl-Trp-Glu-Glu-Trp-Asp-Arg-Glu-Ile-Asn-Asn-Tyr-Thr-(N-[2-[2-(N-(3-maleimidepropionyl) amino) ethoxy] ethoxy] acetyl) Lys-Leu-Ile-His-Glu-Leu-Ile-Glu-Glu-Ser-Gln-Asn-Gln-Glu-Glu-Lys-Asn-Glu-Glu-Leu-Leucinamide

Chemical structure:



Ac-Trp-Glu-Glu-Trp-Asp-Arg-Glu-Ile-Asn-Asn-Tyr-Thr-Lys-Leu-Ile-His-Glu-Leu-Ile-Glu-Glu-Ser-Gln-Asn-Gln-Glu-Glu-Lys-Asn-Glu-Gln-Glu-Leu-Leu-NH_2

Molecular formula: $C_{281}H_{386}N_{74}O_{72}$
Molecular weight: 4666.93
This product contains no pharmaceutical excipients.

[Description]
Off-white or yellowish porous cake or powder.

[Indications]
Albuvirtide is a human immunodeficiency virus type 1 (HIV-1) fusion inhibitor indicated in combination with other antiretroviral agent(s) for treatment of HIV-1 infection in treatment-experienced patients with HIV-1 replication despite ongoing antiretroviral therapy.

[Strength]
160 mg/vial.

[Dosage and Administration]
1. Dosage regimen
For adults 18 years old and above, AIKENING is administered by intravenous infusion at a dose of 320 mg once a day on Day 1, 2, 3, and 8, and thereafter once a week.
Children
The safety and efficacy of AIKENING have not been established in children under 18 years old.
Geriatric
No adequate human data are available in geriatric patients aged over 60 years; it is unknown whether their response to AIKENING is different from young people.

2. Preparation of AIKENING

Step 1	Step 2	Step 3	Step 4		
Number of AIKENING vial	Volume of 5% sodium bicarbonate solution for injection	Volume of 0.9% sodium chloride solution for infusion	Volume of 0.9% sodium chloride solution for infusion in the infusion bag	Total infusion Volume	IV infusion time
2	1.2 mL to each vial	6 mL to each vial	~76 mL	~90 mL	~45 ± 8 min

Step 1: Determine number of AIKENING vial(s) needed for infusion based on assigned dosage (see table above). For 320mg dose, two vials are needed.
- Have all the materials ready before starting the dose preparation to minimize the overall preparation time. Use aseptic technique when preparing and administering the dose.
- From a 100 mL infusion bag (bottle) of 0.9% sodium chloride solution withdraw 12

mL to discard. The remaining 88 mL of 0.9% sodium chloride solution will be used for the AIKENING reconstitution.
Step 2: Inject 1.2 mL of 5% sodium bicarbonate solution into each vial, shake or vortex the vial thoroughly to form solution.
- When preparing for two vials of AIKENING, do not withdraw 2.4 mL of sodium bicarbonate solution in one syringe and attempt to split the volume into two vials.
- **Note:** It will be difficult to control the volume of sodium bicarbonate solution injected into the vial as the vials are sealed under vacuum (negative air pressure) which will likely create a suction.
- Upon addition of sodium bicarbonate, immediately vibrate the vial (within 30 seconds) using a vortex mixer at a setting of 2500 rpm to dissolve AIKENING powder into the sodium bicarbonate solution.
- The complete dissolution is normally achieved within 5 min; if undissolved solid is observed after 5 min of mixing, continue using a vortex mixer or manually shaking till a complete dissolution. Discard the vial if a complete dissolution was not achieved in 20 min of mixing; re-prepare the dose with a fresh vial.

Step 3: Withdraw 6 mL of sodium chloride solution from remaining 88 mL of 0.9% sodium chloride solution in Step 1 and inject into each AIKENING vial to mix thoroughly.
- Gently mix AIKENING solution in sodium bicarbonate with sodium chloride solution in the vial to avoid excessive bubbling. The resulted solution should be clear, transparent, and free of visible particulate.

Step 4: Withdraw entire contents of vial(s) and inject back into the original bag (bottle) of the remaining 0.9% sodium chloride solution in Step 3 to get a final total of infusion volume of ~90 mL AIKENING solution.
- The prepared dose should be administered as soon as possible (or within 30 minutes after end of reconstitution). Discard the dose if the infusion is not started within 30 min after the end of dose preparation and re-prepare the dose with a fresh vial.
- The storage of reconstituted drug product in refrigerator or freezer is not allowed.

3. Administration
Administer AIKENING solution by intravenous infusion via a peripheral vein in one of the upper extremities for 45 ± 8 minutes at speed of about 2ml/minute.

[Adverse Reactions]
Two Phase 1, one Phase 2 and one Phase 3 clinical studies of AIKENING have been completed. A total of 272 patients with HIV-1 infection have received at least one dose of AIKENING treatment. The safety assessment of AIKENING was primarily based on the randomized, controlled phase 3 clinical study (TALENT study) in treatment-experienced, HIV-1 infected patients, in which ABT group received the AIKENING and LPV/r combination therapy, and NRTI group received the standard 3-drug regimen of LPV/r + Tenofovir (TDF) or Zidovudine (AZT) + Lamivudine (3TC). In this phase 3 study, 401 subjects received at least one dose of drugs, of whom 195 received AIKENING treatment. The incidences of adverse drug reactions (ADRs) in ABT group and NRTI group showed no significant difference, and no serious adverse reactions (SARs) occurred in ABT group.

Adverse reactions
Table 1 summarizes grade 2 to 4 ADRs with incidence rates ≥ 2% in phase 3 study. The most common ADRs in ABT group were blood triglycerides increased and blood cholesterol increased, followed by hyperlipidaemia and hypercholesterolaemia. Abnormal blood lipid metabolism is the ADRs with the highest incidence, but since this is a combination treatment, moreover, dyslipidemia and diarrhea are common adverse reactions of LPV/r, it couldn't be excluded the relationship to LPV/r.

Table 1. Grade 2 to 4 ADRs with Incidence Rates ≥ 2%

System Organ Classification (SOC) Preferred Term (PT)	ABT group (N=195)	NRTI group (N=206)
Laboratory tests		
Blood triglycerides increased	10%	11%
Blood cholesterol increased	11%	5%
Blood bilirubin increased	3%	2%
Laboratory tests		
Gamma-glutamyl Transferase increased	<1%	2%
Gastrointestinal disorders		
Diarrhoea	<1%	2%
Metabolic and nutritional disorders		
Hyperlipidaemia*	5%	2%
Hypercholesterolaemia	3%	1%
Hepatobiliary disorders		
Hepatic function abnormal#	2%	1%

*: Both levels of Blood triglycerides and cholesterol increased
#: 2-3 items increased in AST, ALT and γ-GT simultaneously

[Contraindications]
This product is contraindicated in patients allergic to its ingredients.

[Precautions]
1. This product should be clear, transparent solution after being dissolved, and must not be used if turbidity, precipitate or foreign substances are observed.
2. The reconstituted solution should be infused for once, and it should not be used separately.
3. The safety and efficacy of AIKENING have not been established in children under 18 years old.
4. No adequate human data are available in geriatric patients aged over 60 years; it is unknown whether their response to AIKENING is different from young people.

[Pregnancy and breastfeeding]
In the reproductive toxicity studies in rat and rabbit, the No Observed Adverse Effect Level (NOAEL) of albuvirtide intravenously injected were 4 folds and 2 folds of human equivalent dose, respectively, and no toxicity to parental fertility and embryonic development was observed. Since no clinical data are available in pregnant women, it could only be used when there is a clear clinical need and the expected benefit is greater than the risk to the pregnant women.

It is unknown whether albuvirtide is excreted in human breast milk. HIV-infected women should not breastfeed infants so as to avoid HIV transmission. Lactating women should not breastfeed infants if they are receiving AIKENING.

[Drug Interactions]
In the *in vitro* human liver microsome test, albuvirtide was demonstrated not a CYP450 enzyme inhibitor, and had no significant inhibition effect on the activity of human liver microsomal enzymes CYP1A2, 2C8, 2C9, 2C19, 2D6 and 3A4.

In the *in vitro* anti-HIV-1 combination therapy, albuvirtide had synergistic effect with zidovudine (AZT) and saquinavir (SQV), and additive effect with efavirenz (EFV) and enfuvirtide (T20).

Combination of AIKENING and lopinavir/ritonavir (LPV/r) did not change the pharmacokinetics profile of albuvirtide, the *in vivo* exposure to LPV/r was reduced, and no dose adjustments are needed.

[Overdose]
At present there is no information on overdose of AIKENING in humans. Six subjects with HIV-1 infections in clinical trials received single intravenous infusion at highest dose of 640 mg, but no drug-related adverse reaction was observed. There is currently no specific antidote against overdose of AIKENING.

[Effects on Ability to Drive and Use Machine]
No studies on the effects on the ability to drive and use machines have been performed. There is no evidence that albuvirtide may alter the patients' ability to drive and use machines, however, the adverse event profile should be taken into account.

[Clinical Studies]
The efficacy of AIKENING is mainly based on analysis of data from a dose exploration study and a pivotal study (TALENT study).

The dose-exploration phase 2 study was an open, parallel study designed to evaluate the efficacy and safety of combination AIKENING and lopinavir/ritonavir (LPV/r) for the treatment of HIV-1 infection. Twenty treatment-naive HIV-1 infected patients were randomized and received AIKENING 160 mg or 320 mg on Day 5, 6, 7, 12, 19, 26, 33 and 40 by intravenous infusion, both combination with LPV/r twice daily orally from Day 1 to 46. The primary efficacy endpoint was the change of HIV-1 RNA from baseline to the end of treatment. The results showed that after 47-day treatment with combination of AIKENING and LPV/r, HIV-RNA decreased significantly in all 20 subjects. The changes in HIV-RNA in 160 mg group and 320 mg group were -1.91 ± 0.36 and -2.20± 0.33 $\log_{10}$ copies/mL, respectively. The CD4 cell count increased from baseline to different extents. The antiviral effect of AIKENING 320 mg group was significantly better than that of the 160 mg group.

TALENT study was a multicenter, open-label, randomized, non-inferiority phase 3 study. The objective was to evaluate the safety and efficacy of AIKENING combined with LPV/r for treatment of HIV-1 infected patients who failed standard first-line ART. A total of 401 subjects were received at least one dose of drugs. Subjects in ABT group received AIKENING (320 mg once a day on Day 1, 2, 3 and 8, and then once a week by intravenous infusion), combined with LPV/r (400 mg/100 mg twice daily orally) for 48 weeks. Subjects in NRTI group received a 3-drug combination of LPV/r + Tenofovir (TDF) or Zidovudine (AZT) + Lamivudine (3TC) for 48 weeks. LPV/r was administered twice daily orally, while TDF, AZT and 3TC were administered once daily orally. The primary efficacy endpoint was the percentage of subjects with the HIV RNA < 50 copies/mL at Week 48. The second efficacy endpoints included the logarithm value changes of HIV RNA, percentage of

subjects with the HIV RNA < 400 copies/mL, and changes of CD4 cell count.

At baseline, the mean ages in ABT group and NRTI group were 39.8 ± 10.82 and 39.3 ± 10.27 years old, the proportions of male were 74.4 and 71.4%, the proportions of Chinese Han nationality were 97.9% and 97.6%, respectively. The mean HIV-RNA levels in ABT group and NRTI group were 3.94 ± 0.98 and 3.94 ± 0.99 $\log_{10}$ copies/mL, among which, 15.1% and 15.7% subjects had HIV-RNA level ≥ 100000 copies/mL, respectively. The mean baseline CD4 cell counts were 230 ± 190 and 210 ± 160 cells/μL, among which, 25.4% and 23.7% subjects had CD4 cell count < 100 cells/μL, respectively. The percentages of genotypic resistance to at least one drug were 81.3% and 83.9% in ABT group and NRTI group, and 72.0% and 75.0% subjects had two or more classes of drugs resistance, respectively. These baseline characteristics were similar and comparable between the two treatment groups.

At Week 48, the percentages of subjects with the primary efficacy endpoint HIV-RNA < 50 copies/mL were 75.7% and 77.3% in ABT group and NRTI group, respectively, the ABT group was non-inferior to NRTI group. For the secondary efficacy endpoint, 88.1% and 85.4% had HIV-RNA < 400 copies/mL in ABT group and NRTI group, respectively, the ABT group was non-inferior to NRTI group. Logistic regression analysis showed that there was no statistically significant difference in the percentage of subjects with HIV-RNA < 50 copies/mL between ABT group and NRTI group ($P > 0.05$) after adjusting for gender, baseline HIV-RNA and baseline CD4 as independent variables. AIKENING could effectively suppress virus replication in HIV-infected subjects with the viral load ≥ 100,000 copies/mL and those with CD4 cell count < 100 cells/μL (see Table 2).
Other secondary efficacy endpoints including logarithm value changes of HIV RNA and CD4 cell count after treatment were consistent with the result of primary efficacy endpoint.

Table 2. Efficacy Endpoints After 48-week Treatment

TALENT Study	ABT group N=185	NRTI group N=198
Efficacy endpoints analysis		
Percentage of subjects with HIV-RNA < 50 copies/mL (%)	75.7%	77.3%
Percentage of subjects with HIV-RNA < 400 copies/mL (%)	88.1%	85.4%
Mean change of HIV-RNA from baseline ($\log_{10}$ copies/mL)	-2.16±1.00	-2.11±1.16
Mean change of CD4 cell count from baseline (cell/μL)	139.1±142.3	142.3±127.6
< 50 copies/mL stratified analysis		
Baseline HIV-RNA		
< 100000 copies/mL	77.7%	78.4%
≥ 100000 copies/mL	64.3%	71.0%
Baseline CD4 cell count		
< 100 cells/μL	83.0%	83.0%
≥ 100 cells/μL	73.2%	75.5%
Gender		
Male	78.4%	80.4%
Female	67.4%	69.1%

[Pharmacology and Toxicology]

Pharmacology
Mechanism of action:
Albuvirtide is an HIV fusion inhibitor targeting the HIV-1 viral envelope subunit glycoprotein 41 (gp41). It inhibits the fusion of viruses with human target cells, thus blocking viruses from entering cells.

Antiviral activity:
In vitro antiretroviral activity albuvirtide-albumin conjugates against various HIV-1 strains showed the IC_{50} of albuvirtide against 8 HIV-1 subtypes (A, B, C, G and EA recombinants) was 0.5 ~ 4.8 nM in human peripheral blood mononuclear cells (PBMCs). The mean IC_{50} of albuvirtide against 28 prevalent strains of CRF07-BC, CRF01-AE, and B' subtypes from China were 5.2 nM, 6.9 nM and 9.5 nM, respectively.

The *in vivo* antiviral activity of subcutaneous injection of albuvirtide was evaluated in SCID-hu Thy/Liv mice model that was constructed by transplantation of human fetal thymus and liver into immunodeficient CB-17-SCID mice and inoculation with HIV-1. Albuvirtide showed strong antiviral activity in mice at a dose of 10 mg/kg whether albuvirtide was administered by subcutaneous injection once a day or every other day (equal to around 2 and 4 half-life intervals of mouse albumin, respectively).

Drug resistance:
In vitro selection of resistant viruses to albuvirtide showed that albuvirtide showed a high resistance gene barrier. The resistant virus was achieved by 9 passages of HIV-1 in the presence of albuvirtide with a sensitivity decrease of 159 folds, and the resistant viruses were across resistant to T20. The main mutations were Q40K, N126K and K114I.

In the phase 3 study of albuvirtide, there were 11 and 15 patients in ABT and NRTI group

with HIV-1 RNA >400 copies/mL at Week 48. Nine percent (1/11) of patients in ABT group developed new NRTIs resistance mutations (K103S, G190A), while 26.7% (4/15) patients in NRTI group developed new NRTIs (M41LM, K70KR, F77FL, F116FY, Q151QKLM), NNRTIs (Y181C, H221Y) and/or PIs (I50V, V82A, L10F, L33F, Q58E, L10LF) resistance mutations. All 11 patients in ABT group had no fusion inhibitor-associated resistance mutations in the viral gp41 sequence and were susceptible to FIs, indicating the high resistance barrier of albuvirtide.

Cross-resistance:
In vitro assay showed that seven laboratory HIV-1 strains resistant to T20 with resistant mutation in the 36, 38, 42 and 43 site were sensitive to albuvirtide.

Clinical trial information:
Please refer to section [Clinical studies].

Toxicology
Genetic toxicity:
The genetic toxicity tests of albuvirtide are negative, including the bacterial reverse mutation test (Ames test), *in vitro* chromosome aberration test of CHL cells and micronucleus test in bone marrow of mice.

Reproductive toxicity:
In the fertility and early embryo development toxicity study in Wistar rats, albuvirtide was administered by intravenous injection at 30, 60 and 120 mg/kg. Male rats of each group were treated from 4 weeks before mating to the dissection, and females were treated from two weeks before mating to the eighth day of pregnancy. The frequency of administration was once every 2 days. In all albuvirtide dose groups; there was no interference or toxic effect on the fertility and early embryo development in male and female rats. The NOAEL of albuvirtide for the reproductive function, formation and development of embryos in the parental rats was determined to be 120 mg/kg, i.e. 4 folds of human equivalent dose calculated in terms of body surface area.

In the embryo-fetal development toxicity study in Wistar rats, the pregnant rats were given albuvirtide by intravenous injection at dose level of 30, 60 and 120 mg/kg once every 2 days from the 6th to 16th day of pregnancy. No significant changes were observed in pregnant rats, embryo and fetal appearance, skeleton and internal organs. The NOAEL of albuvirtide for the parental pregnant rats, and embryos-fetus development were both 120 mg/kg, i.e. 4 folds of human equivalent dose calculated in terms of body surface area. Toxicokinetic study revealed no significant accumulation of albuvirtide in pregnant rats.

In the embryo-fetal development toxicity study in rabbit, the pregnant rabbits were given albuvirtide by intravenous injection at dose levels of 15, 30 and 60 mg/kg once every 3 days from the 6th to 18th day of pregnancy. In the highest dose of 60 mg/kg group, only 1 rabbit (1/13) delivered prematurely, and the percentage of dysostosis of hyoid bone showed an upward trend compared with that of the control group. There were no significant abnormal changes in appearance, bone and internal organs in the other pregnant rabbits and fetal rabbits. The NOAEL of albuvirtide for the parental rabbits, and embryos-fetus development were all 30 mg/kg, i.e. 3.9 folds of human equivalent dose calculated in terms of exposure. Toxicokinetic study showed no significant accumulation of albuvirtide in pregnant rabbits.

[Pharmacokinetics]
Pharmacokinetic studies of single dose and multiple dose intravenous administration of albuvirtide have been conducted in adult subjects with HIV-1 infection. There was a good linear relationship between AUC_{0-t} and dose, indicating that albuvirtide met the linear elimination pattern. The pharmacokinetic parameters of albuvirtide at a single dose of 320 mg by intravenous infusion were AUC_{0-t} 3012.6 ± 373.0 mg•h/L, and C_{max} 61.9 ± 5.6 mg/L. In the multiple dose study, the steady pharmacokinetic parameters of albuvirtide at a dose of 320 mg by intravenous infusion once a week were AUC_{ss} 4946.3 ± 407.1 mg • h/ L, C_{max} 57.0 ± 7.9 mg/ L, and C_{trough} 6.9 mg/ L.

The distribution and excretion study in rats showed that albuvirtide was well distributed in all tissues and organs *in vivo*, and the highest amount of albuvirtide was present in whole blood, followed by kidney, ovary and other tissues, with the least being in brain, body fat and testes. Albuvirtide was mainly eliminated through kidney *in vivo.*

In vitro tests demonstrated that albuvirtide had no significant inhibitory effect on the *in vitro* activity of six major P450 enzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6 and 3A4) in human liver microsomes.

Special Populations
Gender and race:
There are no gender differences in the pharmacokinetics of albuvirtide, and racial differences in pharmacokinetics have not been established yet.

Children and elderly:
The pharmacokinetic study has not yet been conducted in children under 18 years old and elderly above 60 years old.

Hepatic and renal insufficiency:
The pharmacokinetic study has not been conducted in patients with hepatic and renal insufficiency.

[Storage]
Store in a sealed container under refrigerated (2-8°C) condition, protected from light.

[Package]
20 mL injection vials made of brown low borosilicate glass tubing, 1 vial/carton.

[Manufacturer]
Company: Frontier Biotechnologies Inc.
Production address: Building 7, No. 5 Qiande Road, Hi-tech Park, Jiangning District, Nanjing, China

[Date of Revision of Package Insert]
April 16, 2024

BW036-01

客户名称	前沿生物药业(南京)股份有限公司	制　作	李菊
产品名称	注射用艾博韦泰说明书	校　对	李森林
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PT Black 3C

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