Dose Preparation Instructions:

DS-1062a for Injection 100 mg (Lyophilized Powder)

DAIICHI SANKYO

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Approvals

These Dose Preparation Instructions have been reviewed and approved by Daiichi Sankyo.

Daiichi Sankyo, Inc. CMC Author:

Nataliya Bazhina
Print Name

Associate Director, DSI CMC Management and Operations
Title

DocuSigned by:
Nataliya Bazhina
Signature
Signer Name: Nataliya Bazhina
Signing Reason: I approve this document
Signing Time: 10 October 2022 | 12:37:13 PM EDT
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Date (MM DD YYYY)

Daiichi Sankyo, Inc. CMC Technical Approver:

Umang Trivedi
Print Name

Director, DSI CMC Management and Operations
Title

DocuSigned by:
Umang Trivedi
Signature
Signer Name: Umang Trivedi
Signing Reason: I approve this document
Signing Time: 12 October 2022 | 11:53:28 AM EDT
DEAAD67B603E4499A36E801E16FA7ACB
Date (MM DD YYYY)

Daiichi Sankyo Clinical Supply Operations Approval:

Kimura, Eiki
Print Name

Manager, DST Clinical Supply Operations
Title

DocuSigned by:
kimura Eiki
Signature
Signer Name: Kimura Eiki
Signing Reason: I approve this document
Signing Time: 17 October 2022 | 10:56:43 PM JST
222F76A27FD248B48DF508D73739BA98
Date (MM DD YYYY)

Daiichi Sankyo Clinical Operations Approval:

Rim, Choon-Soo
Print Name

Director, DSI Clinical Operations
Title

DocuSigned by:
Choon Soo Rim
Signature
Signer Name: Choon Soo Rim
Signing Reason: I approve this document
Signing Time: 17 October 2022 | 3:19:47 PM EDT
A1AC2D948E3F4E048D71302C7A0C21D1
Date (MM DD YYYY)

Daiichi Sankyo Clinical Operations Approval:

Jikoh, Takahiro
Print Name

Senior Director, DST Clinical Development
Title

DocuSigned by:
Jikoh Takahiro
Signature
署名者名: Jikoh Takahiro
署名理由: この文書を承認する
署名時刻： 18 October 2022 | 8:36:34 AM JST
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Date (MM DD YYYY)

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These Appendices are example documents for DS-1062a for Injection 100 mg, and the site can use their own formats.

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Revision History

Version	Effective Date	Comments
1	30Jun2020	Initial version
2	30Apr2021	Section 4.5 on page 4: • 4.5.2, update the maximum cumulative time at room temperature from 4 hours to 4.5 hours. • Add in 4.5.3, "Please record the start time for dilution, administration start and end time, and storage time." Use-by time check log on page 7 in Appendix: • Add in a column to record Administration start time. • Change the 4 hrs to 4.5 hrs in the "Accumulative time at room temperature at the end of administration" column. • Add "Accumulated time at room temperature = (End of administration time – Dilution start time) – Accumulated time at 2-8□".
3	29Mar2022	Section 4.1.3 on page 7: • Remove: The patient's weight at screening (baseline) will be used to initially calculate the dose, add: The patient weight at baseline will be used to initially calculate the dose • Remove screening from A2 Preparation Worksheet on page 3 and 4
4	10Sep2022	Section 3, Table 1 on page 6: • Updated Component Material Compatibility list. • Updated page numbers in the Appendix.

1. Introduction

This document describes the procedure for DS-1062a for Injection 100 mg, hereinafter DS-1062a Lyo-DP, infusion preparation, compatible materials and storage conditions of infusion solution to support DS-1062a clinical studies.

2. Description of Drug Product

DS-1062a Lyo-DP is a sterile, lyophilized drug product individually packaged in a single-use vial and contained in a carton. DS-1062a Lyo-DP is provided in an amber borosilicate (Type I) glass vial and is reconstituted with 5 mL of water for injection. One strength of DS-1062a, 100 mg/vial, will be provided for DS-1062a clinical studies.

- DS-1062a Lyo-DP should be handled in accordance with an anticancer drug, such as a chemotherapeutic agent.
- Each vial is for single use only.
- Appearance (White to yellowish white cake-like masses).
- DS-1062a Lyo-DP must be administered intravenously.
- DS-1062a Lyo-DP is supplied in labelled cartons each containing 1 labelled vial.
- DS-1062a Lyo-DP should be stored in a secure refrigerator at 2°C to 8°C and protected from light.

3. Diluent, Media and Components

Once reconstituted, DS-1062a Lyo-DP will be diluted with commercially available 5% (w/v) Dextrose Injection infusion solution. The intravenous infusion solution will be prepared using appropriate aseptic technique and administered at the clinical site by a trained pharmacist, or appropriate delegate. Acceptable drug concentration in infusion solution is 0.1 mg/mL to 6.7 mg/mL DS-1062a Lyo-DP.

Components to be used are listed in Table 1. A 0.2 or 0.22 µm filter is mandatory for administration.

Note: DS-1062a Lyo-DP is **not compatible with saline**.

Table 1: Component Material Compatibility list for solution preparation and administration.

Items	Material Type
5% (w/v) Dextrose Injection	Polyolefin Polyethylene Polypropylene PVC
Infusion set and tubing	Polybutadiene Polycarbonate PET Polypropylene Stainless steel Elastomer Fluorosilicone Silicone oil Polyethylene Copolyester Polymethyl methacrylate Polytetrafluoroethylene Silicone rubber ABS resin Acryl Polyisoprene Acrylic copolymer PVC Parylene MBS resin Polyethersulfone Titanium oxide Polyester Thermoplastic Elastomer Silicone Isoprene rubber PVDF Nylon
0.2 or 0.22 µm filter	Polytetrafluoroethylene Polyethersulfone Polysulfone PVDF Polyamide Polyester Acryl

CV Port	Polyacetal Titanium alloy Polyurethane Silicone rubber Polycarbonate Tungsten Barium sulfate Stainless steel Polybutylene terephthalate Heparinized hydrophilic material Epoxy resin Titanium
CSTD Syringe adaptor Vial adaptor Bag spike	Polycarbonate Silicone rubber Fluorosilicone ABS resin Polypropyrene Stainless steel Polyisoprene PVC Elastomer Thermoplastic Elastomer

Please contact Sponsor to confirm the acceptability.

4. Dose Preparation Instruction of Infusion Solution

Pre-determined volume of reconstituted DS-1062a Lyo-DP will be added into a 5% (w/v) Dextrose Injection infusion bag and gently inverting to ensure homogeneity of the dose in the bag. Open labels generated by the clinical site will be affixed to the bag filled with appropriate volume of drug solution. Preparation will be performed using aseptic techniques. The prepared infusion solution is administered intravenously as stated in the protocol.

- All components are sterile and for single use only. The sterility cannot be guaranteed unless the component packaging seal remains intact. Any component with packaging that shows signs of damage or tampering must not be used and must be quarantined.

General Instructions:

- Local controls associated with standard operation procedures for preparing IV doses should be implemented when following this procedure.
- 5% (w/v) Dextrose Injection Solution is abbreviated “Dextrose”.
- Dextrose is used for priming and flushes.

- Document the procedure in the Preparation Worksheet in Appendix A2.
    - Clinical site pharmacies may document study drug preparation in their format per their standard of practice.
- Appearance after dilution with Dextrose: clear to slightly opalescent and colorless to light yellow solution.
- DS-1062a Lyo-DP vials are for one time use only.

4.1 Dose Calculation

4.1.1 Calculate the volume of reconstituted DS-1062a Lyo-DP based on the body weight of the patient (kg) and planned dose (mg/kg) according to the following formula:

$$\text{Volume of DS-1062a Lyo-DP solution (mL)} = \frac{\text{Dose (mg/kg)} \times \text{Body Weight (kg)}}{20\ \text{(mg/mL)}}$$

4.1.2 Round the drug solution volume to a whole number.

4.1.3 The patient's weight at baseline will be used to initially calculate the dose. If the patient's weight changed by ≥ ± 10% of the baseline weight, the dose needs to be recalculated**.** After recalculation, the updated subject's weight will be used as the new baseline weight. The site may follow local institutional policy for recalculating dose based on weight changes less than 10%.

4.1.4 Calculate the number of vials required for the dose preparation:

$$\text{Vial number (round up)} = \frac{\text{DS-1062a (mL)}}{5\ \text{(mL)}}$$

4.2 Vial inspection

4.2.1 Remove DS-1062a Lyo-DP vials required for a planned dose from storage from the refrigerator.

4.2.2 DS-1062a Lyo-DP should be handled in accordance with an anticancer drug, such as a chemotherapeutic agent.

4.2.3 Outer carton box(es) must remain together with vial(s) until DS-1062a solution preparation is complete.

4.3 Reconstitution

4.3.1 Add 5 mL of sterile Water for Injection to a concentration of 20 mg/mL DS-1062a.

4.3.2 Gently swirl the solution until all solids are dissolved.

4.3.3 Do not vortex or vigorously agitate the vial.

4.3.4 Visually inspect the solution to ensure that the entire content of the lyophilized cake is completely reconstituted.

4.3.5 The reconstituted solution should appear clear to slightly opalescent and colorless to light yellow. Dilution start time is recorded upon vial(s) reconstitution.

4.3.6 Once the vials are reconstituted, preparation of DS-1062a infusion solution is conducted immediately.

4.4 Preparation of DS-1062a Lyo-DP infusion solution

4.4.1 Add calculated volume of DS-1062a Lyo-DP drug product solution from the vials to Dextrose infusion bag.

4.4.2 The infusion bag should be gently inverted to thoroughly mix the solution. Do NOT shake the bag.

4.4.3 Label the infusion bag with a subject number and initials, the initials of the person who prepared the infusion, preparation date, solution prepared time, and use by time per instruction in **Step 4.5** and date. Clinical sites may use site-own label according to site procedures as long as these ensure potential errors in dosing and/or preparation errors do not occur.

4.4.4 Cover the labeled bag with a light protection cover. This is end of preparation time.

4.5 Important notes:

4.5.1 It is recommended to use the prepared infusion immediately. If not used immediately, the storage period must not be longer than 24-hours at 2°C to 8ºC with protection from light. This 24-hour period is from Dilution (Reconstitution) start time until the start of infusion.

4.5.2 It is recommended that the infusion solution be allowed to reach room temperature prior to administration, to ensure that the infusion is comfortable for the patient. The prepared infusion solution may be stored at room temperature for up to 4.5 hours in total. This 4.5-hour period is the cumulative time at room temperature from Dilution (Reconstitution) start time until the end of infusion.

4.5.3 Please record the start time for dilution, administration start and end time, and storage time.

4.5.4 Document all procedures.

Appendix

A1 Preparation Record Sheets For DS-1062a Lyo-DP
A2 Preparation Worksheet
A3 Use-by Time Check Log

A1 Preparation Record Sheets for DS-1062a Lyo-DP

Instructions:

All preparation records should be stored in a secure location within the pharmacy.

Use a Daily Pharmacy Signature Log on each day of dosing. Duplicate the sheets as needed.

Daily Pharmacy Signature Log

Name (Please print.)	Initials	Signature	Date (DDMMMYYYY)
Pharmacy operation done by			
Witnessed by (if locally required)			

A2 Preparation Worksheet

Date of Preparation:	
Cohort/if applicable:	
Subject ID:	**Subject Initials**:

Instructions:

- Local controls for preparing IV doses should be implemented when following this procedure.
- 5% (w/v) Dextrose Injection Solution is abbreviated "Dextrose".
- Upon completion of each step or immediately upon completion of procedure, fill in the provided space with required information or mark off each box.
- The witness should initial in the right-hand column of the Preparation Worksheet of the same row if a witness is locally required.
- Appearance after dilution with Dextrose: clear to slightly opalescent and colorless to light yellow solution.
- When exact delivery volumes are prepared, flush administration line with a volume of Dextrose equal to the line volume.

Procedures	***Pharmacy Operation by (Initials)***	***Witnessed by (if locally required)***
1. Record patient's weight (kg): _____._____kg (at baseline _____._____kg) a. The patient's weight at baseline will be used to initially calculate the dose. b. If the patient's weight changed by > ± 10% of the baseline weight, the dose will be recalculated. c. After recalculation, the updated subject's weight will be used as the new baseline weight. The site may follow local institutional policy for recalculating dose based on weight changes less than 10%. ☐ Read and Understand [Please check.]		

A2 Preparation Worksheet

Date of Preparation:	
Cohort/if applicable:	
Subject ID:	**Subject Initials**:

Procedures	*Pharmacy Operation by (Initials)*	*Witnessed by (if locally required)*
2. Calculate component volumes to prepare an IV bag with dextrose solution using reconstituted DS-1062a Lyo-DP and commercial Dextrose as per **Step 4.1** in the Pharmacy Instruction. a. Calculate the volume of reconstituted DS-1062a Lyo-DP to be added to the IV bag with Dextrose using the following formula: Total volume of reconstituted DS-1062a Lyo-DP (mL) $= \frac{\text{Dose (mg/kg)} \times \text{Body Weight (kg)}}{\text{20 (mg/mL)}}$ b. Round the drug solution volume to whole number: Reconstituted DS-1062a Lyo-DP volume to add_____mL The patient's weight at baseline will be used to initially calculate the dose. If the patient's weight changed by ≥ ± 10% of the baseline weight, the dose will be recalculated. After recalculation, the updated subject's weight will be used as the new baseline weight. The site may follow local institutional policy for recalculating dose based on weight changes less than 10%. c. Calculate the number of vials required for the dose preparation $\text{Vial number (round up)} = \frac{\text{DS-1062a (mL)}}{\text{5 (mL)}}$ Number of vial(s) used _____vials		

A2 Preparation Worksheet

Date of Preparation:	
Cohort/if applicable:	
Subject ID:	**Subject Initials**:

Procedures	*Pharmacy Operation by (Initials)*	*Witnessed by (if locally required)*
3. Reconstitution of DS-1062a Lyo-DP **DS-1062a Lyo-DP should be handled in accordance with an anticancer drug, such as a chemotherapeutic agent.** a. Remove vials from 2-8ºC storage and inspect as per **Step 4.2** and reconstitute with 5mL water for injection per vial as per **Step 4.3** in the instruction b. Record dilution start time upon vial(s) reconstitution: Date:_____ (24-hour clock):_____**:**_____ Note: Outer carton box(es) must remain together with vial(s) until DS-1062a solution preparation is complete.		
4. Preparation of Infusion Solution as per **Step 4.4** in the instruction Once the vials are reconstituted, Preparation of DS-1062a Infusion solution is conducted immediately as per **Step 4.5** in the instruction. Reconstituted DS-1062a Lyo-DP added: _____ mL Total Preparation Volume: _____ mL ☐ confirm [Please check.]		
5. Appearance of the infusion solution a. DS-1062a infusion solution is a clear to slightly opalescent and colorless to light yellow solution. ☐ confirm [Please check.] Inspect for absence of un-dissolved matter in the bag. ☐ confirm [Please check.]		

A2 Preparation Worksheet

Date of Preparation:	
Cohort:/if applicable	
Subject ID:	**Subject Initials**:

Procedures	*Pharmacy Operation by (Initials)*	*Witnessed by (if locally required)*
6. Affix appropriate label for each subject on the prepared infusion solution as per **Step 4.4.3** ☐ confirm [Please check.]		
7. Place infusion solution bag(s) into a light protection cover ☐ confirm [Please check.]		

A3 Use-by Time Check Log

Date of Preparation:	
Cohort:/if applicable	
Subject ID:	**Subject Initials**:

1. Record storage times.
   a. IV bag placed in 2-8ºC storage (if needed):

      Date:_____ (24-hour clock):_____:_____

   b. IV bag removed from 2-8ºC storage (if needed):

      Date:_____ (24-hour clock):_____:_____

      Accumulated time at 2-8ºC :_____

   c. Start of warming period (if needed):

      Date:_____ (24-hour clock):_____:_____

   d. End of warming period (if needed):

      Date:_____ (24-hour clock):_____:_____

      Accumulated time at Room Temperature:_____

2. Set Infusion set with 0.2 or 0.22 μm filter and tubing
   ☐ confirm [Please check.]

Upon completion of administration, start time of dilution on Worksheets and administration start and end time should be transcribed on Use-by Time Check Log.

Cohort	Subject ID	Dilution start time (date: DDMMMYYYY) (time: 24-h clock)	Administration start time (date: DDMMMYYYY) (time: 24-h clock)	End of administration (date: DDMMMYYYY) (time: 24-h clock)	Accumulated time at 2-8ºC	Accumulated time at room temperature at the end of administration*
					Must not exceed 24hrs	**Must not exceed 4.5hrs**

* Accumulated time at room temperature= (End of administration time – Dilution start time) – Accumulated time at 2-8ºC

Signature of person who transcribed