Patisiran: Total Dilution Volume

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SUMMARY

- In the APOLLO, APOLLO-B, and Global OLE studies, the total amount of patisiran prepared to be infused at each dosing visit was 200 mL.[1–3]

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CLINICAL TRIAL EXPERIENCE

The final total volume of the prepared patisiran dose should be 200 mL. If using a 250 mL infusion bag of normal saline, it is necessary to withdraw 50 mL of normal saline plus an additional volume of normal saline that matches the amount of patisiran to be administered, to ensure that the total final volume is 200 mL.[4]

RELEVANT CLINICAL TRIALS

APOLLO was a multicenter, international, randomized (2:1), double-blind, placebo-controlled, phase 3 study designed to assess the efficacy and safety of IV patisiran 0.3 mg/kg every 3 weeks (n=148) versus placebo (n=77) in patients with hATTR-PN. The primary endpoint was the change from baseline in the mNIS+7 at 18 months.[5]

APOLLO-B was a multicenter, randomized (1:1), double-blind, placebo-controlled, phase 3 study designed to evaluate the efficacy and safety of IV patisiran 0.3 mg/kg every 3 weeks (n=181) versus placebo (n=179) in patients with ATTR-CM, including both hATTR and wtATTR. The primary endpoint was the change from baseline in the 6-MWT at 12 months. After the 12-month double-blind treatment period, all patients received patisiran in an OLE period.[6]

The Global OLE study (N=211) was a multicenter, international study designed to evaluate the long-term safety and efficacy of IV patisiran in patients with hATTR-PN. Patients with hATTR-PN who completed the patisiran phase 2 OLE study or phase 3 APOLLO study and met eligibility criteria were able to start or continue IV patisiran 0.3 mg/kg every 3 weeks for up to 5 years. The study enrolled 25 patients from the patisiran phase 2 OLE study (phase 2 OLE-patisiran group), 137 patients from the APOLLO-patisiran arm (APOLLO-patisiran group), and 49 patients from the APOLLO-placebo arm (APOLLO-placebo group).[7]

In the APOLLO, APOLLO-B, and Global OLE studies, the total amount of patisiran prepared to be infused at each dosing visit was 200 mL. Administration of a total amount of 250 mL was not studied.[1–3]

STABILITY STUDIES

A stability study was performed to evaluate the patisiran drug product admixture under simulated conditions of use. The patisiran drug product admixtures were prepared at two concentration levels to simulate patient weights of approximately 50 kg and 104 kg and at a dose of 0.3 mg/kg under aseptic conditions using commercially prepared normal saline. The total volume of the admixture for administration was 200 mL. Experiments with a total volume of 250 mL were not performed.[8]

Two concentrations of patisiran drug product admixture were tested[8]:

- Low concentration = 0.074 mg/mL
- High concentration = 0.158 mg/mL

The admixture was held under simulated conditions of use (i.e., under ambient lighting and simulated motion via repeated inversions) at 30 ± 2 ºC / 75 ± 5 % relative humidity. Samples were analyzed using a combination of visual and stability tests. The data confirmed that the admixture was chemically and physically stable under simulated conditions of use in accordance with the Prescribing Information.[9]

ONPATTRO PRESCRIBING INFORMATION – RELEVANT CONTENT

The DOSAGE AND ADMINISTRATION section provides the following information[10]:

Preparation Instructions

ONPATTRO must be filtered and diluted prior to intravenous infusion. The diluted solution for infusion should be prepared by a healthcare professional using aseptic technique as follows:

- *Remove ONPATTRO from the refrigerator and allow to warm to room temperature. Do not shake or vortex.*
- *Inspect visually for particulate matter and discoloration. Do not use if discoloration or foreign particles are present. ONPATTRO is a white to off-white, opalescent, homogeneous solution. A white to off-white coating may be observed on the inner surface of the vial, typically at the liquid-headspace interface. Product quality is not impacted by presence of the white to off-white coating.*
- *Calculate the required dose of ONPATTRO based on the recommended weight-based dosage.*
- *Withdraw the entire contents of one or more vials into a single sterile syringe.*
- *Filter ONPATTRO through a sterile 0.45 micron polyethersulfone (PES) syringe filter into a sterile container.*
- *Withdraw the required volume of filtered ONPATTRO from the sterile container using a sterile syringe.*
- *Dilute the required volume of filtered ONPATTRO into an infusion bag containing 0.9% Sodium Chloride Injection, USP for a total volume of 200 mL. Use infusion bags that are di(2-ethylhexyl)phthalate-free (DEHP-free).*
- *Gently invert the bag to mix the solution. Do not shake. Do not mix or dilute with other drugs.*
- *Discard any unused portion of ONPATTRO.*
- *ONPATTRO does not contain preservatives. The diluted solution should be administered immediately after preparation. If not used immediately, store in the infusion bag at room temperature (up to 30°C [86°F]) for up to 16 hours (including infusion time). Do not freeze.*

Infusion Instructions

- *Use a dedicated line with an infusion set containing a 1.2 micron polyethersulfone (PES) in-line infusion filter. Use infusion sets and lines that are DEHP-free.*
- *Infuse the diluted solution of ONPATTRO intravenously, via an ambulatory infusion pump, over approximately 80 minutes, at an initial infusion rate of approximately 1 mL/min for the first 15 minutes, then increase to approximately 3 mL/min for the remainder of the infusion. The duration of infusion may be extended in the event of an IRR.*
- *Administer only through a free-flowing venous access line. Monitor the infusion site for possible infiltration during drug administration. Suspected extravasation should be managed according to local standard practice for non-vesicants.*
- *Observe the patient during the infusion and, if clinically indicated, following the infusion.*
- *After completion of the infusion, flush the intravenous administration set with 0.9% Sodium Chloride Injection, USP to ensure that all ONPATTRO has been administered.*

Dosing Information

ONPATTRO should be administered by a healthcare professional.

ONPATTRO is administered via intravenous (IV) infusion. Dosing is based on actual body weight.

For patients weighing less than 100 kg, the recommended dosage is 0.3 mg/kg once every 3 weeks.

For patients weighing 100 kg or more, the recommended dosage is 30 mg once every 3 weeks.

ABBREVIATIONS

6-MWT = 6-minute walk test; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; DEHP = di(2-ethylhexyl)phthalate; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IRR = infusion-related reaction; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; OLE = open-label extension; PES = polyethersulfone; USP = United States Pharmacopeia; wtATTR = wild-type transthyretin amyloidosis.

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