AMONDYS 45 (casimersen) Injection for Intravenous Use Product Summary

INDICATION: AMONDYS 45 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 45 skipping. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in patients treated with AMONDYS 45. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

DOSAGE AND ADMINISTRATION: The recommended dose of AMONDYS 45 is 30 mg/kg administered once weekly as a 35 to 60-minute intravenous infusion via an in-line 0.2-micron filter. If a dose of AMONDYS 45 is missed, it may be administered as soon as possible after the scheduled dose.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS: Kidney toxicity was observed in animals who received casimersen. Although kidney toxicity was not observed in the clinical studies with AMONDYS 45, kidney toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. Kidney function should be monitored in patients taking AMONDYS 45. Because of the effect of reduced skeletal muscle mass on creatinine measurements, creatinine may not be a reliable measure of kidney function in DMD patients. Serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio should be measured before starting AMONDYS 45. Consider also measuring glomerular filtration rate using an exogenous filtration marker before starting AMONDYS 45. During treatment, monitor urine dipstick every month, and serum cystatin C and urine protein-to-creatinine ratio (UPCR) every three months. Only urine expected to be free of excreted AMONDYS 45 should be used for monitoring of urine protein. Urine obtained on the day of AMONDYS 45 infusion prior to the infusion, or urine obtained at least 48 hours after the most recent infusion, may be used. Alternatively, use a laboratory test that does not use the reagent pyrogallol red, as this reagent has the potential to cross react with any AMONDYS 45 that is excreted in the urine and thus lead to a false positive result for urine protein.

If a persistent increase in serum cystatin C or proteinuria is detected, refer to a pediatric nephrologist for further evaluation.

ADVERSE REACTIONS: The most common adverse reactions (incidence greater or equal than 20% and at least 5% higher than placebo) were upper respiratory tract infection (65%, 55%), cough (33%, 26%), pyrexia (33%, 23%), headache (32%, 19%), arthralgia (21%, 10%), and oropharyngeal pain (21%, 7%). Other adverse reactions that occurred in at least 10% of patients treated with AMONDYS 45, and that were reported at a rate at least 5% more frequently in the AMONDYS 45 group than in the placebo group, were: ear pain, nausea, ear infection, post-traumatic pain, and dizziness and light-headedness.

DRUG INTERACTIONS: Based on *in vitro* data, casimersen has a low potential for clinically relevant drug-drug interactions with major CYP enzymes and transporters.

CLINICAL STUDIES: The effect of AMONDYS 45 on dystrophin production was evaluated in one study in male DMD patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 45 skipping (study 1).

Study 1 is an ongoing, double-blind, placebo-controlled, multicenter study designed to evaluate the safety and efficacy of AMONDYS 45 in ambulatory patients. The study is planned to enroll a total of 111 patients, age 7 to 13 years, randomized to AMONDYS 45 or placebo in a 2 to 1 ratio. An interim analysis demonstrated a statistically significant increase in dystrophin expression among patients treated with casimersen (n=27) compared to those who received placebo (n=16). Dystrophin levels, as assessed by the Sarepta Western blot assay, increased from 0.93% (SD 1.67) of normal at baseline to 1.74% (SD 1.97) of normal after 48 weeks of treatment with casimersen, representing a mean change from baseline in dystrophin of 0.81% (SD 0.70) of normal levels ($P<0.001$). Patients who received casimersen showed a significantly greater increase in dystrophin protein levels from baseline to Week 48 compared to those who received placebo (mean difference of 0.59%; $P = 0.004$).

Dystrophin levels assessed by western blot can be meaningfully influenced by differences in sample processing, analytical technique, reference materials, and quantitation methodologies. Therefore, comparing dystrophin results from different assay protocols will require a standardized reference material and additional bridging studies.