Recombinant Factor VIII (Page 1 of 2)

Product Specifics	ADVATE® Shire	ADYNOVATE® Shire	AFSTYLA™ CSL Behring	ELOCTATE™ Bioverativ	Helixate® FS CSL Behring
Indications	Indicated for use in children and adults with hemophilia A (congenital factor VIII deficiency) for: • Control and prevention of bleeding episodes. • Perioperative management. • Routine prophylaxis to prevent or reduce the frequency of bleeding episodes. ADVATE is not indicated for the treatment of von Willebrand disease.	ADYNOVATE, Antihemophilic Factor (Recombinant), PEGylated, is a human antihemophilic factor indicated in adolescent and adult patients (12 years and older) with hemophilia A (congenital factor VIII deficiency) for: • On-demand treatment and control of bleeding episodes • Routine prophylaxis to reduce the frequency of bleeding episodes ADYNOVATE is not indicated for the treatment of von Willebrand disease	AFSTYLA®, Antihemophilic Factor (Recombinant), Single Chain, is a recombinant, antihemophilic factor indicated in adults and children with hemophilia A (congenital Factor VIII deficiency) for: • On-demand treatment and control of bleeding episodes • Routine prophylaxis to reduce the frequency of bleeding episodes • Perioperative management of bleeding. AFSTYLA is not indicated for the treatment of von Willebrand disease.	In adults and children with Hemophilia A (congenital Factor VIII deficiency) for: • Control and prevention of bleeding episodes • Perioperative management • Routine prophylaxis to prevent or reduce the frequency of bleeding episodes. ELOCTATE is not indicated for the treatment of von Willebrand disease.	On-demand treatment and control of bleeding episodes in adults and children with hemophilia A; Perioperative management of bleeding episodes in adults and children with hemophilia A; and Routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with hemophilia A and reduce the risk of joint damage in children without pre-existing joint damage. Helixate FS is not indicated for the treatment of von Willebrand disease.
Contraindications	ADVATE is contraindicated in patients who have life-threatening hypersensitivity reactions, including anaphylaxis, to mouse or hamster protein or other constituents of the product	ADYNOVATE is contraindicated in patients who have had prior anaphylactic reaction to ADYNOVATE, to the parent molecule (ADVATE), mouse or hamster protein, or excipients of ADYNOVATE (e.g. Tris, mannitol, trehalose, glutathione, and/or polysorbate 80).	Do not use in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis to AFSTYLA or its excipients, or hamster proteins.	Do not use in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis, to ELOCTATE or excipients of ELOCTATE (sucrose, sodium chloride, L-histidine, calcium chloride and polysorbate 20).	Do not use in patients who have life-threatening hypersensitivity reactions, including anaphylaxis to mouse or hamster protein or other constituents of the product.
Nutrient in Cell Culture	ADVATE is a purified glycoprotein consisting of 2,332 amino acids that is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line but does not contain plasma or albumin. The CHO cell line employed in the production of ADVATE is derived from that used in the biosynthesis of RECOMBINATE.	The cell culture, pegylation, purification process and formulation used in the manufacture of ADYNOVATE do not use additives of human or animal origins.	No human or animal derived proteins are used in the purification or formulation processes.	BDD-rFVIIIFc is produced by recombinant DNA technology from a human embryonic kidney (HEK) cell line, which has been extensively characterized. The HEK cell line expresses BDD-rFVIIIFc into a defined, cell culture medium that does not contain any proteins derived from animal or human sources.	The cell culture medium contains Human Plasma Protein Solution (HPPS) and recombinant insulin, but does not contain any proteins derived from animal sources.
Stabilizer in Final Formulation	Mannitol, trehalose, sodium, histidine, Tris, calcium chloride, polysorbate-80, glutathione	Tris (hydroxymethyl) aminomethane, Calcium Chloride, Mannitol, Sodium Chloride, Trehalose Dihydrate, Glutathione, Histidine, Polysorbate. There are no additives of human or animal origin.	The reconstituted product contains the excipients: L-Histidine, polysorbate 80, calcium chloride, sodium chloride, sucrose, water for injection.	The reconstituted product contains the excipients: sucrose, sodium chloride, L-histidine, calcium chloride and polysorbate 20.	Sucrose (0.9-1.3%), Glycine (21-25 mg/mL), and Histidine (18-23 mM/L) in 250 IU, 500 IU, 1,000 IU Sucrose (0.9-1.2%), Glycine (20-24 mg/mL and Histidine (17-22 mM/L) in 2000 IU, 3000 IU
Viral Safety Processes	Immunoaffinity chromatography. Solvent/Detergent Treatment.	ADVATE is purified from the culture medium using a series of chromatography columns. The purification process includes an immunoaffinity chromatography step in which a monoclonal antibody directed against factor VIII is employed to selectively isolate the factor VIII from the medium. The production process includes a dedicated, viral inactivation solvent-detergent treatment step. The ADVATE molecule is then covalently conjugated with the polyethylene glycol, which mainly targets lysine residues.	AFSTYLA is purified by a controlled multi-step process including two virus reduction steps complementing each other in their mode of action.	BDD-rFVIIIFc is purified using a series of chromatography steps, including affinity capture with a recombinant, single chain antibody fragment produced in a yeast expression system. No human or animal derived proteins are used in the purification or formulation processes. The production process also incorporates two dedicated viral clearance steps - a detergent treatment step for inactivation and a 15 nm filtration step for removal of viruses.	The purification process includes a solvent/detergent virus inactivation step in addition to the use of the purification methods of ion exchange chromatography, monoclonal antibody immunoaffinity chromatography, along with other chromatographic steps designed to purify recombinant factor VIII and remove contaminating substances.
Product Half Life	Adults >16 years: 12.0 ± 4.2, infants 8.7 ± 1.4, 2 to < 5 year olds: 9.5 ± 1.8, 5 to <12 year olds 11..2 ± 3.5, 12 to <16 year olds 12.0 ± 2.9	12 to <18 years; 13.43 ± 4.05 ≥18 years; 14.69 ± 3.79	0 to <6 years: 10.4 (28.7) ≥6 to <12 years: 10.2 (19.4) 12 to <18 years: 14.3 (33.3) ≥18 years: 14.2 (26.0)	Adults: 19.7 (17.4, 22.0) 12-17 years: 16.4 (14.1, 18.6) 6-11 years: 14.9 (12.0, 17.8) 1-5 years: 12.7 (11.2, 14.1)	Adults: 13.74 ± 1.82 hours Children: 10.7 hours (7.8-15.3)
Product Recovery Percentage	Recovery IU/dL/IU/kg in vivo adults: 2.6 ± 0.5, IU/dL/IU/kg infants: 2.1 ± 0.5 2 to <5 years 1.8 ± 0.4, 5 to <12 years 2.1 ± 0.6, 12 to <16 years 2.1 ± 0.5	12 to <18 years; 2.12 ± 0.60 ≥18 years; 2.66 ± 0.68	0 to <6 years: 1.6 (21.1) ≥6 to <12 years: 1.66 (19.7) 12 to <18 years: 1.69 (24.8) ≥18 years: 2.00 (20.8)	Adults: 2.26 (2.13, 2.40) IU/dL per IU/kg 12-17 years: 1.85 (1.58, 2.12) IU/dL per IU/kg 6-11 years: 2.44 (2.07, 2.80) IU/dL per IU/kg 1-5 years: 1.92 (1.80, 2.04) IU/dL per IU/kg	Adults: 2.20 ± 0.34 IU/dL/IU/kg Children: 1.9 (1.25-2.76) IU/dL/IU/kg
Storage Requirements	2°-8°C (36°-46°F). May be stored at room temperature, up to 30°C (86°F) for up to 6 months not to exceed the expiration date. Do not freeze.	Store ADYNOVATE in powder form at 2°to 8°C (36°to 46°F). Do not freeze. ADYNOVATE may be stored at room temperature not to exceed 30°C (86°F) for a period of up to 1 month not to exceed the expiration date. If stored at room temperature, write the date on the carton when ADYNOVATE is removed from refrigeration. After storage at room temperature, do not return the product to the refrigerator. Do not use beyond expiration date printed on the carton or housing. Store ADYNOVATE in the original box and protect from extreme exposure to light. Administer ADYNOVATE as soon as possible, but no later than 3 hours after reconstitution. Do not refrigerate after reconstitution	• Store AFSTYLA in the original package to protect the AFSTYLA vials from light. • Store AFSTYLA in powder form at 2°C to 8°C (36°F to 46°F). Do not freeze to avoid damage to the diluent vial. AFSTYLA can be stored at room temperature, not to exceed 25°C (77°F), for a single period of up to 3 months, within the expiration date printed on the carton and vial labels. • Record the starting date of room temperature on the unopened product carton. Once stored at room temperature, do not return the product to the refrigerator. The shelf-life then expires after storage at room temperature for 3 months, or after the expiration date on the product vial, whichever is earlier. • Do not use AFSTYLA after the expiration date indicated on the vial. • The reconstituted product (after mixing dry product with diluent) can be stored at2°C to 8°C (36°F to 46°F), or at room temperature, not to exceed 25°C (77°F), for up to 4 hours. • Protect from direct sunlight. • After reconstitution, if the product is not used within 4 hours, it must be discarded. • Do not use AFSTYLA if the reconstituted solution is cloudy or has particulate matter. • Discard any unused AFSTYLA.	Prior to Reconstitution: • Store ELOCTATE in the original package to protect the ELOCTATE vials from light. • Store ELOCTATE in powder form at 2°C to 8°C (36°F to 46°F). Do not freeze to avoid damage to the pre-filled diluent syringe. • ELOCTATE may be stored at room temperature, not to exceed 30°C (86°F), for a single period of up to 6 months, within the expiration date printed on the label. • If stored at room temperature, record the date that ELOCTATE is removed from refrigeration on the carton in the area provided. After storage at room temperature, do not return the product to the refrigerator. • Do not use beyond the expiration date printed on the vial or 6 months after the date that was written on the carton, whichever is earlier. After Reconstitution: • The reconstituted product may be stored at room temperature, not to exceed 30°C (86°F), for up to 3 hours. • Protect from direct sunlight. After reconstitution, if the product is not used within 3 hours, it must be discarded. • Do not use ELOCTATE if the reconstituted solution is cloudy or has particulate matter. • Discard any unused ELOCTATE.	Store in refrigerator at 2-8°C (36-46°F) for up to 30 months from the date of manufacture. Within this period, Helixate FS may be stored for a period of up to 12 months at temperatures up to +25°C (77°F). Record the starting date of room temperature storage on the unopened product carton. Once stored at room temperature, do not return the product to the refrigerator. The shelf-life then expires after storage at room temperature, or after the expiration date on the product vial, whichever is earlier. Do not use Helixate FS after the expiration date indicated on the vial. Do not freeze. Protect from extreme exposure to light and store the lyophilized powder in the carton prior to use.
Shelf Life from Date of Manufacture	24 months	24 months	36 months	36 months from date of manufacture	30 months under refrigeration, shelf-life expires after storage at room temperature, or after the expiration date on the vial, whichever is earlier.
How Supplied / Diluent Volume	2 mL, 5 mL	5 mL	250, 500, 1000 IU in 2.5mL or 2000 IU, 3000 IU in 5mL	250, 500, 750, 1000, 1500, 2000, 3000, 4000, 5000 and 6000 IU - all sizes in 3mL	250 IU - 2.5 mL, 500 IU - 2.5 mL, 1,000 IU - 2.5 mL, 2,000 IU - 5 mL, 3,000 IU - 5mL

Recombinant Factor VIII (Page 2 of 2)

Product Specifics	Kogenate® FS Bayer	KOVALTRY® Bayer	Novoeight® Novo Nordisk	NUWIQ Octapharma	Recombinate Shire	XYNTHA® Pfizer
Indications	• On demand treatment and control of bleeding episodes in adults and children with hemophilia A. • Peri-operative management in adults and children with hemophilia A. • Routine prophylaxis to reduce the frequency of bleeding episodes in children with hemophilia A and to reduce the risk of joint damage in children without pre-existing joint damage. • Routine prophylaxis to reduce the frequency of bleeding episodes in adults with hemophilia A.	Indicated for use in adults and children with hemophilia A (congenital Factor VIII deficiency) for: • On-demand treatment and control of bleeding episodes • Perioperative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes. KOVALTRY is not indicated for the treatment of von Willebrand disease	Indicated for use in adults and children with hemophilia A (congenital factor VIII deficiency or classic hemophilia) for: • Control and Prevention of bleeding • Perioperative management • Routine prophylaxis to prevent or reduce the frequency of bleeding episodes. Novoeight® is not indicated for the treatment of von Willebrand disease.	NUWIQ is a recombinant antihemophilic factor [blood coagulation factor VIII (Factor VIII)] indicated in adults and children with Hemophilia A for: • On-demand treatment and control of bleeding episodes • Perioperative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes NUWIQ is not indicated for the treatment of von Willebrand Disease.	RECOMBINATE is indicated in Hemophilia A for the prevention and control of hemorrhagic episodes. Also indicated in the perioperative management of patients with Hemophilia A.	XYNTHA, Antihemophilic Factor (Recombinant), is indicated for use in adults and children with hemophilia A (congenital factor VIII deficiency) for control and prevention of bleeding episodes and for perioperative management. XYNTHA does not contain von Willebrand factor, and therefore is not indicated in von Willebrand's disease.
Contraindications	Do not use in patients who have life-threatening hypersensitivity reactions, including anaphylaxis to mouse or hamster protein or other constituents of the product	Do not use in patients who have history of hypersensitivity reactions to the active substance, mouse or hamster protein, or other constituents of the product	Do not use in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis, to Novoeight® or its components (including traces of hamster proteins)	NUWIQ is contraindicated in patients who have manifested life-threatening hypersensitivity reactions, including anaphylaxis, to the product or its components.	In patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including bovine, mouse, or hamster proteins.	Do not use in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including hamster proteins.
Nutrient in Cell Culture	The cell culture medium contains human plasma protein solution and recombinant insulin, but does not contain any proteins derived from animal sources. No human or animal proteins, such as albumin, are added during the purification and formulation processes of Kogenate FS	Human- and animal-derived raw materials are not added to the cell culture, purification, or formulation processes	Novoeight® is produced using a defined cell culture medium which does not contain any proteins derived from human or animal sources	BDD-rFVIII is produced by recombinant DNA technology in genetically modified human embryonic kidney (HEK) cells with no animal or human derived materials added during the manufacturing process or to the final product.	Bovine serum albumin and aprotinin	The cell line is grown in a chemically defined cell culture medium that contains recombinant insulin, but does not contain any materials derived from human or animal sources.
Stabilizer in Final Formulation	Sucrose: 0.9-1.3% (250 IU, 500 IU, 1,000 IU); 0.9-1.2% (2,000 IU, 3,000 IU) Glycine: 21–25 mg/mL (250 IU, 500 IU, 1,000 IU); 20-24 mg/mL (2,000 IU, 3,000 IU) Histidine: 18–23 mmol/L(250 IU, 500 IU, 1,000 IU); 17–22 mmol/L (2,000 IU, 3,000 IU)	2.2% glycine, 1% sucrose, 30 mM sodium chloride, 2.5 mM calcium chloride, 20 mM histidine and 80 ppm polysorbate 80.	18 mg/mL sodium chloride, 1.5 mg/mL L-histidine, 3 mg/mL sucrose, 0.1 mg/mL polysorbate 80, 0.055 mg/mL L-methionine, 0.25 mg/mL calcium chloride dihydrate	The reconstituted product contains the following excipients per mL: 18 mg sodium chloride, 5.4 mg sucrose, 5.4 mg L-arginine hydrochloride, 0.3 mg calcium chloride dihydrate, 1.2 mg poloxamer 188, and 1.2 mg sodium citrate dihydrate.	Human albumin, calcium, polyethylene glycol, sodium, histidine, polysorbate 80.	Sucrose
Viral Safety Processes	The purification process includes a solvent/detergent virus inactivation step in addition to the use of the purification methods of ion exchange chromatography, monoclonal antibody immunoaffinity chromatography, along with other chromatographic steps designed to purify recombinant factor VIII and remove contaminating substances.	The production process incorporates two dedicated viral clearance steps: (1) a detergent treatment step for inactivation and (2) a 20 nanometer filtration step for removal of viruses and potential protein aggregates.	The production process includes two dedicated viral clearance steps: • A detergent treatment step for inactivation • A 20 nm filtration step for removal of viruses	The active substance is concentrated and purified by a series of chromatography steps, which also includes two dedicated viral clearance steps: solvent/detergent (S/D) treatment for virus inactivation and 20 nm nanofiltration for removal of viruses.	Immunoaffinity chromatography	The purification process uses a series of chromatography steps, one of which is based on affinity chromatography using a patented synthetic peptide affinity ligand. The process also includes a solvent-detergent viral inactivation step and a virus-retaining nanofiltration step.
Product Half Life	13.74 ± 1.82 hours	0 to <6 yrs : 12.1 ± 2.7 hours 6 to <12 yrs: 12.0 ± 2.1 hours 12 to 17 yrs: 14.4 ± 5.5 hours ≥18 yrs: 14.2 ± 3.5 hours	Adults/adolescents with hemophilia A: 10.8-12 hours Children with hemophilia A: 7.7-10 hours	In adults: 17.1 + 11.2 In children 2 to 5 years: 11.9 + 5.4 In children 6 to 12 years: 13.1 + 2.6	14.6 ± 4.9 hours	Adults and Adolescents (≥12 years): 11.2 + 5.0 hours (initial visit); 11.8 ± 6.2 (month 6); 16.7 ± 5.4 (pre-surgery Adolescents (14-15 years): 6.9 ± 2.4h Children (3.7 years to 5.8 years): 8.3 ± 2.7h
Product Recovery Percentage	2.20 ± 0.34	0 to <6 yrs; 1.6 (IU/dL)/(IU/kg) 6 to 12 yrs; 1.7 (IU/dL)/(IU/kg) ≥12 yrs; 2.3 (IU/dL)/(IU/kg)	Adults/adolescents with hemophilia A: 0.02 + 0.002 - 0.028 + 0.006 (IU/mL per IU/kg) Children with hemophilia A: 0.018 + 0.007-0.025 + 0.006 (IU/mL per IU/kg)	In adults: 2.1 + 0.3 In children 2 to 5 years: 1.6 + 0.2 In children 6 to 12 years: 1.6 + 0.4	Calculated ratio of actual to expected recovery; 121.2 ± 48.9%. Actual baseline recovery observed was 123.9 ± 47.7 IU/dL.	Adults and Adolescents (≥12 years): 2.15 ± 0.44 IU/dL per IU/kg (initial visit); 2.47 ± 0.84 (month 6); 2.17 ± 0.47 (pre-surgery) Adolescents (14-15 years): 1.95 ± 0.41IU/dL per IU/kg Children (3.7 years to 5.8 years): 1.52 ± 0.69 IU/dL per IU/kg
Storage Requirements	Product as Packaged for Sale: Store Kogenate® FS at +2°C to +8°C (36°F to 46°F) for up to 30 months from the date of manufacture. Within this period, Kogenate® FS may be stored for a period of up to 12 months at temperatures up to +25°C or 77°F. The starting date of room temperature storage should be clearly recorded on the unopened product carton. Once stored at room temperature, the product must not be returned to the refrigerator. The shelf-life then expires after the storage at room temperature, or the expiration date on the product vial, whichever is earlier. Do not use Kogenate® FS after the expiration date indicated on the vial. Do not freeze. Protect from extreme exposure to light and store the lyophilized powder in the carton prior to use. Product After Reconstitution: Administer Kogenate® FS within 3 hours after reconstitution. It is recommended to use the administration set provided.	Store KOVALTRY at +2°C to +8°C (36°F to 46°F) for up to 30 months from the date of manufacture. Do not freeze. Within this period, KOVALTRY may be stored for a single period of up to 12 months at temperatures up to +25°C or 77°FRecord the starting date of room temperature storage on the unopened product carton. Once stored at room temperature, do not return the product to the refrigerator. The shelf-life then expires after storage at room temperature for 12 months, or after the expiration date on the product vial, whichever is earlier. Do not use KOVALTRY after the expiration date indicated on the vial. Protect KOVALTRY from extreme exposure to light and store the vial with the lyophilized powder in the carton prior to use.	Store Novoeight® in the original package to protect from light. Store under refrigeration at a temperature of 36–46°F (2-8°C) for up to 30 months from the date of manufacture until the expiration date stated on the label. Within the 30-month period, Novoeight® may also be stored at room temperature not to exceed 86°F (30°C) for up to 12 months. When stored at room temperature, clearly record the date when product was removed from the refrigerator in the space provided on the outer carton. Total storage time at room temperature should not exceed 12 months. Do not return the product to the refrigerator. Do not use Novoeight® after the end of the 12-month period at room temperature storage, or after the expiration date stated on the vial, whichever occurs earlier. Do not freeze Novoeight®. Use Novoeight® within 4 hours after reconstitution when stored at room temperature. Store reconstituted product in the vial. Discard any unused reconstituted product stored at room temperature for more than 4 hours.	Store NUWIQ in the original package to protect the NUWIQ vials from light. Store in powder form at 2 – 8°C (35 – 46°F) for up to 24 months. Do not freeze. During the shelf life, the product may be kept at room temperature [up to 25°C (77°F)] for a single period not exceeding 3 months. After storage at room temperature, do not return the product to the refrigerator. Do not use after the expiration date. Keep the reconstituted solution at room temperature. Do not refrigerate after reconstitution. Use the reconstituted solution immediately or within 3 hours after reconstitution. Discard any remaining solution.	RECOMBINATE can be refrigerated [2° - 8°C (36° - 46°F)] or stored at room temperature, not to exceed 30°C (86°F). Avoid freezing to prevent damage to the diluent vial. Do not use beyond the expiration date printed on the box.	XYNTHA: Store XYNTHA under refrigeration at a temperature of 2° to 8°C (36° to 46°F) for up to 36 months from the date of manufacture until the expiration date stated on the label. XYNTHA may also be stored at room temperature not to exceed 25°C (77°F) for up to 3 months. After room temperature storage, XYNTHA can be returned to the refrigerator until the expiration date. Do not store XYNTHA at room temperature and return it to the refrigerator more than once. Clearly record the starting date at room temperature storage in the space provided on the outer carton. At the end of the 3-month period, immediately use, discard, or return the product to refrigerated storage. The diluent syringe may be stored at 2° to 25°C (36° to 77°F). Do not freeze, to prevent damage to the pre-filled syringe. During storage, avoid prolonged exposure of XYNTHA to light. XYNTHA SOLOFUSE: Store XYNTHA® SOLOFUSE™ under refrigeration at a temperature of 2° to 8°C (36° to 46°F) for up to 36 months from the date of manufacture until the expiration date stated on the label. Within the expiration date, XYNTHA® SOLOFUSE™ also may be stored at room temperature not to exceed 25°C (77°F) for up to 3 months. Clearly record the starting date at room temperature storage in the space provided on the outer carton. At the end of the 3-month period, immediately use or discard the product. Do not put the product back into the refrigerator.
Shelf Life from Date of Manufacture	30 months	30 months	30 months under refrigeration (may also be stored at room temperature not to exceed 86°F (30°C) for up to twelve (12) months)	24 months	36 months	Shelf life for both vial and Dual Chamber Syringe presentations are 36 months at the recommended storage conditions.
How Supplied / Diluent Volume	250 IU - 2.5 mL, 500 IU - 2.5 mL, 1,000 IU - 2.5 mL, 2,000 IU - 5 mL, 3,000 IU - 5 mL	250 IU - 2.5mL, 500 IU - 2.5mL, 1000 IU - 2.5mL, 2000 IU - 5mL, 3000 IU - 5mL	4mL (250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU, 3000 IU vials) The diluent for reconstitution of Novoeight® is 0.9% sodium chloride solution and is supplied as a clear colorless solution in a pre-filled diluent syringe.	250, 500, 1000, 2000, 2500, 3000, 4000 IU; Pre-filled syringe with 2.5mL diluent (WFI)	5 mL	250 IU - 4 mL, 500 IU - 4 mL, 1,000 IU - 4 mL, 2,000 IU - 4 mL, 3,000 IU - 4 mL