HYPERTET- tetanus immune globulin (human) injection
GRIFOLS USA, LLC

Tetanus Immune Globulin (Human)

HyperTET®

250 Units

DESCRIPTION

Tetanus Immune Globulin (Human) — Hyper**TET**® is a clear or slightly opalescent, and colorless or pale yellow or light brown sterile solution of human tetanus immune globulin for intramuscular administration. Hyper**TET** contains no preservative. HyperTET is prepared from pools of human plasma collected from healthy donors by a combination of cold ethanol fractionation, caprylate precipitation and filtration, caprylate incubation, anion exchange chromatography, nanofiltration and low pH incubation. Hyper**TET** consists of a 15% to 18% protein solution at a pH of 4.1 to 4.8 in 0.16 M to 0.26 M glycine. The product is standardized against the U.S. Standard Antitoxin and the U.S. Control Tetanus Toxin and contains not less than 250 tetanus antitoxin units per 1 mL.

When medicinal biological products are administered, the risk of infectious diseases due to transmission of pathogens cannot be totally excluded. However, in the case of products prepared from human plasma, the risk of transmission of pathogens is reduced by epidemiological surveillance of the donor population and selection of individual donors by medical interview; testing of individual donations and plasma pools; and the presence in the manufacturing processes of steps with demonstrated capacity to inactivate/remove pathogen.

In the manufacturing process of Hyper**TET,** there are several steps with the capacity for viral inactivation or removal.(1) The main steps of the manufacturing process that contribute to the virus clearance capacity are as follows:

- Caprylate precipitation/depth filtration
- Caprylate incubation
- Depth filtration
- Column chromatography
- Nanofiltration
- Low pH final container incubation

To provide additional assurance of the pathogen safety of the final product, the capacity of the Hyper**TET** manufacturing process to remove and/or inactivate viruses has been demonstrated by laboratory spiking studies on a scaled down process model using a wide range of viruses with diverse physicochemical properties.

The caprylate/chromatography manufacturing process was also investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the variant Creutzfeldt-Jakob disease (vCJD), and Creutzfeldt-Jakob disease (CJD) agents.(1) These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if

present in the starting material, would be removed by the caprylate/chromatography manufacturing process.

CLINICAL PHARMACOLOGY

The occurrence of tetanus in the United States has decreased dramatically from 560 reported cases in 1947, when national reporting began, to a record low of 48 reported cases in 1987.(2) The decline has resulted from widespread use of tetanus toxoid and improved wound management, including use of tetanus prophylaxis in emergency rooms.(3)

Hyper**TET** supplies passive immunity to those individuals who have low or no immunity to the toxin produced by the tetanus organism, *Clostridium tetani*. The antibodies act to neutralize the free form of the powerful exotoxin produced by this bacterium. Historically, such passive protection was provided by antitoxin derived from equine or bovine serum; however, the foreign protein in these heterologous products often produced severe allergic manifestations, even in individuals who demonstrated negative skin and/or conjunctival tests prior to administration. Estimates of the frequency of these foreign protein reactions following antitoxin of equine origin varied from 5%–30%.(4-7) If passive immunization is needed, human tetanus immune globulin (TIG) is the product of choice. It provides protection longer than antitoxin of animal origin and causes few adverse reactions.(3)

Several studies suggest the value of human tetanus antitoxin in the treatment of active tetanus.(8,9) In 1961 and 1962, Nation et al,(8) using Hyper-Tet treated 20 patients with tetanus using single doses of 3,000 to 6,000 antitoxin units in combination with other accepted clinical and nursing procedures. Six patients, all over 45 years of age, died of causes other than tetanus. The authors felt that the mortality rate (30%) compared favorably with their previous experience using equine antitoxin in larger doses and that the results were much better than the 60% national death rate for tetanus reported from 1951 to 1954.(10) Blake et al,(11) however, found in a data analysis of 545 cases of tetanus reported to the Centers for Disease Control from 1965 to 1971 that survival was no better with 8,000 units of TIG than with 500 units; however, an optimal dose could not be determined.

Serologic tests indicate that naturally acquired immunity to tetanus toxin does not occur in the United States. Thus, universal primary vaccination, with subsequent maintenance of adequate antitoxin levels by means of appropriately timed boosters, is necessary to protect persons among all age groups. Tetanus toxoid is a highly effective antigen; a completed primary series generally induces protective levels of serum antitoxin that persist for ≥10 years.(3)

Passive immunization with Hyper**TET** may be undertaken concomitantly with active immunization using tetanus toxoid in those persons who must receive an immediate injection of tetanus antitoxin and in whom it is desirable to begin the process of active immunization. Based on the work of Rubbo,(12) McComb and Dwyer,(13) and Levine et al,(14) the physician may thus supply immediate passive protection against tetanus, and at the same time begin formation of active immunization in the injured individual which upon completion of a **full toxoid series** will preclude future need for antitoxin.

Peak blood levels of IgG are obtained approximately 2 days after intramuscular injection. The half-life of IgG in the circulation of individuals with normal IgG levels is approximately 23 days.(15)

In a clinical study in 12 healthy human adults receiving another hyperimmune immune globulin product, Rabies Immune Globulin (Human), Hyper**RAB**® , prepared by the same manufacturing process, detectable passive antibody titers were observed in the serum of all subjects by 24 hours post injection and persisted through the 21 day study period.

INDICATIONS AND USAGE

Hyper**TET** is indicated for prophylaxis against tetanus following injury in patients whose immunization is incomplete or uncertain (see below). It is also indicated, although evidence of effectiveness is limited, in the regimen of treatment of active cases of tetanus.(8,9,16)

A thorough attempt must be made to determine whether a patient has completed primary vaccination. Patients with unknown or uncertain previous vaccination histories should be considered to have had no previous tetanus toxoid doses. Persons who had military service since 1941 can be considered to have received at least one dose, and although most of them may have completed a primary series of tetanus toxoid, this cannot be assumed for each individual. Patients who have not completed a primary series may require tetanus toxoid and passive immunization at the time of wound cleaning and debridement.(3)

The following table is a summary guide to tetanus prophylaxis in wound management:

Guide to Tetanus Prophylaxis in Wound Management(3)

History of Tetanus Immunization (Doses)	Clean, Minor Wounds		All Other Wounds*	
	Td†	TIG‡	Td	TIG
Uncertain or less than 3	Yes	No	Yes	Yes
3 or more§	No¶	No	No#	No

* Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns and frostbite.

† Adult type tetanus and diphtheria toxoids. If the patient is less than 7 years old, DT or DTP is preferred to tetanus toxoid alone. For persons ≥7 years of age, Td is preferred to tetanus toxoid alone. (see Dosage and Administration)

‡ Tetanus Immune Globulin (Human).

§ If only three doses of fluid tetanus toxoid have been received, a fourth dose of toxoid, preferably an adsorbed toxoid, should be given.

¶ Yes if more than 10 years since the last dose.

Yes if more than 5 years since the last dose. (More frequent boosters are not needed and can accentuate side effects).

CONTRAINDICATIONS

None known.

WARNINGS

HyperTET is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, and, theoretically, the Creutzfeldt-Jakob Disease (CJD) agent that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Therapeutics LLC [1-800-520-2807].

The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient.

Hyper**TET** should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immunoglobulin preparations.

In patients who have severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections, Hyper**TET** should be given only if the expected benefits outweigh the risks.

PRECAUTIONS

General

HyperTET should not be given intravenously. Intravenous injection of immunoglobulin intended for intramuscular use can, on occasion, cause a precipitous fall in blood pressure, and a picture not unlike anaphylaxis. Injections should only be made **intramuscularly** and care should be taken to draw back on the plunger of the syringe before injection in order to be certain that the needle is not in a blood vessel. Intramuscular injections are preferably administered in the deltoid muscle of the upper arm or lateral thigh muscle. The gluteal region should not be used as an injection site because of the risk of injury to the sciatic nerve.(17)

Chemoprophylaxis against tetanus is neither practical nor useful in managing wounds. Wound cleaning, debridement when indicated, and proper immunization are important. The need for tetanus toxoid (active immunization), with or without TIG (passive immunization), depends on both the condition of the wound and the patient's vaccination history. Rarely has tetanus occurred among persons with documentation of having received a primary series of toxoid injections.(3) See table under See table under INDICATIONS AND USAGE.

Skin tests should not be done. The intradermal injection of concentrated IgG solutions often causes a localized area of inflammation which can be misinterpreted as a positive allergic reaction. In actuality, this does not represent an allergy; rather, it is localized tissue irritation. Misinterpretation of the results of such tests can lead the physician to withhold needed human antitoxin from a patient who is not actually allergic to this material. True allergic responses to human IgG given in the prescribed intramuscular manner are rare.

Although systemic reactions to human immunoglobulin preparations are rare, epinephrine should be available for treatment of acute anaphylactic reactions.

Drug Interactions

Antibodies in immunoglobulin preparations may interfere with the response to live viral vaccines such as measles, mumps, polio, and rubella. Therefore, use of such vaccines should be deferred until approximately 3 months after Tetanus Immune Globulin (Human) — Hyper**TET**® administration.

No interactions with other products are known.

Pregnancy

Animal reproduction studies have not been conducted with Hyper**TET**. It is also not known whether Hyper**TET** can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Hyper**TET** should be given to a pregnant woman only if clearly needed.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

ADVERSE REACTIONS

Slight soreness at the site of injection and slight temperature elevation may be noted at times. Sensitization to repeated injections of human immunoglobulin is extremely rare.

In the course of routine injections of large numbers of persons with immunoglobulin there have been a few isolated occurrences of angioneurotic edema, nephrotic syndrome, and anaphylactic shock after injection.

OVERDOSAGE

Although no data are available, clinical experience with other immunoglobulin preparations suggests that the only manifestations would be pain and tenderness at the injection site.

DOSAGE AND ADMINISTRATION

Routine prophylactic dosage schedule:

- *Adults and children 7 years and older:* Hyper**TET**, 250 units should be given by deep intramuscular injection (see PRECAUTIONS). At the same time, but in a different extremity and with a separate syringe, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use) (Td) should be administered according to the manufacturer's package insert. Adults with uncertain histories of a complete primary vaccination series should receive a primary series using the combined Td toxoid. To ensure continued protection, booster doses of Td should be given every 10 years. (3)

- *Children less than 7 years old:* In small children the routine prophylactic dose of Hyper**TET** may be calculated by the body weight (4.0 units/kg). However, it may be advisable to administer the entire contents of the syringe of Hyper**TET** (250 units) regardless of the child's size, since theoretically the same amount of toxin will be produced in the child's body by the infecting tetanus organism as it will in an adult's body. At the same time but in a different extremity and with a different syringe, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP) or Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) (DT), if pertussis vaccine is contraindicated, should be administered per the manufacturer's package insert.

- Note: The single injection of tetanus toxoid only initiates the series for producing active immunity in the recipient. The physician must impress upon the patient the need for further toxoid injections in 1 month and 1 year. Without such, the active immunization series is incomplete. If a contraindication to using tetanus toxoid-containing preparations exists for a person who has not completed a primary series of tetanus toxoid immunization and that person has a wound that is neither clean nor minor, *only* passive immunization should be given using tetanus immune globulin.(3) See table under INDICATIONS AND USAGE.

- Available evidence indicates that complete primary vaccination with tetanus toxoid provides long lasting protection ≥10 years for most recipients. Consequently, after complete primary tetanus vaccination, boosters-even for wound management-need be given only every 10 years when wounds are minor and uncontaminated. For other wounds, a booster is appropriate if the patient has not received tetanus toxoid within the preceding 5 years. Persons who have received at least two doses of tetanus toxoid rapidly develop antibodies. (3) The prophylactic dosage schedule for these patients and for those with incomplete or uncertain immunity is shown on the table in INDICATIONS AND USAGE.

- Since tetanus is actually a local infection, proper initial wound care is of paramount importance. The use of antitoxin is adjunctive to this procedure. However, in approximately 10% of recent tetanus cases, no wound or other breach in skin or mucous membrane could be implicated. (18)

Treatment of active cases of tetanus:

- Standard therapy for the treatment of active tetanus including the use of Hyper**TET** must be implemented immediately. The dosage should be adjusted according to the severity of the infection. (8,9)

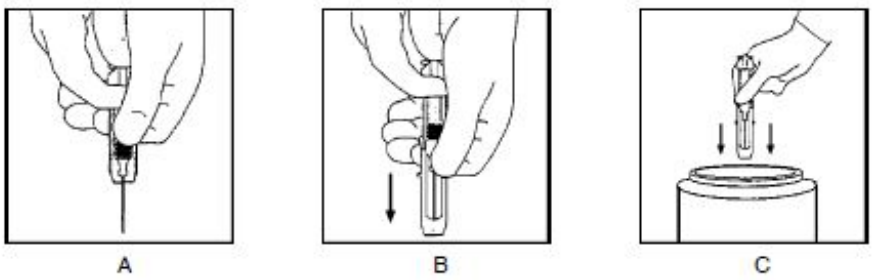
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to

administration, whenever solution and container permit. They should not be used if particulate matter and/or discoloration are present.

Hyper**TET** is supplied with a syringe and an attached UltraSafe® Needle Guard for your protection and convenience. Please follow instructions below for proper use of syringe and UltraSafe® Needle Guard.

Directions for Syringe Usage

1. Remove the prefilled syringe from the package. Lift syringe by barrel, **not** by plunger.
2. Twist the plunger rod clockwise until the threads are seated.
3. With the needle shield secured on the syringe tip, push the plunger rod forward a few millimeters to break any friction seal between the stopper and the glass syringe barrel.
4. Remove the needle shield and expel air bubbles. [Do not remove the needle shield to prepare the product for administration until immediately prior to the anticipated injection time.]
5. Proceed with hypodermic needle puncture.
6. Aspirate prior to injection to confirm that the needle is not in a vein or artery.
7. Inject the medication.
8. Keeping your hands behind the needle, grasp the guard with free hand and slide forward toward needle until it is completely covered and guard clicks into place. If audible click is not heard, guard may not be completely activated. (See Diagrams A and B)
9. Place entire prefilled glass syringe with guard activated into an approved sharps container for proper disposal. (See Diagram C)



A number of factors could reduce the efficacy of this product or even result in an ill effect following its use. These include improper storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration, and biological differences in individual patients. Because of these factors it is important that this product be stored properly and that the directions be followed carefully during use.

HOW SUPPLIED

Hyper**TET** is supplied in 250 unit prefilled disposable syringes with attached needles.
Hyper**TET** contains no preservative and is not made with natural rubber latex.

NDC Number	Size
13533-634-02	250 unit syringe

STORAGE

Store at 2–8°C (36–46°F). Solution that has been frozen should not be used. Discard unused portion.

CAUTION

Rx only

U.S. federal law prohibits dispensing without prescription.

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4. Moynihan NH: Tetanus prophylaxis and serum sensitivity tests. *Br Med J* 1:260-4, 1956.
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Rev. 12/2020

GRIFOLS

Grifols Therapeutics LLC
Research Triangle Park, NC 27709 USA
U.S. License No. 1871

3059641

PACKAGE LABEL

Tetanus Immune Globulin (Human)

Hyper**TET**®
250 Units/ 1 mL

Solution for Intramuscular Injection

Contents: One single-dose disposable syringe with attached needle.

Tetanus Immune Globulin (Human) is a sterile solution of immunoglobulin containing 15%–18% protein stabilized with 0.16 M to 0.26 M glycine. The pH is adjusted with sodium carbonate.

The potency of each syringe is not less than 250 antitoxin units based on the U.S. Standard Antitoxin and the U.S. Control Tetanus Toxin.

FOR INTRAMUSCULAR INJECTION ONLY. DO NOT GIVE INTRAVENOUSLY.

Store at 2 to 8°C (36 to 46°F).
Do not freeze.

1 mL 1 mL

NDC 13533-634-02

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The patient and physician should discuss the risks and benefits of this product.

For complete dosage and administration information, read enclosed package insert.

For directions for syringe usage, see enclosed package insert.

Do not use if the syringe is prematurely engaged.

Not returnable for credit or exchange.

Rx only

Not made with natural rubber latex.

No preservative

The potency of each syringe is not less than 250 antitoxin units based on the U.S. Standard Antitoxin and the U.S. Control Tetanus Toxin.

Discard unused portion.

1 mL 1 mL

Grifols Therapeutics LLC
Research Triangle Park,
NC 27709 USA
U.S. License No. 1871

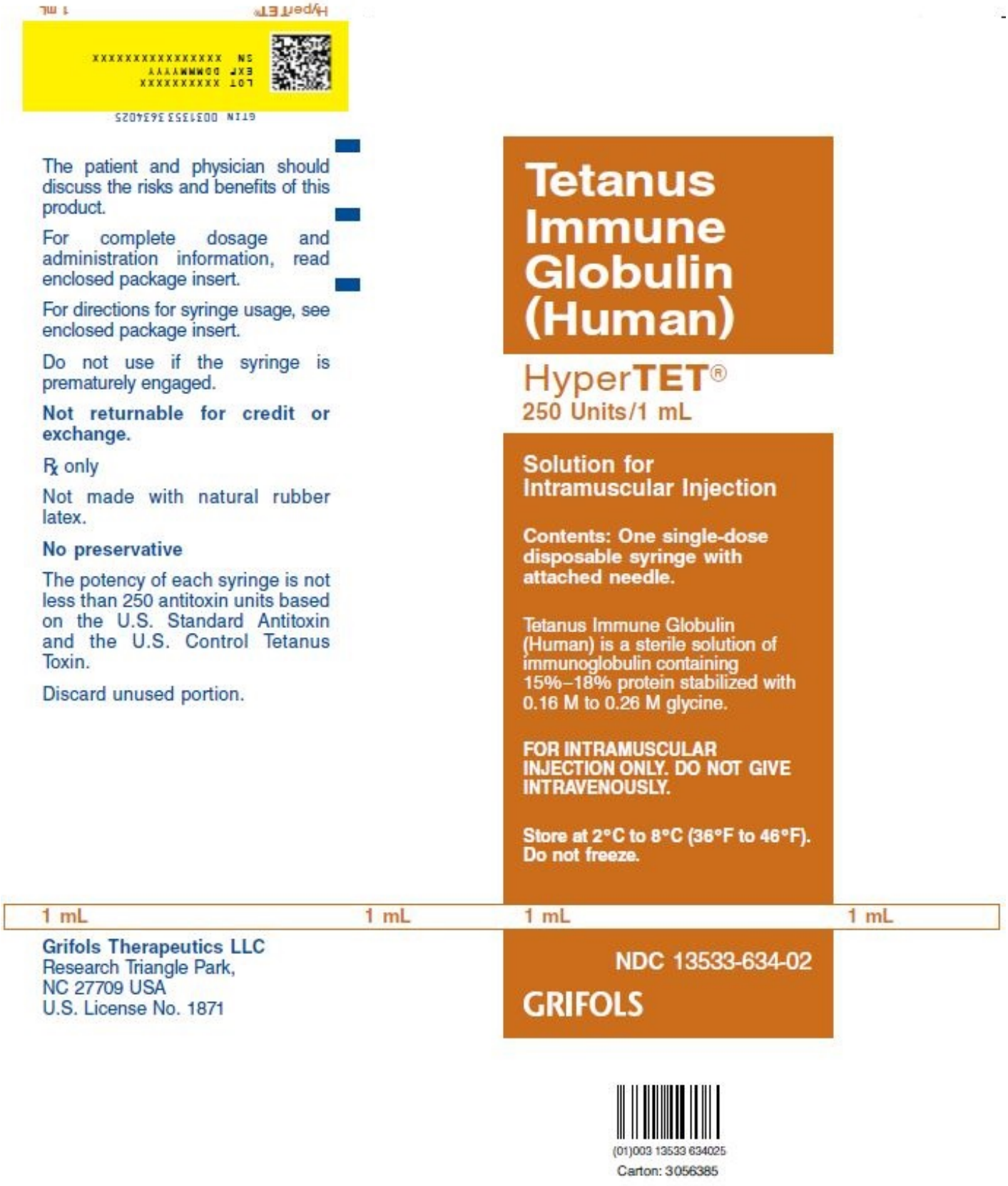
Carton: 3056385

GTIN 00313533634025

LOT XXXXXXXXXX

EXP DDMMMYYYY

SN XXXXXXXXXXXXXXX



Tetanus Immune Globulin (Human).

Hyper**TET**® **250 Units/1 mL**

- **One 1 mL Single Dose**

Grifols Therapeutics LLC
Research Triangle Park,
NC 27709 USA
U.S. License No. 1871

The patient and physician should discuss the risks and benefits of this product.

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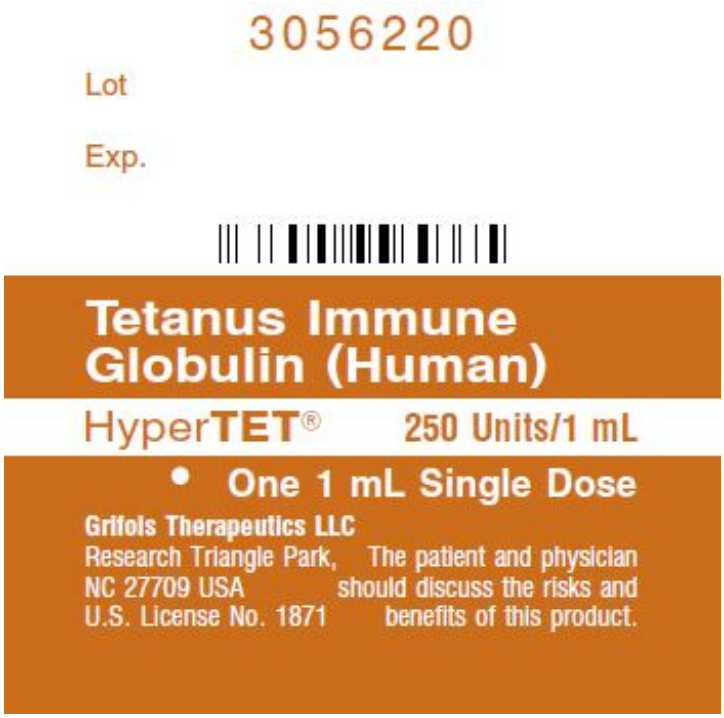
Lot

Exp.



HYPERTET

tetanus immune globulin (human) injection

Product Information			
Product Type	PLASMA DERIVATIVE	**Item Code (Source)**	NDC:13533-634
Route of Administration	INTRAMUSCULAR		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
Human Clostridium Tetani Toxoid Immune Globulin (UNII: V4SWI4RF4J) (Human Clostridium Tetani Toxoid Immune Globulin - UNII:V4SWI4RF4J)	Human Clostridium Tetani Toxoid Immune Globulin	250 [iU] in 1 mL

Inactive Ingredients

Ingredient Name	Strength
Glycine (UNII: TE7660XO1C)	
Water (UNII: 059QF0KO0R)	

Product Characteristics			
Color	YELLOW (colorless or pale yellow or light brown)	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13533-634-02	1 in 1 BOX		
1	NDC:13533-634-20	1 mL in 1 SYRINGE, GLASS; Type 3: Prefilled Biologic Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA101142	08/14/1996	

Labeler - GRIFOLS USA, LLC (048987452)

Establishment

Name	Address	ID/FEI	Business Operations
Grifols Therapeutics LLC		611019113	manufacture(13533-634)

Revised: 12/2020 GRIFOLS USA, LLC