



drotrecogin alfa (activated)

DOSING GUIDELINES— 100-mcg/mL and 200-mcg/mL Fixed Concentrations

XIGRIS DOSING CALCULATION

Xigris is indicated for the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death (e.g., as determined by APACHE II*).

Xigris is not indicated in adult patients with severe sepsis and lower risk of death. Xigris is not indicated in pediatric patients with severe sepsis.

MANUAL DOSING CALCULATION

Step 1. Calculate the amount of Xigris needed for the infusion period

- Actual Patient Weight (kg) x Dose (24 mcg/kg/hr) = Amount of Xigris needed/hr (mcg/hr)
- Amount of Xigris needed/hr (mcg/hr) x Time (# of hours) ÷ 1000 = Amount of Xigris needed for infusion period (mg)
- The amount of Xigris should be rounded up or down to the nearest 5-mg increment

Step 2. Check the concentration in the bag

- Amount of Xigris needed (mg) for infusion period (FROM STEP 1) x 1000 ÷ Total volume of bag (eg, 100 or 250 mL) = Final bag concentration (mcg/mL)
- The solution of reconstituted Xigris is typically diluted into an infusion bag to a final concentration of between 100 mcg/mL and 200 mcg/mL.

Step 3. Calculate the final rate

- Amount of Xigris/hr (mcg/hr; FROM STEP 1) ÷ Final concentration (mcg/mL; FROM STEP 2) = Rate (mL/hr)

Xigris should be administered intravenously at a continuous infusion rate of 24 mcg/kg/hr (based on actual body weight at start of infusion), for a total duration of infusion of 96 hours

- The dose should not be adjusted during the infusion for changes in actual body weight.
- Complete each IV administration within 12 hours after solution is prepared.
- If the infusion is interrupted, Xigris should be restarted at the initial infusion rate and continued to complete the recommended duration of infusion.
- Should clinically important bleeding occur, immediately stop the infusion of Xigris.
- No titration is necessary. Bolus dosing or dose escalation is not recommended.
- No dosage adjustment is required regardless of age, hepatic impairment, or renal impairment.

Bleeding is the most common adverse reaction associated with Xigris therapy. Please see Important Safety Information for Xigris on page 4.



XIGRIS INTRAVENOUS DOSING – 100-mcg/mL AND 200-mcg/mL FIXED CONCENTRATIONS

All doses require a 100-mL intravenous infusion bag*

Actual Patient Weight	Amount of Xigris	Concentration	Rate	Approximate Time to Infuse	Actual Patient Weight	Amount of Xigris	Concentration	Rate	Time to Infuse
kg	mg	mcg/mL	mL/hr	hours	kg	mg	mcg/mL	mL/hr	hours
40	10	100	9.6	10					
41	10	100	9.8	10	88	20	200	10.6	9
42	10	100	10.1	10	89	20	200	10.7	9
43	10	100	10.3	10	90	20	200	10.8	9
44	10	100	10.6	9	91	20	200	10.9	9
45	10	100	10.8	9	92	20	200	11.0	9
46	10	100	11.0	9	93	20	200	11.2	9
47	10	100	11.3	9	94	20	200	11.3	9
48	10	100	11.5	9	95	20	200	11.4	9
49	10	100	11.8	9	96	20	200	11.5	9
50	10	100	12.0	8	97	20	200	11.6	9
51	10	100	12.2	8	98	20	200	11.8	9
52	10	100	12.5	8	99	20	200	11.9	8
53	10	100	12.7	8	100	20	200	12.0	8
54	10	100	13.0	8	101	20	200	12.1	8
55	10	100	13.2	8	102	20	200	12.2	8
56	10	100	13.4	7	103	20	200	12.4	8
57	10	100	13.7	7	104	20	200	12.5	8
58	10	100	13.9	7	105	20	200	12.6	8
59	10	100	14.2	7	106	20	200	12.7	8
60	10	100	14.4	7	107	20	200	12.8	8
61	10	100	14.6	7	108	20	200	13.0	8
62	10	100	14.9	7	109	20	200	13.1	8
63	10	100	15.1	7	110	20	200	13.2	8
64	10	100	15.4	7	111	20	200	13.3	8
65	10	100	15.6	6	112	20	200	13.4	7
66	10	100	15.8	6	113	20	200	13.6	7
67	20	200	8.0	12	114	20	200	13.7	7
68	20	200	8.2	12	115	20	200	13.8	7
69	20	200	8.3	12	116	20	200	13.9	7
70	20	200	8.4	12	117	20	200	14.0	7
71	20	200	8.5	12	118	20	200	14.2	7
72	20	200	8.6	12	119	20	200	14.3	7
73	20	200	8.8	11	120	20	200	14.4	7
74	20	200	8.9	11	121	20	200	14.5	7
75	20	200	9.0	11	122	20	200	14.6	7
76	20	200	9.1	11	123	20	200	14.8	7
77	20	200	9.2	11	124	20	200	14.9	7
78	20	200	9.4	11	125	20	200	15.0	7
79	20	200	9.5	11	126	20	200	15.1	7
80	20	200	9.6	10	127	20	200	15.2	7
81	20	200	9.7	10	128	20	200	15.4	7
82	20	200	9.8	10	129	20	200	15.5	6
83	20	200	10.0	10	130	20	200	15.6	6
84	20	200	10.1	10	131	20	200	15.7	6
85	20	200	10.2	10	132	20	200	15.8	6
86	20	200	10.3	10	133	20	200	16.0	6
87	20	200	10.4	10	134	20	200	16.1	6
					135	20	200	16.2	6

*To ensure the correct dose is administered, the volume of diluent in the vials needs to be accounted for.

Bleeding is the most common adverse reaction associated with Xigris therapy. Please see Important Safety Information for Xigris on page 4.



XIGRIS PREPARATION AND ADMINISTRATION INSTRUCTIONS

1. Use appropriate aseptic technique during the preparation of Xigris for intravenous administration.
2. Calculate the approximate amount of Xigris needed based upon the patient's actual body weight and duration of this infusion period. The maximum duration of infusion from one preparation step is 12 hours. Multiple infusion periods will be needed to cover the entire 96-hour duration of administration.

$$\text{mg of Xigris} = (\text{patient weight, kg}) \times 24 \text{ mcg/kg/hr} \times (\text{hours of infusion}) \div 1000$$

Round the actual amount of Xigris to be prepared to the nearest 5 mg increment to avoid discarding reconstituted Xigris.
3. Determine the number of vials of Xigris needed to make up this amount.
4. Reconstitute each vial of Xigris with Sterile Water for Injection, USP. The 5 mg vials must be reconstituted with 2.5 mL; the 20 mg vials with 10 mL. Slowly add the Sterile Water for Injection, USP to the vial and avoid inverting or shaking the vial. Gently swirl each vial until the powder is completely dissolved. The resulting Xigris concentration of the solution is 2 mg/mL.
5. Xigris contains no antibacterial preservatives; the intravenous solution should be prepared immediately after reconstitution of the Xigris in the vial(s). If the vial of reconstituted Xigris is not used immediately, it may be held at controlled room temperature 20° to 25°C (68° to 77°F), but must be used within 3 hours.
6. Inspect the reconstituted Xigris in the vials for particulate matter and discoloration before further dilution. Do not use vials if particulate matter is visible or the solution is discolored.
7. Xigris should be administered via a dedicated intravenous line or a dedicated lumen of a multilumen venous catheter. The ONLY other solutions that can be administered through the same line are 0.9% Sodium Chloride Injection, USP; Lactated Ringer's Injection, USP; Dextrose Injection, USP; and Dextrose and Sodium Chloride Injection, USP.
8. Avoid exposing Xigris solutions to heat and/or direct sunlight. Studies conducted at the recommended concentrations indicate the Xigris intravenous solution to be compatible with glass infusion bottles, and infusion bags and syringes made of polyvinylchloride, polyethylene, polypropylene, or polyolefin.

Xigris is available in 5-mg and 20-mg single-use vials containing sterile, preservative-free, lyophilized drotrecogin alfa (activated).

Xigris should be stored in a refrigerator at 2° to 8°C (36° to 46°F). Do not freeze. Protect unreconstituted vials of Xigris from light. Retain in carton until time of use. Do not use beyond the expiration date stamped on the vial.

Bleeding is the most common adverse reaction associated with Xigris therapy. Please see Important Safety Information for Xigris on page 4.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Xigris increases the risk of bleeding. Xigris is contraindicated in patients with the following clinical situations in which bleeding could be associated with a high risk of death or significant morbidity:

- Active internal bleeding
- Recent (within 3 months) hemorrhagic stroke
- Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma
- Trauma with an increased risk of life-threatening bleeding
- Presence of an epidural catheter
- Intracranial neoplasm or mass lesion or evidence of cerebral herniation

Xigris is contraindicated in patients with known hypersensitivity to drotrecogin alfa (activated) or any component of this product.

WARNINGS

Bleeding

Bleeding is the most common serious adverse effect associated with Xigris therapy. Each patient being considered for therapy with Xigris should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

Certain conditions, many of which led to exclusion from the Phase 3 trial, are likely to increase the risk of bleeding with Xigris therapy. Therefore, for patients with severe sepsis who have one or more of the following conditions, the increased risk of bleeding should be carefully considered when deciding whether to use Xigris therapy:

- Concurrent therapeutic heparin to treat an active thrombotic or embolic event
- Platelet count < 30,000 x 10⁶/L, even if the platelet count is increased after transfusions
- Prothrombin time-INR > 3.0
- Recent (within 6 weeks) gastrointestinal bleeding
- Recent administration (within 3 days) of thrombolytic therapy
- Recent administration (within 7 days) of oral anticoagulants or glycoprotein IIb/IIIa inhibitors
- Recent administration (within 7 days) of aspirin > 650 mg per day or other platelet inhibitors
- Recent (within 3 months) ischemic stroke
- Intracranial arteriovenous malformation or aneurysm
- Known bleeding diathesis
- Chronic severe hepatic disease
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

Invasive procedures increase the risk of bleeding among patients receiving Xigris. Xigris should be discontinued prior to the performance of invasive surgical procedures or other procedures associated with special risks for bleeding.

Mortality in Patients with Single Organ Dysfunction and Recent Surgery

Among the small number of patients enrolled in PROWESS with single organ dysfunction and recent surgery (surgery within 30 days prior to study treatment) all-cause mortality was numerically higher in the Xigris group (28-day: 10/49; in-hospital: 14/48) compared to the placebo group (28-day: 8/49; in-hospital: 8/47).

In an analysis of the subset of patients with single organ dysfunction and recent surgery from a separate, randomized, placebo-controlled study (ADDRESS) of septic patients not at high risk of death all-cause mortality was also higher in the Xigris group (28-day: 67/323; in-hospital: 76/325) compared to the placebo group (28-day: 44/313; in-hospital: 62/314). Patients with single organ dysfunction and recent surgery may not be at high risk of death irrespective of APACHE II score and therefore not among the indicated population.

Clinicians should consider continuing prophylactic heparin when initiating Xigris therapy, unless discontinuation is considered medically necessary

In a randomized study of prophylactic heparin versus placebo in 1935 adult severe sepsis patients treated with Xigris, mortality and the rate of serious adverse events were increased in the subgroup of 434 patients whose low-dose heparin was stopped on study entry by randomization to placebo. This finding was based on prospectively defined exploratory subgroup analyses; however, the explanation for the finding is unclear.

Adverse Reactions

Bleeding is the most common adverse reaction associated with Xigris therapy. In the Phase 3 study, serious bleeding events were observed during the 28-day study period in 3.5% of Xigris-treated and 2.0% of placebo-treated patients. The difference in serious bleeding occurred primarily during infusion. The incidence of intracranial hemorrhage (ICH) was 0.2% for Xigris-treated and 0.1% for placebo-treated patients. ICH has been reported in Xigris-treated patients in non-placebo controlled trials with an incidence of approximately 1% during infusion. The risk of ICH may be increased in patients with risk factors for bleeding such as severe coagulopathy and severe thrombocytopenia. Should clinically important bleeding occur, immediately stop the Xigris infusion.

*APACHE (Acute Physiology And Chronic Health Evaluation).

Please refer to the full Prescribing Information for Xigris.

FOR MORE INFORMATION, PLEASE VISIT www.Xigris.com

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Lilly