## Linezolid-Resistant MRSA Reported in Spain

## BY KERRI WACHTER Senior Writer

WASHINGTON — An outbreak of methicillin-resistant Staphylococcus aureus in a Spanish hospital may be the first reported appearance of a linezolid-resistant strain of the organism, according to data reported Oct. 27.

Between April and June of this year, 12 patients in an intensive care unit at the Hospital Clinico San Carlos in Madrid

rt For Full Prescribing Information

sonce. mentivity **Exections:** Serious hypersensitivity reactions have been reported in patients receiving Ve d in the clinical studies. Several cases of mild or moderate hypersensitivity reactions were observed

The use of Vender<sup>®</sup> is contraindicated in patients with evidence of iron overload, in patients with known hypersensitivity to Vender<sup>®</sup> or any of its inactive co and in patients with anemia not caused by iron deficiency. WARNINGS

ECUTIONS mark Because body iron excretion is limited and excess tissue iron can be hazardous, caution should be exercised to withhold iron administration in the presence vidence of tissue iron overload. Patients receiving Vender<sup>®</sup> require periodic monitoring of hemotiopic and hemotinc parameters (hemotion). Interatorit, semu itin and transferrin calcuration), iron therapy should be withheld in patients with exidence of iron overload. Clarasterin saturation values increase regivity atter V ministration of iron success; thus, serum iron values may be reliably obtained 48 hours after 17 dosing. See **DOSAGE AND ADMINISTRATION** and

coserved in the clinical studies. Several classes of mild or moderate hypersensibility reactors were observed in three studies. There are post-markeling sportaneous reports of the threatening hypersensibility reactors in patients receiving lenders. See **ADVERSE REACTIONS**. **Mypotension:** Hypotension has been reported frequently in hereal disks dependent chronic kidney dessee patients receiving intravenous iron. Hypotension in Hypotension has been reported in non-disks dependent chronic kidney dessee patients receiving intravenous iron. Hypotension flowing administration of Version may be an equipment and patients and advise dependent chronic kidney dessee patients receiving intravenous iron. Hypotension flowing administration of Version may be related to rate of administration and total does administered. Caution should be taken to administer Verolet<sup>®</sup> according to **Detromogeneois Matements and Herstream ADVERSE FLOWED ADVERSE FLOWED**.

duit instance of dickines. See DOSAGE AND Automost instance. Carcinogenesis, Mutagenesis, and Impairment of Farility: No long-term studies in instance have been performed to exaltive the carcinogenic potential of Verofer®. No long-term studies in the Ames test, the mouse lymphona cell (.5178//TK+/-) forward mutation test, the human lymphocyle chromosome aberration test, in the Ames test, the mouse lymphona cell (.5178//TK+/-) forward mutation test, the human lymphocyle chromosome aberration test,

cented. Warsing Mothers: Veroler"'s excreted in mik of rats, it is not known whether this drug is excreted in human mik, zaution should be exercised when Veroler" is administered to a nursing woman.

cation Should be excised when Veroff<sup>4</sup> is administred to a runsing wormen. **Pediatric Uses**: Stay and effectiveses: Voncel<sup>41</sup> is pediately featers have not been established. In a country where Veroff<sup>41</sup> is available for use in children, at a single site, the premature infants (weight less than 1.250 g) developed neorotizing entercoolitis and two of the file expired during or finding a period when they received Veroff<sup>41</sup>, several other medicators and erythropoietin. Vecontizing entercoolitis may be a complication of prematurity in very two him weight infants. No casal relationship to Veroff<sup>42</sup> or any other drugs could be satisfied. **Gerdaritic Uses**: The line privated initial triats drive includes sufficient numbers of subjects and young a subject, and other period driving entercool taken rule in the line of differently from charding differences in responses between the eddenty and younger palents, but greater sensibility of some obler individuals cannot be ruled out. **AUMENESS: REACTIONIS** 

REACTIONS ments observed in all treated populations ny of adverse events associated with the use of Venofe<sup>re</sup> has been documented in six randomized clinical triats involving 231 hemotialysis dependent alysis dependent and 75 pertineral clashis dependent-OVD patients; and in two post-marketing safety studies involving 1,051 hemotialysis dependent is na tablia of 1,446 patients. In addition, one 2,000 patients treated with Venole<sup>re</sup> have been reported in the medical literature.

reactions have been reported with injectable iron products. See PRECAUTIONS and ADVERSE REACTIONS.

Venofer

iron sucrose injection, USP

PRECAUTIONS

of evidence un ferritin and tr

Hyperse

ADVERSE REACTIONS

Brief Summary (See Package Inse

were identified as having methicillinresistant Staphylococcus aureus (MRSA) that was also resistant to linezolid (Zyvox). Dr. Miguel Sanchez, an internist at the hospital, reported the outbreak during a press briefing at the jointly held annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the annual meeting of the Infectious Diseases Society of America (IDSA).

Linezolid-resistant MRSA was identi-

culture from eight men and four women in the ICU-eight patients were critically ill, three were surgical cases, and one was a trauma patient.

LR-MRSA caused infection in 11 patients—5 with ventilator-associated pneumonia, 5 with primary bacteremia, and 1 with catheter-related sepsis.

Five patients died, but they had cleared the infection at the time of death. No deaths were attributed to LR-MRSA.

Patients had a mean ICU stay of about

a month (34 days) before the index culture. At the index culture, all patients were intubated, had been on prolonged broadspectrum antibiotic therapy, and had concomitant linezolid-susceptible MRSA. Eleven of the patients had received intravenous linezolid, one of the oxazolidinone class of antibiotics.

Hospital staff members were able to quickly control the outbreak by stepping up routine surveillance and isolating these patients. Patients identified with LR-MRSA were sampled once a week at three different sites.

Surveillance of the environment and staff also was performed. Only 1 of 91 environmental surface samples tested positive for LR-MRSA. This sample was taken

## **LR-MRSA** caused infection in 11 patients— 5 with ventilatorassociated pneumonia, 5 with primary bacteremia, and 1 with catheterrelated sepsis.

from an intravenous catheter connection.

The hands of health care personnel also were sampled, and none was positive for LR-MRSA. Genotyping revealed that a single clone was responsible for 10 infections.

As a result of the outbreak, hospital personnel reviewed their antibiotic use. Subsequent use of linezolid was limited to either documented or suspected cases of respiratory tract MRSA infections.

As a result, use of linezolid at the hospital dropped from 202 defined daily doses in April to 25 in July.

The LR-MRSA was susceptible to vancomycin, daptomycin (Cubicin), and tigecycline (Tygacil), which were used to treat these patients. For comparison, the minimum inhibitory concentration was greater than 8 mg/L for linezolid but less than 0.32 mg/L for tigecycline and daptomycin.

"Linezolid is a relatively new drug," noted Dr. Robert S. Daum, a pediatric infectious diseases specialist at the University of Chicago who spoke at the press conference but was not involved with the Spanish outbreak.

"In general, resistance has been very infrequent. We've seen some in Chicago ... but it's actually quite rare in this country.

He attributed this to antibiotic stewardship programs at many U.S. hospitals. "In our hospital, we have a very tight grip on linezolid use." The drug can be prescribed only with the approval of an infectious disease specialist. Limiting use of the drug limits the chances for an organism to develop resistance to it.

Dr. Sanchez agreed, noting that "the take-home message for us is that we have to find ways to administer antibiotics prudently. ... We also have to find ways to shorten antibiotic courses."

Dr. Sanchez and his colleagues are planning a case-control study to investigate the means of LR-MRSA transmission.

Dr. Sanchez did not report whether he had any conflicts of interest. 

fied during surveillance and/or diagnostic eference: 1. Van Wyck DB, Roppolo M, Martinez CO, Mazey RM, McMurray S, for the United States Iron Sucrose (Venofer®) Clinical Trials Group. A randor (Table 2 continued) Adverse Events (Preferred Term) Brief Summary (see reasonance) Therapequic Cases: Hematinic CUNICAL INDICATIONS AND USAGE Vender" (from succes hjection, USP) is indicated in the treatment of iron deficiency anemia in the following pat vender" (from succes hjection), USP) is indicated in the treatment of iron deficiency anemia in the following pat vender" (from succes hjection), USP) is indicated in the treatment of iron deficiency anemia in the following pat • non-dialysis dependent-chronic kidney disease (NDD-CKD) patients not receiving an erythropoietin • non-dialysis dependent-chronic kidney disease (NDD-CKD) patients not receiving an erythropoietin

ent CKD. Kidney Int. 2005;68:2846-2856. 2. Data on file. American Regent, Inc., Shirley, NY (Table 3 continued) NDD-CKD mg 500 mg NDD-CKD Venofer® Oral Iron 200 mg 500 mg (N=109) (N=30) Adverse Events (N=139) (N=139) (Preferred Term) % % % `% Musculoskeletal and Connective Musculoskeletal and Connective **Tissue Disorders** 46 3.3 Back pain Muscle cramp 2.2 0.7 3.6 4.3 Nervous System Disorders 5.5 3.7 10.0 0 Respiratory, Thoracic and Mediastinal Disorders Nervous Syst em Disorders 6.5 2.9 0.7 1.4 0.7 0.7 Cough 0.9 1.8 6.7 10.0 Respiratory, Thoracic and Mediastinal Disorders Pharyngitis Skin and Subcutaneous Tissue Disord 0.9 6.7 0.7 0.7 0.7 2.2 0 2.2 2.2 3.6 2.2 1.4 Vascular Disorders 6.4 0.9 lypertension NOS lypotension NOS 6.7 6.7 yspnea exacerbated Nasal congestion Pharyngitis Rhinitis allergic NOS 0 0.7 Skin and Subcut 2.2 1.4 4.3 2.2 Vascular Disorders Hypertension NOS Hypotension NOS 6.5 2.2 4.3 0.7

No tong-term studies in animals have been performed to exaluate the carcinopanic potential of Veroder<sup>e</sup>. Vector<sup>2</sup> was not queototic in the Annes test, the mouse kymphoma cell (.5178VTK+/) forward mutation test, the human lymphocyte chromosome aberration test, or the mouse micronucleus test. Vectore<sup>2</sup> at N doess up to 15 mg inn/kg/dkg/ (about 1.2 times the recommended maximum human dose on a body surface area basis) was found to have no effect on teltity and regootable performance of male and female etas. on herling and reproductive performance of male and terate rats. Pergnamo, Categoorg, BB: Tetatolog solations have been performed in rats at IV doese up to 13 mg ironkg/day (about 0.5 times the recommended maximum human does on a hody surface area tasks) and rabitis at IV doese up to 13 mg ironkg/day (about 1 times the recommended maximum human does on aboy surface area does) and have newated no exidence of impraind fertility on time to the tasks due to Hordrer<sup>1</sup>. These area, however, no adaquet and evel controlled studies in pregnart women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if dearly worked. \*NOS=Not otherwise specified \*NOS=Not otherwise specified Drug related adverse events reported by  $\geq$  2% of Venofer<sup>®</sup> (iron sucrose injection, USP) treated patients are shown by dose group in Table 4.

Table 4. Most Common Adverse Events Related to Study Drug Reported in ≥ 2% of Patients with NDD-CKD by Dose Group (Multidose Safety Population)

	NDD-CKD		
Adverse Events	200 mg	500 mg	
(Preferred Term)	(N=109)	(N=30)	
	%	%	
Subjects with any adverse event	23.9	20.0	
Gastrointestinal Disorders			
Diarrhea NOS*	0	0	
Dysgeusia	7.3	3.3	
Nausea	2.8	0	
General Disorders and			
Administration Site Conditions			
Infusion site burning	3.7	0	
Injection site pain	2.8	0	
Péripheral edema	1.8	6.7	
Nervous System Disorders			
Dizziness	2.8	6.7	
Headache	2.8	0	
Vascular Disorders			
Hypotension NOS	0	6.7	
~			

\*NOS=Not otherwise specified

Adverse Events Observed in Non-Dialvsis Dependent Chronic Kidnev Disease (NDD-CKD) Patients Notice to this operation information output operations where we have a set of the probability of the PDC-RD pieters of th

Inpublic son, dispine and masseal, Hypersensitivity Reactions: See WARNINGS and PRECAUTIONS. In finical studies seen labelies operated hypersensitivity reactions presenting with wheezing, dispinea, hypotension, rashes, or puritus. Serious episodes of hypotension occurred in 2 patients treated with Veroler<sup>4</sup> at a close of 500 mg. The post-marketing spontaneous reporting system includes reports of patients who experienced serious or life-threatening reactions (anaphylactic shock, loss of conscisuous ses or collepse, bronchospasm with dysprea, or convulsion) associated with Venote<sup>an</sup> administration. OVERDOSAGE

OVERDOSAGE Doagas of Vandle<sup>4</sup> (ron sucree injection, USP) in eccess of iron needs may lead to accumulation of iron in storage sites leading to hemosidensis. Periodic monitoring of iron parameters such as surum ferritm and transferm situration may assist in recognizing iron accumulation. Venole<sup>44</sup> should not be administered to patients with iron overload and should be discriptioned when serum ferrith levels equal or exceed established guidelines (1). Particular cation should be excreded to avoid iron overlaad where a normal unreprove to treatment this been increded (begingered as iron deficiency arientia. Symptoms associated with overdosage or influsing vendle<sup>44</sup> too rapidly included hypotension, deprea, hexadaete, vomiting, nausea, dizzinees, joint aches, paraterisea, advormina and musche para, and condrovaculor objece. Next symptoms have been successfully treated with W fluids, hydrocortisone, and/or antihistamins, hitusing the solution as recommended or at a sover rate may also alleviate symptoms.

Istamines Influsing the solution as recommended or at a slower rate may also arevaer symptoms. **Jainica Data:** Je IV closes of Venoter<sup>4</sup> at 150 mg iron/kg in mice (about 3 times the recommended maximum human dose on a body surface area basis) and ing iron/kg in rats (about 8 times the recommended maximum human dose on a body surface area basis) were lethal.

wing wing in rais (about 8 times the recommended maximum human of the symptoms of acute toxicity with the second maximum human does on a body surface area basis) were left a symptoms of acute toxicity were sectation, hypoachily, pale eyes, and bleeding in the gestrointestinal tract and lungs. **DOSAGE AND ADMINISTRATION** The dosage of Verolide's expressed in terms of mon of elementations from the terms of the terms of the original terms.

red over sequential sessions, to achieve a favorable

VENIA

Construct Auron Auminius IMAI IUN
 The dosage of Venote<sup>4</sup> is expressed in terms of mg of elemental iron. Each mL contains 20 mg of elemental iron, Most COD patients will require a minimum cumulate engletion dose of 1,000 mg of elemental iron, administer
 Homolphin response and to repletish iron stress (territin, TSAT).
 Administration: Venote<sup>4</sup> must only be administered intravenously either by slow injection or by infusion.
 Recommended Auth Dosage:

Recommended Adult Doesgue: Non John V injection undukationer 2005 Miching Disease Patients (NDP-SKD): Vender" is administered as a bala unukatie ober of 1000 m no solv V injection undukationer 2:to 5 minutes on 5 offerent occesions within he 14 day period. There is imited experience with administr mg sow // injection uncluled over 2 to 5 minutes on 5 different cocessions within the 14 day period. There is limited experience with administration of an industrue of 500 mp or Veroder?, diubed in a maximum d220 mp, of 0.9% k420, ore a period d3.54 hours on day. 1 and day. 144, hours inscoured in 2 d30 patients heated. See CLNICAL RTALAS, Study D: Non-Dialaysis Dependent-Chronic k40mg Disease (NDD-CK0) Patients and ADVERSE REACTIONS, Adverse Events Observed in Non-Dialaysis Dependent-Chronic K40mg Diseases (NDD-CK0) Patients sections.)

nuw SuPFLIEU Verofer® supplied in 5 mL and 10 mL single dose vials. Each 5 mL vial contains 100 mg elemental ion ,20 mg/mL) and each 10 mL vial contains 200 mg elemental ion ,20 mg/mL). Contains no presentalises. Store in original cartun at 25°C (77°F). Excursions permitted to 15°-30°C (69°-86°F), (See the LBP controlled com temperature). Do not treeze.

Starie NDC-0517-2340-01 100 mg/5 mL Single Dose Vial Individually Boxed | NDC-0517-2310-01 200 mg/10 mL Single Dose Vial Individually Boxe NDC-0517-2340-10 100 mg/5 mL Single Dose Vial Packages of 10 NDC-0517-2340-25 100 mg/5 mL Single Dose Vial Packages of 25 NDC-0517-2340-25 100 mg/5 mL Single Dose Vial Packages of 10

Rx Only REFERENCE: [11] National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease, 2000. Am J Kidney Dis an under some (in and in an anomalian and in a statement of the statement of th

AMERICAN<sup>®</sup> REGENT Ducumu Rev. 10/08 Venofet<sup>a</sup> is manufactured under license from Vifor (International) Inc., Switzerland. Rev 10/2008 © 2008 American Regent, Inc

able 2. Most Common Treatment-Er leported in ≥ 2% of Patients with NI Multidose Safety Population)			Reported in ≥ 2% of Patients with NI (Multidose Safety Population)	ID-ČKD by Dose	Group	
Adverse Events	NDD Venofer®	-CKD Oral Iron	Adverse Events	NDD- 200 mg	D-CKD 500 ma	
(Preferred Term)	(N=139)	(N=139)	(Preferred Term)	(N=109)	(N=30)	
(i totorioù torniy	%	%		%	<u>(11=00)</u> %	
bubjects with any adverse event	76.3	73.4	Subjects with any adverse event	75.2	80.0	
ar and Labyrinth Disorders	10.0		Ear and Labyrinth Disorders			
ar Pain	2.2	0.7	Ear Pain	0.9	6.7	
ve Disorders	L.L.	0.7	Eve Disorders	0.0	0.7	
Coniunctivitis	0	0	Conjunctivitis	0	0	
astrointestinal Disorders	-		Gastrointestinal Disorders			
bdominal pain NOS*	1.4	2.9	Abdominal pain NOS*	1.8	0	
Constitution	4.3	12.9	Constipation	3.7	6.7	
Jiarrhea NOS	7.2	10.1	Diarrhea NOS	6.4	10.0	
Nsoeusia	7.9	0	Dysoeusia	9.2	3.3	
lausea	8.6	12.2	Nausea	9.2	6.7	
lomiting NOS	5.0	8.6	Vomiting NOS	5.5	3.3	
eneral Disorders and	0.0	0.0	General Disorders and			
dministration Site Conditions			Administration Site Conditions			
sthenia	0.7	2.2	Asthenia	0.9	0	
hest pain	1.4	0	Chest pain	0.9	3.3	
dema NOS	6.5	6.5	Edema NOS	7.3	3.3	
atique	3.6	5.8	Fatique	4.6	0.0	
eelina abnormal	0	0	Feeling abnormal	0	Ő	
fusion site burnina	3.6	Ō	Infusion site burning	3.7	3.3	
jection site extravasation	2.2	ŏ	Injection site pain	2.8	0.0	
njection site pain	2.2	Ō	Peripheral edema	5.5	13.3	
eripheral edema	7.2	5.0	Pvrexia	0.9	0	
Vrexia	0.7	0.7	Infections and Infestations			
fections and Infestations			Catheter site infection	0	0	
atheter site infection	0	0	Nasopharyngitis	0.9	0	
lasopharvnoitis	0.7	2.2	Peritoneal infection	0.5	0	
eritoneal infection	0.7	0	Sinusitis NOS	0	3.3	
inusitis NOS	0.7	0.7	Upper respiratory tract infection NOS	0.9	0	
lpper respiratory tract infection NOS	0.7	1.4	Injury, Poisoning and Procedural	0.5	0	
Irinary tract infection NOS	0.7	5.0	Complications			
njury, Poisoning and Procedural	0.7	3.0	Graft complication	1.8	0	
complications			Investigations	1.0	0	
Formplications	1.4	0	Cardiac murmur NOS	2.8	0	
nvestigations	1.4	U	Fecal occult blood positive	2.8	0	
nvestigations 'ardiac murmur NOS	2.2	2.2	Metabolism and Nutrition Disorders		U	
	2.2	2.2	Fluid overload		0	
ecal occult blood positive Aetabolism and Nutrition Disorders		3.0	Fluid ovenoad Gout	1.8 1.8	6.7	
		0.7		3.7	0.7	
luid overload	1.4	0.7	Hyperglycemia NOS	3.7	0	
	2.9	1.4 0	Hypoglycemia NOS	0.9	U	
iout			Musculoskeletal and Connective	1		
lyperglycemia NOS	2.9					
lyperglycemia NOS lypoglycemia NOS	2.9 0.7	0.7	Tissue Disorders			
lyperglycernia NOS lypoglycernia NOS <b>Ausculoskeletal and Connective</b>			Tissue Disorders Arthralgia	0.9	3.3	
yperglycemia NOS lypoglycemia NOS <b>Ausculoskeletal and Connective</b> <b>Tissue Disorders</b>	0.7	0.7	<b>Tissue Disorders</b> Arthralgia Back pain	1.8	3.3	
lyperglycernia NOS lypoglycernia NOS <b>Ausculoskeletal and Connective</b>			Tissue Disorders Arthralgia			

Kill         Kill <th< th=""><th></th><th>NDD</th><th>-CKD</th></th<>		NDD	-CKD
%         %         %           Subjects with any adverse event         75.2         60.0           Subjects with any adverse event         75.2         60.0           Ear Pain         0.9         6.7           Egr Diagram         0.9         6.7           Egr Diagram         0.9         6.7           Egr Diagram         0.9         6.7           Egr Diagram         0.9         6.7           Conjunchits         0         0           Gastrointestinal Disorders         0.0         0           Abdominal pain NOS*         1.8         0           Constigation         3.7         6.7           Diarrhea NOS         6.4         10.0           Operation         9.2         6.7           General Disorders and         Administration Site Conditions           Adhenia         0.9         0           Chest pain         0.3         3.3           Edment Disorders and         0         0           Adhenia         0.9         0           Intestion and Infestations         0         0           Carlage training pain         2.8         0           Infections and Infestations         0.9         <		200 mg	
Subjects with any adverse event         75.2         80.0           Ear and Labyrinth Disorders	(Preferred Term)	(N=109)	(N=30)
Ear and Labyrinth Disorders         0.9         6.7           Ear Pain         0.9         6.7           Ear Pain         0.9         6.7           Conjunchitis         0         0           Gastrointestinal Disorders         0         0           Conjunchitis         0         0           Constration NOS*         1.8         0           Constration NOS*         6.4         10.0           Disorders and Administration Site Conditions         9.2         3.3           Administration Site Conditions         4.6         0           Administration Site Conditions         7.3         3.3           Edema NOS         7.3         3.3              Edema NOS         7.3         3.3           Edema NOS         7.3         3.3           Injection sells pain         2.8         0           Pertiheral edema         0.9         0           Indictoring and Infestations         0.9         0           Struct respitoring and Procedu		%	%
Ear Pain         0.9         6.7           Eye Disorders         O         O           Gastrointestinal Disorders         Abdominal pain NOS"         1.8         0           Constignation         3.7         6.7         1.8         0           Constignation         3.7         6.7         1.8         0           Constignation         3.7         6.7         1.8         0           Operation Scores and Automotic Pain NOS         5.5         3.3         General Disorders and Athenia         0.9         0           Administration Site Conditions         Adhenia         0.9         0         0           Chest pain         0.9         3.3         3         General Disorders and Athenia         0         0           Adhenia Consorters and Athenia         0.9         0         1.8         0         0           Infusion site burning         3.7         3.3         0         0         0         0           Infusion site burning         3.7         3.3         0         0         0         0           Infusion site burning         3.7         3.3         0         0         0         0           Staprexia         0.9         0         0<	Subjects with any adverse event	75.2	80.0
Ear Pain         0.9         6.7           Eye Disorders         O         O           Gastrointestinal Disorders         Abdominal pain NOS"         1.8         0           Constignation         3.7         6.7         1.8         0           Constignation         3.7         6.7         1.8         0           Constignation         3.7         6.7         1.8         0           Operation Scores and Automotic Pain NOS         5.5         3.3         General Disorders and Athenia         0.9         0           Administration Site Conditions         Adhenia         0.9         0         0           Chest pain         0.9         3.3         3         General Disorders and Athenia         0         0           Adhenia Consorters and Athenia         0.9         0         1.8         0         0           Infusion site burning         3.7         3.3         0         0         0         0           Infusion site burning         3.7         3.3         0         0         0         0           Infusion site burning         3.7         3.3         0         0         0         0           Staprexia         0.9         0         0<	Ear and Labyrinth Disorders		
Conjunctitis         0         0           Gastrointistinal Disorders         Achonnal pan NOS"         1.8         0           Carstipation         3.7         6.7           Durrhea NOS         6.4         10.0           Dysgeusia         9.2         3.3           Nausca         9.2         6.7           Administration Site Conditions         Administration Site Conditions         Administration Site Conditions           Asthenia         0.9         0         0           Chest pain         0.9         3.3         3           Fabrenia         0.9         0         0           Chest pain         2.8         0         0           Indiction sand and the burning         3.7         3.3         3           Injection sand Infestations         0         0         0           Influstion sand Infestations         0         0         0           Strustins NOS         0.9         0         0         3.3           Influctions and Infestations         0         0         3.3           Cardiac mummur NOS         2.8         0         0           Factin count placing and Procedural Count place infection NOS         0.9         0	Ear Pain	0.9	6.7
Conjunctitis         0         0           Gastrointistinal Disorders         Achonnal pan NOS"         1.8         0           Carstipation         3.7         6.7           Durrhea NOS         6.4         10.0           Dysgeusia         9.2         3.3           Nausca         9.2         6.7           Administration Site Conditions         Administration Site Conditions         Administration Site Conditions           Asthenia         0.9         0         0           Chest pain         0.9         3.3         3           Fabrenia         0.9         0         0           Chest pain         2.8         0         0           Indiction sand and the burning         3.7         3.3         3           Injection sand Infestations         0         0         0           Influstion sand Infestations         0         0         0           Strustins NOS         0.9         0         0         3.3           Influctions and Infestations         0         0         3.3           Cardiac mummur NOS         2.8         0         0           Factin count placing and Procedural Count place infection NOS         0.9         0	Eve Disorders		
Gastrointestinal Disorders         1.8         0           Abdomine plain NGS         1.8         0           Constipation         3.7         6.7           Diarrhea NOS         6.4         10.0           Digentesia         9.2         6.7           Nausea         9.2         6.7           Vorniting NOS         5.5         3.3           Rausea         9.2         6.7           Administration Stet Conditions         Administration Stet Conditions         Administration Stet Conditions           Astheria         0.9         0         0           Feeling adnormal         0         0         0           Influxing and Infestations         0.3         0         0           Influxing and Infestations         0.9         0         0           Influxing and Infestations         0         0         0           Sinustis NOS         0.3         0         0         0           Influxing infection Intection NOS         0.9         0         0         0           Carditer numm NDS         2.8         0         0         0         0           Graft complication         1.8         0         0         0         0		0	0
Abdominal pain NOS*         1.8         0           Correligation         3.7         6.7           Diarrhaa NOS         6.4         10.0           Opspessia         9.2         3.3           Reareal Disorders and Administration Site Conditions         -         -           Chest pain         0.9         0         -           Chest pain         0.9         0         -           Chest pain         0.9         0         -           Inficient site burning         3.7         3.3         -           Again Site Conditions         0.9         0         -           Parational infections and Infestations         0.9         0         -           Inflactions and Infestations         0.9         0         -         -           Situatis Notacy         0.9         0         -         -           Situatis Notacy         0.8         0         -         -           Situatis Notacy         1.8         0         -         -		-	-
Constipation         37         6.7           Diarrhea NOS         6.4         1000           Dipartea NOS         6.4         1000           Vorgensia         9.2         6.7           Vormiting NDS         5.5         3.3           General Disorders and Administration Site Conditions Asthenia         0.9         0.0           Chest pain         0.9         0.3           Edmen MOS         7.3         3.3           Edman MOS         7.3         3.3           Injuscion site burning         3.7         6.7           Numsion site burning         0.9         0.3           Injuscion site burning         3.7         3.3           Injuscion site burning         3.7         3.3           Injuscion site burning         3.7         3.3           Injuscion site burning         3.7         3.1           Networks and Infestations         0         0           Catheter site infection         0         0           Infections and Infestations         0         0           Suspitabry Disoning and Procedural Complication         1.8         0           Complication         1.8         0           Metabolism and Nutrition Disorders Huid veritoa		1.8	0
Diarrhéa NOS         6.4         100           Opgeusia         9.2         3.3           Mausa         9.2         6.7           Vorniting NOS         5.5         3.3           General Discorders and Administration Site Conditions         9         0           Asthenia         0.9         0           Chest pain         0.9         0.3           Edema NOS         7.3         3.3           Edema NOS         7.3         3.3           Edema NOS         7.3         3.3           Injection site burning         3.7         3.3           Injection site pain         2.8         0           Peripheral detma         0.9         0           Intections and Infestations         0.9         0           Gartherer Isel infection         0         0         0           Nasopharyngtis         0.9         0         0           Garto corplications         0         0         0           Garto corplication         0         0         0           Seatt complications         2.8         0         Feature           Carditer mum NOS         2.8         0         0           Featu coult blood posit			
Nausea         9.2         6.7           Vornting NOS         5.5         3.3           Administration Site Conditions         Administration Site Conditions           Asthenia         0.9         0           Chest pain         0.9         3.3           Edman Disorders and         0.9         0           Asthenia         0.9         0           Chest pain         0.9         3.3           Edman NUS         7.3         3.3           Taflupe         4.6         0           Feeling adnormal         0         0           Influsion site burning         3.7         3.3           Previous         0.9         0           Influctions and Infestations         0         0           Catheter site infection         0         0           Nascynaryngits         0.9         0           Peritorneal infection         0         3.3           Gradies murmur NOS         2.8         0           Fecal accutt blood positive         1.8         0           Gradie curum NOS         3.7         0           Houger respiratory tract infection NOS         0.9         0           Cardiac murum NOS         2.8 <td>Diarrhea NOS</td> <td>6.4</td> <td>10.0</td>	Diarrhea NOS	6.4	10.0
Nausea         9.2         6.7           Vornting NOS         5.5         3.3           Administration Site Conditions         Administration Site Conditions           Asthenia         0.9         0           Chest pain         0.9         3.3           Edman Disorders and         0.9         0           Asthenia         0.9         0           Chest pain         0.9         3.3           Edman NUS         7.3         3.3           Taflupe         4.6         0           Feeling adnormal         0         0           Influsion site burning         3.7         3.3           Previous         0.9         0           Influctions and Infestations         0         0           Catheter site infection         0         0           Nascynaryngits         0.9         0           Peritorneal infection         0         3.3           Gradies murmur NOS         2.8         0           Fecal accutt blood positive         1.8         0           Gradie curum NOS         3.7         0           Houger respiratory tract infection NOS         0.9         0           Cardiac murum NOS         2.8 <td>Dysneusia</td> <td>9.2</td> <td>3.3</td>	Dysneusia	9.2	3.3
Vomiting NDS         5.5         3.3           General Disorders and Administration Ste Conditions         -           Astheria         0.9         0.           Astheria         0.9         3.3           Edema NOS         7.3         3.3           Edema NOS         7.3         3.3           Edema NOS         7.3         3.3           Fatigue         4.6         0           Peripheral edema         5.5         13.3           Nigeton site pain         2.8         0.9           Partipheral edema         5.5         13.3           Name         0.9         0           Influctions and Infestations         0         0           Influctions and Infestations         0.9         0           Sinustis NOS         0.9         0         0           Vigor respiratory that: infection NOS         0.9         0           Influctioning and Procedural         Conditioning and Procedural         0           Cardier onrumi NOS         2.8         0           Featal occult blood positive         1.8         0           Morating min MOS         3.7         0           Musculoskeietal and Connective         1.8         6.7	Nausea		
General Disorders and Administration Site Conditions Administration Site Conditions Administration Site Conditions Schema NOS         0.9         0.0           Chest pain         0.9         3.3         3.3           Edema NOS         7.3         3.3           Failuge         4.6         0           Feeling ahormal         0         0           Indicision site burning         3.7         3.3           Injection site pain         2.8         0.9           Paripheral edema         5.5         13.3           Sprexia         0.9         0           Inflections and Infestations         0         0           Catheter site infection         0         0           Nascipharyngtis         0.9         0           Influxing Neisoning and Procedural Complication         0.9         0           Cardiac murum NOS         2.8         0           Feal acouti biood positive         1.8         0           Matabolism and Nutrition Disorders         1.8         0           Huid overlicad         1.8         0           Musculaskeletal and Connective Tissue Disorders         3.3           Musculaskeletal and Connective Tissue Disorders         3.3           Antrialgia         0.9	Vomiting NOS	5.5	
Administration Site Conditions		0.0	0.0
Asthenia         0.9         0           Chest pain         0.9         3.3           Edema NOS         7.3         3.3           Faligue         4.6         0           Indigo         7.3         3.3           Faligue         4.6         0           Indigo         3.7         3.3           Ingiction site burning         3.7         3.3           Injection site pain         2.8         0           Pertipheral edema         5.5         13.3           Pyrexia         0.9         0           Influctions and Infestations         0         0           Catheter site infection         0         0           Nasoptraryngtils         0.9         0           Influery, Poisoning and Procedural         0         3.3           Cardiac murmur NOS         2.8         0           Fecal accut blood positive         1.8         0           Goat         1.8         0           Goat         1.8         0.7           Goat         3.7         0           Investigations         0.9         0           Mathemation         1.8         0.7           Operalocutal toi			
Chest pain         0.9         3.3           Chest pain         0.9         3.3           Edema NOS         7.3         3.3           Edema NOS         7.3         3.3           Edema NOS         7.3         3.3           Injuction set and mormal         0         0           Injuction site pain         2.8         0           Peripheral edema         5.5         13.3           prexia         0.9         0           Inflections and Infestations         0         0           Catheter site infection         0         0           Nascyntaryngits         0.9         0           Peritoneal infection         0         0.3           Upper respiratory tract infection NOS         0.9         0           Cardac murmum XDS         2.8         0           Grafts complication         1.8         0           Graft conglicitions         1.8         0           Grafts manner NDS         2.9         0           Heabolism and Nutrition Disorders         1.8         0           Hypedynemia NOS         0.9         0         0           Mitabolism and Nutrition Disorders         1.8         0         0		0.9	0
Edema NOS         7.3         3.3           Falique         4.6         0           Falique         4.6         0           Infusion site burning         3.7         3.3           inpicton site pain         2.8         0           Peripheral edema         5.5         13.3           Pyrexia         0.9         0           Catheler site infection         0         0           Nacophayngitis         0.9         0           Periodications         0         0           Sinustis NOS         0         3.3           Uper respiratory tract infection NOS         0.9         0           Injury, Poisoning and Procedural         Conditions         0           Cardiac mumplication         1.8         0           Gradia count blood positive         1.8         0           Fecal occult blood positive         1.8         0           Gout         1.8         0.7         0           Mato evering         0.9         0         0           True of third overlinda         1.8         0.7         0           Mato everlind         1.8         0.9         0           Muscle carian unumar NOS         2.9 <td></td> <td></td> <td></td>			
Fatigue         4.6         0           Feding admormal         0         0         0           Feding admormal         0         0         0         0           Infection site burning         3.7         3.3         3.4         3.3			
Feeling abnormal         0         0           Inflacting abnormal         3.7         3.3           Inflacting be burning         3.7         3.3           Peripheral edema         5.5         13.3           Prinzent ale infection         0         0           Infections and Infestations         0         0           Catheter stein infection         0         0           Nascynaryngitis         0.9         0           Peritoneal infection         0         0           Sinustis NOS         0         3.3           Upper respiratory tract infection NOS         0.9         0           Complications         0         0.3           Graft complications         2.8         0           Fecal accut blood positive         1.8         0           Metabolism and Nutrition Disorders         1.8         0.3           Fuid werkinds         3.7         7           Hypoglycennia NOS         3.7         0           Musculoskeletal and Connective         1.8         0.3           Tissue Disorders         4.9         3.3           Back pain         1.8         3.3			
Infusion alle burning         3.7         3.3           Injection site pain         2.8         0           Pretional eldema         5.5         13.3           Pretional eldema         5.5         13.3           Pretional infections and Infestations         0         0           Catheter site infection         0         0         0           Nasoptaryngtils         0.9         0         0           Nasoptaryngtils         0.9         0         0           Sirustils NOS         0         3.3         0           Injuer, Poisoning and Procedural Complications         0         3.3         0           Grat complications         2.8         0         0           Grat complication         1.8         0         0           Grat complication         1.8         0         0           Gratic murmur NOS         2.8         0         0         0           Feed accut blood positive         1.8         0         0         0           Fuid overload         1.8         0.7         0         0           Muscle and Nutrition Disorders         1.8         0.7         0         0           Muscle blog acity         3.7			
Injection site pain         2.8         0           Peripheral eldema         5.5         13.3           Peripheral eldema         5.5         13.3           Cathetar site infection         0         0           Infections and Infestations         0         0           Cathetar site infection         0         0           Nascyntaryngits         0.9         0           Peritoneal infection         0         0           Sussitis NOS         0.9         0           Upper respiratory tract infection NOS         0.9         0           Complications         Complications         Cardiac murmur NOS         2.8         0           Graft complication         1.8         0         0         0           Metabolism and Nutrition Disorders         1.8         0         0           Metabolism and Nutrition Disorders         1.8         0         0           Mudi werkinda         1.8         0         0         0           Missue obsorders         0.9         0         0         0           Mudi werkinda         1.8         0.9         0         0           Mud werkinda         0.9         0         0         0 <t< td=""><td></td><td></td><td>33</td></t<>			33
Peripheral elema         5.5         13.3           Pprexia         0.9         0           Inflections and Infestations         0         0           Catheler sile inflection         0         0           Nasopharyngits         0.9         0           Peritoneal inflection         0         0           Sinustils NOS         0         3.3           Upper respiratory tract inflection NOS         0.9         0           Graft complications         Graft complications         Graft complications           Graft complications         0         2.8         0           Fecal accut blood positive         1.8         0         0           Fuid welficiation         1.8         0.7         0           Graft acmplications         3.7         0         0           Fuid welficiation         1.8         0.7         0           Graft accut blood positive         1.8         0.7         0           Musculoskeletal and Connective         1.8         0.7         0           Tissue Disorders         Hardigia         0.9         3.3         3           Arthraigia         0.9         3.3         3         3			
Pyrexia         0.9         0           Inflections and Infestations         Cathers site infection         0         0           Nasopharyngitis         0.9         0         0           Nasopharyngitis         0.9         0         0           Sinsulis NOS         0         3.3         0         0           Sinsulis NOS         0.9         0         0         0         0           Sinsulis NOS         0.9         0			
Infections and Infestations         0         0           Catheler site infection         0         0         0           Nascyharyngits         0.9         0         0           Peritoneal infection         0         0         33           Sinusitis NOS         0.9         0         33           Upper respiratory tract infection NOS         0.9         0         10           Complications         Complications         0         33         0           Graft complication         1.8         0         0         18         0           Cardiac numm NDS         2.8         0         Feal accut blood positive         1.8         0           Graft complications         1.8         0         0         33         0           Heid welficida         1.8         0			
Catheter site infection         0         0           Nasopharyngtils         0.9         0           Nasopharyngtils         0.9         0           Sirnuslis NOS         0         3.3           Upper respiratory tract infection NDS         0.9         0           Sirnuslis NOS         0         3.3           Upper respiratory tract infection NDS         0.9         0           Graft complications         Graft complication         1.8         0           Cardie nurmur NOS         2.8         0         Percal coult blood positive         1.8         0.7           Fead coult blood positive         1.8         0.7         0         0         0           Fuld overload         0.5         3.7         0         0         0         0           Fuld overload         0.5         0.9         0			
Nasspharyngitis         0.9         0           Pertineal infection         0         0           Sinsulis NOS         0         3.3           Upper respiratory tract infection NOS         0.9         0           Sinsulis NOS         0.9         0           Omplications         0         0           Graft complications         0         0           Cardac mumur NOS         0.9         0           Fecal acoult blood positive         1.8         0           Metabolism and Nutrition Disorders         1.8         0           Modult blood positive         1.8         0           Hoperlycemia NOS         3.7         0           Hypoglycemia NOS         0.9         0           Arthratiga         0.9         0           Musculeskeletal and Connective         Tissue Disorders           Tasue Disorders         4.3         3.3           Macsch pain         1.8         3.3		0	0
Peritoneal infection         0         0         3.3           Sinustis NOS         0         3.3         0         3.3           Upper respiratory tract infection NOS         0.9         0         0         1.8         0           Complications         Complications         0         2.8         0         1.8         0           Carit complications         2.8         Caritics mumm NOS         2.8         0         1.8         0           Fecal accut blood positive         1.8         0         0         0         0         0           Hetabolism and Nutrition Disorders         1.8         0			
Sinustis NOS         0         3.3           Upper respiratory tract infection NOS         0.9         0           Injury, Poisoning and Procedural Complications		0.0	
Upper respiratory tract infection NOS         0.9         0           Injury, Poisoning and Procedural Complications         Complication         1.8         0           Graft complications         2.8         0         6         6           Graft complications         2.8         0         6         7         7         6         6         7         7         0         6         0         9         0         6         0         9         0         6         0         9         0         0         0         Musculskeletal and Connective Trassue Disorders         Trassue Disorders         6         7         0         0         0         3         3         3         3         3         3         3         3         3         3         3         3         3         3         3         3         3			
Injury, Poisoning and Procedural Complications         Important           Complications         0           Card complications         0           Cardia communications         0           Cardia communications         0           Cardia communications         0           Cardia communications         1.8           Cardia communications         1.8           Pical overlinad         1.8           Gout         1.8           Hyperglycemia NOS         3.7           Musculoskeletal and Connective         Tissue Disorders           Tissue Disorders         0.9         3.3           Anthralgia         0.9         3.3           Back pain         1.8         3.3			
Complications         1.8         0           Graft complication         1.8         0           Investigations         2.8         0           Cardiac murmur NOS         2.8         0           Fead occut blood positive         1.8         0           Metabolism and Nutrition Disorders         1.8         0           Fuid overload         1.8         0           Gout         1.8         6.7           Hyperglycemia NOS         3.7         0           Hyperglycemia NOS         0.9         0           Musculoskeletal and Connective Tissue Disorders         1.8         3.3           Arthraliga         0.9         3.3         3.3           Muscle cramp         0         3.3         3.3		0.0	0
Craft complication         1.8         0           Investigations         Cardac mumm NOS         2.8         0           Fecal occult blood positive         1.8         0           Metabolism and Nutrition Disorders         1.8         0           Metabolism and Nutrition Disorders         1.8         0           Gout         1.8         0           Hypedynemia NOS         3.7         0           Hypedynemia NOS         0.9         0           Musculoskeletal and Connective         Tissue Disorders           Arthralgia         0.9         3.3           Back pain         1.8         3.3           Muscle camp         0         3.3			
Investigations         2.8         0           Cardia: mumur NOS         2.8         0           Cardia: mumur NOS         1.8         0           Metabolism: and Nutrition Disorders         1.8         0           Fluid overload         1.8         0           Gout         1.8         0           Hyperglycemia NOS         3.7         0           Hypoglycemia NOS         0.9         0           Musculoskeletal and Connective Tissue Disorders         4           Arthraligia         0.9         3.3           Back pain         1.8         3.3           Muscle camp         0         3.3		1.8	0
Fecal occuit blood positive         1.8         0           Metabolism and Nutrition Disorders         1.8         0           Fluid overliad         1.8         0           Gout         1.8         6.7           Hyperglycemia NOS         3.7         0           Musculoskeletal and Connective         Tissue Disorders         3           Tissue Disorders         0.9         3.3           Back pain         1.8         3.3           Muscle camp         0         3.3	Investigations		
Metabolism and Nutrition Disorders	Cardiac murmur NOS	2.8	0
Fluid overload         1.8         0           Gout         1.8         6.7           Mpperglycemia NOS         3.7         0           Hypoglycemia NOS         0.9         0           Musculoskeletal and Connective Tissue Disorders         1.8         0.9           Arthratiga         0.9         3.3           Back pain         1.8         3.3           Muscle camp         0         3.3	Fecal occult blood positive	1.8	0
Fluid overload         1.8         0           Gout         1.8         6.7           Mpperglycemia NOS         3.7         0           Hypoglycemia NOS         0.9         0           Musculoskeletal and Connective Tissue Disorders         1.8         0.9           Arthratiga         0.9         3.3           Back pain         1.8         3.3           Muscle camp         0         3.3	Metabolism and Nutrition Disorders		
Gout         1.8         6.7           Hyperglycemia NOS         3.7         0           Hypoglycenia NOS         0.9         0           Musculoskeletal and Connective         Tissue Disorders	Fluid overload	1.8	0
Hypoglycemia NOS         0.9         0           Musculoskeletal and Connective Tissue Disorders         1         3         3           Arthratigia         0.9         3.3         3         3           Back pain         1.8         3.3         3         3           Muscle cramp         0         3.3         3         3	Gout		6.7
Hypoglycemia NOS         0.9         0           Musculoskeletal and Connective Tissue Disorders         1         3         3           Arthratigia         0.9         3.3         3         3           Back pain         1.8         3.3         3         3           Muscle cramp         0         3.3         3         3	Hyperalycemia NOS		0
Musculoskeletal and Connective Tissue Disorders Antralgia 0.9 3.3 Back pain 1.8 3.3 Muscle cramp 0 3.3			Ő
Tissue Disorders           Arthraligia         0.9         3.3           Back pain         1.8         3.3           Muscle cramp         0         3.3	Musculoskeletal and Connective	2.0	
Arthralgia         0.9         3.3           Back pain         1.8         3.3           Muscle cramp         0         3.3	Tissue Disorders		
Back pain         1.8         3.3           Muscle cramp         0         3.3		0.9	3.3
Muscle cramp 0 3.3			
	Myalqia	2.8	6.7