הודעה על החמרה (מידע בטיחות)

תאריך: 13.8.2012

שם תכשיר באנגלית: VANCOMYCIN MYLAN 500 MG, VANCOMYCIN MYLAN 1 G

מספר רישום: (30297.00 , 30297.11 , 30298.00 , 30298.11) :

שם בעל הרישום: ג'נמדיקס

השינויים בעלון מסומנים על רקע צהוב

בעלון לרופא

פרטים על השינוי/ים המבוקש/ים		
טקסט חדש	**טקסט נוכחי**	**פרק בעלון**
Intravenous administration Solution concentrations of no more than 5 mg/ml are recommended. In selected patients in need of fluid restriction, solution concentration up to 10 mg/ml may be used; use of such higher concentrations may increase the risk of infusion-related events (see section 6.6). Infusions should be given over at least 60 minutes. In adults, if doses exceeding 500 mg are used, a rate of infusion of no more than 10 mg/min is recommended. Infusion-related adverse events are related to both concentration and rate of administration of vancomycin. The duration of treatment is guided by the severity of the infection and its clinical and bacteriological progression. **Patients with normal renal and hepatic functions** *Adult and adolescents above 12 years of age:* The recommended daily intravenous dose is 2000 mg (2g), divided into doses of 500mg every 6 hours or 1000mg every 12 hours. For bacterial endocarditis, the generally accepted regimen is 1000 mg of vancomycin intravenously every 12 hours for 4 weeks either alone or in combination with other antibiotics	For intravenous infusion only and not for intramuscular administration. Infusion-related adverse events are related to both concentration and rate of administration of Vancomycine. Concentrations of no more than 5mg/ml are recommended. In selected patients in need of fluid restriction, a concentration up to 10mg/ml may be used; use of such higher concentrations may increase the risk of infusion-related events. Infusions should be given over at least 60 minutes. In adults, if doses exceeding 500mg are used, a rate of infusion of no more than 10mg/min is recommended. Infusion-related events may occur, however, at any rate or concentration. **Intravenous infusion in patients with normal renal function:** *Adults*: The usual intravenous dose is 500mg every six hours or 1g every 12 hours, in Sodium Chloride Intravenous Infusion BP or 5% Dextrose Intravenous Infusion BP. Each dose should be administered at no more than 10mg/min. Other patient factors, such as age, obesity or pregnancy, may call for modification of the usual daily dose. The majority of patients with infections caused by organisms sensitive to the antibiotic show a therapeutic response within 48-72 hours. The total duration of therapy is determined by the type and severity of the infection and the clinical response of the patient. In staphylococcal endocarditis, treatment for three weeks or longer is recommended. *Pregnancy*: It has been reported that significantly increased doses may be required to achieve therapeutic serum concentrations in pregnant patients, but see 'Warnings'.	**4.2. Posology and method of administration**

(gentamicin plus rifampin, gentamicin, streptomycin). Enterococcal endocarditis is treated for 6 weeks with vancomycin in combination with an aminoglycoside – according to national recommendations.

Children 1 month to 12 years of age:
The recommended intravenous dose is 10mg/kg, every 6 hours.

Infants and newborn:
The recommended initial dose is 15 mg/kg, followed by 10 mg/kg every 12 hours during the first week of life and every 8 hours after that age and up to 1 month of age. Careful monitoring of serum concentration of vancomycin is recommended (see below).

Elderly patients:
Lower maintenance doses may be required due to the age – related reduction in renal function.

Obese patients:
Modification of the usual daily doses may be required.

Patients with impaired hepatic function
There is no evidence that the dose has to be reduced in patients with impaired hepatic function.

Patients with impaired renal function
The dose must be adjusted in patients with impaired renal function and the following nomogram can serve as guidance. Careful monitoring of serum concentration of vancomycin is recommended (see below)

The elderly: Dosage reduction may be necessary to a greater extent than expected because of decreasing renal function (see below). Monitor auditory function - see 'Warnings' and 'Precautions'.

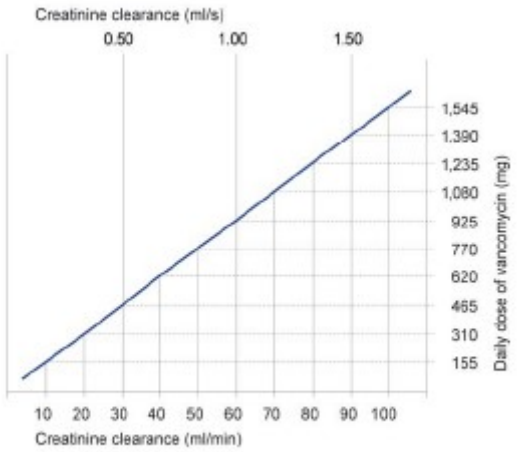
Children: The usual intravenous dosage is 10mg/kg per dose given every 6 hours (total daily dosage 40mg/kg of body weight). Each dose should be administered over a period of at least 60 minutes.

In neonates and young infants, the total daily dosage may be lower. An initial dose of 15mg/kg is suggested, followed by 10mg/kg every 12 hours in the first week of life and every 8 hours thereafter until one month of age. Each dose should be administered over 60 minutes. Close monitoring of serum Vancomycine concentrations may be warranted in these patients.

Patients with impaired renal function: Dosage adjustments must be made to avoid toxic serum levels. In premature infants and the elderly, greater dosage reductions than expected may be necessary because of decreased renal function. Regular monitoring of serum levels is advised in such patients, as accumulation has been reported, especially after prolonged therapy. Vancomycine serum concentrations may be determined by use of a microbiological assay, radioimmunoassay, fluorescence polarisation immunoassay, fluorescence immunoassay or high-pressure liquid chromatography. The following table, based on creatinine clearance values, is provided:

Dosage for vancomycin in patients with impaired renal function:

Creatinine Clearance (ml/min/kg)	Vancomycin Dose (mg/kg/24	Vancomycin Clearance (ml/min/kg)	Creatinine Clearance (ml/min/kg)	Vancomycin Dose (mg/kg/24	Vancomycin Clearance (ml/min/kg)



Dosing nomogram for adults with impaired renal function

If the creatine clearance is not available, the following formula may be applied to calculate the creatinine clearance from the patients age, sex and serum creatinine:

Men: $\frac{\text{Weight [kg]} \times (140 - \text{age [years]})}{72 \times \text{serum creatinine [mg/100 ml]}}$

Women: 0.85 x value calculated by the above formula.

Where possible, the creatinine clearance should always be determined.

In patients with mild or moderate renal failure, the starting dose must not be less than 15 mg/kg. In patients with severe renal failure, it is preferable to administer a maintenance dose between 250 mg and 1000 mg at a spacing of several days rather than administer lower daily doses.

Patients with *anuria* (with practically no renal function) should receive a dose of 15 mg/kg body weight until the therapeutic serum concentration is reached. The maintenance doses are 1.9 mg/kg body weight per 24 hours. In order to facilitate the procedure, adult patients with

	hours)			hours)	
0.1	1.5	0.071	1.1	17.0	0.808
0.2	3.1	0.147	1.2	18.5	0.879
0.3	4.6	0.219	1.3	20.1	0.955
0.4	5.2	0.247	1.4	21.6	1.027
0.5	7.7	0.366	1.5	23.2	1.103
0.6	9.3	0.442	1.6	24.7	1.174
0.7	10.8	0.513	1.7	26.3	1.250
0.8	12.4	0.589	1.8	27.8	1.321
0.9	13.9	0.661	1.9	29.3	1.393
1.0	15.4	0.732	2.0	30.9	1.487

The table is not valid for functionally anephric patients on dialysis. For such patients, a loading dose of 15mg/kg body weight should be given to achieve therapeutic serum levels promptly, and the dose required to maintain stable levels is 1.9mg/kg/24 hours. Since individual maintenance doses of 250mg to 1g are convenient, in patients with marked renal impairment a dose may be given every several days rather than on a daily basis. In anuria a dose of 1g every 7 to 10 days has been recommended.

Preparation of solutions: See 'Instructions for use/handling'.

strongly impaired renal function may obtain a maintenance dose of 250 - 1000 mg at intervals of several days instead of a daily dose. *Dosage in case of haemodialysis* For patients without any renal function, even under regular hemodialysis, the following dosage is also possible: Saturating dose 1000 mg, maintenance dose 1000 mg every 7 - 10 days. If polysulfone membranes are used in haemodialysis (high flux dialysis), the half-life of vancomycin is reduced. An additional maintenance dose may be necessary in patients on regular haemodialysis. Monitoring of vancomycin serum concentrations: The serum concentration of vancomycin should be monitored at the second day of treatment immediately prior to the next dose, and one hour post infusion. Therapeutic vancomycin blood levels should be between 30 and 40 mg/l (maximum 50 mg/l) one hour after the end of the infusion, the minimum level (short prior to the next administration) between 5 and 10 mg/l. The concentrations should normally be monitored twice or three times per week. **Oral administration** **Treatment of colitis due to *C. difficile*** *Adults:* The usual daily dose is 0,5g to 2 g given in 4 divided doses (125 mg to 500 mg per dose) for 7 to 10 days. *Children:* The usual daily dose is 40 mg/kg/day given in 4 divided doses, up to a maximum of 250 mg/dose, for 7 to 10 days. **Method of administration** For intravenous infusion only, and not for intramuscular administration. Parenterally vancomycin shall only be administered as slow intravenous infusion (not more than 10 mg/min – over at least 60 min) which is sufficiently diluted (at least 500 mg/100ml or at least 1000mg/200 ml).	**Measurement of serum concentrations:** Following multiple intravenous doses, peak serum concentrations, measured 2 hours after infusion is complete, range from 18-26mg/l. Trough levels measured immediately prior to the next dose should be 5-10mg/l. Ototoxicity has been associated with serum drug levels of 80-100mg/l, but this is rarely seen when serum levels are kept at or below 30mg/l. **Method of administration:** Intravenous use Dissolve the vial contents as follows: VANCOMYCIN MYLAN 1 G: 1000 mg in 20 ml of water for injections. VANCOMYCIN MYLAN 500 MG: 500 mg in 10 ml of water for injection.	

Patients requiring fluid restriction can receive a solution of 500 mg /50 ml or 1000 mg /100 ml. With these higher concentrations the risk for infusion related side effects can be increased. The reconstituted solution may also be used for oral administration. Therapeutic indications for intravenous and oral administration are different. Both administration routes could not be commuted. For information about the preparation of the solution, please refer to section 6.6 special precautions for disposal and other handling.	**NEVER INJECT THE SOLUTION AS IS, BUT DILUTE IT AS FOLLOWS:** The route of administration of choice is by intermittent infusion. Add the primary solution to 100ml or 200ml of diluent. The resulting dilution may be administered by infusion over 60 minutes every 6 hours. In the case of continuous infusion, add two to four vials of the above primary solution to a sufficient volume so as to be administering the desired daily dose slowly, by intravenous drip, over a 24-hour period	
Warnings: If severe acute hypersensitivity reactions occurs (e.g. anaphylaxis), treatment with vancomycin has to be discontinued immediately and the usual appropriate emergency measures have to be started (e.g antihistaminics, corticosteroids, and –if necessary- artificial respiration). Rapid bolus administration (e.g., over several minutes) may be associated with severe hypotension, (including shock and rare cardiac arrest), histamine like responses and maculopapular or erythematous rash (“red man’s syndrome” or “red neck syndrome”). Vancomycin should be infused in a dilute solution (2.5 to 5.0g/l) at a rate not greater than 10 mg/min and over a period of not less than 60 minutes to avoid rapid infusion-related reactions. Stopping the infusion usually results in a prompt cessation of these reactions. Nephrotoxicity: vancomycin must be used with caution in patients with renal failure as the possibility of developing toxic effects is much higher in the presence of prolonged high blood concentrations. In the treatment of these patients and in those who are receiving concomitant treatment with other nephrotoxic active substances (i.e. aminoglycosides),	*Warnings* Rapid bolus administration (e.g., over several minutes) may be associated with exaggerated hypotension, including shock, and, rarely, cardiac arrest. Vancomycine should be infused in a dilute solution over a period of not less than 60 minutes to avoid rapid infusion-related reactions. Stopping the infusion usually results in a prompt cessation of these reactions (see 'Posology and method of administration' and 'Undesirable effects' sections). Some patients with inflammatory disorders of the intestinal mucosa may have significant systemic absorption of oral Vancomycine and, therefore, may be at risk for the development of adverse reactions associated with the parenteral administration of Vancomycine. The risk is greater in patients with renal impairment. It should be noted that the total systemic and renal clearances of Vancomycine are reduced in the elderly. Due to its potential ototoxicity and nephrotoxicity, Vancomycine should be used with care in patients with renal insufficiency and the dose should be reduced according to the degree of renal impairment. The risk of toxicity is appreciably increased by high blood concentrations or prolonged therapy. Blood levels should be monitored and renal function tests should be performed regularly. Vancomycine should also be avoided in patients with previous hearing loss. If it is used in such patients, the dose should be regulated, if possible, by periodic determination of the drug level in the blood. Deafness may be preceded by tinnitus. The elderly are more susceptible to auditory damage. Experience with other antibiotics suggests that deafness may be progressive despite cessation of	**4.4 Special warnings and precautions for use**

serial tests of renal function must be performed and the appropriate dose regimens adhered to in order to reduce the risk of nephrotoxicity to a minimum (see section 4.2). Ototoxicity: Ototoxicity, which may be transitory or permanent, has been reported in patients with prior deafness, who have received excessive intravenous doses, or who receive concomitant treatment with another ototoxic active substance such as an aminoglycoside. Deafness may be preceded by tinnitus. Experience with other antibiotics suggests that deafness may be progressive despite cessation of treatment. To reduce the risk of ototoxicity, blood levels should be determined periodically and periodic testing of auditory function is recommended. Clinically significant serum concentrations have been reported in some patients being treated for active *C. difficile*-induced pseudomembranous colitis after multiple oral doses of vancomycin. Therefore, monitoring of serum concentrations may be appropriate in these patients. **<u>Precautions:</u>** Vancomycin is very irritating to tissue and causes injection site necrosis if injected intramuscularly. Pain and thrombophlebitis may occur in many patients receiving vancomycin and are occasionally severe. The frequency and severity of thrombophlebitis can be minimized by administering the medicinal product slowly as a dilute solution (see section 6.6) and by changing the sites of infusion regularly. Vancomycin should be used with caution in patients with allergic reactions to teicoplanin, since crossed hypersensitivity reactions between vancomycin and teicoplanin have been reported. Anaesthetic induced myocardial depression may be enhanced by vancomycin. During anaesthesia, doses must be well diluted and administered slowly with close cardiac monitoring. Position changes should be delayed until the infusion is completed to allow for postural adjustment.	treatment. *Usage in paediatrics*: In premature neonates and young infants, it may be appropriate to confirm desired Vancomycine serum concentrations. Concomitant administration of Vancomycine and anaesthetic agents has been associated with erythema and histamine-like flushing in children. *Usage in the elderly*: The natural decrement of glomerular filtration with increasing age may lead to elevated Vancomycine serum concentrations if dosage is not adjusted (see 'Posology and method of administration'). *Precautions* Clinically significant serum concentrations have been reported in some patients being treated for active C. difficile-induced pseudomembranous colitis after multiple oral doses of Vancomycine. Therefore, monitoring of serum concentrations may be appropriate in these patients. Patients with borderline renal function and individuals over the age of 60 should be given serial tests of auditory function and of Vancomycine blood levels. All patients receiving the drug should have periodic haematological studies, urine analysis and renal function tests. Vancomycine is very irritating to tissue, and causes injection site necrosis when injected intramuscularly; it must be infused intravenously. Injection site pain and thrombophlebitis occur in many patients receiving Vancomycine and are occasionally severe. The frequency and severity of thrombophlebitis can be minimised by administering the drug slowly as a dilute solution (2.5 to 5.0g/l) and by rotating the sites of infusion. The administration of vancomycin by intraperitoneal injection during continuous ambulatory peritoneal dialysis has been associated with a syndrome of chemical peritonitis. Prolonged use of Vancomycine may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs	

All patients who receive vancomycin should be periodically examined for hematological and renal function parameters and also for auditory functions. With prolonged duration of use, regular monitoring of vancomycin blood levels is indicated during therapy, particularly in patients with renal dysfunction or impaired hearing, or if ototoxic or nephrotoxic substances are co-administered, such as aminoglycosides. In such cases, renal function should be regularly monitored and the dosage adjusted to the reduction in renal function. Regular monitoring of auditory function is required in patients with impaired auditory function, or if ototoxic medications are co-administered and in cases of renal dysfunction. <u>Use in paediatric population:</u> In premature neonates and young infants, it may be appropriate to confirm desired vancomycin serum concentrations. Concomitant administration of vancomycin and anaesthetic agents has been associated with erythema and histamine-like flushing in children <u>Use in the elderly:</u> The natural decrement of glomerular filtration with increasing age may lead to elevated vancomycin serum levels. The elderly are particularly susceptible to auditory damage and should be given serial tests for auditory function if over the age of 60. Concurrent or sequential use of other nephrotoxic substances	during therapy, appropriate measures should be taken. In rare instances, there have been reports of pseudomembranous colitis, due to Clostridium difficile, developing in patients who received intravenous Vancomycine. Vancomycin should be used with caution in patients with allergic reactions to teicoplanin, since crossed hypersensitivity reactions between vancomycin and teicoplanin have been reported. Anaesthetic induced myocardial depression may be enhanced by vancomycin. During anaesthesia, doses must be well diluted and administered slowly with close cardiac monitoring. Position changes should be delayed until the infusion is completed to allow for postural adjustment	
<u>Other potentially nephrotoxic or ototoxic medications</u> Concurrent or sequential administration of vancomycin with other potentially neurotoxic or/and nephrotoxic active substances particularly gentamycin, amphotericin B, streptomycin, neomycin, kanamycin, amikacin, tobramycin, viomycin, bacitracin, polymyxin B, colistin and cisplatin may potentiate the nephrotoxicity and/or ototoxicity of vancomycin and consequently requires careful monitoring of the patient. Because of synergic action (e.g. with gentamycin) in these	Concomitant administration of Vancomycine and anaesthetic agents has been associated with erythema, histamine-like flushing and anaphylactoid reactions. There have been reports that the frequency of infusion-related events increases with the concomitant administration of anaesthetic agents. Infusion-related events may be minimised by the administration of Vancomycine as a 60-minute infusion prior to anaesthetic induction. Concurrent or sequential systemic or topical use of other potentially neurotoxic or nephrotoxic drugs, such as amphotericin B, aminoglycosides (eg. gentamycin, streptomycin, neomycin, kanamycin, amikacin, tobramycin), bacitracin, polymixin B,	**4.5 Interaction with other medicinal products and other forms of interaction**

cases the maximum dose of vancomycin has to be restricted to 500 mg every 8 hours.	colistin, viomycin or cisplatin, when indicated, requires careful monitoring. If vancomycin is administered during or directly after surgery, the effect (neuromuscular blockade) of muscle relaxants (such as succinylcholine) concurrently used can be enhanced and prolonged.	
Pregnancy: No sufficient safety experience is available regarding vancomycin during human pregnancy. Reproduction toxicological studies on animals do not suggest any effects on the development of the embryo, foetus or gestation period (see section 5.3). However, vancomycin penetrates the placenta and a potential risk of embryonal and neonatal ototoxicity and nephrotoxicity cannot be excluded. Therefore vancomycin should be given in pregnancy only if clearly needed and after a careful risk/benefit evaluation. Breastfeeding: Vancomycin is excreted in human milk and should be therefore used in lactation period only if other antibiotics have failed. Vancomycin should be cautiously given to breast-feeding mothers because of potential adverse reactions in the infant (disturbances in the intestinal flora with diarrhoea, colonisation with yeast-like fungi and possibly sensibilisation). Considering the importance of this medicine for nursing mother, the decision should to stop breastfeeding should be considered. Fertility No fertility (male or female) study is available for vancomycin.	*Usage in pregnancy*: Teratology studies have been performed at 5 times the human dose in rats and 3 times the human dose in rabbits, and have revealed no evidence of harm to the foetus due to Vancomycine. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of Vancomycine hydrochloride on infants were evaluated when the drug was administered to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancomycine hydrochloride was found in cord blood. No sensorineural hearing loss or nephrotoxicity attributable to Vancomycine was noted. One infant, whose mother received Vancomycine in the third trimester, experienced conductive hearing loss that was not attributable to Vancomycine. Because Vancomycine was administered only in the second and third trimesters, it is not known whether it causes foetal harm. Vancomycine should be given in pregnancy only if clearly needed and blood levels should be monitored carefully to minimise the risk of foetal toxicity. It has been reported, however, that pregnant patients may require significantly increased doses of Vancomycine to achieve therapeutic serum concentrations. *Usage in nursing mothers*: Vancomycine hydrochloride is excreted in human milk. Caution should be exercised when Vancomycine is administered to a nursing woman. It is unlikely that a nursing infant can absorb a significant amount of Vancomycine from its gastro-intestinal tract.	**4.6 Fertility, Pregnancy and lactation**
Vancomycin has no or negligible influence on the ability to drive and use machines.	Not applicable	**4.7 Effects on ability to drive and use machines**
The adverse reactions listed below are defined using the following MedDRA convention and system organ class database: very common (≥ 1/10); common (≥ 1/100 to <	*Infusion-related events*: During or soon after rapid infusion of Vancomycine, patients may develop anaphylactoid reactions including hypotension, wheezing, dyspnoea, urticaria or pruritus. Rapid infusion may also cause flushing of the upper-body ('red-	**4.8 Undesirable effects**

1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
The most common adverse reactions are phlebitis and pseudo-allergic reactions in connection with too rapid intravenous use of vancomycin.

System Organ Class	Frequency grouping
Blood and lymphatic system disorders	Rare - thrombocytopenia - neutropenia, - agranulocytosis, - eosinophilia.
Immune system disorders	Rare - anaphylactic reactions, - hypersensitivity reactions.
Ear and labyrinth disorders	Uncommon - transient or permanent loss of hearing. Rare - tinnitus, - dizziness.
Cardiac disorders	Very Rare - cardiac arrest.
Vascular disorders	Common - decrease in blood pressure, - thrombophlebitis. Rare - vasculitis.
Respiratory, thoracic and mediastinal disorders	Common - dyspnoea, - stridor.
Gastrointestinal disorders	Rare - nausea Very Rare

neck syndrome') or pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may persist for several hours. In animal studies, hypotension and bradycardia occurred in animals given large doses of Vancomycine at high concentrations and rates. Such events are infrequent if Vancomycine is given by slow infusion over 60 minutes. In studies of normal volunteers, infusion-related events did not occur when Vancomycine was administered at a rate of 10mg/min or less.

Nephrotoxicity: Rarely, renal failure, principally manifested by increased serum creatinine or blood urea concentrations, have been observed, especially in patients given large doses of intravenously administered Vancomycine. Rare cases of interstitial nephritis have been reported. Most occurred in patients who were given aminoglycosides concomitantly or who had pre-existing kidney dysfunction. When Vancomycine was discontinued, azotaemia resolved in most patients.

Ototoxicity: Hearing loss associated with intravenously administered Vancomycine has been reported. Most of these patients had kidney dysfunction, pre-existing hearing loss, or concomitant treatment with an ototoxic drug. Vertigo, dizziness and tinnitus have been reported rarely.

Haematological: Reversible neutropenia, usually starting one week or more after onset of intravenous therapy or after a total dose of more than 25g. Neutropenia appears to be promptly reversible when Vancomycine is discontinued. Thrombocytopenia has rarely been reported. Reversible agranulocytosis (less than 500 granulocytes per mm3) has been reported rarely, although causality has not been established.

Miscellaneous: Phlebitis, hypersensitivity reactions, anaphylaxis, stridor, nausea, chills, drug fever, decrease in blood pressure, thrombophlebitis, eosinophilia, rashes (including exfoliative dermatitis) and rare cases of vasculitis. Vancomycine has been associated with the bullous eruption disorders Stevens-Johnson syndrome, toxic epidermal necrolysis, exanthema and mucosal inflammation, Lyell's syndrome and linear IgA bullous dermatosis. If a bullous disorder is suspected, the drug should be discontinued and specialist dermatological assessment should be carried out.

	- pseudomembranous enterocolitis after intravenous administration.
Skin and subcutaneous tissue disorders	Common - exanthema and mucosal inflammation, - pruritus, - urticaria. Very Rare - exfoliative dermatitis, - Stevens-Johnson syndrome, - Lyell's syndrome, - IgA induced bullous dermatitis.
Renal and urinary disorders	Common - renal insufficiency manifested primarily by increased serum creatinine or serum urea concentrations. Rare - interstitial nephritis, - acute renal failure.
General disorders and administration site conditions	Common - redness of the upper body and the face, - pain and spasm of the chest and back muscles. Rare - drug fever, - shivering.

During or shortly after rapid infusion anaphylactic reactions may occur, including hypotension, dyspnea, urticaria or pruritus. The reactions abate when administration is stopped, generally between 20 minutes and 2 hours after having stopped administration.
Ototoxicity has primarily been reported in patients given high doses, or concomitant treatment with other ototoxic medicinal products, or with pre-existing reduction in kidney

function or hearing. After oral administration, as vancomycine could be absorbed in case of digestive lesion, the risk of the above mentioned undesirable effects described cannot be eliminated.		
Toxicity due to overdose has been reported. 500 mg IV to a child, 2 year of age, resulted in lethal intoxication. Administration of a total of 56 g during 10 days to an adult resulted in renal insufficiency. In certain high-risk conditions (e. g. in case of severe renal impairment) high serum levels and oto- and nephrotoxic effects can occur. *Measures in case of overdose* • A specific antidote is not known. • Symptomatic treatment while maintaining renal function is required. Vancomycin is poorly removed from the blood by haemodialysis or peritoneal dialysis. Haemofiltration or haemoperfusion with polysulfone resins have been used to reduce serum concentrations of vancomycin.	Supportive care is advised, with maintenance of glomerular filtration. Vancomycine is poorly removed from the blood by haemodialysis or peritoneal dialysis. Haemoperfusion with Amberlite resin XAD-4 has been reported to be of limited benefit.	**4.9 Overdose**
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity. Limited data on mutagenic effects show negative results, long-term studies in animals regarding a carcinogenic potential are not available. In teratogenicity studies, where rats and rabbits received doses approximately corresponding to the human dose based on body surface (mg/m^2), no direct or indirect teratogenic effects were observed. Animal studies of the use during the perinatal/postnatal period and regarding effects on fertility are not available.	Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of vancomycin was found in standard laboratory tests. No definitive fertility studies have been performed.	**5.3 Preclinical safety data**

פרטים על השינוי/ים המבוקש/ים		
פרק בעלון	טקסט נוכחי	טקסט חדש
	לא רלוונטי.	