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REVIEW

Glomerular hyperfiltration of antibiotics

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Abstract

Normal glomerular filtration rate (GFR) declines with age and in disease. Diminished GFRs are seen in many patients on the ICU. The clearance of toxins and pharmaceuticals might be (temporarily) diminished especially in patients with septic or circulatory shock. Most physicians are aware of this and adjust the dosage of antibiotics accordingly: the dosage is reduced or the administration interval is prolonged. However, some patients have an increased clearance of antimicrobials, so-called glomerular hyperfiltration. Glomerular hyperfiltration is present whenever the GFR exceeds 160 ml/min/1.73 m^2 in men and 150 ml/min/1.73 m^2 in women. This is especially seen in young, male patients after neurotrauma, polytrauma or burn patients. The consequences of glomerualr hyperfiltration might be that antibiotics are cleared more rapidly and concentrations fall below optimal levels. This compromises effective antimicrobial therapy when it is most important: directly from the beginning of treatment. Therapeutic Drug Monitoring (TDM) of all classes of antibiotics is needed in ICUs that treat critically ill patients at risk of glomerular hyperfiltration.

Acute kidney injury on the ICU

Acute kidney injury is a common complication of acute illness, affecting approximately 2-7% of hospitalised patients and more than 35% of critically ill patients.[1] Acute kidney injury (AKI) consists of a rapid and sustained decline in the glomerular filtration rate (GFR) that results in the inability of the kidneys to eliminate waste products, toxins, antibiotics and other medications, or to maintain proper fluid and electrolyte balances.[2] Most ICUs measure creatinine levels on a daily basis. Whenever creatinine levels increase (and estimated GFRs diminish) we interpret these changes as renal dysfunction, particularly in combination with oliguria (urine output <0.5 mL/kg/h). Whenever this occurs, most clinicians are quite eager to modify their dosage schemes of renally excreted antibiotics: either the dosage is reduced or the administration interval is prolonged. However, it remains questionable whether this is a sound decision in all circumstances.

Hyperdynamic circulation and glomerular hyperfiltration

The hemodynamic manifestations Systemic Inflammatory Response Syndrome (SIRS) are low systemic vascular resistance and a high cardiac output. The impact of this hyperdynamic circulation upon renal function is still being studied. In animal models of early sepsis, renal blood flow has been documented to increase parallel to cardiac output.[10] In a later phase of sepsis the renal blood flow is diminished, resulting in decreased creatinine clearance.[11] One of the first measures to improve cardiovascular function in patients with SIRS is fluid resuscitation followed by the application of vasopressors. Again, animal research has shown that crystalloids and vasoactive drugs can result in an increase of creatinine clearance.[12,13] Data from these studies suggest that in critically ill patients without significant renal dysfunction and in whom adequate resuscitation has been achieved, renal clearance might actually be increased in the acute phase: this is known as glomerular hyperfiltration.

How do we measure GFR when renal function is unstable?

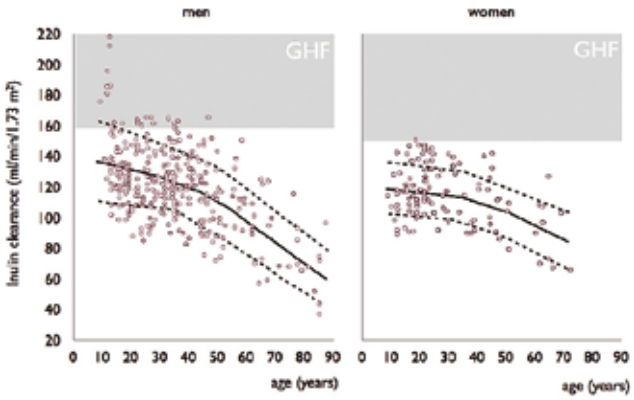
The gold standard estimations of GFR include urinary clearance of iohexal and clearance of various radionuclide markers, among which 99mTc-labeled diethylenetriaminepentaacetic acid (DTPA), 51Cr-labeled EDTA, and 125I-labeled iothalamate.[9] However, these test methods are cumbersome and are almost never used in daily practice. Numerous equations have been used to estimate the GFR from serum creatinine levels in patients with chronic kidney diseases. The Modification of Diet in Renal Disease (MDRD), the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and

Cockcroft-Gault formula are the most widely used estimations for GFR in patients with chronic but stable kidney disease. Unfortunately, all have a poor application in the critically ill, especially when renal function is not stable.[3-5] Although these calculations are somewhat more useful than a single creatinine concentration, the use of such equations to estimate the GFR should be discouraged in critically ill patients.[3,6,7] A possible better way to estimate GFR in critically ill patients is a urinary creatinine collection taken over 4 to 12 hours.[8,9] However, the optimal time period in which creatinine clearance should be measured in unstable critically ill patients is still debatable. The GFR is influenced by circadian rhythm and intra-individual variability is likely to be substantial. Because rapid changes in renal function might occur in the critically ill, more frequent sampling of urine creatinine collection has been advocated.

What is glomerular hyperfiltration?

One of the most important functions of the kidney is to excrete circulating metabolites, toxins, waste products and pharmaceutical products such as antibiotics. This can be achieved by a combination of glomerular filtration, tubular secretion and reabsorption. Glomerular hyperfiltration means that the renal clearance of waste products and antibiotics is above normal limits. Accurately defining this is difficult because we cannot agree upon "normal renal function" in any population, let alone in critically ill patients! However, the most accepted definition of "normal renal function" is the GFR of approximately 130 mL/min/1.73 m^2 in young, healthy, adult males and 120 ml/min/1.73 m^2 in young, healthy, adult females.[14] Importantly, these values decline over age (*figure 1*). One of the most sensible definitions of "glomerular hyperfiltration" is a GFR >10% higher than the normal limits. This means a GFR of >160 mL/min/1.73 m^2 in young men and a GFR >150 mL/min/1.73 m^2 in young women.[8] These conservative thresholds are likely to identify patients that truly have "glomerular hyperfiltration". In a single-centre observational cohort (n=89) 17.9% of the patients had such "glomerular hyperfiltration" on admission and 75% had hypoalbuminaemia.[15] During the first week of admission, the percentage of patients with glomerular hyperfiltration rose to 30%. The patients with an elevated GFR were primarily younger, polytrauma victims or postoperative patients, were less severely ill (lower APACHE II scores) and had higher urine outputs. In a subgroup of patients with traumatic brain injury, who received norepinephrine treatment, increased creatinine clearance had been noticed. These increased GFRs (>150 mL/min/1.73 m^2) were already present before the initiation of norepinephrine treatment and remained elevated for the duration of this study (24 hours).[16] Quite similar results had been found in a much older study. Here the effects of a combination of dopamine and norepinephrine were studied in 20 young, stable patients with brain trauma. The mean GFR at

Figure 1. Declining creatinine clearances over age.



Normal values for inulin clearance are shown for men and women of various ages, with the GFR measured as the urinary clearance of inulin. A GFR value of 60 ml/min/1.73 m^2 is the threshold for the definition of chronic kidney disease. Solid lines represent the mean value of GFR per decade of age, and dashed lines represent the value 1 standard deviation from the mean value of GFR per decade of age. A GFR >160 ml/min/1.73 m^2 in men and >150 ml/min/1.73 m^2 in women is considered glomerular hyperfiltration (grey area). Adapted from Stevens et al. NEJM 2006;354:2473-2483. With permission from the Massachusetts Medical Society.

the beginning of the study was 152 mL/min/1.73 m^2.[17] Recently these results have been confirmed in another study involving patients with brain trauma.[7] Based upon the definitions of glomerular hyperfiltration as stated above, they found that in 17 out of 20 (85%) patients, renal clearance was clearly increased (mean GFR of 179 with interquartile range of 159-198 mL/min/1.73 m^2). The mean age of this population was 26 years and they were receiving 3% NaCl infusions and vasopressor therapy to maintain a cerebral perfusion pressure >60 mmHg. From these small and uncontrolled case series, which all used proper creatinine clearance in urine samples, it follows that younger patients, admitted after trauma and/or brain trauma are at particular risk of developing glomerular hyperfiltration. However, higher than normal antimicrobial clearances have been documented in patients with sepsis[18,19], haematological malignancies[20,21] and patients with burns[22,23] as well.

What are the consequences of glomerular hyperfiltration?

Why should we be bothered with glomerular hyperfiltration? A faster excretion of waste products and toxins is a good thing and the effects of other pharmaceuticals can be dosed according to their pharmacodynamic effect. If midazolam metabolites are excreted in a more rapid fashion, we will just increase the infusion rates until the patient is sufficiently sedated. Unfortunately, not all effects of pharmaceuticals are directly evident. If antibiotics are administered inadequately

this might result in slower eradication of the infection or even introduce resistance.[24] Unfortunately, resolution of infection takes time and recognizing whether the antibiotics are working properly will take days. Therefore, glomerular hyperfiltration might be the cause of ineffective antimicrobial therapy just at the time when it counts most: at the start of treatment!

Pharmacodynamics and glomerular hyperfiltration

Different classes of antibiotics possess different pharmacodynamic properties. Some antibiotics have concentration dependent killing, while others typically demonstrate time depending killing (see *figure 2*).

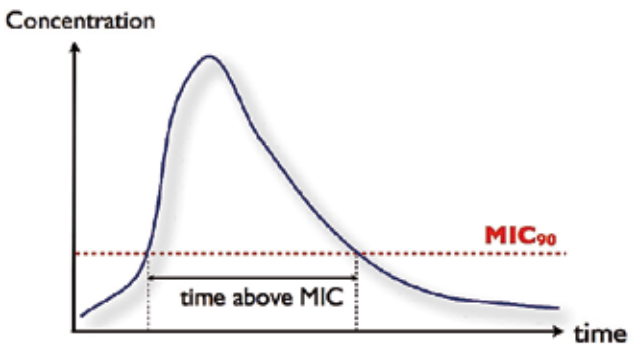
Aminoglycosides, like gentamicin and tobramycin, are classical examples of antibiotics that exhibit concentration dependent killing properties. The higher the peak concentration (also called maximum concentration, C_{max}) in relation to the minimum inhibitory concentration (MIC) of a bacterium the better the killing.[25] The killing of bacteria is optimal whenever the C_{max}/MIC >10. This means that the peak concentration of an aminoglycoside, in the organ you are trying to treat, should be 10x higher than the MIC of the bacterium. The peak concentration depends on the loading dose of the aminoglycoside and its immediate dilution in the extracellular fluid compartment (the so-called volume of distribution, V_d). Aminoglycosides are hydrophilic, rather large molecules. Therefore, their apparent V_d is rather small (no penetration into cells, no penetration into lipophilic compartments) and almost the entire aminoglycoside loading dose is present in a free and unbound fashion. Modern dosage schemes are >7 mg/kg once daily.[25,26] Glomerular hyperfiltration will not influence the V_d and therefore have no influence on the loading dose. However, the clearance of aminoglycosides might be faster than in patients with a normal GFR. Therefore, the frequency of the maintenance dose might be increased to once every 18 hours instead of once daily.[8] Indeed, the V_d of aminoglycosides is unpredictable in critically ill patients and the penetration into organs (like the lung and the abdominal cavity) is limited.[27,28] As a consequence, the pharmacodynamic goal (C_{max}/MIC>10) is often not attained in critically ill patients.[27]

Beta-lactam antibiotics (penicillins, cephalosporins, monobactams and carbapenems) demonstrate time dependent killing (see *figure 2*). This means that the killing of bacteria by beta-lactam antibiotics is maximal whenever the free and unbound concentration of beta-lactams is higher than the minimum inhibitory concentration (*fu*T>MIC) during 70-100% of the time.[7,25] Again, the direct concentration depends on the loading dose and its immediate dilution into the V_d. Unfortunately, the V_d can be highly variable in critically ill patients. Just consider a patient in septic shock who is being aggressively resuscitated with fluids. In such patients, the V_d for hydrophilic antimicrobials (like aminoglycosides, beta-lactams, and vancomycin) might even be doubled. For this reason, a one-size-fits-all loading dose cannot be established in critically ill patients.

However, the trough levels (also called minimum levels, C_{min}) are dependent on binding to proteins and excretion by the liver and kidneys. Whenever there is glomerular hyperfiltration, the beta-lactams will be excreted more efficiently and minimal levels will be reached earlier. Given the pharmacodynamic goal of keeping the trough level above the MIC for as long as possible, the dosage frequency may have to be increased. Just giving higher dosages might lead to higher free fractions and more clearance of antibiotics. An alternative is to administer beta-lactams by continuous infusion. Theoretically the trough levels will be above MIC for all of the time (*fu*T>MIC = 100%). Again, in critically ill patients the volume of distribution and renal clearance are not stable over time.

The range of protein binding of beta-lactams is enormous. Some beta-lactams are predominantly bound to albumin, like ceftriaxone (85-95% is protein bound), while others are hardly bound to albumin, like amoxicillin (17-20% is protein bound).[29] Unfortunately, critically ill patients often have hypoalbuminaemia. In the Saline versus Albumin Fluid Evaluation (SAFE)-study, hypoalbuminaemia (<25 g/L) was seen in 40.5% of the patients on admission to the ICU.[30] Hypoalbuminaemia

Figure 2. Concentration dependent killing and time dependent killing.



Some antibiotics exhibit so-called concentration-dependent killing properties. This means that the higher the peak concentration in relation to minimum inhibitory concentration where 90% of the bacteria are killed (MIC_{90}) the better bacteria are killed (peak/MIC-ratio). A peak/MIC-ratio >10 results in optimal killing for aminoglycosides, like gentamicin and tobramycin.

Other antimicrobials exhibit time dependent killing properties (e.g. beta-lactam antibiotics, like penicillins, cephalosporins, monobactams and carbapenems). This means that the longer the concentration stays above the MIC the better the bacteria are killed. Peak concentrations are not needed. The free and unbound concentration of beta-lactams (fuT>MIC) needs to be above the MIC 70-100% of the time for optimal killing.

Table 1. Suggested reading

Suggested reading
Marta Ulldemolins and co-authors emphasise how often hypoalbuminaemia is seen in the ICU. They highlight the consequences of hypoalbuminaemia on different classes of antibiotics. A list of antibiotics with their estimated protein binding is included. Clin Pharmacokinet. 2011;50:99-110.
Frederico Pea and Pierluigi Viale describe which chemical properties are important for an antimicrobial in order to reach its target organ. They also explain the concentration needed for optimal killing and conclude that certain antimicrobials (especially the aminoglycosides) do not attain sufficient concentrations in target organs. This seriously limits their use. A list with proposed antimicrobial dosage schemes is included. Crit Care. 2009;13:214.
Andrew Udy and co-authors describe the consequences of augmented renal clearance (=glomerular hyperfiltration) of various antibiotic classes. They describe the difficulties of assessing glomerular filtration rate in critically ill patients and suggest that creatine clearance in urine is probably the best estimation. Clin Pharmacokinet. 2010;49:1-16.

results in a higher free and unbound antibiotic fraction. Although this means that the "active fraction" has increased it also means that the fraction available for renal clearance is higher. This is particularly true for beta-lactam antibiotics with a high protein binding, like ceftriaxone. In patients with hypoalbuminaemia (and normal GFR) ceftriaxone clearance might be doubled, leading to trough levels below the MIC too early.[31] The pharmacodynamic goal (*fu*T>MIC 70-100%) might, therefore, not be reached.

Clearly, we cannot predict the initial V_d, the GFR and the hypoalbuminaemia in critically ill patients and changes over time are commonplace on the ICU. A prerequisite for the administration of beta-lactams in critically ill patients is therapeutic drug monitoring (TDM). We have to assure whether the free and unbound trough levels remain above the MIC whenever something changes in our patients. Additionally, TDM can minimise the risk of toxicity in excessive dosing. At present only very few hospitals in the Netherlands are able to provide this necessary TDM.

Conclusions

Glomerular hyperfiltration (>150 ml/min/1.73m^2 in women and >160 ml/min/1.73 m^2 in men) is seen in a substantial subpopulation on the ICU. Especially younger patients with neurotrauma, polytrauma, burns or sepsis, appear to be at risk of higher than normal clearance of antibiotics. In addition, hypoalbuminaemia causes higher free and unbound fractions of antibiotics, and thereby further increases renal clearance of protein bound antibiotics. Both lead to suboptimal concentrations of antibiotics and possibly less effective antimicrobial therapy. Creatinine concentrations and estimations of the glomerular filtration rate (GFR) are inadequate for measuring such elevated clearance in clinical practice. Because rapid changes in renal function might occur in the critically ill, measuring creatinine clearance with short period urine collections seems the best available option. All kinds of pharmacokinetic conditions, like hypoalbuminaemia, clearance and volume of distribution, are constantly changing in critically ill patients. Therefore, Therapeutic Drug Monitoring (TDM) of all antimicrobials (including beta-lactam antibiotics) should be available in hospitals treating critically ill patients.

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VERKORTE PRODUCTINFORMATIE
CANCIDAS® 50 mg poeder voor concentraat voor oplossing voor intraveneuze infusie.
CANCIDAS® 70 mg poeder voor concentraat voor oplossing voor intraveneuze infusie.
Samenstelling
CANCIDAS 50 mg bevat 50 mg caspofungin (als acetaat).
CANCIDAS 70 mg bevat 70 mg caspofungin (als acetaat).
Indicaties
- Behandeling van invasieve candidiasis bij volwassen patiënten of kinderen.
- Behandeling van invasieve aspergillose bij volwassen patiënten of kinderen die niet reageren op amfotericine B, toedieningsvormen van amfotericine B met lipiden en/of itraconazol of deze niet verdragen.
- Empirische therapie voor vermoede schimmelinfecties (zoals *Candida* of *Aspergillus*) bij volwassen patiënten of kinderen met koorts en neutropenie.

Contra-indicaties
Overgevoeligheid voor het actieve bestanddeel of één van de hulpstoffen.
Waarschuwingen en voorzorgen
De werkzaamheid van caspofungine tegen de minder vaak voorkomende niet-*Candida*-gisten en niet-*Aspergillus*-schimmels is niet vastgesteld.
Bij gelijktijdig gebruik van CANCIDAS met ciclosporine werden geen ernstige bijwerkingen aan de lever opgemerkt. Sommige gezonde volwassen vrijwilligers die ciclosporine samen met caspofungine kregen, vertoonden een voorbijgaande verhoging van het alaninetransaminase (ALT) en aspartaattransaminase (AST) van minder dan of gelijk aan 3 maal de bovenste waarde van het normale bereik (ULN), die bij stopzetting van de behandeling verdween. CANCIDAS kan gebruikt worden bij patiënten die ciclosporine krijgen als de mogelijke voordelen opwegen tegen de potentiële risico's. Zorgvuldige controle van de leverenzymen moet worden overwogen als CANCIDAS en ciclosporine gelijktijdig worden gebruikt.
Bij een matige leverfunctiestoornis wordt een verlaging van de dagelijkse dosis naar 35 mg aanbevolen. Er is geen klinische ervaring met ernstige leverinsufficiëntie of bij kinderen met elke mate van leverinsufficiëntie. Te verwachten valt dat de blootstelling hoger is dan bij matige leverinsufficiëntie; bij deze patiënten moet CANCIDAS voorzichtig worden toegepast.
De gegevens over de veiligheid van een behandeling die langer duurt dan 4 weken zijn beperkt.
Bijwerkingen
Volwassen patiënten
Flebitis was in alle patiëntpopulaties een vaak gemelde lokale bijwerking op de injectieplaats. Andere lokale reacties waren erytheem, pijn/gevoeligheid, jeuk, afschеiding, en een brandend gevoel.
De gemelde klinische en laboratoriumafwijkingen bij alle met CANCIDAS behandelde volwassenen waren over het algemeen licht en maakten zelden stopzetting noodzakelijk.
De volgende bijwerkingen zijn gemeld:
[Zeer vaak (≥1/10), Vaak (≥1/100 tot <1/10), Soms (≥1/1.000 tot <1/100)]
Vaak: verlaagd hemoglobine, verlaagd hematocriet, verminderd aantal leukocyten, hypokaliëmie, hoofdpijn, flebitis, dyspnoe, misselijkheid, diarree, braken, verhoogde leverwaarden (AST, ALT, alkalische fosfatase, direct en totaal bilirubine), uitslag, pruritus, erytheem, hyperhidrose, artralgie, koorts, rillingen, pruritus op infusieplaats.
Soms: anemie, trombocytopenie, coagulopathie, leukopenie, verhoogd aantal eosinofielen, verminderd aantal trombocyten, verhoogd aantal trombocyten, verminderd aantal lymfocyten, verhoogd aantal leukocyten, verminderd aantal neutrofielen, vochtophoping, hypomagnesiëmie, anorexia, gestoorde elektrolytenbalans, hyperglykemie, hypocalciëmie, metabole acidose, angst, desoriëntatie, slapeloosheid, duizeligheid, dysgeusie, paresthesie, slaperigheid, tremoren, hypo-esthesie, oculaire icterus, wazig zien, oedeem van het ooglid, verhoogde traanvorming, palpitaties, tachycardie, aritmieën, atriumfibrilleren, hartfalen, tromboflebitis, flushing, opvliegers, hypertensie, hypotensie, verstopte neus, faryngolaryngeale pijn, tachypnoe, bronchospasmen, hoest, paroxysmale dyspnoe 's nachts, hypoxie, rhonchi, wheezing, buikpijn, pijn in de bovenbuik, droge mond, dyspepsie, last van de maag, opgezwollen buik, ascites, constipatie, dysfagie, winderigheid, cholestase, hepatomegalie, hyperbilirubinemie, geelzucht, gestoorde leverfunctie, hepatotoxiciteit, leveraandoening, erythema multiforme, maculaire uitslag, maculopapulaire uitslag, pruritische uitslag, urticaria, allergische dermatitis, gegeneraliseerde pruritus, erythemateuze uitslag, gegeneraliseerde uitslag, morbilliforme uitslag, huidlaesie, rugpijn, pijn in extremiteiten, botpijn, spierzwakte, myalgie, nierfalen, acuut nierfalen, pijn, pijn rond catheter, vermoeidheid, koud gevoel, warm gevoel, erytheem op infusieplaats, verharding op infusieplaats, pijn op infusieplaats, zwelling op infusieplaats, flebitis op injectieplaats, perifeer oedeem, gevoeligheid, ongemak op de borst, pijn op de borst, aangezichtsoedeem, gevoel van andere lichaamstemperatuur, verharding, extravasatie op infusieplaats, irritatie op infusieplaats, flebitis op infusieplaats, uitslag op infusieplaats, urticaria op infusieplaats, erytheem op injectieplaats, oedeem op injectieplaats, pijn op injectieplaats, zwelling op injectieplaats, malaise, oedeem.
Onderzoeken:
Vaak: verlaagd kalium in bloed, verlaagd bloedalbumine.
Soms: verhoogd bloedcreatinine, positief voor rode bloedcellen in urine, verlaagd totaal eiwit, eiwit in urine, verlengde protrombinetijd, verkorte protrombinetijd, verlaagd natrium in bloed, verhoogd natrium in het bloed, verlaagd calcium in bloed, verhoogd calcium in bloed, verlaagd chloride in bloed, verhoogd glucose in bloed, verlaagd magnesium in bloed, verlaagd fosfor in bloed, verhoogd fosfor in bloed, verhoogd ureum in bloed, verhoogd gamma-glutamyltransferase, verlengde geactiveerde partiële tromboplastinetijd, verlaagd bicarbonaat in bloed, verhoogd chloride in bloed, verhoogd kalium in bloed, verhoogde bloeddruk, verlaagd urinezuur in bloed, bloed in urine, afwijkende ademgeluiden, verlaagd kooldioxide, verhoogde concentratie immunosuppressivum, verhoogde INR, cilinders in urinesediment, positief op witte bloedcellen in urine, en verhoogde pH van urine.
Kinderen
Het algehele veiligheidsprofiel van CANCIDAS bij kinderen is over het algemeen vergelijkbaar met dat bij volwassenen.
Zeer vaak: koorts.
Vaak: verhoogd aantal eosinofielen, hoofdpijn, tachycardie, flushing, hypotensie, verhoogde leverenzymen (AST, ALT), uitslag, pruritus, rillingen, pijn op de injectieplaats.
Onderzoeken:
Vaak: verlaagd kalium, hypomagnesiëmie, verhoogd glucose, verlaagd fosfor en verhoogd fosfor.
Post-marketingervaring
Sinds de introductie van het product zijn de volgende bijwerkingen gemeld:
leverfunctiestoornis, zwelling en perifeer oedeem, hypercalciëmie.

Farmacotherapeutische groep
Antimycotica voor systemisch gebruik, ATC-code: J 02 AX 04
Afleverstatus
UR
Verpakking
CANCIDAS 50 mg is beschikbaar in een verpakking met 1 injectieflacon.
CANCIDAS 70 mg is beschikbaar in een verpakking met 1 injectieflacon.
Vergoeding
CANCIDAS wordt volledig vergoed.
Raadpleeg de volledige productinformatie (SPC) voor meer informatie over CANCIDAS.

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