Linezolid

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.3. Reserve group antibiotics

EMLc | Codes ATC: J01XX08

Indication	Vancomycin resistant Enterococcus — Code ICD11: MG51.20
INN	Linezolid
Type de médicament	Chemical agent
Groupes d'antibiotiques	R RESERVE
Type de liste	Liste complémentaire
Additional notes	The square box applies only to the listing of linezolid on the EML
Formulations	**Parenteral > General injections > IV:** 2 mg per mL in 300 mL bag **Oral > Liquid:** 100 mg per 5 mL powder for oral liquid **Oral > Solid > dispersible tablet:** 150 mg (EMLc) **Oral > Solid > tablet:** 600 mg (EML)
Historique des statuts LME	Ajouté pour la première fois en 2019 (TRS 1021) Modifié en 2023 (TRS 1049)
Sexe	Tous
Âge	Aussi recommandé pour les enfants
Équivalence thérapeutique	tedizolid (Codes ATC: J01XX11)
Renseignements sur le brevet	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Lire la suite sur les brevets.
Wikipédia	Linezolid
DrugBank	Linezolid

Recommandation du comité d'experts

1. Application for the addition of tedizolid phosphate to the complementary list of the EML as a reserve group antibiotic for use in the treatment of confirmed or suspected acute skin and skin structure infections caused by susceptible Gram-positive bacteria, including multidrug-resistant strains. The Expert Committee noted that MRSA remains a major cause of severe bacterial infections in many settings, and that the pathogen is designated by WHO as high priority for which new therapeutic options are needed. The Committee acknowledged the activity of tedizolid phosphate against high-priority drug-resistant Gram-positive pathogens, mainly S. aureus including MRSA and also vancomycin-resistant enterococci. The Committee noted that clinical trial data suggest tedizolid phosphate is non-inferior to linezolid for the treatment of acute bacterial skin and skin structure infections, including infections caused by MRSA. The Committee also noted the advice of the EML Antimicrobial Working Group that tedizolid phosphate is associated with less bone marrow suppression and gastrointestinal toxicity than linezolid and that it is administered once daily for generally shorter treatment courses than linezolid which is administered twice daily . The Committee noted that the application failed to include any information on the cost and cost–effectiveness of tedizolid phosphate. The Expert Committee also noted the advice of the EML

Antimicrobial Working Group that tedizolid phosphate is more expensive than linezolid and is still under patent protection (either primary or secondary) until at least 2030, whereas linezolid is already available in generic versions. Taking these issues into consideration, the Expert Committee recommended the inclusion of tedizolid phosphate as a Reserve group antibiotic on the EML as a therapeutic alternative to linezolid under a square box listing. The representative medicine should be linezolid because of its wider availability and lower price. The Committee noted that the application requested inclusion specifically for treatment of acute bacterial skin and skin structure infections. However, the Committee recommended that tedizolid phosphate be included on the EML for the same indications as linezolid, which are currently pathogen- rather than infection-based, namely infections caused by MRSA, vancomycin-resistant S. aureus and vancomycin-resistant enterococci. ======= 2. Review of the age-appropriateness of formulations of essential medicines for children. In consideration of the review of the age appropriateness of formulations of medicines on the EMLc, and the comparison report of the EML versus EMLc, the Expert Committee recommended changes to the EMLc for addition of new, age-appropriate formulations and strengths of existing essential medicines, deletion of unavailable or age-inappropriate formulations and strengths, and other listing modifications as proposed in the application. The Committee also endorsed the proposals for further review of the public health relevance and evidence for specific medicines for use in children for potential future consideration for inclusion on the EMLc. The Committee noted and welcomed the ongoing review being coordinated by the Secretariat for the remaining sections of the EMLc for consideration by the 2025 Expert Committee. As a result of the review of the age-appropriateness of formulations on the EMLc, the Expert Committee recommended the addition of linezolid 150 mg dispersible tablets to the EMLc, the removal of linezolid 400 mg tablets from the EML and EMLc, and the removal of linezolid 600 mg tablets from the EMLc.

Contexte

1. Application for the addition of tedizolid phosphate to the complementary list of the EML as a reserve group antibiotic for use in the treatment of confirmed or suspected acute skin and skin structure infections caused by susceptible Gram-positive bacteria, including multidrug-resistant strains. Tedizolid phosphate has not previously been considered for inclusion on the EML. It is classified as a Reserve group antibiotic under the AWaRe (Access–Watch–Reserve) classification. =======

Pertinence pour la santé publique

1. Application for the addition of tedizolid phosphate to the complementary list of the EML as a reserve group antibiotic for use in the treatment of confirmed or suspected acute skin and skin structure infections caused by susceptible Gram-positive bacteria, including multidrug-resistant strains. Worldwide in 2019, an estimated 4.95 million people died with drug-resistant bacterial infections. Of these deaths, 1.27 million were directly attributable to resistant infections and most were concentrated in low- and middle-income countries. Methicillin-resistant Staphylococcus aureus (MRSA) remains one of the most important causes of antimicrobial resistance and hospital-acquired infections worldwide. In 2019, it was estimated that drug-resistant S. aureus infections were responsible for 178 000 deaths globally – almost a quarter of all deaths caused by drug-resistant organisms (1). In 2017, WHO designated vancomycin-resistant S. aureus and MRSA as high priority pathogens in need of new therapeutic options (2). =======

Bénéfices

1. Application for the addition of tedizolid phosphate to the complementary list of the EML as a reserve group antibiotic for use in the treatment of confirmed or suspected acute skin and skin structure infections caused by susceptible Gram-positive bacteria, including multidrug-resistant strains. In-vitro studies The application stated that tedizolid (the active metabolite of the prodrug tedizolid phosphate) has demonstrated at least four-fold greater potency in vitro against susceptible strains of staphylococci (including MRSA), enterococci and streptococci compared with linezolid, based on a minimum inhibitory concentration to inhibit growth of 90% of organisms (MIC90) (3,4). There is no cross-resistance with linezolid-resistant cfr-positive S. aureus in the absence of chromosomal mutations (5). Randomized clinical trials ESTABLISH 1 was a randomized, double-blind, non-inferiority, phase III trial comparing oral tedizolid (200 mg once daily for 6 days) with oral linezolid (600 mg twice

daily for 10 days) for the treatment of 667 adults with acute bacterial skin and skin structure infections (6). The primary endpoint was clinical response defined as ≥ 20% decrease from baseline in lesion area at 48–72 hours. Results of the sensitivity analysis in all randomized patients (i.e. intention-to-treat population) showed that 78.0% of patients in the tedizolid group and 76.1% in the comparator group met the primary endpoint (absolute treatment difference 1.9%, 95% confidence interval (CI) –4.5% to 8.3%) favouring tedizolid but with no statistically significant difference between the two groups. Tedizolid met the criteria for non-inferiority to linezolid with a prespecified 10% margin. Of note, the sensitivity analysis excluded temperature 37.6 °C at 48–72 hours as a variable for the definition of clinical response. For the intention-to-treat population, sustained clinical response measured at the end of treatment (day 11 relative to the first dose) was 69.3% in the tedizolid group and 71.9% in the linezolid group (absolute treatment difference –2.6%, 95% CI –9.6% to 4.2%). Clinical response 7–14 days after the end of treatment was 85.5% in the tedizolid group and 86.0% in the linezolid group (difference –0.5%, 95% CI –5.8% to 4.9%). ESTABLISH 2 was a randomized, double-blind, non-inferiority, phase III trial comparing the same regimens compared in the ESTABLISH 1 trial but with an intravenous to oral switch. A total of 666 patients were randomized to receive either tedizolid (n = 332) or linezolid (n = 334) (7). All baseline pathogens were susceptible to vancomycin and linezolid. For the primary efficacy endpoint (≥ 20% decrease from baseline in lesion area at 48–72 hours), in the intention-to-treat population, 85% (283/332) in the tedizolid group and 82.6% in the comparator group responded to treatment (treatment difference 2.6%, 95% CI –3.0% to 8.2%). Tedizolid met the criteria for non-inferiority to linezolid with a prespecified 10% margin. Other endpoints evaluated in the intention-to-treat population included clinical success 7–14 days after the end of treatment (88.0% in the tedizolid group and 87.7% in the comparator group; treatment difference 0.3%, 95% CI –4.8% to 5.3%) and clinical success at the day 11 end of treatment (87.0% in the tedizolid group and 88.0% in the linezolid group; treatment difference –1.0%, 95% CI –6.1% to 4.1%). The primary efficacy endpoint in patients with MRSA infections was evaluated by pooling ESTABLISH 1 and ESTABLISH 2 results in the microbiological intention-to-treat population. In this subgroup analysis, clinical success was reported in 83.7% (118/141) of patients in the tedizolid group and 81.5% (119/146) in the comparator group. In these trials, MRSA was the causative pathogen in 16–27% of all patients and 27–43% of patients with a positive culture. Observational studies The application reported the results of a case series of four patients with cellulitis and wound infections treated with tedizolid phosphate (8). Two were obese patients with severe cellulitis complicated by sepsis and myositis: one patient received tedizolid after failure of first-line therapy with cefalotin, clindamycin and imipenem, and the other was started on tedizolid and clindamycin but clindamycin was stopped on day 3 due to an adverse event. Both patients improved within 72 hours of starting tedizolid with normalized laboratory results within a week. A third patient had a surgical site infection and was treated empirically with tedizolid for 7 days because of a history of previous MRSA bacteraemia; this patient and had a clinical response within 72 hours. The fourth patient also had a surgical site infection treated with tedizolid for 14 days and also improved within 72 hours. =======

Torts

1. Application for the addition of tedizolid phosphate to the complementary list of the EML as a reserve group antibiotic for use in the treatment of confirmed or suspected acute skin and skin structure infections caused by susceptible Gram-positive bacteria, including multidrug-resistant strains. Safety data from the ESTABLISH 1 and ESTABLISH 2 trials were reported in the application (6,7). Overall, the proportion of patients experiencing drug-related treatment-emergent adverse events was similar between groups (22.4% and 27.9% in the tedizolid phosphate and linezolid groups, respectively). Less than 0.5% were serious (0 events with tedizolid and 2 with linezolid). Fewer patients in the tedizolid group had gastrointestinal adverse events (16.0% versus 23.0%) and low platelet counts (< 150 000 cells/mm3) during the postbaseline period (6.5% with tedizolid versus 12.6% with linezolid). Tedizolid was not associated with nephrotoxicity or postbaseline serum creatinine, and blood urea nitrogen increase was low (< 0.5%) in both treatment groups. Tedizolid is a weak and reversible inhibitor of monoamine oxidase. The interaction with monoamine oxidase inhibitors could not be evaluated in the phase III trials as the patients receiving these medicines were excluded because linezolid has a warning in its prescribing information against use in patients using serotonergic psychiatric medications because of the potential risk of serotonin syndrome. However, based on a murine serotonergic model, tedizolid has not shown a propensity for

serotonergic effects when given at doses up to almost 30 times higher than the human equivalent (9). Based on this evidence, the United States Food and Drug Administration has not put any warning or restriction for the use of tedizolid with serotonergic medications. =======

Preuves supplémentaires

1. Application for the addition of tedizolid phosphate to the complementary list of the EML as a reserve group antibiotic for use in the treatment of confirmed or suspected acute skin and skin structure infections caused by susceptible Gram-positive bacteria, including multidrug-resistant strains. A randomized, double-blind, phase III study compared tedizolid phosphate with linezolid for treatment of 726 ventilated patients with Gram-positive hospital-acquired or ventilator-associated bacterial pneumonia (10). The overall incidence of MRSA was 31.3%. The primary efficacy endpoints were day 28 all-cause mortality and investigator-assessed clinical response at test of cure in the intention-to-treat population. All-cause mortality at 28 days was 28.2% and 26.4% in the tedizolid and linezolid arms, respectively (treatment difference –1.8%, 95% CI –8.2% to 4.7%). Non-inferiority of tedizolid was demonstrated using a non-inferiority margin of 10%. For investigator-assessed clinical response at test of cure, rates were 56.3% and 63.9% for tedizolid and linezolid groups, respectively (treatment difference –7.6, 97.5% CI –15.7% to 0.5%). Non inferiority of tedizolid was not demonstrated for this outcome measure based on a non-inferiority margin of 12.5%. =======

Rapport coût/efficacité

1. Application for the addition of tedizolid phosphate to the complementary list of the EML as a reserve group antibiotic for use in the treatment of confirmed or suspected acute skin and skin structure infections caused by susceptible Gram-positive bacteria, including multidrug-resistant strains. Information regarding the cost and comparative cost–effectiveness of tedizolid phosphate was not presented in the application. =======

Directives de l'OMS

1. Application for the addition of tedizolid phosphate to the complementary list of the EML as a reserve group antibiotic for use in the treatment of confirmed or suspected acute skin and skin structure infections caused by susceptible Gram-positive bacteria, including multidrug-resistant strains. Tedizolid phosphate is not currently included in existing WHO guidelines. Tedizolid phosphate is included as a treatment option for MRSA skin and soft tissue infections in guidelines issued by the World Society for Emergency Surgery (11), the Surgical Infection Society (12) and in a consensus statement by the Italian Infectious Diseases Society (13). =======

Disponibilité

1. Application for the addition of tedizolid phosphate to the complementary list of the EML as a reserve group antibiotic for use in the treatment of confirmed or suspected acute skin and skin structure infections caused by susceptible Gram-positive bacteria, including multidrug-resistant strains. Tedizolid phosphate has regulatory approval in 43 countries globally, however market availability is limited to only 14 upper middle- and high-income countries. =======

Autres considérations

1. Application for the addition of tedizolid phosphate to the complementary list of the EML as a reserve group antibiotic for use in the treatment of confirmed or suspected acute skin and skin structure infections caused by susceptible Gram-positive bacteria, including multidrug-resistant strains. The AMR Global Coordination department reviewed the application and advised that it supported the inclusion of tedizolid phosphate on the EML as a reserve group antibiotic for treatment of confirmed or suspected infections caused by multidrug-resistant Gram-positive organisms. The technical department stressed that the use tedizolid phosphate must be always informed by evidence-based guidance and strong stewardship activities, and that access and affordability of the medicine must be considered, particularly for patients in low- and middle-income countries. The EML Antimicrobial Working Group reviewed the application and advised that it supported the inclusion of tedizolid phosphate on the

EML as a reserve antibiotic for the treatment of infections caused by multidrug-resistant organisms as a therapeutic alternative to linezolid. The indications for use of tedizolid should be aligned with those for linezolid as described in the WHO AWaRe antibiotic book (14). The Working Group highlighted that MRSA remains a major global public health concern as a cause of severe bacterial infections, with significant mortality associated with invasive disease as noted in the recent Global Research on Antimicrobial Resistance Project (GRAM) study (1). The Working Group also noted that tedizolid is given only once daily, and generally for shorter treatment courses than linezolid, which is given twice daily. Tedizolid has good bioavailability and has both an intravenous and oral preparation, encouraging oral treatment only or rapid switch from intravenous to oral treatment in stable patients. No dose adjustments need to be made in patients with hepatic or renal disease. The Working Group considered that the main advantage of tedizolid over linezolid was the significantly lower incidence of bone marrow suppression and gastrointestinal toxicity. The Working Group noted that tedizolid is more expensive than generic linezolid, however shorter treatment courses may affect the relative costs. Based on current patent status, generic versions of tedizolid are unlikely to be widely available before the 2030s. Cost–effectiveness data are scarce in low- and middle-income settings. =======

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