MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

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TEBIPENEM PIVOXIL HYDROBROMIDE IN COMPLICATED URINARY TRACT INFECTION

Keywords: tebipenem pivoxil hydrobromide, orapenem, complicated urinary tract infection, acute pyelonephritis

SUMMARY OF TECHNOLOGY

Tebipenem pivoxil hydrobromide (brand name Orapenem) is a broad-spectrum orally-administered antibiotic, from the carbapenem subgroup of β-lactam antibiotics to treat complicated urinary tract infections (cUTI) including pyelonephritis.[1] It has been studied under various investigational product names including SPR994, L-084, L-036, LJC 11,036, SPR 859, and ME1211.[1] This antibiotic provides alternative to intravenous carbapenem antibiotic therapy.[1]

This first carbapenem in prodrug form is formulated as the ester tebipenem pivoxil due to the higher absorption rate and improved bioavailability of this form compared to other prodrugs of beta-lactam antibiotics.[2] Tebipenem also contains a 1- β- methyl group, which provides stability against hydrolysis by renal dehydropeptidase- I (DHP- I), allowing use without the DHP- I inhibitor, cilastatin.[3]

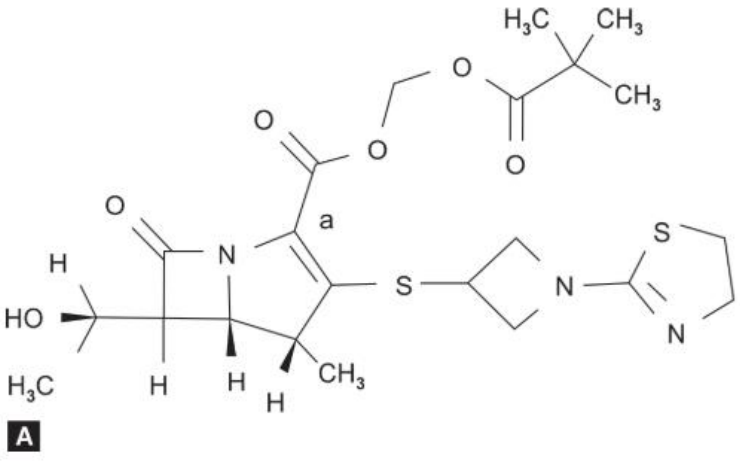

Figure 1: Chemical structures of Tebipenem-pivoxil[1]

Tebipenem pivoxil is prepared for oral formulation by combination with the hydrobromide salt to enhance stability and facilitate administration of larger doses than the previous formulation.[4]

It has a broad spectrum in vitro and in vivo activity against gram-negative and gram-positive pathogens, including resistant strains like extended spectrum β-lactamases (ESBL)-producing Enterobacteriaceae and strains resistant to fluoroquinolones and trimethoprim sulfamethoxazole.[5]

The mechanism of action of tebipenem is like other beta-lactam antibiotics, penetrates through the outer membrane and into the periplasmic region.[1] After acylation of tebipenem in the periplasmic region, the penicillin-binding proteins (PBPs) are inhibited.[1] As a result, the production of cell wall peptidoglycan is catalysed, weakening the peptidoglycan, resulting in bacterial cell lysis.[1]

Tebipenem is currently licensed in Japan only for paediatrics use in otolaryngologic infections and respiratory infections at the dosage of 0.04 gram per kilogram of body weight 2 times a day, after meals for maximum of seven days. The U.S. Food and Drug Administration (FDA) has granted Priority Review designation and confirmed the acceptance for substantive review of the New Drug Application (NDA) for treatment in adult patients with complicated urinary tract infections (cUTI), including acute pyelonephritis, caused by susceptible microorganisms.[6] This antibiotic has also been granted Qualified Infectious Disease Product (QIDP) and Fast Track designations for these cUTI indications.[6] The FDA is planning to hold an Advisory Committee meeting to discuss this application and has also set a Prescription Drug User Fee Act (PDUFA) target action date of June 27, 2022.[6]

INNOVATIVENESS

Novel, completely new	/
Incremental improvement of the existing technology	
New indication of an existing technology	

DISEASE BURDEN

Urinary tract infections (UTIs) are the most frequent outpatient infections caused by Gram-negative bacteria in the United States.[7] Changes in frequency, dysuria, urgency, and the presence or absence of vaginal discharge are the most common signs of urinary tract infections, however, urinary tract infections can present differently in older women.[8] Clinically, UTIs are categorised as uncomplicated or complicated.[9] Uncomplicated UTIs affect people who are generally healthy and have no structural or neurological problems

in their urinary system; they are classified into lower UTIs (cystitis, prostatitis) and upper UTIs (pyelonephritis).[9] Complicated UTIs are defined as UTIs associated with factors that compromise the urinary tract or host defense, including urinary obstruction, urinary retention caused by neurological disease, immunosuppression, renal failure, renal transplantation, pregnancy and the presence of foreign bodies such as calculi, indwelling catheters or other drainage devices.[9]

There are more than 404.6 million incident cases of UTIs occurred worldwide, and nearly 236 786 people died of UTIs in 2019.[10] In 2019, more than 404.6 million (95% CI 359.4-446.5) incident cases of UTIs occurred worldwide, and nearly 236 786 people died of UTIs.[10] Urinary tract infections contributed to 5.2 million DALYs worldwide with an age-standardised DALY rate of 67.2 (57.6-73.7) per 100 000 populations in 2019.[10] The prevalence in women over 65 years of age is approximately 20%, compared with approximately 11% in the overall population.[11] The prevalence of UTIs increases with age with the exception of a spike in young women aged 14−24 years old.[8] The prevalence of healthcare-associated UTIs ranges between 1.4% and 5.1%, and the majority of them are catheter-related UTIs.[12]

Urinary tract infections are also common among inpatients. In 2004, a study conducted in 49 Swiss hospitals showed that 1.5% of hospitalised patients developed symptomatic UTIs.[10] In 2007, in the United States alone, there were an estimated 10.5 million office visits for UTI symptoms (constituting 0.9% of all ambulatory visits) and 2–3 million emergency department visits.[13] Complicated UTIs in particular constitute a huge burden on healthcare systems as a frequent reason for hospitalisations and thus entail a significant financial burden on healthcare systems resources.[12] Common organisms that caused complicated UTIs were Enterobacteriaceae, Enterococci and Pseudomonas sp.[14] The main reason for increased expenses was prolongation of hospital stay for the antibiotic's treatment.[12]

Complicated urinary tract infections impose a high burden on healthcare systems and a frequent cause of hospitalisations.[15,16] In the United States, the overall incidence of complicated UTIs was 1.01%, equating to approximately 2 882 195 annuals complicated UTIs cases.[16] In the inpatient cohort, overall median (interquartile range [IQR]) 30-day health care costs were $13 028 ($4855–$26 781).[16] Median (IQR) costs for the initial admission were $9441 ($2079–$19 027), with median (IQR) length of stay (LOS) of 4 (3–8) days.[16] Among inpatient patients, 12 933 (12.3%) had a subsequent readmission. In the outpatient's cohort, median (IQR) 30-day health care costs were $1531 ($305–$4998).[16] In the outpatient patients' populations, 40 457 (9.2%) had a 30-day admission.[17]

In Malaysia, UTI's are the most common type of infection among the elderly population and the most common cause of hospitalisations due to bacterial infections.[17,17] In the study conducted at the Department of Urology, Hospital Pulau Pinang, Malaysia on the

geriatric patients, cystitis (37.6%) was the most prevalent UTI among the study population followed by asymptomatic bacteriuria (ASB) (31.9%), pyelonephritis (13.9%), urosepsis(10.2%), and prostatitis (6.4%).[17]

In diabetes mellitus (DM) patients, UTIs are considered as complicated and may have a bad prognosis.[18] In a cross-sectional study done in a tertiary hospital in Malaysia, there was high prevalence of UTIs among DM patients.[18] Urinary tract infections were found in 140 (40.2%) of 348 DM patients.[18] Most of the UTI cases in this study (89.3%) were found in DM patients with poorly uncontrolled glycaemia.[18] In controlled glycaemic DM patients, 10.7% of UTI cases were reported.[18] Prevalence of UTI was higher among females (54.9%) than males (23.8%).[18] Prevalence of UTI among Chinese and Malays were nearly equivalent with slightly higher among Chinese while Indians had the lowest prevalence than both above mentioned ethnic groups.[18] Cystitis and ASB were the most common type of UTI followed by pyelonephritis, urosepsis and prostatitis.[18]

In the management of complicated UTIs, carbapenems is the gold standard for treating multidrug-resistant Gram-negative bacterial infections and only available via intravenous administration. Thus, treatment by oral carbapenem will provide additional option and could help patients avoid the unnecessary cost and risk of hospitalisations for infections.

CURRENT OPTIONS FOR PATIENTS

According to the National Antimicrobial Guideline 2019, in acute uncomplicated cystitis, nitrofurantoin or cephalexin is the suggested treatment.[14] Alternatively, cefuroxime or amoxicillin/clavunate or ampicillin/sulbactam may be given to treat the conditions.[14] Fosfomycin may be considered for patients suspected to have multi drug resistance gram negative infections.[14] In uncomplicated pyelonephritis, outpatient patients may be given oral antibiotics of amoxicillin/clavunate or ampicillin/sulbactam for 14 days as the outpatient treatment while for the inpatients, treatments may be provided with amoxicicilin/ clavunate, cefuroxime and ampicillin/sulbactam intravenously. Ceftriaxone may also be given alternatively intravenously.[14]

In the complicated UTIs, once culture results are available, broad-spectrum, empiric antibiotics should be switched to a targeted narrow-spectrum antibiotic.[19] Initial broad-spectrum choices tend to be penicillins or beta-lactams, cephalosporins, fluoroquinolones, and carbapenems especially if dealing with an ESBL organism.[19] Based on the National Antimicrobial Guideline 2019, the preferred oral therapy are amoxicillin/clavunate and cephaxalin for seven days.[14] The suggested parenteral therapy is amoxicillin/clavulanate, ampicillin/sulbactam and cefuroxime with plus or minus aminoglycoside.[14] Ceftriaxone plus minus aminoglycoside can be given as an alternative.[14] Once a patient can tolerate orally and is afebrile for more than 48 hours, antibiotics may be reduced to oral antibiotics based on culture and sensitivity results.[14]

POTENTIAL IMPACT OF TECHNOLOGY

a. Clinical Impact

Based on available evidence up to 25 April 2022, the latest clinical trials on oral tebipenem pivoxil hydrobromide in complicated urinary tract infection is the phase 3 international ADAPT-PO trial.[20] Previously, there were two phase 1 clinical trials on tebipenem pivoxil hydrobromide conducted to study the safety and pharmacokinetics of tebipenem.[21,22]

The randomized, double- blind, double-dummy, noninferiority trial was conducted at 95 sites in Central and Eastern Europe, South Africa, and the United States.[20] The primary outcome was to evaluate the efficacy and safety of oral tebipenem pivoxil hydrobromide as compared to intravenous ertapenem in hospitalised adult patients with complicated urinary tract infection or acute pyelonephritis.[20] An overall response was seen in 264 of 449 patients (58.8%) who received tebipenem pivoxil hydrobromide, as compared to 258 of 419 patients (61.6%) who received ertapenem.[20] Eligible patients were randomly assigned to receive either tebipenem pivoxil hydrobromide at a dose 600mg for every 8 hours plus a dummy infusion of ertapenem or ertapenem at a dose of 1g administered intravenously for every 24hours plus dummy tebipenem pivoxil hydrobromide for seven to ten days.[20]

Oral tebipenem pivoxil hydrobromide was non-inferior to intravenous ertapenem with respect to the primary end point of overall response at the test-of-cure visit (58.8% and 61.6% of the patients, respectively. The weighted difference of −3.3 percentage points (95% CI; −9.7 to 3.2) did not reach the noninferiority margin of 12.5%.[20] Overall response at the end-of-treatment visit was 97.3% in the tebipenem pivoxil hydrobromide group and 94.5% in the ertapenem group.[20] Among patients with bacteraemia at baseline, overall responses were 93.6% with tebipenem pivoxil hydrobromide and 96.2% with ertapenem at the end-of-treatment visit and 72.3% and 66.0%, respectively, at the test-of-cure visit.[20] The clinical cure with tebipenem pivoxil hydrobromide was 99.3% versus 97.9% with ertapenem (difference of 1.4%, CI of −0.1 to 3.4).[20] Clinical cure at test of cure was 93.1% and 93.6% for tebipenem pivoxil hydrobromide and ertapenem arms, respectively, (−0.6%, 95% CI −4.0 to 2.8) whereas microbiological eradication at test of cure was 59.5% for patients treated with tebipenem pivoxil hydrobromide and 63.5% for patients treated with ertapenem (−4.5%, CI −10.8 to 1.9).[20] For the late follow- up period, sustained clinical cure was 88.6% with tebipenem pivoxil hydrobromide and 90% with ertapenem (−1.5%, 95% CI −5.7 to 2.6). The microbiological response at the end of treatment was 97.8% with tebipenem pivoxil hydrobromide and 96.2% with ertapenem (−1.5%, 95% CI −0.8 to 4.1).[20] The microbiological response at the late follow- up period was 57.2% with tebipenem pivoxil hydrobromide and 58.2% with ertapenem (1.5%, CI −7.9 to 5.0).[20] Thus,

tebipenem pivoxil hydrobromide was noninferior to intravenous ertapenem for the treatment of patients with complicated urinary tract infection or acute pyelonephritis.

b. Cost

There was no retrievable evidence on the cost of tebipenem pivoxil hydrobromide.

However, tebipenem pivoxil hydrobromide is available for paediatric use in Japan in the form of fine granules 10% 0.5g at the price from USD 5.8 (MYR 25.23; 1 USD=MYR 4.35) depending on the provider company.[23]

c. Societal/ethical

Considering complicated urinary tract infections are the most prevalent cause of hospitalisations, administering antibiotics effectively and immediately to treat them can improve clinical outcomes and reduce mortality. Carbapenems are considered as the last resort of antimicrobial agents of choice for treatment of complicated UTIs and acute pyelonephritis, particularly severe infections, due to ESBLs- enterobacteriaceae.[24]

Since tebipenem pivoxil hydrobromide is a broad-spectrum orally-administered antibiotic, from the carbapenem group, there are possibility of overuse and self-prescribed antibiotic which may lead to spread of drug-resistant bacteria and increased the relative risk of infection with drug-resistant Gram-negative bacteria. Thus, usage restriction of this orally carbapenem group for the management and treatment of UTIs must be warranted to be prescribed with the proper consultation from an infectious diseases specialist and microbiologist, or antimicrobial stewardship team.

d. Safety

Based on the phase 3 ADAPT-PO trial, the safety profile of tebipenem pivoxil hydrobromide was consistent with a carbapenem antibiotic; the incidence of adverse events and laboratory abnormalities was similar in both treatment groups and was representative of the carbapenem class.[20] The overall incidence of adverse events was approximately 26% in both treatment groups.[20] Diarrhoea, headache, and nausea were the only adverse events reported in more than 1% of the patients in either treatment group.[20] Most adverse events were mild or moderate in severity and non–treatment-limiting.[20] No serious adverse events in the tebipenem pivoxil hydrobromide group were assessed by the investigator as being related to the trial drug.[20]

In the phase 1 trial, the most common adverse events associated with tebipenem pivoxil hydrobromide in both the single ascending dose (SAD) and the multiple ascending dose (MAD) phase were gastrointestinal effects, mainly diarrhoea.[22] No participants receiving tebipenem pivoxil hydrobromide had a severe treatment-emergent adverse events,

discontinued the study drug, or withdrew from the trial in either the SAD or MAD phase.[22] The pharmacokinetics (PK) profile of tebipenem generally was dose proportional and linear after single doses of 100 to 900 mg.[22] Results from the MAD phase indicate dose proportionality and approximately linear PK with 300 and 600 mg q8h, with no accumulation over 14 days.[22]

Besides that, in another phase 1 trial, the safety and PK of tebipenem pivoxil hydrobromide was studied in patients with various degrees of renal impairment.[21] Tebipenem pivoxil hydrobromide plasma area under the curve increase with decreased in renal function.[21] Thus, a reduced dosage of tebipenem pivoxil hydrobromide may be needed as with other carbapenems in patients with end stage renal disease receiving haemodialysis and severe renal impairment.[21] However, the safety and tolerability profile of tebipenem pivoxil hydrobromide was not impacted by the degree of renal impairment.[21]

CONCLUSIONS

Oral tebipenem pivoxil hydrobromide was associated with overall response that were similarly effective and shown similar safety profile as intravenous ertapenem in patients with complicated urinary tract infections. The adverse event was generally well-tolerated at various doses and comparable with placebo.

Thus, in the absence of other effective oral agents, tebipenem pivoxil hydrobromide has the potential to provide an option for the treatment of complicated urinary tract infection and reduce the need for intravenous antibiotic therapy in the hospital or outpatient setting. However, further evidence on cost-implication is needed.

In addition, it is crucial to use this orally administered carbapenem group antibiotics as only the last-resort treatments when UTIs caused by MDR-organisms that resistant to old antimicrobial options are confirmed or strongly suspected and prescribed by the consultation with an infectious diseases specialist, microbiologist, or antimicrobial stewardship team to avoid antibiotics resistance development.

EVIDENCE

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