Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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ceftolozane/tazobactam 1g/0.5g powder for concentrate for solution for infusion (Zerbaxa®) SMC No. (1146/16)

Merck, Sharp & Dohme Ltd

08 April 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

ceftolozane/tazobactam (Zerbaxa®) is not recommended for use within NHS Scotland.

Indication under review: for the treatment of the following infections in adults:
- Complicated intra-abdominal infections
- Acute pyelonephritis
- Complicated urinary tract infections

In a phase III, randomised, double-blind study, ceftolozane/tazobactam, in combination with metronidazole, demonstrated non-inferior efficacy to a carbapenem in patients with complicated intra-abdominal infections.

In a phase III, randomised, double-blind study, ceftolozane/tazobactam demonstrated non-inferior efficacy to a quinolone antibiotic in patients with acute pyelonephritis or complicated urinary tract infections.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

for the treatment of the following infections in adults:
- Complicated intra-abdominal infections (cIAI)
- Acute pyelonephritis (AP)
- Complicated urinary tract infections (cUTI)

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Dosing Information

The recommended dose regimen (for patients with creatinine clearance >50mL/minute) is 1g ceftolozane/0.5g tazobactam by intravenous (IV) infusion (over one hour) every eight hours. Duration of treatment is four to fourteen days for cIAI and seven days for both cUTI and AP. In cIAI when anaerobic pathogens are suspected, concomitant metronidazole should also be administered.

Refer to the Summary of Product Characteristics (SPC) for ceftolozane/tazobactam dosage in patients with creatinine clearance ≤50mL/minute.

Product availability date

16 November 2015

Summary of evidence on comparative efficacy

Ceftolozane/tazobactam is a new, fixed-combination, parenteral antimicrobial medicine comprising a novel fifth generation cephalosporin, ceftolozane, and an established beta-lactamase inhibitor, tazobactam. Ceftolozane binds to penicillin-binding proteins resulting in inhibition of bacterial cell wall synthesis and subsequent cell death.[1] The combination treatment is active against many Gram-negative pathogens including multidrug-resistant *Pseudomonas aeruginosa* and most extended-spectrum beta-lactamase (ESBL)–producing *Enterobacteriaceae*.[2,3] The submitting company has requested that SMC reviews ceftolozane/tazobactam when positioned for use following empiric therapy, where the bacterial organism is resistant to/or is considered non-susceptible to the initial agent, but susceptible to ceftolozane/tazobactam.

The evidence supporting the marketing authorisation is from two phase III, double-blind, randomised-controlled, non-inferiority studies: in patients with cIAI (ASPECT-cIAI) and in patients with cUTI or AP (ASPECT-cUTI).[3,4]

ASPECT-cIAI recruited adults with clinical evidence of cIAI in whom operative or percutaneous drainage of an infectious focus was either planned or had been performed in the previous 24 hours, confirming the presence of cIAI.[3] A total of 993 patients were randomised, in a 1:1 ratio, stratified by primary site of infection (bowel versus other site) and by investigational site, to receive IV ceftolozane/tazobactam (1.5g [1g ceftolozane plus 0.5g tazobactam] every eight hours) plus IV metronidazole (500mg every eight hours), or IV meropenem (1g every eight hours) plus placebo (sodium chloride 0.9% infusions), for four to ten days. Doses were adjusted as required for renal impairment.[3,5] Treatment could be continued for up to 14 days in patients who had one of the following: multiple abscesses, non-appendix-related diffuse peritonitis, failure of prior antimicrobial therapy, or hospital-acquired infection. Patients were required to stay in hospital until they had received at least the first nine doses of study treatment.[5] No information on stopping criteria was provided in the company submission or published study report.

The primary outcome was clinical cure rate at the test-of-cure visit (24 to 32 days from treatment initiation) in the microbiological intention-to-treat (ITT) population, defined as all randomised patients with at least one baseline pathogen identified in abscess or peritonitis fluid, regardless of susceptibility to study drug. The primary analysis population included 81% (806/993) of all randomised patients. Clinical cure rates were 83% (323/389) in the ceftolozane/tazobactam plus metronidazole group and 87% (364/417) in the meropenem group; treatment difference: −4.2% (95% confidence interval [CI]: −8.91% to 0.54%). As the lower limit of the 95% CI was greater than -10%, the non-inferiority criterion was met.[3]

Subgroup analyses showed lower cure rates for ceftolozane/tazobactam plus metronidazole versus meropenem across all subgroups. Treatment failures in the ceftolozane/tazobactam plus metronidazole versus meropenem groups were more likely to occur in the elderly (44% versus 27%), in patients with peritonitis (77% versus 64%) and in those who had a laparotomy (65% versus 49%).[2]

The key secondary outcome evaluated the primary endpoint in the microbiologically evaluable (ME) population consisting of all randomised patients who received protocol specified amount of study drug, met the protocol specific disease definition of cIAI, adhered to study procedures, had a test-of-cure visit within the specified window and had at least one baseline infecting pathogen identified that was susceptible to study drug. The clinical cure rate at the test-of-cure visit in the ME population was 94% (259/275) in the ceftolozane/tazobactam plus metronidazole group, and 95% (304/321) in the meropenem group; difference of −1.0 (95% CI: −4.52% to 2.59%).[3]

ASPECT-cUTI recruited adults with pyuria and a diagnosis of pyelonephritis or cUTI, who had been admitted to hospital for IV antibiotic therapy and had a urine culture specimen obtained in the 36 hours before the initiation of study drug treatment. Diagnosis of pyelonephritis required at least two of the following symptoms: fever (oral temperature >38°C) accompanied by rigors, chills, or warmth; flank pain; costovertebral angle or suprapubic tenderness on physical examination; or nausea or vomiting. Diagnosis of cUTI included all of the above symptoms plus suprapubic pain, dysuria, urinary frequency or urgency, and at least one of the following: male sex with urinary retention, indwelling urinary catheter, current obstructive uropathy, or any functional or anatomical urogenital-tract abnormality.[4]

A total of 1,083 patients were randomised, in a 1:1 ratio, stratified by study site, to receive seven days IV treatment with ceftolozane/tazobactam 1.5g every eight hours or levofloxacin 750mg once daily.[4] Doses were adjusted as required for renal impairment.[4,2] Antibiotics (non-study) were permitted if they had Gram-positive activity only. All patients received study drugs prior to the results of urine culture being available. If the results showed resistance to either or both of the study drugs, a non-study antibiotic could be used in addition to, or instead of, the study treatment.[4] No information on stopping criteria was provided in the company submission or published study report.

The primary outcome was the proportion of patients with composite cure (both microbiological eradication and clinical cure) at the test-of-cure visit (five to nine days after the last dose).[4] Microbiological eradication was defined as a test-of-cure urine culture with $<10^3$ colony-forming units per mL of the baseline uropathogen.[2] Clinical cure was defined as complete resolution, substantial improvement (ie, reduction in severity of all baseline signs and symptoms and worsening of none), or return to pre-infection signs and symptoms of cUTI or pyelonephritis without the need for additional antibiotic therapy.

The primary analysis was performed on the microbiological modified ITT population which included all patients who had received at least one dose of study drug (modified ITT population) and had growth of one or two uropathogens of at least 10^5 colony-forming units per mL in urine culture. The microbiological modified ITT population included 74% (800/1,083) of all randomised patients. Composite cure was achieved in 77% (306/398) of patients receiving ceftolozane/tazobactam compared with 68% (275/402) of patients receiving levofloxacin, a difference of 8.5% (95% CI: 2.3% to 14.6%). Results of the separate components of the composite cure for ceftolozane/tazobactam versus levofloxacin were microbiological eradication: 80% (320/398) versus 72% (290/402) treatment difference 8.3% (95% CI: 2.4% to 14.1%) and clinical cure: 92% (366/398) versus 87% (356/402); treatment difference 3.4% (95% CI: 0.7% to 7.6%). Ceftolozane/tazobactam was considered to be non-inferior to levofloxacin. Superiority of ceftolozane/tazobactam to levofloxacin was not a pre-specified outcome; however, the study investigators deemed that superiority was shown as the treatment difference was positive and the lower bound of the 95% CI was above zero.[4]

Subgroup analysis suggested greater efficacy in the primary outcome for ceftolozane/tazobactam than levofloxacin among: older patients (≥65 years versus <65 years); patients with cUTI versus AP (although the number of patients with cUTI was small); presence versus absence of bacteraemia; levofloxacin-resistant versus susceptible pathogens; and ESBL-producing versus non-producing pathogens.[4] Sensitivity analysis showed that in the subgroup of patients with levofloxacin-susceptible baseline uropathogens, ceftolozane/tazobactam was still non-inferior to levofloxacin, but was not superior.[2]

Composite cure was assessed as a secondary outcome in the per-protocol (PP) population which included patients in the microbiological modified ITT population who adhered to the treatment protocol and had a clinical assessment and interpretable urine culture at the test-of-cure visit; if patients had received concomitant active non-study antibiotics and failed to respond, they were included in the per-protocol population, and, if they responded to non-study treatment, they were excluded. Composite cure was achieved in 83% (284/341) of patients receiving ceftolozane/tazobactam compared with 75% (266/353) of patients receiving levofloxacin; a difference of 8.0% (95% CI: 2.0 to 14.0). Sustained clinical cure rates in the clinically assessable population at 21 to 42 days after the end of study treatment were 96% (319/331) and 95% (314/329) in the ceftolozane/tazobactam and levofloxacin groups, respectively.[4]

Summary of evidence on comparative safety

In ASPECT-cIAI, adverse events were reported in 44% (212/482) of patients in the ceftolozane/tazobactam plus metronidazole group and in 43% (212/497) of the meropenem group. Serious adverse events were reported in 8.1% (39/482) and 7.2% (36/497) of patients in the respective groups. Most adverse events were mild to moderate in severity and the most common events in the ceftolozane/tazobactam plus metronidazole versus meropenem groups were: nausea (7.9% versus 5.8%); diarrhoea (6.2% versus 5.0%); vomiting (3.3% versus 4.0%) and pyrexia (5.2% versus 4.0%). Treatment-related serious adverse events occurred in one patient in each treatment group (both *Clostridium difficile* infection).[3] There were eleven deaths (2.3%) in the ceftolozane/tazobactam plus metronidazole group and eight deaths (1.6%) in the meropenem group. None was considered by the investigators to be related to study treatment, although inadequate treatment efficacy cannot be excluded as a contributing factor.[3,5]

In ASPECT-cUTI, adverse events were reported in 35% (185/533) of patients in the ceftolozane/tazobactam group and in 34% (184/535) of patients in the levofloxacin group. These were categorised as serious adverse events in 2.8% (15/533) and 3.4% (18/535) of patients in the respective groups. The most frequent adverse events in both treatment groups were headache and gastrointestinal symptoms. Most adverse events were mild to moderate. Treatment–related adverse events were reported in 10% (55/533) of patients in the ceftolozane/tazobactam group and in 12% (64/535) of the levofloxacin group.[2] Two serious adverse events (*Clostridium difficile* infection) in the ceftolozane-tazobactam group were considered study treatment-related. Both patients recovered by the late follow-up visit, (within 42 days of the end of treatment).[4]

Summary of clinical effectiveness issues

Complicated intra-abdominal infections invade tissue, producing abscesses or generalised peritonitis and surgical intervention is needed to remove the source of infection.[3] Complicated urinary tract infections involve additional challenges to eradication of the infection and increase vulnerability to re-infection. These include indwelling catheters, urinary obstruction, instrumentation of the urinary tract, or other functional or anatomical abnormalities of the urogenital tract.[2] Pyelonephritis is an infection of one or both kidneys.[2] Ceftolozane has activity against Gram-negative organisms including *Pseudomonas aeruginosa*, and to some streptococci and a few selected anaerobes. Tazobactam can inhibit many class A and some class C beta-lactamases, potentially protecting ceftolozane from hydrolysis and thereby widening its spectrum to include a range of ESBL-producing *E. coli, K. pneumoniae* and other *Enterobacteriaceae*.[1,2]

The submitting company has requested that SMC reviews ceftolozane/tazobactam when positioned for use following empiric therapy, where the bacterial organism is resistant to/or is considered non-susceptible to the initial agent, but susceptible to ceftolozane/tazobactam. Clinical expert opinion indicates that a number of different antibiotics are currently used second-line depending on culture results.

Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely lack of effective antimicrobial agents for drug-resistant infections.

Ceftolozane/tazobactam (plus metronidazole) was non-inferior (though numerically less efficacious) to meropenem with respect to clinical cure rate in patients with cIAI.[3] Subgroup analysis demonstrated significantly higher rates of treatment failure for ceftolozane/tazobactam plus metronidazole compared with meropenem in the elderly, in patients with peritonitis and in those who had a laparotomy.[2,5]

The ASPECT-cIAI study population did not adequately reflect the range of possible infections in practice, as 48% of patients had infection originating in the appendix. This contributed to a less severe disease profile as demonstrated by low Acute Physiology and Chronic Health Evaluation (APACHE) II scores and the fact that half of all study patients received four to seven days therapy. The European Medicines Agency (EMA) recommends that, in clinical studies of antibiotics in cIAI, the proportion of patients with infections originating in the appendix should not exceed 30%.[2] Most patients in ASPECT-cIAI had community-acquired IAI whereas the risk of antibiotic resistance is much higher in nosocomial infections.[2,3] It is not known if this influenced the treatment effect of ceftolozane/tazobactam. It is not clear if the study patients reflected the severity of illness required to be eligible to receive either ceftolozane/tazobactam or meropenem in practice.

In ASPECT-cUTI, ceftolozane/tazobactam was non-inferior to levofloxacin with respect to the composite outcome of microbiological eradication plus clinical cure.[4] Although superiority of

ceftolozane/tazobactam over levofloxacin was claimed, this was not a pre-specified outcome and was driven by the presence of levofloxacin-resistant bacteria.

Most patients in ASPECT-cUTI had pyelonephritis and there is limited evidence in cUTI as only 60 microbiologically evaluable patients with this diagnosis received ceftolozane/tazobactam.[1] The EMA advises that patients with AP do not always require parenteral treatment and that it is preferable to evaluate efficacy in cUTI and AP in separate studies. If they are evaluated in the same study, then stratification at randomisation with capping of the proportion with AP is recommended.[2] In ASPECT-cUTI, 82% of patients had AP but, as the study predated the EMA advice, stratification according to diagnosis was not performed. There were marked differences in demographics between the two disease subgroups, including that a higher proportion of patients with AP were younger, female and generally had better renal function compared to patients with cUTI.[1,2] Baseline resistance of Gram-negative pathogens to ceftolozane/tazobactam was much lower than to levofloxacin (2.7% versus 27%).[4] The daily dose of levofloxacin used was 750mg, rather than the recommended UK dose of 500mg.[7]

The submitting company acknowledged that levofloxacin is unlikely to be used in patients with cUTI in Scotland and therefore ciprofloxacin was used in the economic case.

In both ASPECT-cIAI and ASPECT-cUTI, treatment was administered on an empiric basis, whereas the proposed positioning is targeted treatment on the basis of culture sensitivity results after failure of empiric treatment.[3,4] In both studies, 75% of patients lived in Eastern Europe where rates of ESBL antibiotic resistance are higher than in Scotland.[9] It is not clear how differences in clinical practice and microbiological resistance patterns may affect the generalisability of the study results to the Scottish population.

In Scottish practice, specific restrictions advise limiting the use of antibiotics which promote *Clostridium difficile* infection including carbapenem antibiotics and cephalosporins. It is recommended that they should only be prescribed on the advice of a microbiologist or infectious diseases physician.[10]

Clinical experts consulted by SMC considered that ceftolozane/tazobactam is a potential carbopenem-sparing option for inclusion on the restricted list of antibiotics for very specific situations involving resistant micro-organisms.

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The submitting company presented cost-minimisation analyses (CMA) for two patient groups: cIAI and cUTI/AP. For both groups, the submitting company positioned the medicine for use in complicated intra-abdominal infections and complicated urinary tract infections (including pyelonephritis) following empiric therapy, where the bacterial organism is resistant to/or is considered non-susceptible to the initial agent but susceptible to ceftolozane/tazobactam. For cIAI, the main comparator was meropenem. Additional analysis was also provided against piperacillin/tazobactam. For cUTI/AP, the main comparator was ciprofloxacin. Additional analysis was provided using piperacillin/tazobactam and also levofloxacin as comparators. The time horizon for the analysis was the duration of antibiotic treatment, including the hospitalisation related to the episode. For the cIAI patients, this was assumed to be 7 days. For the cUTI/AP patients, the treatment duration was 7 to 10 days.

For the main comparison against meropenem in the cIAI population, the source of clinical data to underpin the CMA was the non-inferiority ASPECT-cIAI study. An NMA was used to support the CMA in the case of the alternative comparison against piperacillin/tazobactam. In the case of the cUTI analyses, the source of the evidence of similar effect was also a NMA.

Costs in the analysis related to medicines acquisition cost and the costs of preparing and administering the medicines. No adverse event or subsequent treatment costs were assumed on the basis that outcomes were equivalent between treatments. Monitoring costs for meropenem were included.

The result for the base case comparison in the cIAI patients versus meropenem was that ceftolozane/tazobactam was associated with an incremental cost difference of £1,110. In the base case comparison in cUTI/AP patients versus ciprofloxacin, ceftolozane/tazobactam was also not cost-minimising given an incremental cost difference of £434.

A range of scenario analyses were provided. For the cIAI group the results were:

- The additional cost of ceftolozane/tazobactam increased to £3,161 if a treatment duration of 14 days was assumed, or dropped to an additional cost of £232 if treatment duration was 4 days.
- If piperacillin/tazobactam was used as the comparator, ceftolozane/tazobactam was still not cost-minimising and associated with an additional cost of £1,141.

For the cUTI/AP group:

- If the dose of the comparator (ciprofloxacin) was increased to 3 times per day for 21 days, ceftolozane/tazobactam became the preferred treatment on cost-minimisation grounds, with a cost saving of £1,056. This was the only scenario where the treatment would be judged cost-effective, but assumes the use of IV treatment for the 21 day duration, which seemed unlikely in practice. However, if the comparator was used twice daily for 7 days, the incremental costs of ceftolozane/tazobactam increased to £1,119.
- If levofloxacin was used as the comparator, the additional cost of ceftolozane/tazobactam increased to £906.
- If piperacillin/tazobactam was used as the comparator, the additional cost of ceftolozane/tazobactam increased to £1,140.

In addition to the medicine not demonstrating cost-minimisation, a number of weaknesses were noted with the analysis:

- There are weaknesses in the evidence base underpinning the various CMAs. In the case of the cIAI group for the main comparison with meropenem, the evidence came from a non-inferiority study. Against the other comparison of piperacillin/tazobactam, the evidence came from an NMA, which was associated with significant limitations. For the cUTI/AP group, the evidence against the comparators came from another NMA, and again, this was associated with a number of limitations. It is also noted that the two pivotal studies used treatment on an empirical basis, which is not as per the positioning proposed by the submitting company. Given this, there are uncertainties associated with the evidence base used to support the CMAs presented.
- There may be some uncertainty associated with the choice of comparators in practice, but those selected seem broadly reasonable for the position sought.

Given the incremental costs associated with the medicine and the weaknesses noted, the economic case has not been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- A submission was received from The UK Sepsis Trust, which is a registered charity.
- The patient group has not received any pharmaceutical company funding in the past two years.
- This submission focused on the impact of sepsis, which may result from a complicated infection. Sepsis is a life threatening condition that arises when the body's response to an infection injures its own tissues and organs. Sepsis leads to shock, multiple organ failure and death especially if not recognised early and treated promptly.
- Timely use of the right antibiotic to treat an infection is key to preventing the spread, thus reducing the risk of the infection becoming systemic and the risk of sepsis developing. Having access to new antibiotics is critical in this setting to ensure that clinicians are armed with the most effective antibiotic treatment in order to contain the spread of infection.
- New antibiotics which demonstrate proven efficacy have a valuable role in ensuring effective treatment of infections. The experience of patients - their recovery and long-term outcomes - is critically reliant on effectively controlling the source of the infection as soon as possible.

Additional information: guidelines and protocols

In 2012, the Scottish Intercollegiate Guidelines Network (SIGN) published an updated national clinical guideline for the management of suspected bacterial urinary tract infection (UTI) in adults. Treatment of recurrent infections or complicated infections is not specifically covered, although, the guidelines note that UTI in men are generally viewed as complicated because they result from an anatomic or functional anomaly or instrumentation of the genitourinary tract. The document states that no high quality evidence for the treatment of bacterial UTI in men was identified but recommends that bacterial UTI in men with symptoms suggestive of prostatitis should be treated empirically with a quinolone.[11]

In 2015, the European Association of Urology (EAU) published its guideline for urological infections. The document states that with a complicated UTI, the spectrum of bacteria which can cause the infection is broader and bacteria are more likely to show antimicrobial resistance, particularly where the complicated UTI is related to treatment. It provides advice on prescribing empirical treatment and states that, whenever possible, this should be replaced by a therapy adjusted for the specific infective organisms identified in the urine culture. There is no evidence to support superiority of any agent or class of agents in cases in which the infective organism is susceptible to the drug administered.[12]

World Society of Emergency Surgery (WSES) guidelines for management of intra-abdominal infections, published in 2013, state that both surgical and antibiotic therapy are required in the treatment of complicated intra-abdominal infections. Empirical treatment is usually initiated and depending on the requirements of antimicrobial coverage, intra-abdominal infections can be treated with either single or multiple antimicrobial regimens. The guidance states that, in recent years, complicated infections have more commonly been treated with a combination of ciprofloxacin/metronidazole.[13]

Additional information: comparators

The comparators in the cost table are those used in the company submission. In practice, the relevant comparators would be the antibiotics with activity against the infection based on culture results.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Ceftolozane/tazobactam (cIAI) **(**plus metronidazole)	**By intravenous infusion 1.5g every eight hours for 4 to 14 days** (500mg every eight hours for 7 to 10 days)	**804 to 2,815** (plus 65 to 93)
Ceftolozane/tazobactam (cUTI)	**By intravenous infusion 1.5g every eight hours for 7 days**	**1,408**
Ciprofloxacin (cUTI)*	By intravenous infusion 400mg twice or three times daily for 7 to 21 days Orally 500mg to 750mg twice daily for 10 to 21 days	320 to 1,439 2 to 8
Meropenem (cIAI or cUTI)	By intravenous infusion 500mg to 1g every eight hours for 4 to 14 days	124 to 866
Piperacillin/tazobactam (cIAI or cUTI)	By intravenous infusion 4.5g every eight hours for 5 to 14 days	237 to 663
Levofloxacin (cUTI)*	By intravenous infusion 500mg once daily for 7 to 14 days Orally 500mg once daily for 7 to 14 days	176 to 351 11 to 22

Doses are for general comparison and do not imply therapeutic equivalence.
cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; IV=intravenous
Costs from evadis except (ceftolozane/tazobactam, intravenous levofloxacin and metronidazole from dm&d site) on 31.01.16
Costs are based on licensed treatment durations except for meropenem as no specific licensed duration, therefore the same duration range as ceftolozane/tazobactam is used.
*In practice, patients receiving levofloxacin or ciprofloxacin have the option to switch to an oral formulation if their condition allows.

Additional information: budget impact

Complicated intra-abdominal infections

The company estimated there would be 916 patients eligible for treatment with ceftolozane/tazobactam in each year. The uptake rate was estimated to be 2% in year 1 (18 patients) and 8% in year 5 (73 patients). A mortality rate of 11% was assumed and no patients were assumed to discontinue.

The gross impact on the medicines budget was estimated to be £26k in year 1, rising to £105k in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be £20k in year 1 and £80k in year 5.

Complicated urinary tract infections, including acute pyelonephritis

The company estimated there would be 3,283 patients eligible for treatment with ceftolozane/tazobactam in each year. The uptake rate was estimated to be 2% in year 1 (66 patients) and 8% in year 5 (263 patients). A mortality rate of 11% was assumed and no patients were assumed to discontinue.

The gross impact on the medicines budget was estimated to be £92k in year 1, rising to £370k in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be £32k in year 1 and £130k in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Ceftolozane/Tazobactam 1g/0.5g powder for concentrate for solution for infusion (Zerbaxa®). Summary of product characteristics. Merck Sharp & Dohme Limited. Electronic Medicines Compendium www.medicines.org.uk/emc/ last updated 11 November 2015.

2. European Medicines Agency (EMA) European Public Assessment Report. Ceftolozane/tazobactam (Zerbaxa®). 23/07/2015, EMEA/H/C/003772/0000. www.ema.europa.eu.

3. Solomkin J, Hershberger E, Miller B et al. Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: results from a randomized, double-blind, phase 3 trial (ASPECT-cIAI). Clinical Infectious Diseases 2015; 60(10):1462-71 plus supplementary material.

4. Wagenlehner F, Umeh O, Steenbergen J et al. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). The Lancet 2015; 385 (9981): 1949–1956.

5. United States Food and Drug Administration Center for Drug Evaluation and Research. Application number 206829Orig1s000 M Ceftolozane/tazobactam. Medical review 2014.

6. *Commercial in Confidence*

7. Levofloxacin 5mg/mL solution for infusion (Evoxil®). Summary of product characteristics. Beacon Pharmaceuticals. Electronic Medicines Compendium www.medicines.org.uk/emc/ last updated 30 October 2014.

8. *Commercial in Confidence.*

9. Prevalence of antimicrobial resistance in the World Health Organisation (WHO) European Region. http://www.euro.who.int/en/health-topics/disease-prevention/antimicrobial-resistance/data-and-statistics/prevalence-of-antimicrobial-resistance-in-the-who-european-region

10. Scottish Medicines Consortium. Scottish Antimicrobial Prescribing Group Good practice recommendations for hospital antimicrobial stewardship in NHS Scotland December 2014.

11. Scottish Intercollegiate Guidelines Network SIGN 88. Management of suspected bacterial urinary tract infection in adults. http://www.sign.ac.uk/pdf/sign88.

12. Grabe (M, Bartoletti R, Bjerklund Johansen TE et al. Guidelines on urological infections. European Association of Urology 2015.

13. Sartelli M, Viale P, Catena F et al. World Society of Emergency Surgery (WSES) guidelines for management of intra-abdominal infections. World Journal of Emergency Surgery 2013, 8:3 http://www.wjes.org/content/8/1/3.

This assessment is based on data submitted by the applicant company up to and including 11 March 2016**.**

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.