Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

moxifloxacin intravenous, 400mg/250mL, solution for infusion (Avelox®)

SMC No. (650/10)

Bayer Schering

05 November 2010

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission

moxifloxacin intravenous (Avelox®) is accepted for restricted use within NHS Scotland.

Indication under review: the treatment of community acquired pneumonia (CAP). It should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

SMC restriction: use only on the advice of microbiologists or specialists in infectious diseases.

In several studies, sequential intravenous/oral moxifloxacin has been shown to be non-inferior to a range of comparative therapies.

Intravenous moxifloxacin is also licensed for the treatment of complicated skin and skin structure infections. The manufacturer's submission related only to use in CAP, therefore SMC cannot recommend its use in the treatment of skin infections.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Moxifloxacin intravenous (iv) is indicated for the treatment of community acquired pneumonia (CAP). It should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Moxifloxacin iv is also indicated for the treatment of complicated skin and skin structure infections. Evidence for this indication was not included in the manufacturer's submission therefore it has not been considered by SMC.

Dosing Information

400mg infused intravenously over 60 minutes, once daily.

Initial intravenous treatment may be followed by oral treatment with moxifloxacin 400mg tablets when clinically indicated. In clinical studies, most patients switched to oral therapy within 4 days. The recommended total duration of intravenous and oral treatment is 7 to 14 days.

Product availability date

March 2010

Summary of evidence on comparative efficacy

Community acquired pneumonia (CAP) is defined as pneumonia acquired in the community or within two days of hospitalisation, and is a common, acute infection of the pulmonary parenchyma. *Streptococcus pneumoniae* is the leading aetiological agent among adult patients, either as a single causative agent or in cases of mixed aetiology. Moxifloxacin is a synthetic broad spectrum antibacterial agent effective against Gram-positive cocci and with a good coverage of atypical pathogens while maintaining the Gram-negative activity of existing quinolones. Moxifloxacin covers all the key pathogens involved in CAP and it is also active against emerging strains of antibiotic resistant bacteria.

In 2003, the Scottish Medicines Consortium accepted the oral formulation of moxifloxacin for restricted use, with the recommendation that it was reserved as a second-line treatment for community acquired pneumonia. The manufacturer proposes that intravenous (iv) moxifloxacin should be used for the treatment of adult patients with CAP requiring initial treatment with iv antibiotics who are not suitable for treatment with co-amoxiclav plus clarithromycin. The patient population therefore largely consists of patients who are allergic to penicillin based antibiotics.

Evidence for iv moxifloxacin in the treatment of CAP comes from six randomised active-controlled studies, which shared a similar design, five of which will be discussed. In all five studies, adult patients diagnosed with CAP, with specified clinical signs and symptoms, and who required iv antibiotic therapy were enrolled.

Patients were stratified according to disease severity (usually mild/moderate or severe), then randomised to receive either iv/oral moxifloxacin or the comparator for 7 to 14 days. The switch to oral therapy was at the investigators' discretion, based on clinical response and the ability to tolerate oral therapy.

The primary objective of all studies was to evaluate the clinical response to the sequential treatment with iv/oral moxifloxacin versus comparators, with clinical response being defined as the disappearance of acute signs and symptoms related to infection or sufficient improvement such that additional or alternative antibiotic therapy was not required. All studies were designed to show non-inferiority or equivalence of moxifloxacin to the comparator, based on clinical response at the test-of-cure visit, in the clinically valid (per protocol) population.

In the first, double-blind, study 516 patients with CAP of any severity were randomised to either sequential iv/oral moxifloxacin 400mg once daily or iv alatrofloxacin/oral trovafloxacin 200mg once daily. Due to safety concerns, the comparator was changed during the study to iv/oral levofloxacin 500mg once daily. Data from the two comparator regimens were not significantly different and so were pooled for the purposes of analysis, and referred to as "the comparator". In the clinically valid population (n=356), the overall clinical cure rate 7 to 30 days post-therapy was similar between the two groups: 88% (155/177) in the moxifloxacin group and 89% (160/179) in the comparator group (95% confidence intervals (CI) for the difference: -7.3 to 5.6). Equivalence had been defined as occurring when the lower limit of the 95% CI was greater than -15%, therefore moxifloxacin treatment was shown to be equivalent to the comparator. This result was supported by a similar finding in the ITT population (all patients who received a dose of study drug). Exploratory analysis found that higher response rates were achieved in patients with mild/moderate CAP compared to severe CAP. In patients with severe disease, the clinical cure rate was 79% (48/61) in the moxifloxacin group and 80% (39/49) in the comparator group.

In the second, open-label, study 628 patients with CAP of any severity were randomised to either sequential iv/oral moxifloxacin 400mg once daily or co-amoxiclav 1.2g iv then 625mg orally, three times daily, in combination with clarithromycin 500mg twice daily (if cover for atypical organisms was required), either iv or orally. In the clinically valid population (n=538), the clinical cure rate 5 to 7 days after the end of the drug treatment period was 93% (241/258) in the moxifloxacin group and 85% (239/280) in the comparator group (a difference of 8.0%; 95% CI: 2.9 to 13.2). With a pre-specified equivalence margin of 10%, equivalence of the two treatment regimens was demonstrated but further statistical analysis showed that moxifloxacin was superior to the comparator regimen in this population. This was supported by a similar result in the intention to treat (ITT) population. In the clinically valid population, the higher rate of clinical cure with moxifloxacin was irrespective of whether or not clarithromycin was part of the comparator regimen. In both populations, clinical cure rate was also significantly better for the moxifloxacin group 21 to 28 days post-therapy. In patients with severe disease, clinical cure rates were 92% for the moxifloxacin group and 85% for the comparator group.

In the third, double-blind, study 738 patients with scores on the Pneumonia Severity Index (PSI) of III to V only were enrolled, stratified according to PSI class III or IV/V then randomised to either sequential iv/oral moxifloxacin 400mg once daily or iv ceftriaxone 2g once daily plus iv/oral levofloxacin 500mg twice daily. In the clinically valid population (n=569), the clinical cure rate 4 to 14 days after completion of study treatment was 87% (253/291) for the moxifloxacin group and 90% (250/278) for the comparator group (95% CI for the difference: -8.1 to 2.2). Non-inferiority of moxifloxacin was to be concluded if the lower limit of the CI was greater than -10% and the upper limit was >0, therefore moxifloxacin was shown to be non-inferior to the comparator regimen in patients with PSI class III, IV or V CAP.

In the fourth, double-blind, study 401 patients aged 65 or over only were randomised to receive either sequential iv/oral moxifloxacin 400mg once daily or sequential iv levofloxacin 500mg once daily then oral 250mg to 500mg once daily. In the clinically valid population (n=281), the clinical cure rate 5 to 21 days after the end of therapy was 93% for the moxifloxacin group and 88% for the levofloxacin group (95% CI for the difference: -1.9 to 11.9), demonstrating the non-inferiority of moxifloxacin. During treatment (between days 3 and 5 of treatment), in the same population, 98% of the moxifloxacin group and 90% of the levofloxacin patients had achieved clinical recovery (95% CI for the difference: 1.7 to 14.1). In patients with severe CAP (n=45), the rates of clinical cure were 95% in the moxifloxacin arm and 85% in the levofloxacin group (a non-significant difference).

In the fifth, open-label, study 397 patients were randomised to receive either sequential iv/oral moxifloxacin 400mg once daily or iv ceftriaxone 2g once daily with or without iv erythromycin 1g three or four times daily. In the per protocol population (n=317), the rate of continued clinical resolution 5 to 20 days after the end of therapy was 86% (138/161) in the moxifloxacin group and 86% (135/156) in the comparator group (95% CI for the difference: -7.9 to 7.1). With the lower limit of the CI being greater than -15%, equivalence of moxifloxacin and the comparator was demonstrated. This was supported by analysis in the ITT population.

Summary of evidence on comparative safety

In all studies, there were no significant differences between moxifloxacin and the relevant comparators in terms of drug-related adverse events (AEs), discontinuations due to AEs and serious AEs. In general, gastrointestinal AEs were the most common with diarrhoea and nausea reported similarly for all treatment groups.

With regard to AEs of concern, the second study reported one incident of treatment-emergent significant QTc prolongation in the comparator (co-amoxiclav ± clarithromycin) group. Drug-related cardiac AEs occurred in 6.6% of moxifloxacin patients and 10% of patients in the comparator group. In the third study, the incidence of adverse events that could be considered a clinical surrogate for QTc prolongation (e.g. cardiac arrest, ventricular tachycardia, and sudden death) was similar in the two treatment groups and only one (ventricular tachycardia) was considered to be drug related (in the comparator group). The fourth study had a composite cardiac safety variable as a primary end-point and was observed in 8.3% of moxifloxacin patients and 5.1% of levofloxacin patients, demonstrating non-inferiority of moxifloxacin.

Only the fourth study specifically discussed *Clostridium difficile* infection, and reported incidences of 0.5% in the moxifloxacin group and 3.0% in the comparator (levofloxacin) group. One case (in the comparator group) was reported in the third study, although there was no routine screening.

Abnormal liver function tests (LFTs) were reported as the most common drug-related AE in both groups in the second study, and the first study reported frequencies of 4.0% (10/249) in the moxifloxacin group and 2.3% (6/258) in the comparator group.

Summary of clinical effectiveness issues

The studies were well conducted, although two were open-label and two studies (the second and third) had reduced power to detect a difference in the primary endpoint, as the required numbers of patients were not recruited. All studies were similar in design although one enrolled patients with severe CAP only and one included only patients ≥ 65 years. In the first study, there was a slight discrepancy between groups with regard to baseline characteristics, with patients in the moxifloxacin group being more severely ill than those in the comparator group. In the fifth study, only 38% of patients in the comparator group received both antibiotics and patients in this group were not given the opportunity to switch to oral therapy (unlike those in the moxifloxacin group). It is likely that the criteria used to classify the severity of disease in studies are not the same as those commonly used in Scotland (the CURB-65 score); the clinical significance of this is uncertain.

All studies showed moxifloxacin to be equivalent or non-inferior to the respective comparator, and in one, it was shown to be superior.

The licence for iv moxifloxacin states that it is indicated for the treatment of CAP only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections. This specific patient population was not investigated in any of the studies although the manufacturer has assumed this would be patients with penicillin allergy.

Guidelines for the treatment of CAP agree that the treatment of mild disease should be with oral agents and intravenous agents should be used in severe disease. In four of the five studies discussed previously, patients with mild CAP were enrolled and given intravenous agents. Only one study limited recruitment to patients with more severe disease, however results are supported by post-hoc sub-group analyses of other studies. The licence does not specify disease severity.

The studies were conducted up to 11 years ago, which may have implications for drug sensitivities and resistance of the infecting organism(s). The comparator drug regimens used in the studies appear to concur with current UK prescribing guidelines, although it should be noted that two of the studies (the first and fourth) used a dose of levofloxacin only recommended for moderate disease (once daily monotherapy instead of twice daily in combination). Some of the classes of antibiotics recommended in the guidelines such as cephalosporins and quinolones have been strongly associated with *Clostridium difficile*-associated diarrhoea (CDAD) and methicillin-resistant *Staphylococcus aureus* (MRSA), and as a result hospitals in Scotland have moved away from cephalosporins in the treatment of CAP. Quinolones such as levofloxacin are reserved for patients with severe CAP and a history of penicillin allergy; ciprofloxacin has poor activity against *Streptococcus pneumoniae* and is not recommended for CAP.

No significant safety concerns were identified in any of the studies, but the licence contraindicates use of iv moxifloxacin in patients with specific cardiac conditions and impaired liver function. Hepatotoxicity, the subject of an MHRA safety warning, was specifically discussed only in the first study, when this was given as the reason for changing the original quinolone comparator arm.

Summary of comparative health economic evidence

The manufacturer submitted two cost-minimisation analyses comparing sequential iv/oral moxifloxacin 400 mg once daily to i) sequential iv/oral levofloxacin 500mg twice daily plus iv ceftriaxone 2g once daily and ii) iv ceftriaxone ± iv erythromycin for the treatment of adult patients with CAP requiring initial treatment with iv antibiotics who are not suitable for treatment with co-amoxiclav plus clarithromycin. The patient population therefore largely consisted of patients who are allergic to penicillin. Antibiotic regimens currently used in this situation in Scotland include levofloxacin monotherapy, clarithromycin plus vancomycin and levofloxacin plus vancomycin.

The duration of treatment was assumed to be 12-21 days in analysis i) and 7-14 days in analysis ii).

The clinical evidence used to support the assumption of non-inferiority was based on two efficacy studies that compared sequential iv/oral moxifloxacin to i) sequential iv/oral levofloxacin 500 mg twice daily plus iv ceftriaxone 2g once daily and ii) iv ceftriaxone ± iv erythromycin. Non-inferiority was demonstrated in both studies.

The analyses compared the average total cost per patient treated with moxifloxacin to that of those treated with the treatment(s) in the comparator arms. The costs were based on resource use recorded in the clinical trials. The total cost included iv and oral drug costs, costs associated with iv infusion and the hospital length of stay. The results showed that the total average cost was £5,336 per patient treated with moxifloxacin and £5,688 per patient treated with levofloxacin plus ceftriaxone, equating to a saving of £352 with moxifloxacin. From the second analysis, the total average cost was £4,823 per patient treated with moxifloxacin and £5,604 per patient treated with ceftriaxone ± erythromycin, equating to a saving of £781 with moxifloxacin. The savings were due to fewer iv doses per day and less days on iv treatment in the moxifloxacin group, and decreased length of stay in the second analysis. As such, the manufacturer claimed that moxifloxacin would be the preferred treatment on cost-minimisation grounds versus the two selected comparators.

The sensitivity analyses explored the effect of removing the cost of ceftriaxone from the comparator arm in analysis i) (i.e. comparing against levofloxacin monotherapy); using drug and administration costs associated with clarithromycin instead of erythromycin and equalising length of stay in analysis ii). The key finding was that the estimated base case results remained robust. However, the analyses did not explore the impact of reducing the number of days of iv treatment in the comparator arm in analysis ii).

Limitations of the analysis include:

- not considering all comparator antibiotic regimens used in Scottish practice;
- the clinical data used are not in the second-line positioning, e.g. in penicillin allergic patients; and
- analysis ii) did not allow an oral switch in the comparator arm which would not reflect clinical practice and would be likely to result in more iv doses being given and increased length of stay in the comparator arm.

Despite these limitations, the economic case was considered demonstrated for the patient group proposed by the manufacturer due to savings through reduced drug acquisition and iv administration costs.

Summary of patient and public involvement

A Patient Interest Group submission was not made.

Additional information: guidelines and protocols

The British Thoracic Society produced updated "Guidelines for the management of community acquired pneumonia in adults" in 2009. They recommend that most patients with low and moderately severe CAP can be treated with oral antibiotics but those with high severity disease should be treated with parenteral therapy. For low and moderately severe disease, parenteral therapy involves amoxicillin, benzylpenicillin or clarithromycin (together with clarithromycin in moderate disease). In those with severe disease, co-amoxiclav together with clarithromycin is recommended. In moderate disease, the recommendations for penicillin-intolerant patients are levofloxacin monotherapy or a second or third generation cephalosporin with clarithromycin, whilst in severe disease, the recommendation is for a second or third generation cephalosporin with clarithromycin. These guidelines are endorsed by the Scottish Antimicrobial Prescribing Group.

A Cochrane review published in 2008 entitled "Empiric antibiotic coverage of atypical pathogens for community acquired pneumonia in hospitalised adults" concluded that "No benefit of survival or clinical efficacy was shown to empirical atypical coverage in hospitalised patients with community acquired pneumonia. This conclusion relates mostly to the comparison of quinolone monotherapy to beta-lactams or cephalosporins monotherapy. Further trials, comparing beta-lactam or cephalosporin therapy to beta-lactams or cephalosporins combined with a macrolide in this population, using mortality as its primary outcome, should be performed."

The European Respiratory Society's "Guidelines for the management of adult lower respiratory tract infections" published in 2005, suggests moxifloxacin, along with levofloxacin, as an alternative treatment in non-severe CAP (although this is usually treated with oral therapy) and as an alternative, in combination with a 3rd generation cephalosporin, in severe disease.

All guidelines preceded the licensing of the iv formulation of moxifloxacin.

Additional information: comparators

Antibiotics commonly used are intravenous amoxicillin, benzylpenicillin, co-amoxiclav or clarithromycin (as monotherapy or in combination).

In those intolerant of penicillins, the choices would be levofloxacin monotherapy, clarithromycin plus vancomycin or levofloxacin plus vancomycin.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
moxifloxacin	**400mg daily, iv**	**120**
cefotaxime	2g to 12g daily, iv	27 to 162
levofloxacin	500mg once or twice daily, iv	79 to 158
ceftriaxone	2g to 4g daily, iv	60 to 120
vancomycin	750mg every 48 hours to 1.25g twice daily, iv	26 to 117
clarithromycin	500mg twice daily, iv	57
cefuroxime	750mg three times daily to 1.5g four times daily, iv	20 to 54
co-amoxiclav	1.2g three or four times daily, iv	24 to 31
benzylpenicillin	2.4g to 4.8g daily, iv	11 to 23
amoxicillin	500mg three times daily to 1g four times daily, iv	9 to 23

Costs have been calculated for a 3 day course of intravenous therapy. Drugs are listed individually, but can be combined as per guidelines. Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 8 and 28 September 2010.

Additional information: budget impact

The manufacturer estimated that approximately 201 to 336 patients would be eligible for treatment and that uptake would be 10% in year 1, rising to 50% by year 5. On this basis 20 to 34 patients would be treated with iv moxifloxacin in year 1, rising to 108 to 180 by year 5. The corresponding net drug budget impact was estimated to be a saving ranging from approximately £1,000 to £1,700 in year 1, increasing to approximately £5,600 to £9,300 in year 5. Feedback from SMC clinical experts suggest that the manufacturer's uptake estimates may be high.

References

The undernoted references were supplied with the submission.

File TM, Jr., Larsen LS, Fogarty CM et al. Safety and efficacy of sequential (IV to PO) moxifloxacin for the treatment of community-acquired pneumonia in hospitalized patients. Today's Therapeutic Trends 19(4) (pp 251-270), 2001 Date of Publication: 2001 2001;(4):251-70.

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Torres A, Garau J, Arvis P et al. Moxifloxacin monotherapy is effective in hospitalized patients with community-acquired pneumonia: The MOTIV study - A randomized clinical trial. Clinical Infectious Diseases 2008; 46(10):1499-509.

Anzueto A, Niederman MS, Pearle J et al. Community-acquired pneumonia recovery in the elderly (CAPRIE): Efficacy and safety of moxifloxacin therapy versus that of levofloxacin therapy. Clinical Infectious Diseases 2006; 42(1): 73-81.

Morganroth J, Dimarco JP, Anzueto A et al. A randomized trial comparing the cardiac rhythm safety of moxifloxacin vs levofloxacin in elderly patients hospitalized with community-acquired pneumonia. Chest 2005; 128(5): 3398-406.

Welte T, Petermann W, Schurmann D et al. Treatment with sequential intravenous or oral moxifloxacin was associated with faster clinical improvement than was standard therapy for hospitalized patients with community-acquired pneumonia who received initial parenteral therapy. Clinical Infectious Diseases 2005; 41(12): 1697-705.

This assessment is based on data submitted by the applicant company up to and including **15 October 2010.**

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. 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.