

**diclofenac, 75mg/2ml of solution for intravenous injection
(Dyloject®) No. (446/08)**

Javelin Pharmaceuticals UK Ltd

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The Scottish Medicines Consortium 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

diclofenac (Dyloject®) is accepted for restricted use within NHS Scotland for the treatment or prevention of post-operative pain by intravenous injection, in supervised healthcare settings.

When given as an intravenous bolus, it showed non-inferiority to a comparator non-steroidal anti-inflammatory drug infusion at providing pain relief over an initial 4 hour period and caused less thrombophlebitis.

The manufacturer's submission related only to intravenous use of diclofenac (Dyloject®) in the post-operative setting. SMC cannot recommend its use by the intramuscular route.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

By the intravenous route, treatment or prevention of post-operative pain in supervised healthcare settings.

By the intramuscular route, the solution for injection is effective in acute forms of pain, including renal colic, exacerbations of osteo- and rheumatoid arthritis, acute back pain, acute gout, acute trauma and fractures, and post-operative pain.

Dosing information

Prevention of post-operative pain: 25mg to 50mg as a single IV bolus dose after surgery, followed by additional injections up to a maximum of 150mg within 24 hours.

Treatment of post-operative pain: 75mg/2ml as a single IV bolus dose, up to 150mg within 24 hours. Solution for injection should not be used for more than 2 days.

Product availability date

December 2007

Summary of evidence on comparative efficacy

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) which is commonly used in the post-operative setting. Although licensed for both the intramuscular and intravenous (IV) routes and a variety of indications, evidence is only provided for intravenous use in the post-operative setting.

This submission is based on a change in drug administration due to the development of a new formulation. Currently, the licensed intravenous preparation (Voltarol[®]) has to be given by infusion over 30-120 minutes. The subject of the submission (Dyloject[®]) can be given by intravenous bolus injection (only). Both preparations are licensed for intramuscular use.

A phase II/III double-blind, randomised, single centre, placebo and comparator-controlled single dose trial provided the evidence. 155 patients, aged between 18 and 65 years, who experienced moderate to severe pain within 6 hours following third molar extraction, were recruited to the study. Patients were randomised 1:1:1 to receive a single intravenous dose of diclofenac 75mg as Dyloject[®] (the study drug) by bolus injection, Voltarol[®] 75mg (the comparator) by infusion, or placebo. Patients were required to receive the allocated treatment within 15 minutes of establishing that they qualified for the trial. The treatment period was defined as the 12-hour period immediately following drug administration. Pain relief was evaluated via a 100mm visual analogue scale (VAS) and a categorical 5-point scale. Pain intensity was similarly measured on a VAS scale and a 4-point categorical scale. A global evaluation was also conducted. Patients were assessed for pain control at regular intervals. Rescue analgesia was permitted, but meant that no further pain assessments were carried out. The primary efficacy endpoints were superiority of the study drug to placebo and non-inferiority to the comparator in total pain relief over 0-4 hours (TOTPAR4), as determined by summing assessments recorded on the VAS. The non-inferiority margin was set at 15 points on the VAS, which equates to 60mm.hours for TOPPAR4. Analyses were carried out on the intention to treat population and missing values were imputed either by linear interpolation or by the last observation carried forward method, if more than three consecutive assessments were missing.

The primary efficacy endpoints were met. The study drug and the comparator were statistically superior to placebo in providing pain relief on the VAS scale over the 4 hour period following IV treatment. The mean scores (\pm standard deviation) in mm.hours for the study drug, the comparator and placebo were 300.6 ± 73.6 , 266.2 ± 91.6 and 52.5 ± 88.8 respectively. The mean differences from placebo (\pm standard error) were therefore 247.7 ± 16.6 (95% confidence intervals (CI): 215.2 to 280.2) and 213.3 ± 16.8 (95% CI: 180.4 to 246.3) for the study drug and the comparator respectively. For the other primary endpoint, non-inferiority of the study drug to the comparator was demonstrated with a treatment difference (\pm standard error) of 34.4 ± 16.7 mm.hours (95% CI: 1.6 to 67.1).

Secondary endpoint results included the study drug being statistically superior to the comparator with respect to total pain relief on the VAS scale over the 0 to 2 hour period, with no statistical difference demonstrated over the 0 to 6 and 8 hour periods. Pain relief measured on the categorical scale showed that the study drug was superior to the comparator only over the first 2 hours. On both scales, pain relief was significantly greater at 15 and 30 minutes for the study drug compared with the comparator. Both drugs had similar peak pain relief scores on both scales. Duration of analgesic effect was similar for each drug. In the patient global evaluation, no significant differences were noted between the two active drugs.

Summary of evidence on comparative safety

It should be noted that the comparative safety data relate to the administration of single doses only.

The majority of reported adverse events were mild to moderate in severity and typical of those generally observed following administration of diclofenac. There were a total of 36/155 (23%) reported treatment-related adverse events: 31% in the placebo group, 20% in the comparator group (Voltarol[®]) and 19% in the study drug group (Dyloject[®]).

Thrombophlebitis was assessed on a 6-point scale from grade 0 (no reaction) to grade 5 (thrombosis with overt infection). It was reported most frequently in the comparator group (12% (6/50), vs 5.7% (3/53) for the study drug and 1.9% (1/52) for placebo). During a clinical assessment, 2 patients in each of the study drug and comparator groups were found to have vein tenderness, with a further 2 patients in the comparator group only assessed as having "continuous tenderness or pain with redness." No patients had a more severe score.

Summary of clinical effectiveness issues

A major limitation of the trial is that it was a single-dose study. As the licence permits the use of up to 4 doses over a 48 hour period, neither the efficacy nor safety data are based on proposed patterns of use.

The licence also extends to prevention of post-operative pain and intramuscular use for a variety of other conditions, neither of which are covered by the pivotal trial.

Risk management issues should be highlighted with regard to the potential availability of two formulations of the same drug in a clinical area which must be given by different routes and which cannot be interchanged.

Summary of comparative health economic evidence

The manufacturer submitted a cost-minimisation analysis comparing IV bolus injection of diclofenac (Dyloject,[®] the study drug) with diclofenac (Voltarol,[®] the comparator) 75mg administered by slow iv infusion for post-operative pain. Equal efficacy was assumed based on non-inferiority results from a phase II/III pivotal trial comparing a single dose of the study drug and the comparator. Resource use estimates (primarily nurse time) for drug administration, adverse events and use of rescue medication were provided by an expert panel consisting of anaesthetists, nurses and pharmacists. Additional study drug acquisition costs (£10.50 per patient for the study drug v £1.62 for the comparator) were offset by savings in the cost of nurse time for drug administration, lower cost of consumable items and less rescue medications and adverse event costs. This produced an estimated £45 saving per patient receiving the study drug after an inpatient procedure in Scotland. Financial savings associated with reduced use of consumable items only were estimated to be in the order of £13 per patient.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The European Society of Regional Anaesthesia and Pain Therapy guidelines, published in 2005, discuss step-wise management of post-operative pain and include NSAIDs (including diclofenac) at each step.

Additional information: previous SMC advice

In the absence of a submission, the Scottish Medicines Consortium issued advice on 7th April 2006 that oxycodone (OxyNorm[®]) injection is not recommended for use within NHS Scotland for the treatment of post-operative pain.

After review of a full submission, the Scottish Medicines Consortium issued advice on 10th January 2003 that parecoxib (Dynastat[®]) is not recommended for use within NHS Scotland. There is no evidence that the parenteral COX-2 selective non-steroidal anti-inflammatory drug (NSAID), parecoxib, is associated with a reduction in clinically significant post-operative haemorrhagic or gastro-intestinal complications compared with the non-selective NSAIDs. Parecoxib is substantially more expensive than non selective NSAIDs and should therefore not replace these drugs.

Additional information: comparators

Voltarol[®] solution for injection, as used in the trial, is used, along with the other non-opioids which can be given intravenously for post-operative pain.

Cost of relevant comparators

Drug	Dose regimen	Cost per course (£)
diclofenac (Dyloject®)	75mg by iv bolus for up to 4 doses	5 – 20 *
parecoxib	40mg then 20-40mg as needed by iv injection up to 80mg per day	5 – 40 ***
paracetamol	1g as needed by iv infusion up to 4g per day	2 – 13 ***
ketorolac	10mg then 10-30mg as needed by iv injection up to 90mg per day	1 – 17 **
diclofenac (Voltarol®)	75mg by iv infusion for up to 4 doses	1 – 3 *

Doses are for general comparison and do not imply therapeutic equivalence. * Costs from eVadis on 27th November 2007. ** Costs from eVadis on 19th December 2007. *** Costs from the Monthly Index of Medical Specialities December 2007 edition. All costs were based on use for up to 2 days.

Additional information: budget impact

The manufacturer estimated that 22% of all patients undergoing surgical procedures in Scotland currently receive injectable NSAIDs, and estimated that all these patients (estimated at 76,000 in 2007-08) would switch to the study drug (Dyloject®). The manufacturer estimated a direct drug cost in 2008 of £825K rising to £920K by 2012. Net budget impact after displacement of the comparator was estimated at £673K in 2008 and £778K by 2012. The manufacturer estimated that overall there would be a net resource saving due to reductions in the use of rescue medication and consumables. Savings in nurse time spent on drug administration may not be realised.

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.

This assessment is based on data submitted by the applicant company up to and including 10 January 2008.

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.