

**DYLOJECT[®] 75MG/2ML SOLUTION FOR INJECTION
PL 25053/0001**

UKPAR

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**DYLOJECT® 75MG/2ML SOLUTION FOR INJECTION
PL 25053/0001**

LAY SUMMARY

The MHRA granted Javelin Pharmaceuticals (UK) Limited a Marketing Authorisation (licence) for the medicinal product Dyloject® 75mg/2ml Solution for Injection (PL 25053/0001) on 30th October 2007. This is a prescription only medicine (POM) to relieve the symptoms of inflammation and pain.

Dyloject® 75mg/2ml Solution for Injection contains the active ingredient diclofenac sodium which is a non-steroidal anti-inflammatory drug (NSAID).

The test product has satisfactorily been demonstrated as therapeutically equivalent to the reference product Voltarol® Ampoules 75mg/3ml (Novartis Pharmaceuticals UK Limited) based on the clinical studies submitted. No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Dyloject® 75mg/2ml Solution for Injection outweigh the risks; hence Marketing Authorisations has been granted.

**DYLOJECT[®] 75MG/2ML SOLUTION FOR INJECTION
PL 25053/0001**

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Dyloject® 75mg/2ml Solution for Injection (PL 25053/0001) to Javelin Pharmaceuticals (UK) Limited on 30th October 2007. The product is a prescription-only medicine.

This application was submitted as an abridged application according to Article 10.3 of Directive 2001/83/EC, as amended, referring to the original product Voltarol® Ampoules 75mg/3ml (PL 00101/0466) granted to Novartis Pharmaceuticals UK Ltd on 6th August 1981.

The product contains the active ingredient diclofenac sodium and is indicated for rheumatoid arthritis, osteoarthritis, low back pain, relief of pain from fractures, sprains, strains and dislocations; acute gout; pain relief from kidney stones and post-operative pain.

Diclofenac sodium is an NSAID and acts by inhibiting the body's ability to synthesize prostaglandins. The body produces prostaglandins in response to tissue injury that in turn results in inflammation and pain.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

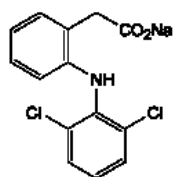
Diclofenac Sodium

INN: Diclofenac sodium

Chemical Name: 2-[(2,6-dichlorophenyl) amino]benzeneacetic acid,

CAS No: 15307-79-6

Structural Formula:



Molecular formula: C₁₄H₁₀Cl₂ NNaO₂

Molecular weight: 378.13

Physical form: White or slightly yellowish, crystalline powder, slightly hygroscopic.

An appropriate specification based on the European Pharmacopeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active diclofenac sodium is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Satisfactory batch analysis data and certificates of analysis have been provided and comply with the proposed specification.

Appropriate stability data have been generated supporting a retest period of 30 months when stored in the proposed packaging.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of pharmaceutical excipients, namely hydroxypropylbetadex (HPβCD), monothioglycerol, water for injection, and sodium hydroxide and/or hydrochloric acid (to adjust pH). All excipients used comply with their respective European Pharmacopoeial monograph specifications. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used are novel or contain material of animal or human origin. No overages were applied to the formulation.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on three batches of the medicinal product. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The primary packaging consists of 2ml Type I glass vials and 13mm siliconised butyl rubber stoppers. Specifications and Certificates of Analysis for both packaging types used have been provided and these are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 30 months has been set, which is satisfactory. Storage conditions are “Store below 30 degrees”, “Do not freeze” and “Keep vials in the outer carton in order to protect from light”.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

Dyloject® 75mg/2ml Solution for Injection has been shown to be a generic medicinal product of Voltarol® Ampoules 75mg/3ml. The proposed drug product corresponds to the current EU definition of a generic product as it complies with the criteria of having the same qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence as the reference product.

PRECLINICAL ASSESSMENT

No new preclinical data has been supplied with this application and none is required for an application of this type.

CLINICAL ASSESSMENT

INTRODUCTION AND BACKGROUND

Voltarol[®] Ampoules 75 mg/3 ml was first approved in the United Kingdom on 6th August 1981. The Marketing Authorisation Holder was Ciba-Geigy at the time, and the MAA number was PL 00001/0091. Hence, the marketing authorization application for Dyloject[®] is “abridged” in accordance with Article 10 paragraph 3 of Directive 2001/83/EC as amended.

Dyloject[®] is a soluble aqueous solution that can be administered directly from a vial. Dyloject[®] 75mg/2ml and Voltarol[®] Ampoules 75 mg/3 ml both contain the same therapeutic moiety: diclofenac. They differ in the concentration of diclofenac and the components of the formulation (specific excipients) as well as absorption rate and maximum plasma concentration following IV/IM administration. The solubilising agent used is HP β CD which allows the same dose of the active ingredient in a smaller volume (2 ml rather than 3 ml), and as a bolus injection rather than as an IV infusion. Voltarol[®] Ampoules 75 mg/3 ml is an insoluble pharmaceutical formulation that must be buffered and diluted.

The objective of the European DIC075V development program was to demonstrate therapeutic equivalence (non-inferiority) to the approved reference medicinal product Voltarol[®] Ampoules (diclofenac sodium 75 mg/3 ml, solution for injection) manufactured by Novartis Pharmaceuticals in the European Union.

GCP issues (Check)

The MHRA have been reassured that all studies conducted in the Dyloject[®] clinical development program were performed in accordance with the ICH Good Clinical Practice and the Declaration of Helsinki.

Pharmacotherapeutic group

Non-steroidal anti-inflammatory drugs (NSAIDs). ATC code M01AB

CLINICAL BACKGROUND

Dyloject[®] (diclofenac sodium) is a NSAID as a 75 mg/2 ml injection for parenteral use. Diclofenac is the first phenylacetic acid derivative to be approved as an NSAID. Diclofenac produces analgesic, antipyretic, and anti-inflammatory activity secondary to inhibition of cyclooxygenases COX-1 and COX-2. Parenteral Voltarol[®] is the leading NSAID for post-operative pain relief in the United Kingdom. As with other NSAIDs, its mode of action is not known; its ability to inhibit prostaglandin synthesis, however, may be involved in its anti-inflammatory activity, as well as contribute to its efficacy in relieving pain related to inflammation and primary dysmenorrhea.

Dyloject[®] (DIC075V) was developed as 75 mg/2 ml injection for parenteral use with claimed similar bioavailability and bioequivalence to the reference product Voltarol[®], however, with the additional benefit of more rapid uptake and clinically meaningful plasma levels expected soon after IV bolus administration. This more rapid T_{max} and greater C_{max} for DIC075V, were reflected in the efficacy findings of the pivotal trial DFC-001. Another claim of advantage with this formulation is the observed decreased incidence of certain side effects, such as phlebitis.

A pivotal study (DFC-001) was submitted to support the claim of similar efficacy and safety of Dyloject® to intravenous Voltarol®.

INDICATIONS

Intramuscular Use

Dyloject® Vials 75 mg/2 ml 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.

Intravenous Use

For treatment or prevention of post-operative pain in supervised health care settings.

Assessor comments:

Indications are in line with UK approved SPC.

DOSE AND DOSE REGIMEN

Adults

Dyloject 75 mg/2 ml Solution for Injection should not be given for more than two days.

Intramuscular injection: The following directions for intramuscular injection must be adhered to in order to avoid damage to a nerve or other tissue at the injection site.

One vial once (or in severe cases twice) daily, intramuscularly by deep intragluteal injection into the upper outer quadrant of the buttock. If two injections daily are required, it is advised that the alternative buttock be used for the second injection.

Recommended IM injection procedure

1. The patient may lie down or stand, whichever is more comfortable.
2. The exposed buttocks should be inspected to find the most suitable injection site. Avoid scars and lumps and choose the buttock which is free from any problems. If more than one injection needs to be given, the other buttock should be used.
3. The injection site should be thoroughly disinfected, e.g. with alcohol, and allowed to dry.
4. To ensure deep intramuscular injection, give high into upper outer quadrant of the buttock, taking particular care to avoid the sciatic nerve and blood vessels. Avoid injecting into an area where resistance is felt. N.B. In obese patients, avoid deposition of the drug into the subcutaneous fatty tissue. In small thin patients with little muscle bulk, be especially aware of the sciatic nerve, which may be quite superficial.
5. Prior to injection of solution, draw back to ensure that no blood vessel has been penetrated. If blood is drawn, withdraw the needle to another site and check again.

Renal colic: One 75 mg dose intramuscularly. A further dose may be administered after 30 minutes if necessary. The recommended maximum daily dose of Dyloject is 150 mg.

Intravenous use: Dyloject 75 mg/2 ml Solution for Injection may be given as an intravenous bolus injection. Two alternative regimens are recommended for bolus injection.

- For the *treatment* of moderate to severe post-operative pain, 75 mg should be injected intravenously. If necessary, treatment may be repeated after 4 to 6 hours, not exceeding 150 mg within any period of 24 hours.

- For the *prevention* of post-operative pain, a loading dose of 25 mg to 50 mg administered as a 5 to 60 second intravenous bolus after surgery, followed by additional injections up to a maximum daily dosage of 150 mg. If necessary, treatment may be repeated after 4 to 6 hours, not exceeding 150 mg within any period of 24 hours.

Phlebitis: Intravenous drug administration has been associated with the occurrence of Thrombophlebitis. Clinical studies comparing Dyloject 75 mg/2 ml Solution for Injection to Voltarol[®] Ampoules have demonstrated reduced severity and one fourth the incidence of phlebitis (p=0.0032).

Children: Dyloject 75 mg/2 ml Solution for Injection is not recommended for use in children.

Elderly: Although the pharmacokinetics of diclofenac sodium are not impaired to any clinically relevant extent in elderly patients, non-steroidal anti-inflammatory drugs (NSAIDs) should be used with particular caution in such patients who generally are more prone to adverse reactions. In particular it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight (see also *Precautions* in Section 4.4) and the patient should be monitored for gastrointestinal bleeding for 4 weeks following initiation of NSAID therapy. The recommended maximum daily dose of Dyloject 75 mg/2 ml Solution for Injection is 150 mg.

Patients with renal impairment: Hydroxypropylbetadex (HP β CD), when administered intravenously, is predominantly eliminated through glomerular filtration. Therefore, patients with severe renal impairment defined as creatinine clearance below 30 ml/min should not be treated with Dyloject 75 mg/2 ml Solution for Injection. See Section 4.4, *Special warnings and precautions for use*.

Assessor comments:

In the reference drug SPC: Voltarol[®] must not be given as an intravenous bolus injection

LEGAL STATUS

POM

CLINICAL PHARMACOLOGY

The clinical studies submitted to establish essential similarity of the Dyloject[®] to the reference product Voltarol[®] are:

1. DFC-PL1: Phase 1 pharmacokinetic single-dose, four-way, cross-over study of the bioavailability of three infusion rates (0, 30 and 60 seconds) of DIC075V (Test drug) vs. a 30 minute intravenous infusion of Voltarol[®], (N=8).
2. DFC-003: Phase 1 pharmacokinetic single-dose, four-way, cross-over study of the bioavailability of DIC075V vs. Voltarol[®], when administered intramuscularly and intravenously (N=24).
3. DFC-001 study: Is a randomised, double-blind, placebo- and comparator-controlled, single dose, parallel-group comparison of the analgesic efficacy and safety of IV DIC075V (Diclofenac sodium 75 mg) and Voltarol[®] (75 mg) following Dental surgery.

DFCPL1 and DFC-003 were performed to compare the bioequivalence to Voltarol[®]. DFC-PL1 was a pilot study which demonstrated DIC075V is bioequivalent with Voltarol[®] with respect AUC_{0-t} and AUC_∞ regardless of the IV administration rate.

CLINICAL EFFICACY

Introduction

The applicant submitted a phase III pivotal study (study DFC-001) which is a randomised, double-blind, placebo-and comparator controlled, single-dose, parallel-group comparison of the analgesic efficacy and safety of intravenous DIC075V (diclofenac sodium 75 mg) and Voltarol[®] (diclofenac sodium 75 mg) following dental surgery

The primary objectives of this study were to demonstrate the safety and superiority of DIC075V to placebo through the measure of 0 - 4 hour total pain relief (TOTPAR4) and to demonstrate that DIC075V and Voltarol[®] Ampoules 75 mg/3 ml provide equivalent efficacy (non inferiority) when compared to placebo.

The secondary objectives were to demonstrate analgesic efficacy of DIC075V to Voltarol[®] Ampoules 75 mg/3 ml in subjects with moderate or severe postoperative pain and compare the safety and tolerability of DIC075V to placebo and DIC075V to Voltarol[®] Ampoules 75 mg/3 ml in subjects with moderate or severe postoperative pain.

Diagnosis Inclusion criteria: Mod. To severe post-op. pain; VAS: ≥ 50 mm; Categorical: moderate or severe rating.

Subjects had undergone elective extraction of one or more molar teeth.

Duration of Treatment: Approx. 14 hrs in-house, 5-9 day safety visit

Study & Ctrl Drugs: Dose, Route & Regimen:

- DIC075V 75 mg, IV bolus, q.d.
- Voltarol[®] 75 mg, IV infusion, q.d.
- Placebo, IV bolus & IV infusion, q.d.

Statistical and Clinical Assessment of Efficacy

The primary evidence of efficacy is provided in study DFC-001. This was a randomised, double-blind, parallel group comparison of the efficacy and safety of intravenous administration of 75mg of Dyloject[®] and Voltarol[®] following elective extraction of one or more molar teeth. Patients were admitted into the study if they had moderate to severe pain within 6 hours following dental surgery. Moderate to severe pain was measured by a categorical pain intensity scale (“moderate” or “severe” descriptor) and a pain intensity score of 50mm or greater on a 0-100 visual analogue scale (VAS). Patients were randomised to receive a single dose of placebo, Dyloject[®] or Voltarol[®]. The primary efficacy parameter was total pain relief in the 0-4 hours post dose time interval as measured on the VAS. The secondary endpoints were total pain relief, pain intensity reduction, pain intensity difference, and peak pain relief as well as time to onset of analgesia (30% reduction). The non-inferiority of Dyloject[®] to Voltarol[®] was assessed by constructing a 95% confidence interval for the difference in total pain relief in the 0-4 hours post dose period. A clinically meaningful difference of 15mm on the VAS was defined and therefore the chosen non-inferiority margin for the 0-4 hour endpoint was 60mm. Missing values were inputted either by linear interpolation or by carrying forward the last observation (LOCF).

Assessors Comment: *The Applicant was asked to justify the chosen clinically meaningful difference of 15mm in a scientific meeting held at the MHRA. The Applicant has provided a satisfactory justification for the chosen pain intensity VAS score.*

Results:

Approximately two thirds of patients enrolled had a moderate maximum surgical trauma rating and the remaining one third of patients had a severe rating. 57% of patients had moderate baseline pain intensity and 43% of patients had severe baseline pain intensity. The overall mean VAS score was 67.8.

The mean total pain relief for the first 4 hours in the ITT population is summarised in the table below.

Statistics and Comparisons to Dyloject	Dyloject	Voltarol	Placebo
Mean	300.6	266.2	52.5
Standard deviation	73.61	91.63	88.77
Placebo comparison			
Treatment difference (mm*hours)	247.7	213.3	-
Standard error	16.56	16.8	-
95% CI for treatment difference	(215.2,280.2)	(180.4,246.3)	-
p-value	< 0.001	< 0.001	-
Voltarol comparison			
Treatment difference (mm*hours)	34.4	-	-
Standard error	16.72	-	-
95% CI for treatment difference	(1.6,67.1)	-	-

Assessors Comment: *The results on the primary endpoint clearly show that both diclofenac formulations are superior to placebo. The difference between the diclofenac formulations is small. However, the lower limit of the 95% confidence interval is only 1.6 and therefore this provides clear support for the claim that Dyloject[®] is non-inferior to Voltarol[®]. It should be noted that normally in non-inferiority analysis an analysis on the per protocol population is also performed. However as the per protocol population included 97% of the patients from the ITT population the results from this analysis will be very similar to those provided. Also it should be noted that these analyses included imputed data. The linear interpolations performed are acceptable and the use of last observation carried forward should provide a conservative estimate of efficacy as the least favourable of the baseline score and the last pain assessment score was carried forward. Therefore, the only remaining concern is whether the efficacy of Voltarol[®] and Dyloject[®] is different during the first 4 hours although similar when looked at as a whole. However, this possibility is easily discounted by looking at a graphical representation of the pain relief over time. The results seen on the primary endpoint are consistent with those seen on a broad range of secondary endpoints.*

Overall Statistical Conclusion

There are no major methodological concerns with this application. The pivotal study provides clear evidence of superiority for Dyloject over placebo. Good evidence of non-inferiority of Dyloject[®] to Voltarol[®] in terms total pain relief during the first 4 hours since receiving treatment has also been provided. The results of study DFC-001 provide sufficient evidence to establish the efficacy of Dyloject[®] for use as a single dose treatment in patients with moderate to severe pain following dental surgery.

CLINICAL SAFETY

The safety data provide by the pivotal study do not suggest a safety concern in comparison with the previous formulation.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

This is satisfactory.

EXPERT REPORTS

A satisfactory Clinical Expert Report has been submitted with appropriate CV.

PATIENT INFORMATION LEAFLET

This is satisfactory.

LABELLING

This is satisfactory.

RISK BENEFIT

The application contains an adequate review of published clinical data. The reference medicinal product Voltarol[®] ampoules 75mg/3ml, solution for injection contains the widely used and well-known active substance Diclofenac sodium with an established favorable benefit-risk profile. The current applicant has provided satisfactory data to support the indication and a positive benefit–risk ratio has been concluded.

CONCLUSION

Marketing authorisations should be granted for this product.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Dyloject[®] 75mg/2ml Solution for Injection are well-defined and controlled. The specifications and batch analysis results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data was submitted and none is required for an application of this type.

EFFICACY

Diclofenac sodium has been approved as an NSAID for many years and used to manage and treat pain and inflammation. Satisfactory evidence has been provided to demonstrate the efficacy of Dyloject[®] 75mg/2ml Solution for Injection for use as a single dose treatment in patients with moderate to severe pain. This applicant has demonstrated that Dyloject[®] 75mg/2ml Solution for Injection is therapeutically equivalent to the previously granted application for Voltarol[®] Ampoules 75mg/3ml Solution for Injection.(PL 00101/0466).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product and the reference product are interchangeable. Extensive clinical experience with diclofenac sodium is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

**DYLOJECT[®] 75MG/2ML SOLUTION FOR INJECTION
PL 25053/0001**

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 26 th September 2005.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 31 st October 2005.
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 13 th December 2005, and further information relating to the clinical dossier on 18 th December 2006.
4	The applicant responded to the MHRA's requests, providing further information on 21 st June for the quality sections, and again on 21 st February 2007 for the clinical sections.
5	The application was determined on 30 th October 2007

**DYLOJECT[®] 75MG/2ML SOLUTION FOR INJECTION
PL 25053/0001**

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

DYLOJECT[®] 75MG/2ML SOLUTION FOR INJECTION PL 25053/0001

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dyloject[®] 75 mg/2 ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is diclofenac sodium [sodium-(o-[(2,6-dichlorophenyl)-amino]-phenyl)-acetate)]. Each 2 ml vial contains 75 mg of diclofenac sodium. For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Intramuscular use

Dyloject 75 mg/2 ml 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.

Intravenous use

For treatment or prevention of post-operative pain in supervised healthcare settings.

4.2 Posology and method of administration

Instructions on using the vial

1. Remove the green flip cap
2. Aseptically withdraw the appropriate amount (not more than 2 ml) for either IV use or deep IM injection. As with all parenteral products, Dyloject should be inspected visually for particulate matter or discoloration prior to administration.

Adults

Dyloject 75 mg/2 ml Solution for Injection should not be given for more than two days.

Intramuscular injection: The following directions for intramuscular injection must be adhered to in order to avoid damage to a nerve or other tissue at the injection site.

One vial once (or in severe cases twice) daily, intramuscularly by deep intragluteal injection into the upper outer quadrant of the buttock. If two injections daily are required, it is advised that the alternative buttock be used for the second injection.

Recommended IM injection procedure

1. The patient may lie down or stand, whichever is more comfortable.
2. The exposed buttocks should be inspected to find the most suitable injection site. Avoid scars and lumps and choose the buttock which is free from any problems. If more than one injection needs to be given, the other buttock should be used.

3. The injection site should be thoroughly disinfected, e.g. with alcohol, and allowed to dry.
4. To ensure deep intramuscular injection, give high into upper outer quadrant of the buttock, taking particular care to avoid the sciatic nerve and blood vessels. Avoid injecting into an area where resistance is felt. N.B. In obese patients, avoid deposition of the drug into the subcutaneous fatty tissue. In small thin patients with little muscle bulk, be especially aware of the sciatic nerve, which may be quite superficial.
5. Prior to injection of solution, draw back to ensure that no blood vessel has been penetrated. If blood is drawn, withdraw the needle to another site and check again.

Renal colic: One 75 mg dose intramuscularly. A further dose may be administered after 30 minutes if necessary. The recommended maximum daily dose of Dyloject is 150 mg.

Intravenous use: Dyloject 75 mg/2 ml Solution for Injection may be given as an intravenous bolus injection. Two alternative regimens are recommended for bolus injection.

- For the *treatment* of moderate to severe post-operative pain, 75 mg should be injected intravenously. If necessary, treatment may be repeated after 4 to 6 hours, not exceeding 150 mg within any period of 24 hours.
- For the *prevention* of post-operative pain, a loading dose of 25 mg to 50 mg administered as a 5 to 60 second intravenous bolus after surgery, followed by additional injections up to a maximum daily dosage of 150 mg. If necessary, treatment may be repeated after 4 to 6 hours, not exceeding 150 mg within any period of 24 hours.

Phlebitis: Intravenous drug administration has been associated with the occurrence of Thrombophlebitis. Clinical studies comparing Dyloject 75 mg/2 ml Solution for Injection to Voltarol[®] Ampoules have demonstrated reduced severity and one fourth the incidence of phlebitis ($p=0.0032$).

Children: Dyloject 75 mg/2 ml Solution for Injection is not recommended for use in children.

Elderly: Although the pharmacokinetics of diclofenac sodium are not impaired to any clinically relevant extent in elderly patients, non-steroidal anti-inflammatory drugs (NSAIDs) should be used with particular caution in such patients who generally are more prone to adverse reactions. In particular it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight (see also *Precautions* in Section 4.4) and the patient should be monitored for gastrointestinal bleeding for 4 weeks following initiation of NSAID therapy. The recommended maximum daily dose of Dyloject 75 mg/2 ml Solution for Injection is 150 mg.

Patients with renal impairment: Hydroxypropylbetadex (HP β CD), when administered intravenously, is predominantly eliminated through glomerular filtration. Therefore, patients with severe renal impairment defined as creatinine clearance below 30 ml/min should not be treated with Dyloject 75 mg/2 ml Solution for Injection. See Section 4.4, *Special warnings and precautions for use*.

4.3 Contraindications

Patients with a history of, or active or suspected gastrointestinal ulcers or bleeding.

Patients with a history of severe renal, hepatic or gastrointestinal reactions to diclofenac in any form.

Patients who have previously shown hypersensitivity reactions (e.g. asthma, urticaria or acute rhinitis) or hepatic inflammation to diclofenac sodium, aspirin or other NSAIDs.

Patients with a hypersensitivity to the excipients HP β CD or monothioglycerol.

The excipient HP β CD is predominantly eliminated through the kidney by glomerular filtration. Therefore, Dyloject 75 mg/2 ml Solution for Injection is contraindicated in patients with severe renal impairment (defined as creatinine clearance below 30 ml/min). See Section 4.4, *Special warnings and precautions for use*.

Specifically for IV use

Concomitant NSAID or anticoagulant use (including low dose heparin).

A history of haemorrhagic diathesis, a history of confirmed or suspected cerebrovascular bleeding.

Operations associated with a high risk of haemorrhage.

A history of asthma.

Moderate or severe renal impairment (serum creatinine > 160 μ mol/l). Hypovolaemia or dehydration from any cause.

4.4 Special warnings and precautions for use

Gastrointestinal: Close medical surveillance is imperative in patients with symptoms indicative of gastrointestinal disorders, with a history suggestive of gastrointestinal ulceration, with ulcerative colitis or with Crohn's disease.

Gastrointestinal bleeding or ulcerative/perforation, haematemesis and melaena have in general more serious consequences in the elderly. They can occur at any time during treatment, with or without warning symptoms or a previous history. In the rare instances where gastrointestinal bleeding or ulceration occurs in patients receiving Dyloject 75 mg/2 ml Solution for Injection, the drug should be withdrawn.

Hepatic: Close medical surveillance is also imperative in patients suffering from severe impairment of hepatic function.

Hypersensitivity reactions: As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.

Like other NSAIDs, Dyloject 75 mg/2 ml Solution for Injection may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Renal impairment: HP β CD, when administered intravenously, is predominantly eliminated through the kidney by glomerular filtration. Therefore, patients with renal impairment (defined as creatinine clearance below 30 ml/min) should not be treated with Dyloject 75 mg/2 ml Solution for Injection. See Section 5.2, *Pharmacokinetic properties*.

Pregnancy and lactation: Please refer to Section 4.6 for information regarding use in pregnancy or lactation.

Precautions

Renal: Patients with renal, cardiac or hepatic impairment and the elderly should be kept under surveillance, since the use of NSAIDs may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored.

The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or those recovering from major surgery. Effects on renal function are usually reversible on withdrawal of Dyloject 75 mg/2 ml Solution for Injection.

Renal impairment: HP β CD, when administered intravenously, is predominantly eliminated through the kidney by glomerular filtration. Therefore, patients with renal impairment

(defined as creatinine clearance below 30 ml/min) should not be treated with Dyloject 75 mg/2 ml Solution for Injection. See Section 5.2, *Pharmacokinetic properties*.

Hepatic: If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (eosinophilia, rash, etc.), Dyloject 75 mg/2 ml Solution for Injection should be discontinued. Hepatitis may occur without prodromal symptoms.

Use of Dyloject 75 mg/2 ml Solution for Injection in patients with hepatic porphyria may trigger an attack.

Haematological: Dyloject 75 mg/2 ml Solution for Injection may reversibly inhibit platelet aggregation (see *Anticoagulants* in Section 4.5). Patients with defect of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

Long-term treatment: Dyloject 75 mg/2 ml Solution for Injection is not recommended for long term use. Prescribers should select follow-on treatment based on prescribing information for the specific product selected. All patients who are receiving non-steroidal anti-inflammatory agents long term, should be monitored as a precautionary measure, e.g. renal function, hepatic function (elevation of liver enzymes may occur) and blood counts. This is particularly important in the elderly.

Like other drugs that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of, bronchial asthma.

Caution is required in patients with a history of heart failure or hypertension since oedema has been reported in association with NSAID administration.

4.5 Interaction with other medicinal products and other forms of interaction

Lithium and digoxin: Diclofenac may increase plasma concentration of lithium and digoxin.

Anticoagulants: There are isolated reports of an increased risk of haemorrhage with the combined use of diclofenac and anticoagulant therapy. Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other non-steroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

Antidiabetic agents: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of hypoglycaemic and hyperglycaemic effects which have required adjustment to the dosage of hypoglycaemic agents.

Cyclosporin: Cases of nephrotoxicity have been reported in patients receiving concomitant cyclosporine and NSAIDs, including diclofenac. This might be mediated through combined renal antiprostaglandin effects of both the NSAID and cyclosporine.

Methotrexate: Cases of serious toxicity have been reported when methotrexate and NSAIDs are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.

Quinolone antimicrobials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

Other NSAIDs and corticosteroids: Co-administration of diclofenac with aspirin or corticosteroids may increase the risk of gastrointestinal bleeding. Avoid concomitant use of two or more NSAIDs.

Diuretics: Like other NSAIDs, diclofenac may inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, which should therefore be monitored frequently.

Cardiac glycosides: Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce glomerular filtration rate and increase plasma glycoside and HPβCD levels.

Mifepristone: NSAIDs should not be used for 8 to 12 days after mifepristone administration, as NSAIDs can reduce the effect of mifepristone.

Anti-hypertensives: Concomitant use of NSAIDs with antihypertensive drugs (i.e. beta-blockers, angiotensin converting enzyme (ACE) inhibitors, diuretics) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.

4.6 Pregnancy and lactation

Although animal studies have not demonstrated teratogenic effects, diclofenac should not be prescribed during pregnancy unless there are compelling reasons for doing so. The lowest effective dosage should be used.

Congenital abnormalities have been reported in association with the administration of NSAIDs in man; however, these are low in frequency and do not appear to follow any discernible pattern.

In view of the known effects of NSAIDs on the foetal cardiovascular system (e.g. a premature closure of the ductus arteriosus) and in causing uterine inertia, use in late pregnancy should be avoided.

Following doses of 50 mg enteric coated tablets every 8 hours, traces of active substance have been detected in breast milk, but in quantities so small that no adverse effects on the breast-fed infant are to be expected.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness or other central nervous disturbances while taking NSAIDs should refrain from driving or operating machinery.

4.8 Undesirable effects

If serious side effects occur, Dyloject 75 mg/2 ml Solution for Injection should be withdrawn.

Frequency estimate: frequent: >10%; occasional: > 1 to 10%; rare: > 0.001 to 1%; isolated cases: < 0.001%. Side effects observed after parenteral diclofenac administration.

Gastrointestinal tract

Occasional: epigastric pain, other gastrointestinal disorders (e.g. nausea, vomiting, diarrhoea, dyspepsia, flatulence, anorexia)

Rare: gastrointestinal bleeding (haematemesis, melaena, bloody diarrhoea), abdominal pain/tenderness, gastrointestinal ulcers with or without bleeding or perforation, mouth ulcerations, tooth and tongue disorders or dysphagia

In isolated cases: aphthous stomatitis, glossitis, esophageal lesions, lower gut disorders (e.g. non-specific haemorrhagic colitis and exacerbations or ulcerative colitis or Crohn's proctocolitis, colonic damage and stricture formation), pancreatitis, or constipation.

Central nervous system

Occasional: headache, dizziness or vertigo

Rare: drowsiness, tiredness, dysguesia, paraesthesia, balance impairment, aponia, hypoaesthesia, migraine, speech disorder, or trismus

In isolated cases: disturbances of sensation, memory disturbance, disorientation, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions, or aseptic meningitis.

General disorders

Rare: pain, chest pain, chest tightness, malaise, rigors, bloody discharge, feeling abnormal, feeling hot, or pyrexia.

Musculoskeletal and connective tissue disorders

Occasional: pain in jaw

Rare: facial pain, joint stiffness, myalgia, back pain, chest wall pain, neck pain, muscle cramp, or muscle tightness.

Special senses

Rare: eyelid oedema, eyelid pruritus, increased lacrimation, or eye pain

In isolated cases: disturbances of vision (blurred vision, diplopia), impaired hearing, tinnitus, or taste disturbances.

Skin

Occasional: rashes or skin eruptions

Rare: urticaria, pruritus, or sweating increased

In isolated cases: bullous eruptions, eczema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (acute toxic epidermolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reactions, or purpura including allergic purpura.

Kidney

Rare: oedema, renal pain

In isolated cases: acute renal insufficiency, urinary abnormalities (e.g. haematuria, proteinuria), interstitial nephritis, nephritic syndrome, or papillary necrosis.

Liver

Occasional: elevation of serum aminotransferase enzymes (ALT, AST)

Rare: liver function disorders including hepatitis (in isolated cases fulminant) with or without jaundice, or increased lipase.

Blood

Rare: neutrophilia

In isolated cases: thrombocytopenia, leucopenia, agranulocytosis, hemolytic anaemia, or aplastic anaemia.

Hypersensitivity

Rare: hypersensitivity reactions (e.g. bronchospasm, anaphylactic/anaphylactoid systemic reactions including hypotension), respiratory disorder NOS, or rhinorrhoea

In isolated cases: vasculitis, or pneumonitis.

Cardiovascular system

Occasional: haemorrhage

Rare: phlebitis, hypotension, bradycardia, or flushing

In isolated cases: palpitations, chest pain, hypertension, or congestive heart failure.

Laboratory abnormalities

Rare: elevated creatine phosphokinase, ketonuria, haematuria, or bilirubin in urine.

Other organ systems

In isolated cases: impotence.

Reactions to the intramuscular injection

Occasional: reactions such as local pain and induration

In isolated cases: abscesses and local necrosis at the injection site.

Reactions to the intravenous injection

Occasional: thrombophlebitis

Rare: cannula site reaction, infusion site discomfort or burning, injection site stinging, or pyrexia.

4.9 Overdose

Management of acute poisoning with NSAIDs essentially consists of supportive and symptomatic measures. There is no typical clinical picture resulting from diclofenac sodium overdose.

Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal irritation and respiratory depression.

Specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Non-steroidal anti-inflammatory drugs (NSAIDs). ATC code M01AB.

Mechanism of action

Dyloject 75 mg/2 ml Solution for Injection is a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase (cyclo-oxygenase). Diclofenac sodium *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings. When used concomitantly with opioids for the management of post-operative pain, diclofenac sodium often reduces the need for opioids.

5.2 Pharmacokinetic properties

Absorption

Intramuscular injection: After administration of Dyloject 75 mg/2 ml Solution for Injection intramuscularly, absorption sets in immediately, and mean peak plasma concentrations of about 2.569 ± 1.092 µg/ml (2.5 µg/ml equals approximately 8 µmol/l) are reached in 39 minutes. In comparative clinical studies, the rate of absorption for Dyloject 75 mg/2 ml Solution for Injection was more rapid than Voltarol[®] Ampoules - peak plasma concentration for Voltarol[®] was 1.541 ± 0.419 µg/ml at 48 minutes. The extent of absorption of Dyloject 75 mg/2 ml Solution for Injection was bioequivalent to Voltarol[®]

Ampoules. The amount of diclofenac absorbed after IM administration is in linear proportion to the size of the dose.

Intravenous injection: After administration of Dyloject 75 mg/2 ml Solution for Injection intravenously, absorption sets in immediately, and mean peak plasma concentrations of about 15.147 ± 2.829 $\mu\text{g/ml}$ (2.5 $\mu\text{g/ml}$ equals approximately 8 $\mu\text{mol/l}$) are reached in 3 minutes. In comparative clinical studies, the rate of absorption for Dyloject 75 mg/2 ml Solution for Injection was more rapid than Voltarol[®] Ampoules - peak plasma concentration for Voltarol[®] was 5.668 ± 0.974 $\mu\text{g/ml}$ at 30 minutes. The extent of absorption of Dyloject 75 mg/2 ml Solution for Injection was bioequivalent to Voltarol[®] Ampoules.

In clinical studies comparing the analgesic efficacy of Dyloject to Voltarol[®], Dyloject was found to have a more rapid onset of analgesic action. At the 15- and 30-minute post-dose times, Dyloject 75 mg/2 ml Solution for Injection was statistically superior to Voltarol[®] as measured on the VAS and categorical pain intensity and pain relief scales ($p < 0.05$). At 15 minutes after dosing, the proportion of patients reporting a 30% reduction in pain intensity differed significantly for those given Dyloject and Voltarol[®] (52% versus 21%, respectively; $p = 0.0022$). Dyloject was statistically superior to Voltarol[®] over the initial 0-2 hour TOTPAR interval both on the VAS scale ($p = 0.009$) and the categorical scale ($p = 0.019$). The magnitude of pain relief after two hours and the duration of action of Dyloject were found to be similar to Voltarol[®].

Bioavailability

The relative bioavailability of Dyloject 75 mg/2 ml Solution for Injection after IM administration is approximately 100%. The absolute bioavailability of Dyloject 75 mg/2 ml Solution for Injection after IV administration relative to Voltarol[®] Ampoules IV is approximately 100%.

The bioavailability of diclofenac after oral or rectal administration is approximately one half that of IM or IV administration, as these latter routes avoid "first-pass" metabolism.

Distribution

The active substance is 99.7% protein bound, mainly to albumin (99.4%).

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after the peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3 - 6 hours. Two hours after reaching the peak plasma values, concentrations of the active substance are already higher in the synovial fluid than they are in the plasma, and remain higher for up to 12 hours.

Metabolism

Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Elimination

The terminal half-life of Dyloject 75 mg/2 ml Solution for Injection in plasma is 1.17 ± 0.32 hours. In comparative clinical studies, the rate of clearance was more rapid than for Voltarol[®] Ampoules (IM: 1.17 ± 0.29 hours, IV: 1.23 ± 0.31 hours). For Dyloject and Voltarol[®], renal clearance and excretion were found to be bioequivalent. Total systemic clearance of diclofenac in plasma is 263 ± 56 ml/min (mean value \pm SD). Four of the metabolites, including the two active ones, also have short plasma half-lives of 1 - 3 hours.

About 60% of the administered dose is excreted in the urine in the form of the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to

glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

Previous studies with HP β CD at higher doses than what is present in Dyloject 75 mg (667 mg per dose) have shown that the terminal half-life following a single-dose of 2 g of HP β CD administered by a one-hour IV infusion is 1.5 ± 0.3 hours. HP β CD is primarily renally excreted with 93% to 101% excreted unchanged in the urine within 12 hours of administration. In subjects with severe renal impairment (creatinine clearance ≤ 19 ml/min), clearance of HP β CD was reduced 6-fold compared to subjects with normal renal function.

Characteristics in patients

Elderly: No relevant age-dependent differences in the drug's absorption, metabolism or excretion have been reported.

Patients with renal impairment: In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of < 10 ml/min, the calculated steady-state plasma levels of the hydroxyl metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

Patients with hepatic disease: In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

5.3 Preclinical safety data

Nonclinical data on diclofenac, HP β CD and their combination in Dyloject revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction, and local tolerance studies with the following provisions for potential gastrointestinal toxicity and foetal risk of premature closure of the ductus arteriosus in late pregnancy.

A single oral dose of 0.1 mg/kg of diclofenac to pregnant rats on pregnancy day 21 caused a constriction of the ductus arteriosus in the offspring, a known effect of prostaglandin-inhibiting drugs. Administration of diclofenac in late pregnancy is therefore not recommended.

In the 4-week IV toxicity studies conducted with diclofenac in rats (3, 7 and 15 mg/kg/day) and diclofenac and HP β CD in monkeys (3, 15 and 60 mg/kg/day and 533 mg/kg/day respectively) observed effects were essentially similar for both species and were all considered expected. Diclofenac induced a low incidence of mortality/premature sacrifice (due to peritonitis), gastrointestinal toxicity and regenerative anaemia in rats at a dose level of 15 mg/kg/day. Recovery was complete after a 9-week treatment-free period.

In monkeys, diclofenac caused gastrointestinal toxicity, regenerative anaemia and exacerbation of minor tail skin lesions at dose levels of 15 and 60 mg/kg/day. Resolution of these findings could not be assessed in the 60 mg/kg/day dose group, due to premature sacrifice. Findings attributed to HP β CD included very mild to mild renal tubular vacuolization in rats and very mild to mild granular appearance of the renal tubular cells in the medullar rays in monkeys. Following a relatively long treatment-free period as compared to the duration of treatment, partial and complete recovery of HP β CD-associated findings has been demonstrated in rats and monkeys, respectively.

The No Adverse Effect Level for HP β CD-related effects after 4 weeks of administration is lower than 26.6 mg HP β CD/kg/day in both species.

The solubilising agent HP β CD has been found to produce pancreatic hyperplasia and neoplasia when administered orally to rats at doses of 500, 2000 or 5000 mg/kg per day for 25 months. Adenocarcinomas of the exocrine pancreas produced in the treated animals were not seen in the untreated group and are not reported in the historical controls. These findings were not observed in the mouse carcinogenicity study, nor in a 12-month toxicity study in dogs or in a 2-year toxicity study in female cynomolgous monkeys.

In the Dyloject nonclinical studies diclofenac and HP β CD alone and in combination were not mutagenic or clastogenic. Diclofenac has shown no carcinogenic potential. The adenocarcinomas observed in the exocrine pancreas in the 2-year oral carcinogenicity study with HP β CD in rats were not considered a clinical hazard for Dyloject because HP β CD is not genotoxic. Dyloject is intended for short-term treatment only, and no pancreatotrophic changes were observed in the 4 week intravenous studies in rats and monkeys described above.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dyloject 75 mg/2 ml Solution for Injection also contain

- Hydroxypropylbetadex (HP β CD)
- Monothioglycerol
- Water for Injection
- Sodium hydroxide and/or hydrochloric acid (to adjust pH)
- Nitrogen

6.2 Incompatibilities

The vials used IM or IV as a bolus should not be mixed with other injection solutions.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store below 30°C. Do not freeze. Keep vials in the outer carton in order to protect from light.

Keep Dyloject out of reach and sight of children.

The product should not be used if crystals or precipitates are observed.

6.5 Nature and contents of container

The vials are 2 ml Ph. Eur. Type I borosilicate glass vials with 13 mm caps. The vials contain colourless liquid and are supplied in packs of 10.

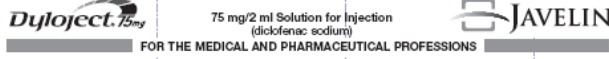
6.6 Special precautions for disposal

The dose should be freshly withdrawn from the vial and used immediately. Once withdrawn, the dose should not be stored.

- 7 MARKETING AUTHORISATION HOLDER**
Javelin Pharmaceuticals UK Limited
Compass House, Vision Park
Chivers Way, Histon
Cambridge CB4 9AD
United Kingdom
- 8 MARKETING AUTHORISATION NUMBER(S)**
PL 25053/0001
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**
30/10/2007
- 10 DATE OF REVISION OF THE TEXT**
30/10/2007
- 11 DOSIMETRY (IF APPLICABLE)**
- 12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS
(IF APPLICABLE)**

PATIENT INFORMATION LEAFLET

DYLOJECT® 75MG/2ML SOLUTION FOR INJECTION PL 25053/0001



1. NAME OF THE MEDICINAL PRODUCT
Dyloject® 75 mg/2 ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
The active ingredient is diclofenac sodium [sodium-(p)-[(2S)-dicloheptano-2-ylidene]phenyl]acetate]. Each 2 ml vial contains 75 mg of diclofenac sodium. For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications
Intramuscular use
Dyloject 75 mg/2 ml Solution for Injection is effective in acute forms of pain, including neuralgia, exacerbations of osteo- and rheumatoid arthritis, acute back pain, acute gout, acute trauma and fractures, and post-operative pain.

Intravenous use
For treatment or prevention of post-operative pain in supervised healthcare settings.

4.2 Posology and method of administration
Instructions on using the vial
1. Remove the cap from the top.
2. Aspirately withdraw the appropriate amount (not more than 2 ml) for either IV use or deep IM injection. As with all parenteral products, Dyloject should be inspected visually for particulate matter or discoloration prior to administration.

Adults
Dyloject 75 mg/2 ml Solution for Injection should not be given for more than two days.

Intramuscular injection: The following directions for intramuscular injection must be adhered to in order to avoid damage to a nerve or other tissue at the injection site.
One vial once (or in severe cases twice) daily intramuscularly by deep intragluteal injection into the upper outer quadrant of the buttock. If two injections daily are required, it is advised that the alternative buttock be used for the second injection.

Recommended IM injection procedure
1. The patient may lie down or stand, whichever is more comfortable.
2. The exposed buttocks should be inspected to find the most suitable injection site. Avoid scars and lacerations of the buttock which is free from any problems. If more than one injection needs to be given, the other buttock should be used.
3. The injection site should be thoroughly disinfected, e.g. with alcohol, and allowed to dry.
4. To ensure deep intramuscular injection, give high into upper outer quadrant of the buttock, taking particular care to avoid the sciatic nerve and blood vessels. Avoid injecting into an area where resistance is felt, i.e. in obese patients, avoid deposition of the drug into the subcutaneous fatty tissue. In small thin patients with little muscle bulk, be especially aware of the sciatic nerve, which may be quite superficial.
5. Prior to injection of solution, draw back to ensure that no blood vessel has been penetrated. If blood is drawn, withdraw the needle to another site and check again.

Renal excretion: One 75 mg dose intramuscularly. A further dose may be administered after 30 minutes if necessary. The recommended maximum daily dose of Dyloject is 150 mg.

Intravenous use: Dyloject 75 mg/2 ml Solution for Injection may be given as an intravenous bolus injection. Two alternative regimens are recommended for bolus injection.
- For the treatment of moderate to severe post-operative pain, 75 mg should be injected intravenously. If necessary, treatment may be repeated after 4 to 6 hours, not exceeding 150 mg within any period of 24 hours.
- For the prevention of post-operative pain, a loading dose of 25 mg to 50 mg administered as a 5 to 10 second intravenous bolus after surgery, followed by additional injections up to a maximum daily dosage of 150 mg. If necessary, treatment may be repeated after 4 to 6 hours, not exceeding 150 mg within any period of 24 hours.

Phlebittis: Intravenous drug administration has been associated with the occurrence of thrombophlebitis. Clinical studies comparing Dyloject 75 mg/2 ml Solution for Injection to Voltarol® have demonstrated reduced severity and one fourth the incidence of phlebittis (p=0.002).

Children: Dyloject 75 mg/2 ml Solution for Injection is not recommended for use in children.

Elderly: Although the pharmacokinetics of diclofenac sodium are not impaired to any clinically relevant extent in elderly patients, non-steroidal anti-inflammatory drugs (NSAIDs) should be used with particular caution in such patients who generally are more prone to adverse reactions. In particular, it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight (see also Precautions in Section 4.4) and the patient should be monitored for gastrointestinal bleeding for 4 weeks following initiation of NSAID therapy. The recommended maximum daily dose of Dyloject 75 mg/2 ml Solution for Injection is 150 mg.

Patients with renal impairment: Hydroxypropylbetadex (HPBCD), when administered intravenously, is predominantly eliminated through glomerular filtration. Therefore, patients with severe renal impairment (defined as creatinine clearance below 30 ml/min) should not be treated with Dyloject 75 mg/2 ml Solution for Injection. See Section 4.4, Special warnings and precautions for use.

4.3 Contraindications
Patients with a history of, or active or suspected gastrointestinal ulcers or bleeding.
Patients with a history of severe renal, hepatic or gastrointestinal reactions to diclofenac in any form.
Patients who have previously shown hypersensitivity reactions (e.g. asthma, urticaria or acute rhinitis) or hepatic inflammation to diclofenac sodium, aspirin or other NSAIDs.
Patients with a hypersensitivity to the excipients HPBCD or monohydroxyacetate. The excipient HPBCD is predominantly eliminated through the kidney by glomerular filtration. Therefore, Dyloject 75 mg/2 ml Solution for Injection is contraindicated in patients with severe renal impairment (defined as creatinine clearance below 30 ml/min). See Section 4.4, Special warnings and precautions for use.

Specifically for IV use
Concomitant NSAID or anticoagulant use (including low dose heparin).
A history of haemorrhagic diathesis, a history of confirmed or suspected cerebrovascular bleeding.
Operations associated with a high risk of haemorrhage.

A history of asthma.
Moderate to severe renal impairment (serum creatinine > 180 µmol/l), hypotension or dehydration from any cause.

4.4 Special warnings and precautions for use
Gastrointestinal: Close medical surveillance is imperative in patients with symptoms indicative of gastrointestinal disorders, with a history suggestive of gastrointestinal ulceration, with ulcerative colitis or with Crohn's disease. Gastrointestinal bleeding or ulceration/perforation, haematemesis and melena have in general more serious consequences in the elderly. They can occur at any time during treatment, with or without warning symptoms or a previous history. In the rare instances where gastrointestinal bleeding or ulceration occurs in patients receiving Dyloject 75 mg/2 ml Solution for Injection, the drug should be withdrawn.
Hepatic: Close medical surveillance is also imperative in patients suffering from severe impairment of hepatic function.

Hypersensitivity reactions: As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.
Like other NSAIDs, Dyloject 75 mg/2 ml Solution for Injection may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Renal impairment: HPBCD, when administered intravenously, is predominantly eliminated through the kidney by glomerular filtration. Therefore, patients with renal impairment (defined as creatinine clearance below 30 ml/min) should not be treated with Dyloject 75 mg/2 ml Solution for Injection. See Section 5.2, Pharmacokinetic properties.
Pregnancy and lactation: Please refer to Section 4.6 for information regarding use in pregnancy or lactation.

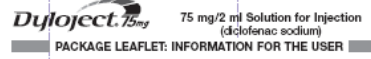
Precautions
Renal: Patients with renal, cardiac or hepatic impairment and the elderly should be kept under surveillance, since the use of NSAIDs may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored.
The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or those recovering from major surgery. Effects on renal function are usually reversible on withdrawal of Dyloject 75 mg/2 ml Solution for Injection.
Renal impairment: When administered intravenously, is predominantly eliminated through the kidney by glomerular filtration. Therefore, patients with renal impairment (defined as creatinine clearance below 30 ml/min) should not be treated with Dyloject 75 mg/2 ml Solution for Injection. See Section 5.2, Pharmacokinetic properties.
Hepatic: If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. anorexia, rash, etc.), Dyloject 75 mg/2 ml Solution for Injection should be discontinued. Hepatitis may occur without prodromal symptoms. Use of Dyloject 75 mg/2 ml Solution for Injection in patients with hepatic pathology may trigger an attack.
Haematological: Dyloject 75 mg/2 ml Solution for Injection may reversibly inhibit platelet aggregation (see Anticoagulants in Section 4.5). Patients with defect of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.
Long-term treatment: Dyloject 75 mg/2 ml Solution for Injection is not recommended for long term use. Prescribers should select follow-on treatment based on prescriber information for the specific product selected. All patients who are receiving non-steroidal anti-inflammatory agents long term, should be monitored as a precautionary measure, e.g. renal function, hepatic function (elevation of liver enzymes may occur) and blood counts. This is particularly important in the elderly.
Like other drugs that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of, bronchial asthma. Caution is required in patients with a history of heart failure or hypertension since oedema has been reported in association with NSAID administration.

4.5 Interaction with other medicinal products and other forms of interaction
Lithium and digoxin: Diclofenac may increase plasma concentration of lithium and digoxin.
Anticoagulants: There are isolated reports of an increased risk of haemorrhage with the combined use of diclofenac and anticoagulant therapy. Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other non-steroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.
Antidiabetic agents: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of hypoglycaemic and hyperglycaemic effects which have required adjustment to the dosage of hypoglycaemic agents.
Cyclosporins: Cases of nephrotoxicity have been reported in patients receiving concomitant cyclosporine and NSAIDs, including diclofenac. This might be mediated through combined renal antiprostaglandin effects of both the NSAID and cyclosporine.
Methotrexate: Cases of serious toxicity have been reported when methotrexate and NSAIDs are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.
Quinolone antimicrobials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.
Other NSAIDs and corticosteroids: Co-administration of diclofenac with aspirin or corticosteroids may increase the risk of gastrointestinal bleeding. Avoid concomitant use of two or more NSAIDs.
Diuretics: Like other NSAIDs, diclofenac may inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, which should therefore be monitored frequently.
Cardiac glycosides: Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce glomerular filtration rate and increase plasma glycoside and HPBCD levels.
Mifepristone: NSAIDs should not be used for 8 to 12 days after mifepristone administration, as NSAIDs can reduce the effect of mifepristone.
Anti-hypertensives: Concomitant use of NSAIDs with antihypertensive drugs (i.e. beta-blockers, angiotensin converting enzyme (ACE) inhibitors, diuretics) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.

4.6 Pregnancy and lactation
Although animal studies have not demonstrated teratogenic effects, diclofenac should not be prescribed during pregnancy unless there are compelling reasons for doing so. The lowest effective dosage should be used. Congenital abnormalities have been reported in association with the administration of NSAIDs in man; however, these are low in frequency and do not appear to follow any discernible pattern.
In view of the known effects of NSAIDs on the fetal cardiovascular system (e.g. a premature closure of the ductus arteriosus) and in causing electrolyte imbalance, use in late pregnancy should be avoided.
Following doses of 50 mg enteric coated tablets every 8 hours, traces of active substance have been detected in breast milk, but in quantities so small that no adverse effects on the breast-fed infant are to be expected.

4.7 Effects on ability to drive and use machines
Patients who experience dizziness or other central nervous system disturbances while taking NSAIDs should refrain from driving or operating machinery.

4.8 Undesirable effects
If serious side effects occur, Dyloject 75 mg/2 ml Solution for Injection should be withdrawn.
Frequency estimate: frequent >10%; occasional > 1 to 10%; rare > 0.001 to 1%; isolated cases < 0.001%. Side effects observed after parenteral diclofenac administration
Gastrointestinal tract
Occasional: epigastric pain, other gastrointestinal disorders (e.g. nausea, vomiting, diarrhoea, dyspepsia, flatulence, anorexia).
Rare: gastrointestinal bleeding (haematemesis, melena, bloody diarrhoea), abdominal pain/tenderness, gastrointestinal ulcers with or without bleeding or perforation, mouth ulcerations, both and tongue disorders or dysphagia.
In isolated cases: aphthous stomatitis, glossitis, esophageal lesions, lower gut disorders (e.g. non-specific haemorrhagic colitis and exacerbations or ulcerative colitis or Crohn's disease), colonic damage and stricture formation, pancreatitis, or constipation.



PACKAGE LEAFLET: INFORMATION FOR THE USER

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Dyloject® is and what it is used for
2. Before you use Dyloject
3. How to use Dyloject
4. Possible side effects
5. How to store Dyloject
6. Further information

1. WHAT DYLOJECT IS AND WHAT IT IS USED FOR
Dyloject is a solution for injection. Dyloject comes in packs of 10 vials. Each vial contains 2 ml of a clear liquid.
Dyloject (diclofenac sodium) is a non-steroidal anti-inflammatory analgesic drug (NSAID). NSAIDs reduce pain and inflammation. Aspirin is another NSAID (see below).
Dyloject is used to treat a number of painful conditions including:
• 'Flare-ups' of joint or back pain
• Attacks of gout
• Pain caused by kidney stones
• Pain caused by injuries, fractures or trauma
It is also used to prevent or treat pain following an operation.

2. BEFORE YOU USE DYLOJECT
Do not use Dyloject
• If you have an ulcer
• If you have kidney or liver disease
• If you are hypersensitive or allergic to diclofenac, aspirin, other NSAIDs, cyclo-oxygenase 2 inhibitors or any of the ingredients in Dyloject
• If you have a history of liver inflammation due to diclofenac, aspirin, or other NSAIDs
• If you have a history of asthma or bleeding
• If you are pregnant, planning to become pregnant or breast feeding
• If you suffer from any bowel disorders, for example ulcerative colitis or Crohn's disease
• If you are taking any other medicines, either bought or prescribed, for long term use or outside of a medically supervised setting

Tell your doctor before you are given Dyloject
• If you have, or have ever had, an ulcer in the gut, stomach or upper bowel, or gastrointestinal bleeding, symptoms of which may include blood in vomit or stool, emptying bowels or black, tarry stools
• If you have had any breathing problems, runny nose, skin rash or other allergic type reaction after taking aspirin or any other NSAID
• If you have, or have ever had, heart, kidney or liver disease
• If you have had a history of or suffer from any bleeding disorders, your doctor may ask you to go for regular check ups while you are being treated with Dyloject
• If you have, or have ever had, bronchial asthma
• If you have, or have ever had, a heart condition or high blood pressure
• If you could be suffering from dehydration
• If you have suffered any heavy loss of blood recently

Take special care with Dyloject
• Dyloject is not suitable for children
• Because it is an anti-inflammatory medicine, Dyloject may reduce the symptoms of infection, for example headache or high temperature. If you feel unwell and need to see a doctor, remember to tell him or her that you are taking Dyloject
• Elderly patients are generally more prone to side effects associated with Dyloject

Pregnancy
You must tell your doctor if you are pregnant or planning to become pregnant as then your doctor will consider whether Dyloject should be used. During the late phase (last 3 months) of pregnancy Dyloject may affect the baby's circulation.

Breast-feeding
You must tell your doctor if you are breast-feeding. If you are breast-feeding, your doctor will consider whether Dyloject should be used.

Driving and using machines
Dyloject makes some people feel dizzy or drowsy. If you feel dizzy or drowsy after taking Dyloject do not drive or operate machinery until its effects have worn off.

Taking other medicines
Some medicines may interfere with the effects of Dyloject.
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed, including:
• Medicines to treat diabetes
• Anticoagulants (blood thinning tablets like warfarin or heparin)
• Diuretics (water tablets)
• Lithium
• Methotrexate
• Cyclosporine
• Antibiotics
• Steroids
• Any other NSAID, for example aspirin or ibuprofen
• Mifepristone (a medicine used during termination of pregnancy)
• Medicines for heart problems or high blood pressure, for example beta blockers or ACE inhibitors

3. HOW TO USE DYLOJECT
Your doctor will decide when and how to treat you with Dyloject, usually in a hospital or medical centre. Your doctor or nurse will take the contents of the Dyloject vial into a syringe and give it to you by an intravenous injection (an injection into a vein) or an intramuscular injection (an injection into a muscle, usually into the buttock).

The usual dose is:
Adults: One or two vials (75 to 150 mg) each day for up to two days.
Elderly: Your doctor may give you a dose that is lower than the usual adult dose if you are elderly.
Children: Not suitable for children.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Dyloject can have side effects.

If you get any of the following, tell your doctor immediately

- Stomach pain, indigestion, heartburn, wind, nausea (feeling sick) or vomiting (being sick)
- Any sign of bleeding in the stomach or intestine, for example when emptying your bowels, blood in vomit or black, tarry stools
- Skin rash, itching, bruising or painful red areas
- Whooshing, shortness of breath or trouble breathing
- Yellowing of your skin or the whites of your eyes
- Persistent sore throat or high temperature
- An unexpected change in the amount of urine produced and/or its appearance
- Pain, redness or lumps at the injection site

If you notice that you are bruising more easily than usual or have frequent sore throats or infections, tell your doctor as soon as possible.

Common side effects (likely to affect between 1 in 100 to 1 in 10 patients) are

- Headache, dizziness, vertigo
- Drowsiness, tiredness
- Nausea, vomiting or other GI disorders
- Diarrhoea, loss of weight or appetite, heartburn
- Skin rash, itch
- Liver problems
- Injection site pain
- Infection of the vein in which Dyloject is injected

Very rare to uncommon side effects (reported in 1 in 100,000 to 1 in 100 people) are

- Stomach ulcers or bleeding
- Mouth or tongue disorders, trouble swallowing, tightening of the jaw muscles, taste disturbances, speech disorder
- Abdominal pain or tenderness, chest pain or tightness, stiffness
- Runny nose, watery eyes, swollen or itchy eyes
- Bronchospasm (symptoms of which include wheezing or difficulty in breathing)
- Hypertension (low blood pressure, symptoms of which may include faintness, dizziness or light-headedness)
- Liver disorders and liver pain, sometimes with jaundice
- Fluid retention, symptoms of which include swollen ankles
- Impaired balance, feeling abnormal, feeling hot
- Sweating, shaking, chills, malaise

Isolated side effects (reported in less than 1 in 100,000 people) include

- Tingling or numbness in the fingers, tremor, blurred or double vision, hearing loss or impairment, tinnitus (ringing in the ears), sleeplessness, nightmares, mood changes, disorientation and loss of memory, fits, headache together with a dilate of bright lights and a stiff neck, disturbances in sensation
- Constipation, inflammation of the tongue, mouth ulcers, taste changes, lower gut disorders (including inflammation of the colon)
- Palpitations (fast or irregular heart beat), chest pain, hypertension (high blood pressure), inflammation of blood vessels (vasculitis), inflammation of the lung (pneumonitis), congestive heart failure, blood disorders (including anaemia)
- Kidney or liver disorders, presence of blood or protein in the urine
- Skin rashes which may be made worse by exposure to sunlight, hair loss
- Inflammation of the pancreas, impotence

Do not be alarmed by this list - most people receive Dyloject without any problems.

If you think your medicine may be causing any of the effects listed above, or any other side effects that are not listed, talk to your pharmacist or doctor.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. HOW TO STORE DYLOJECT

Your doctor, pharmacist or nurse knows how to store Dyloject properly.

The expiry date is on the box and vial label. This medicine should not be used after the expiration date shown on the pack.

Store below 30°C. Do not freeze. Keep vials in the outer carton in order to protect from light.

Keep Dyloject out of reach and sight of children.

6. FURTHER INFORMATION

- What Dyloject contains
 - The active substance is diclofenac sodium
 - Hydrochloric acid
 - Water for Injection
 - Nitrogen
 - The other ingredients are
 - Hydroxypropylbetadex
 - Macroglycol
 - Sodium hydroxide
- The Dyloject 75 mg/2 ml Solution for Injection pack consists of ten 2 ml vials.
- For any information about this medicinal product, please contact the Marketing Authorisation Holder at tel: 0800 066 5446.
- Marketing Authorisation Holder
 - Javelin Pharmaceuticals UK Limited
 - Compass House, Vision Park, Chivers Way, Histon, Cambridge CB4 9AD United Kingdom
 - Manufacturer Responsible for Batch Release
 - Chester Medical Solutions
 - 3-4 Apex Court, Bassendene Road, Bromborough, Wirral CH62 3FE United Kingdom
 - Marketing Authorisation Number(s)
 - PL 25053/0001
 - This leaflet was last approved in October 2007
 - Dyloject[®] is the trademark of Javelin Pharmaceuticals, Inc.



Central nervous system

- Occasional: headache, dizziness or vertigo
- Rare: drowsiness, weakness, dysgeusia, paraesthesia, balance impairment, sponia, hypoaesthesia, migraine, speech disorder, or trismus
- In isolated cases: disturbances of sensation, memory disturbance, disorientation, incoherence, inability to concentrate, depression, anxiety, nightmares, tremor, psychotic reactions, or aseptic meningitis.

- General disorders
 - Rare: pain, chest pain, chest tightness, malaise, rigors, bloody discharge, feeling abnormal, feeling hot, or dryness
 - Musculoskeletal and connective tissue disorders
 - Occasional: pain in jaw
 - Rare: facial pain, joint stiffness, myalgia, back pain, chest wall pain, neck pain, muscle cramp, or muscle tightness
 - Spastic disorders
 - Rare: eyelid oedema, eyelid pruritus, increased lacrimation, or eye pain
 - In isolated cases: disturbances of vision (blurred vision, diplopia, impaired hearing, tinnitus, or taste disturbances).

- Skin
 - Occasional: rash or skin eruptions
 - Rare: urticaria, pruritus, or sweating increased
 - In isolated cases: bullous eruptions, eczema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (acute toxic epidermolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reactions, or purpura including allergic purpura
- Kidney
 - Rare: oedema, renal pain
 - In isolated cases: acute renal insufficiency, urinary abnormalities (e.g. haematuria, proteinuria, interstitial nephritis, nephritic syndrome, or papillary necrosis)
- Liver
 - Occasional: elevation of serum aminotransferase enzymes (ALT, AST)
 - Rare: liver function disorders including hepatitis (in isolated cases fulminant) with or without jaundice, or increased liver enzymes

- Blood
 - Rare: neutropenia
 - In isolated cases: thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia, or aplastic anaemia
- Hypersensitivity
 - Rare: hypersensitivity reactions (e.g. bronchospasm, anaphylactic/anaphylactoid systemic reactions including hypotension), respiratory disorder (COPD or rhinorrhoea)
 - In isolated cases: vasculitis, or pneumonitis.

- Cardiovascular system
 - Occasional: heart rate increase
 - Rare: phlebitis, hypotension, bradycardia, or flushing
 - In isolated cases: palpitations, chest pain, hypertension, or congestive heart failure.
- Labouratory abnormalities
 - Rare: elevated creatine phosphokinase, ketonuria, haematuria, or Bilirubin in urine.
 - Other organ systems
 - In isolated cases: impotence.

- Reactions to the intramuscular injection
 - Occasional: reactions such as local pain and induration
 - In isolated cases: abscesses, allergic contact dermatitis at the injection site.
- Reactions to the intravenous injection
 - Occasional: thrombophlebitis
 - Rare: cannula site reaction, infusion site discomfort or burning, injection site stinging or pruritis.

- 4.8 Overdose
 - Management of acute poisoning with NSAIDs essentially consists of supportive and symptomatic measures. There is no typical clinical picture resulting from diclofenac sodium overdose.
 - Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal inflammation and respiratory depression.
 - Specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in stimulating NSAIDs due to their high level of protein binding and extensive metabolism.

- 5. PHARMACOLOGICAL PROPERTIES
 - 5.1 Pharmacodynamic properties
 - Pharmacotherapeutic group: Non-steroidal anti-inflammatory drugs (NSAIDs). ATC code M01AB.
 - Mechanism of action: Dyloject 75 mg/2 ml Solution for Injection is a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase (cyclo-oxygenase). Diclofenac sodium *in vitro* does not suppress proinflammatory cytokines in cartilage at concentrations equivalent to the concentrations reached in human beings. When used concomitantly with opioids for the management of post-operative pain, diclofenac sodium often reduces the need for opioids.
 - 5.2 Pharmacokinetic properties
 - Absorption:
 - Intramuscular injection: After administration of Dyloject 75 mg/2 ml Solution for Injection intramuscularly, absorption sets in immediately, and mean peak plasma concentrations of about 2.589 ± 1.092 µg/ml (2.5 µg/ml) equals approximately 8 µg/ml as measured in plasma. In comparative clinical studies, the rate of absorption for Dyloject 75 mg/2 ml Solution for Injection was more rapid than Voltarol[®] Ampoules - peak plasma concentration for Voltarol[®] was 1.541 ± 0.419 µg/ml at 45 minutes. The extent of absorption of Dyloject 75 mg/2 ml Solution for Injection was bioequivalent to Voltarol[®] Ampoules. The amount of diclofenac absorbed after IM administration is in linear proportion to the size of the dose.
 - Intravenous injection: After administration of Dyloject 75 mg/2 ml Solution for Injection intravenously, absorption sets in immediately, and mean peak plasma concentrations of about 15.147 ± 2.829 µg/ml (2.5 µg/ml) equals approximately 8 µg/ml are reached in 3 minutes. In comparative clinical studies, the rate of absorption for Dyloject 75 mg/2 ml Solution for Injection was more rapid than Voltarol[®] Ampoules - peak plasma concentration for Voltarol[®] was 5.868 ± 0.974 µg/ml at 30 minutes. The extent of absorption of Dyloject 75 mg/2 ml Solution for Injection was bioequivalent to Voltarol[®] Ampoules.
 - In clinical studies comparing the analgesic efficacy of Dyloject to Voltarol[®], Dyloject was found to have a more rapid onset of analgesic action. At the 15- and 30-minute post-dose times, Dyloject 75 mg/2 ml Solution for Injection was statistically superior to Voltarol[®] as measured on the VAS and categorical pain intensity and pain relief scales (*p* < 0.05). At 15 minutes after dosing, the proportion of patients reporting a 30% reduction in pain intensity differed significantly for those given Dyloject and Voltarol[®] (32% versus 16%, respectively; *p* = 0.002). Dyloject was statistically superior to Voltarol[®] over the initial 0-2 hour TOTPAR interval both on the VAS scale (*p* = 0.009) and the categorical scale (*p* = 0.019). The magnitude of pain relief after two hours and the duration of action of Dyloject were found to be similar to Voltarol[®].
 - Elimination:
 - The relative bioavailability of Dyloject 75 mg/2 ml Solution for Injection after IM administration is approximately 100%. The absolute bioavailability of Dyloject 75 mg/2 ml Solution for Injection after IV administration relative to Voltarol[®] Ampoules IV is approximately 100%. The bioavailability of diclofenac after oral or rectal administration is approximately one half that of IM or IV administration, as these latter routes avoid "first-pass" metabolism.
 - Distribution:
 - The active substance is 99.7% protein bound, mainly to albumin (99.4%). Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after the peak plasma values have been obtained. The apparent half-life for elimination from the synovial fluid is 3 - 6 hours. Two hours after reaching the peak plasma values, concentrations of the active substance are already higher in the synovial fluid than they are in the plasma, and remain higher for up to 12 hours.

Metabolism

Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

The terminal half-life of Dyloject 75 mg/2 ml Solution for Injection in plasma is 1.17 ± 0.32 hours. In comparative clinical studies, the rate of clearance was more rapid than for Voltarol[®] Ampoules (M₁ = 1.17 ± 0.29 hours, M₁ = 1.23 ± 0.31 hours). For Dyloject and Voltarol[®], renal clearance and excretion were found to be bioequivalent. Total systemic clearance of diclofenac in plasma is 263 ± 56 ml/min (mean value ± SD). Four of the metabolites, including the two active ones, also have short plasma half-lives of 1 - 3 hours. About 60% of the administered dose is excreted in the urine in the form of the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

Previous studies with HPPCO at higher doses than what is present in Dyloject 75 mg (867 mg per dose) have shown that the terminal half-life following a single-dose of 2 g of HPPCO administered by a one-hour IV infusion is 1.5 ± 0.3 hours. HPPCO is primarily renally excreted with 99% to 101% excreted unchanged in the urine within 12 hours of administration. In subjects with severe renal impairment (creatinine clearance ≤ 19 ml/min), clearance of HPPCO was reduced 6-fold compared to subjects with normal renal function.

Characteristics in patients

- Elderly: No relevant age-dependent differences in the drug's absorption, metabolism or excretion have been reported.
- Patients with renal impairment: In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics (when applying the usual dosage schedule). At a creatinine clearance of < 10 ml/min, the calculated steady-state plasma levels of the hydroxyl metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.
- Patients with hepatic disease: In patients with chronic hepatitis or non-compensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

5.3 Preclinical safety data

- Nonclinical data on diclofenac, HPPCO and their combination in Dyloject revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction, and local tolerance studies with the following provisions for potential gastrointestinal toxicity and fetal risk of premature closure of the ductus arteriosus in late pregnancy.
 - A single oral dose of 0.1 mg/kg of diclofenac to pregnant rats on pregnancy day 21 caused a constriction of the ductus arteriosus in the offspring, a known effect of prostanoid-inhibiting drugs. Administration of diclofenac in late pregnancy is therefore not recommended.
 - In the 4-week IV toxicity studies conducted with diclofenac in rats (3, 7 and 15 mg/kg/day) and diclofenac and HPPCO in monkeys (3, 15 and 60 mg/kg/day and 533 mg/kg/day respectively) observed effects were essentially similar for both species and were all considered expected. Diclofenac induced a low incidence of mortality/premature sacrifice (due to peritonitis, gastrointestinal toxicity and regenerative anaemia) in rats at a dose level of 15 mg/kg/day. Recovery was complete after a 9-week treatment-free period.
 - In monkeys, diclofenac caused gastrointestinal toxicity, regenerative anaemia and exacerbation of minor tail skin lesions at dose levels of 15 and 60 mg/kg/day. Resolution of these findings could not be assessed in the 60 mg/kg/day resolution group, due to premature sacrifice. Findings attributed to HPPCO included very mild to mild renal tubular vacuolization in rats and very mild to mild granular appearance of the renal tubular cells in the medullary rays in monkeys. Following a relatively long treatment-free period, as compared to the duration of treatment, partial and complete recovery of HPPCO-associated findings has been demonstrated in rats and monkeys, respectively.
- The No Adverse Effect Level for HPPCO-related effects after 4 weeks of administration is lower than 26.6 mg HPPCO/kg/day in both species.
- The stabilising agent HPPCO has been found to produce pancreatic hyperplasia and hyperplasia when administered orally to rats at doses of 500, 2000 or 6000 mg/kg per day for 25 months. Adenocarcinomas of the exocrine pancreas produced in the treated animals were not seen in the untreated group and are not reported in the historical controls. These findings were not observed in the mouse carcinogenicity study nor in a 12-month toxicity study in dogs or in a 2-year toxicity study in female cynomolgus monkeys. In the Dyloject nonclinical studies diclofenac and HPPCO alone and in combination were not mutagenic or clastogenic. Diclofenac has shown no carcinogenic potential. The adenocarcinomas observed in the exocrine pancreas in the 2-year oral carcinogenicity study with HPPCO in rats were not considered a clinical hazard for Dyloject because HPPCO is not genotoxic. Dyloject is intended for short-term treatment only and no pancreatic changes were observed in the 4-week intravenous studies in rats and monkeys described above.

- 6. PHARMACEUTICAL PARTICULARS
 - 6.1 List of excipients
 - Dyloject 75 mg/2 ml Solution for Injection also contain
 - Hydroxypropylbetadex (HPPCO)
 - Macroglycol
 - Water for Injection
 - Sodium hydroxide and/or hydrochloric acid (to adjust pH)
 - Nitrogen
 - 6.2 Incompatibilities
 - The Vials used M or IV as a bolus should not be mixed with other injection solutions.
 - 6.3 Shelf life
 - 30 months.
 - 6.4 Special precautions for storage
 - Store below 30°C. Do not freeze. Keep vials in the outer carton in order to protect from light.
 - Keep Dyloject out of reach and sight of children.
 - The product should not be used if crystals or precipitates are observed.
 - 6.5 Nature and contents of container
 - The Vials are 2 ml fl. Eur. Type I borosilicate glass vials with 10 mm caps. The Vials contain colourless liquid and are supplied in packs of 10.
 - 6.6 Special precautions for disposal
 - The dose should be freshly withdrawn from the vial and used immediately. Once withdrawn, the dose should not be stored.

- 7. MARKETING AUTHORISATION HOLDER
 - Javelin Pharmaceuticals UK Limited
 - Compass House, Vision Park, Chivers Way, Histon, Cambridge CB4 9AD United Kingdom
 - 8. MARKETING AUTHORISATION NUMBER(S)
 - PL 25053/0001
 - 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
 - 30/10/2007
 - 10. DATE OF REVISION OF THE TEXT
 - 30/10/2007
- Dyloject[®] is the trademark of Javelin Pharmaceuticals, Inc. Voltarol[®] is the trademark of Novartis.

**DYLOJECT® 75MG/2ML SOLUTION FOR INJECTION
PL 25053/0001**

LABELLING

