Public Assessment Report

Ketorolac Trometamol 30mg/ml Solution for Injection

Ketorolac Trometamol

PL 18157/0012

Beacon Pharmaceuticals Ltd

Table of Contents

Lay Summary

The MHRA has granted Beacon Pharmaceuticals a Market Authorisation (licence) for the medicinal product Ketorolac trometamol 30mg/ml Solution for Injection (PL 18257/0012) on 30/04/2007. This is a prescription only medication. The active substance is a non-steroidal anti-inflammatory drug (NSAID) with analgesic activity. It is indicated for short-term management of moderate to severe acute postoperative pain.

The test product was considered the same as the reference product Toradol, which contains the same amount of ketorolac trometamol active substance in the same pharmaceutical form. No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Ketorolac trometamol 30mg/ml Solution for Injection outweigh the risks, hence a Marketing Authorisation was granted.

Scientific Discussion

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal product Ketorolac Trometamol 30mg/ml Solution for Injection (PL 18257/0012) on 30/04/2007. This is a prescription only medicine.

The application was a complex abridged application which successfully claimed that the product was a generic medical product of Toradol, which contains the same amount of ketorolac trometamol active substance in the same pharmaceutical form, under Article 10.1 of Directive 2001/83/EC. The reference product PL 00286 / 0111 was held by Syntex Pharmaceuticals Limited, granted 08/06/1990. The reference product was subsequently transferred by Change of Ownership to Roche Products Limited on 31 May 1996, under PL 00031/0481.

The active substance is a non-steroidal anti-inflammatory drug (NSAID) with analgesic activity. It is indicated for short-term management of moderate to severe acute postoperative pain. It is administered by intramuscular injection or by bolus intravenous injection. The recommended initial dose is 10mg followed by 10-30mg every four to six hours if required. Maximum dose is 90mg in non-elderly and 60mg in elderly.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

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

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

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

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 3 years, with no specific storage instructions.

DRUG PRODUCT

Other Ingredients

The other ingredients of the drug product are ethanol, sodium chloride, sodium hydroxide and water for injection. All excipients used comply with their respective European Pharmacopoeial monograph. Satisfactory certificates of analysis have been provided for all excipients.

There are no excipients of human or animal origin.

Impurity profiles

Impurity profiles for both strengths of drug product were found to be similar to those for the reference product.

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 batches of the drug 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 drug product is stored in glass ampoules.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage conditions are “Keep container in original carton”, “Do not store above 30°C” and “Protect from light”..

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation was granted.

PRE-CLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

MEDICAL ASSESSMENT

CLINICAL PHARMACOLOGY

Pharmacodynamics

Ketorolac is a potent analgesic agent of the non-steroidal, anti-inflammatory class (NSAID). It is not an opioid and has no known effects on opioid receptors. Its mode of action is to inhibit the cyclo-oxygenase enzyme system and hence prostaglandin synthesis and it demonstrates a minimal anti-inflammatory effect at its analgesic dose.

Pharmacokinetics

Intramuscular

Following intramuscular administration, ketorolac was rapidly and completely absorbed. A mean peak plasma concentration of 2.2µg/ml occurred an average of 50 minutes after a single 30mg dose. Age, kidney and liver function affect terminal plasma half-life and mean total clearance as outlined in the table below (estimated from a single 30mg IM dose of ketorolac).

Type of subjects	Total clearance (l/hr/kg) mean (range)	Terminal half-life (hrs) mean (range)
Normal subjects (n = 54)	0.023 (0.010 - 0.046)	5.3 (3.5 - 9.2)
Patients with hepatic dysfunction (n = 7)	0.029 (0.013 - 0.066)	5.4 (2.2 - 6.9)
Patients with renal impairment (n = 25) (serum creatinine 160 - 430 micromol/l)	0.016 (0.005 - 0.043)	10.3 (5.9 - 19.2)
Renal dialysis patients (n = 9)	0.016 (0.003 - 0.036)	13.6 (8.0 - 39.1)
Healthy elderly subjects (n = 13) (mean age 72)	0.019 (0.013 - 0.034)	7.0 (4.7 - 8.6)

Intravenous

Intravenous administration of a single 10mg dose of ketorolac resulted in a mean peak plasma concentration of 2.4µg/ml at an average of 5.4 minutes after dosing. The terminal plasma elimination half-life was 5.1 hours, average volume of distribution 0.15 l/kg, and total plasma clearance 0.35ml/min/kg.

The pharmacokinetics of ketorolac in man following single or multiple doses are linear. Steady-state plasma levels are achieved after dosing every six hours for one day. No changes in clearance occurred with chronic dosing. The primary route of excretion of ketorolac and its metabolites is renal: 91.4% (mean) of a given dose being found in the urine and 6.1% (mean) in the faeces.

More than 99% of the ketorolac in plasma is protein-bound over a wide concentration range.

Bioequivalence Study
This application does not require the inclusion of a bioequivalence study as it is an application claiming essential similarity for a parenteral drug containing the same active substance in the same concentration as the reference product.

Efficacy and Safety
No new data are submitted and none are required for this type of application.

Clinical Expert Report
There is a satisfactory clinical expert report written suitably qualified expert.

Summary of Product Characteristics
A satisfactory SPC was arrived at during the procedure which is consistent with the reference product SPC.

Patient Information Leaflet
The Patient Information Leaflet was amended to reflect changes in the SPC. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

Assessors Overall Conclusion
A marketing authorisation may be granted.

Overall Conclusion and Risk/Benefit Analysis

Quality

The important quality characteristics of Ketorolac trometamol 30mg/ml Solution for Injection are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

Pre-Clinical

No new preclinical data were submitted and none are required for applications of this type.

Clinical

A bioequivalence study was not required for this application. No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Toradol.

Risk/Benefit Analysis

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit is, therefore, considered to be positive.

Steps Taken During Assessment

1	The MHRA received the application on 01/08/2003.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 15/10/2003.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 09/06/2004, 09/06/2005, 29/11/2006 and 16/02/2007 on the medical assessment on 25/05/2004 and 15/03/2007.
4	The applicant provided further information in regard to the quality assessment on 08/07/2004, 18/03/2005, 15/02/2007 and 19/02/2007 and on the medical assessment on 09/07/2004 and 29/03/2007.
5	The application was determined on 30/04/2007.

Steps Taken after Assessment

None

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ketorolac trometamol 30mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml ampoule contains 30 mg Ketorolac trometamol
For excipients see section 6.1

3 PHARMACEUTICAL FORM

Solution for Injection
Colourless or slightly yellowish solution in amber glass ampoules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ketorolac Injection is indicated for the short-term management of moderate to severe acute post-operative pain.

4.2 Posology and method of administration

Ketorolac Injection is for administration by intramuscular or bolus intravenous injection. Bolus intravenous doses should be given over at least 15 seconds. Ketorolac Injection should not be used for epidural or spinal administration.

The time to onset of analgesic effect following both IV and IM administration is similar and is approximately 30 minutes, maximum analgesia occurs within one to two hours. Analgesia normally lasts for four to six hours.

Dosage should be adjusted according to the severity of the pain and the patient response. Undesirable effects may be minimised by using the lowest effective dose for the shortest
duration necessary to control symptoms (see section 4.4).

The administration of continuous multiple daily doses of ketorolac intramuscularly or intravenously should not exceed two days because adverse events may increase with prolonged usage. There has been limited experience with dosing for longer periods since the vast majority of patients have transferred to oral medication or no longer require analgesic therapy after this time.

Adults

The recommended initial dose of Ketorolac Injection is 10mg followed by 10 to 30mg every four to six hours as required. In the initial post-operative period, Ketorolac Injection may be given as often as every two hours if needed. The lowest effective dose should be given. A total daily dose of 90mg for non-elderly and 60mg for the elderly, patients with renal impairment and patients less than 50kg should not be exceeded. The maximum duration of treatment should not exceed two days.

The dosage in patients under 50kg should be reduced.

Opioid analgesics (e.g. morphine, pethidine) may be used concomitantly, and may be required for optimal analgesic effect in the early post-operative period when pain is most severe. Ketorolac does not interfere with opioid binding and does not exacerbate opioid-related respiratory depression or sedation. When used in association with Ketorolac Injection, the daily dose of opioid is usually less than that normally required. However, opioid side-effects should still be considered, especially in day-case surgery.

Patients receiving Ketorolac Injection, and who are converted to oral Ketorolac, should receive a total combined daily dose not exceeding 90mg (60mg for the elderly, patients with renal impairment and patients less than 50kg). The oral component should not exceed 40mg on the day the change of formulation is made. Patients should be converted to oral treatment as soon as possible.

Elderly

For patients over 65 years, the lower end of the dosage range is recommended and a total daily dose of 60mg should not be exceeded (see section 4.4 Special warnings and special precautions for use).

Children

Safety and efficacy in children have not been established. Therefore, Ketorolac Injection is not recommended for use in children under 16 years of age.

Renal impairment

Ketorolac Injection should not be used in moderate to severe renal impairment and a reduced dosage given in lesser impairment (not exceeding 60mg/day IV or IM) (see section 4.3 Contra-indications).

4.3 Contraindications

active or previous peptic ulcer. History of upper gastrointestinal bleeding or perforation, related to previous NSAID therapy
suspected or confirmed cerebrovascular bleeding
haemorrhagic diatheses, including coagulation disorders
hypersensitivity to ketorolac trometamol or other NSAIDs and those patients in whom aspirin or other prostaglandin synthesis inhibitors induce allergic reactions (severe anaphylactic-like reactions have been observed in such patients)
the complete or partial syndrome of nasal polyps, angioedema or bronchospasm
concurrent treatment with other NSAIDs including cyclooxygenase 2 specific inhibitors, oxpentifylline, probenecid or lithium salts
hypovolaemia from any cause or dehydration
moderate or severe renal impairment (serum creatinine> 160 micromol/l)
a history of asthma
severe heart failure
patients who have had operations with a high risk of haemorrhage or incomplete haemostasis
patients on anti-coagulants including low dose heparin (2500 - 5000 units twelve hourly)
during pregnancy, labour, delivery or lactation
children under 16 years of age
Ketorolac is contra-indicated as prophylactic analgesia before surgery due to inhibition of platelet aggregation and is contra-indicated intra-operatively because of the increased risk of bleeding
patients currently receiving aspirin

4.4 Special warnings and precautions for use

Physicians should be aware that in some patients pain relief might not occur until 30 minutes or more after IV or IM administration.

Use in the elderly: in common with other NSAIDs, patients over the age of 65 years may be at an increased risk of experiencing adverse events compared to younger patients. The elderly have an increased plasma half-life and reduced

plasma clearance of ketorolac, therefore a total daily dose of greater than 60mg ketorolac is not recommended.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

Gastro-intestinal effects: ketorolac can cause gastro-intestinal irritation, ulcers or bleeding in patients with or without a history of previous symptoms. Elderly and debilitated patients are more prone to develop these reactions. The incidence increases with dose and duration of treatment.

A study has shown increased rates of clinically serious GI bleeding in patients < 65 years of age who received an average daily dose of> 90mg ketorolac IM as compared to those patients receiving parenteral opioids.

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence on the lowest dose available.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrotoxicity or bleeding, such as corticosteroids, or anticoagulants such as warfarin or anti-platelet agents such as aspirin (see section 4.5).

Where GI bleeding or ulceration occurs in patients receiving ketorolac, the treatment should be withdrawn.

Cardiovascular and cerebrovascular effects: Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for ketorolac.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular

disease should only be treated with ketorolac after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Respiratory effects: bronchospasm may be precipitated in patients with a history of asthma.

Renal effects: drugs that inhibit prostaglandin biosynthesis (including non-steroidal anti-inflammatory drugs) have been reported to cause nephrotoxicity including but not limited to: glomerular nephritis, interstitial nephritis, renal papillary necrosis, nephrotic syndrome and acute renal failure. In patients with renal, cardiac or hepatic impairment, caution is required since the use of NSAIDs may result in deterioration of renal function.

As with other drugs that inhibit prostaglandin synthesis, elevations of serum urea, creatinine and potassium have been reported with ketorolac and may occur after one dose.

Patients with impaired renal function: since ketorolac and its metabolites are excreted primarily by the kidney, patients with moderate to severe impairment of renal function (serum creatinine greater than 160 micromol/l) should not receive Ketorolac Injection. Patients with lesser renal impairment should receive a reduced dose of ketorolac (not exceeding 60mg/day IM or IV) and their renal status should be closely monitored.

Female fertility: the use of ketorolac may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation for infertility, withdrawal of ketorolac should be considered.

Caution should be observed in patients with conditions leading to a reduction in blood volume and/or renal blood flow, where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in renal prostaglandin formation and may precipitate overt renal failure. Patients at greatest risk of this reaction are those who are volume depleted because of blood loss or severe dehydration, patients with impaired renal function, heart failure, liver dysfunction, the elderly and those taking diuretics. Discontinuation of NSAID therapy is typically followed by recovery to the pre-treatment state. Inadequate fluid/blood replacement during surgery, leading to hypovolaemia, may lead to renal dysfunction, which could be exacerbated when ketorolac is administered. Therefore, volume depletion should be corrected and close monitoring of serum urea and creatinine and urine output is recommended until the patient is normovolaemic. In patients on renal dialysis, ketorolac clearance was reduced to approximately half the normal rate and terminal half-life increased approximately three-fold.

Fluid retention and oedema have been reported with the use of ketorolac and it should therefore be used with caution in patients with cardiac decompensation, hypertension or similar conditions.

Patients with impaired hepatic function from cirrhosis do not have any clinically important changes in ketorolac clearance or terminal half-life.

Borderline elevations of one or more liver function tests may occur. These abnormalities may be transient, may remain unchanged, or may progress with continued therapy. Meaningful elevations (greater than three times normal) of serum glutamate pyruvate transaminase (SGPT/ALT) or serum glutamate oxaloacetate transaminase (SGOT/AST) occurred in controlled clinical trials in less than 1% of patients. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, ketorolac should be discontinued.

Haematological effects: patients with coagulation disorders should not receive ketorolac. Patients on anti-coagulation therapy may be at increased risk of bleeding if given ketorolac concurrently. The concomitant use of ketorolac and prophylactic low-dose heparin (2500 - 5000 units twelve hourly) has not been studied extensively and may also be associated with an increased risk of bleeding. Patients already on anti-coagulants or who require low-dose heparin should not receive ketorolac. Patients who are receiving other drug therapy that interferes with haemostasis should be carefully observed if ketorolac is administered. In controlled clinical studies, the incidence of clinically significant post-operative bleeding was less than 1%.

Ketorolac inhibits platelet aggregation and prolongs bleeding time. In patients with normal bleeding function, bleeding times were raised, but not outside the normal range of two to eleven minutes. Unlike the prolonged effects from aspirin, platelet function returns to normal within 24 to 48 hours after ketorolac is discontinued.

Post-operative wound haemorrhage has been reported in association with the immediate peri-operative use of ketorolac. Therefore, ketorolac should not be used in patients who have had operations with a high risk of haemorrhage or incomplete haemostasis. Caution should be used where strict haemostasis is critical, e.g. in cosmetic or day-case surgery. Haematomata and other signs of wound haemorrhage and epistaxis have been reported with the use of ketorolac. Physicians should be aware of the pharmacological similarity of ketorolac to other non-steroidal anti-inflammatory drugs that inhibit cyclo-oxygenase and the risk of bleeding, particularly in the elderly.

The risk of clinically serious gastro-intestinal bleeding is dose-dependent. This is particularly true in elderly patients who receive an average daily dose greater than 60mg/day of ketorolac.

Ketorolac is not an anaesthetic agent and possesses no sedative or anxiolytic properties; therefore it is not recommended as a pre-operative medication for the support of anaesthesia when these effects are required.

4.5 Interaction with other medicinal products and other forms of interaction

Ketorolac should not be used with other NSAIDs or in patients receiving aspirin because of the potential for additive side-effects.

Ketorolac is highly bound to human plasma protein (mean 99.2%) and binding is concentration-independent.

Ketorolac did not alter digoxin protein binding. In vitro studies indicated that at therapeutic concentrations of salicylate (300µg/ml) and above, the binding of ketorolac was reduced from approximately 99.2% to 97.5%. Therapeutic concentrations of digoxin, warfarin, paracetamol, phenytoin and tolbutamide did not alter ketorolac protein binding. Because ketorolac is a highly potent drug and present in low concentrations in plasma, it would not be expected to displace other protein-bound drugs significantly.

Care should be taken when administering ketorolac with anti-coagulants since co-administration may cause an enhanced anti-coagulant effect.

There is no evidence in animal or human studies that ketorolac induces or inhibits the hepatic enzymes capable of metabolising itself or other drugs. Hence ketorolac would not be expected to alter the pharmacokinetics of other drugs due to enzyme induction or inhibition mechanisms.

In normovolaemic healthy subjects, ketorolac reduces the diuretic response to frusemide by approximately 20%, so particular care should be taken in patients with cardiac decompensation.

Ketorolac and other non-steroidal anti-inflammatory drugs can reduce the anti-hypertensive effect of beta-blockers and may increase the risk of renal impairment when administered concurrently with ACE inhibitors, particularly in volume depleted patients.

NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels when co-administered with cardiac glycosides.

Caution is advised when methotrexate is administered concurrently, since some prostaglandin synthesis inhibiting drugs have been reported to reduce the clearance of methotrexate, and thus possibly enhance its toxicity.

Probenecid should not be administered concurrently with ketorolac because of increases in ketorolac plasma level and half-life.

As with all NSAIDs caution is advised when cyclosporin is co-administered because of the increased risk of nephrotoxicity.

NSAIDs should not be used for eight to twelve days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

As with all NSAIDs, caution should be taken when co-administering with cortico-steroids because of the increased risk of gastro-intestinal bleeding.

Patients taking quinolones may have an increased risk of developing convulsions.

Co-administration with diuretics can lead to a reduced diuretic effect, and increase the risk of nephrotoxicity of NSAIDs.

Because of an increased tendency to bleeding when oxpentifylline is administered concurrently, this combination should be avoided.

In patients receiving lithium there is a possible inhibition of renal lithium clearance, increased plasma lithium concentration and potential lithium toxicity. (See section 4.3 Contra-indications).

4.6 Pregnancy and lactation

There is no evidence of teratogenicity in rats or rabbits studied at maternally-toxic doses of ketorolac. Prolongation of the gestation period and/or delayed parturition was seen in the rat. Ketorolac and its metabolites have been shown to pass into the foetus and milk of animals. Ketorolac has been detected in human milk at low levels. Safety in human pregnancy has not been established. Congenital abnormalities have been reported in association with NSAID administration in man, however these are low in frequency and do not follow any discernible pattern. Ketorolac is therefore contra-indicated during pregnancy, labour or delivery, or in mothers who are breast-feeding.

4.7 Effects on ability to drive and use machines

Some patients may experience dizziness, drowsiness, visual disturbances, headaches, vertigo, insomnia or depression with the use of ketorolac. If patients experience these, or other similar undesirable effects, they should not drive or operate machinery.

4.8 Undesirable effects

The following side-effects have been reported.

Gastro-intestinal:

Nausea, dyspepsia, gastro-intestinal pain, gastro-intestinal bleeding, abdominal discomfort, haematemesis, gastritis, oesophagitis, diarrhoea, eructation, constipation, flatulence, fullness, melaena, peptic ulcer, non-peptic gastro-intestinal ulceration, rectal bleeding, ulcerative stomatitis, vomiting, haemorrhage, perforation, pancreatitis. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4)

Central nervous/musculoskeletal systems:
Anxiety, drowsiness, dizziness, headache, sweating, dry mouth, nervousness, paraesthesia, functional disorders, abnormal thinking, depression, euphoria, convulsions, excessive thirst, inability to concentrate, insomnia, malaise, fatigue, stimulation, vertigo, abnormal taste and vision, optic neuritis, myalgia, abnormal dreams, hallucinations, hyperkinesia, hearing loss, tinnitus, aseptic meningitis, psychotic reactions.

Renal:
Nephrotoxicity including increased urinary frequency, oliguria, acute renal failure, hyponatraemia, hyperkalaemia, haemolytic uraemic syndrome, flank pain (with or without haematuria), raised serum urea and creatinine, interstitial nephritis, urinary retention, nephrotic syndrome.

Cardiovascular/haematological:
Flushing, bradycardia, pallor, purpura, thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia, hypertension, palpitations, chest pain.
Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).
Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Respiratory:
Dyspnoea, asthma, pulmonary oedema.

Dermatological:
Pruritus, urticaria, skin photosensitivity, Lyell's syndrome, Stevens-Johnson syndrome, exfoliative dermatitis, maculopapular rash.

Hypersensitivity reactions:
Anaphylaxis, bronchospasm, laryngeal oedema, hypotension, flushing and rash. Such reactions may occur in patients with or without known sensitivity to ketorolac or other non-steroidal anti-inflammatory drugs.

These may also occur in individuals with a history of angioedema, bronchospastic reactivity (e.g. asthma and nasal polyps). Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome (see section 4.3 Contra-indications).

Bleeding:
Post-operative wound haemorrhage, haematomata, epistaxis, increased bleeding time.

Reproductive, female:
Infertility

Other:
Asthenia, oedema, weight gain, abnormalities of liver function tests, hepatitis, liver failure, jaundice, fever. Injection site pain has been reported in some patients.

4.9 Overdose

Doses of 360mg given intramuscularly over an eight hour interval for five consecutive days have caused abdominal pain and peptic ulcers that have healed after discontinuation of dosing. Two patients recovered from unsuccessful suicide attempts. One patient experienced nausea after 210mg ketorolac, and the other hyperventilation after 300mg ketorolac.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code M01A

Ketorolac is a potent analgesic agent of the non-steroidal, anti-inflammatory class (NSAID). It is not an opioid and has no known effects on opioid receptors. Its mode of action is to inhibit the cyclo-oxygenase enzyme system and hence prostaglandin synthesis and it demonstrates a minimal anti-inflammatory effect at its analgesic dose.

5.2 Pharmacokinetic properties

Intramuscular
Following intramuscular administration, ketorolac was rapidly and completely absorbed. A mean peak plasma concentration of 2.2µg/ml occurred an average of 50 minutes after a single 30mg dose. Age, kidney and liver function affect terminal plasma half-life and mean total clearance as outlined in the table below (estimated from a single 30mg IM dose of ketorolac).

Type of subjects	Total	Terminal

	clearance (l/hr/kg) mean (range)	half-life (hrs) mean (range)
Normal subjects (n = 54)	0.023 (0.010 - 0.046)	5.3 (3.5 - 9.2)
Patients with hepatic dysfunction (n = 7)	0.029 (0.013 - 0.066)	5.4 (2.2 - 6.9)
Patients with renal impairment (n = 25) (serum creatinine 160 - 430 micromol/l)	0.016 (0.005 - 0.043)	10.3 (5.9 - 19.2)
Renal dialysis patients (n = 9)	0.016 (0.003 - 0.036)	13.6 (8.0 - 39.1)
Healthy elderly subjects (n = 13) (mean age 72)	0.019 (0.013 - 0.034)	7.0 (4.7 - 8.6)

Intravenous
Intravenous administration of a single 10mg dose of ketorolac resulted in a mean peak plasma concentration of 2.4µg/ml at an average of 5.4 minutes after dosing. The terminal plasma elimination half-life was 5.1 hours, average volume of distribution 0.15 l/kg, and total plasma clearance 0.35ml/min/kg.

The pharmacokinetics of ketorolac in man following single or multiple doses are linear. Steady-state plasma levels are achieved after dosing every six hours for one day. No changes in clearance occurred with chronic dosing. The primary route of excretion of ketorolac and its metabolites is renal: 91.4% (mean) of a given dose being found in the urine and 6.1% (mean) in the faeces.

More than 99% of the ketorolac in plasma is protein-bound over a wide concentration range.

5.3 Preclinical safety data

An 18-month study in mice with oral doses of ketorolac trometamol at 2mg/kg/day (0.9 times human systemic exposure at the recommended IM or IV dose of 30mg qid, based on area-under-the-plasma-concentration curve [AUC]), and a 24-month study in rats at 5mg/kg/day (0.5 times the human AUC), showed no evidence of tumourigenicity.

Ketorolac trometamol was not mutagenic in the Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac trometamol did not cause chromosome breakage in the in vivo mouse micronucleus assay.

At 1590µg/ml and at higher concentrations, ketorolac trometamol increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells.

Impairment of fertility did not occur in male or female rats at oral doses of 9mg/kg (0.9 times the human AUC) and 16mg/kg (1.6 times the human AUC) of ketorolac trometamol, respectively.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol, sodium chloride, sodium hydroxide and water for injections

6.2 Incompatibilities

Ketorolac Injection should not be mixed in a small volume (e.g. in a syringe) with morphine sulphate, pethidine hydrochloride, promethazine hydrochloride or hydroxyzine hydrochloride, as precipitation of ketorolac will occur.

It is compatible with normal saline, 5% dextrose, Ringer's, lactated Ringer's or Plasmacyte solutions. Compatibility of Ketorolac Injection with other drugs is unknown.

6.3 Shelf life

Two years

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage time sand conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 30°C. Keep container in the outer carton and protect from light.

6.5 Nature and contents of container

Ampoules, amber type I glass. In cartons containing either 6 or 100 ampoules.

6.6 Special precautions for disposal

There are no special instructions.

7 MARKETING AUTHORISATION HOLDER

Beacon Pharmaceutical Ltd
Tunbridge Wells
Kent TN1 1YG

8 MARKETING AUTHORISATION NUMBER(S)

PL 18157/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/04/2007

10 DATE OF REVISION OF THE TEXT

30/04/2007

Labels and Leaflet

Patient Information Leaflet:

Ketorolac trometamol 30mg/ml Solution for Injection

(Referred to in this leaflet as Ketorolac injection)

Please read this leaflet carefully before being given Ketorolac trometamol 30mg/ml Solution for Injection.

- Keep the leaflet in case you want to refer to it again.
- If you want to know more about your medicine or have any questions, you should ask your doctor or pharmacist.

In this leaflet:

The name of this medicine is Ketorolac trometamol 30mg/ml Solution for Injection (referred to in this leaflet as Ketorolac injection). Ketorolac Injection is a colourless or slightly yellowish solution in amber glass ampoules. Each 1 ml ampoule contains 30mg of the active substance ketorolac trometamol. Each pack contains 6 or 100 ampoules.

The ampoules also contain ethanol, sodium chloride, sodium hydroxide and water for injections.

Marketing authorisation holder: Beacon Pharmaceuticals Ltd. Tunbridge Wells, Kent TN1 1YG

Manufacturer: This medicine is manufactured by Laboratorio Reig Jofré S.A, Barcelona, Spain.

1. What Ketorolac Injection is and what it is used for.

Ketorolac belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs). These medicines are used to treat pain.

Ketorolac Injection is used to relieve moderate or severe pain after a surgical operation.

2. Before you are given Ketorolac Injection

You must not be given Ketorolac Injection and you should talk to your doctor immediately if:

- You are allergic to Ketorolac, any other NSAID, aspirin or other prostaglandin synthetase inhibitors
- You have previously had or have gastric ulcers or gastro-intestinal bleeding
- You have bleeding from a damaged blood vessel in the brain
- You have problems with bleeding or blood clotting disorders
- You have nasal polyps, allergic swellings (of the skin, around the mouth, eyes, nose or the genitals),
- Asthma or a history of asthma
- You are taking other NSAIDs such as ibuprofen, oxpentifylline (to treat circulatory disease), probenecid (to treat gout) or lithium salts (to treat nervous disorders)
- You are taking medicines to thin the blood
- You are dehydrated or have lost a lot of blood
- You have recently had an operation with a high risk of bleeding or bleeding has not been completely stopped
- You are about to have surgery
- You have moderate or severe kidney disease
- You are pregnant, in labour, in delivery or breast feeding
- You are under 16 years of age

Before you are given Ketorolac Injection, tell your doctor if:

- You have stomach problems or are passing black tarry stools or blood.
- You have problems with breathing.
- You have problems with your kidneys or liver.
- You have problems with the clotting of your blood
- You have heart problems or high blood pressure.
- You have a decrease in the usual amount of urine you pass.
- You have swollen hands, feet or other parts of your body.
- You have bleeding or bruising at the site of your operation.
- You are planning to become pregnant

Medicines such as Ketorolac may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment.

If you have heart problems, previous stroke or think that you might be at risk of these conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist.

Pregnancy and breast-feeding

Ask your doctor for advice before taking any medicine.

Ketorolac Injection should not be given if you are pregnant, in labour, during delivery or if you are breast-feeding

Ketorolac Injection may make it more difficult to become pregnant. You should inform your doctor if you are planning to become pregnant or if you are having problems in becoming pregnant

Technical Leaflet:

Ketorolac Trometamol 30mg/ml Solution for Injection

Please read this information carefully before using Ketorolac Injection. Further information is contained in the Summary of Product Characteristics

Presentation

Ketorolac Trometamol 30mg/ml Solution for Injection (referred to as Ketorolac Injection) contains 30mg ketorolac trometamol in each 1 ml ampoule. Also contains ethanol, sodium chloride, sodium hydroxide and water for injections.

Dosage and Method of Administration

Ketorolac Injection is suitable for use as long as it remains clear and free of precipitate. Ketorolac Injection is for administration by intramuscular or bolus intravenous injection. Bolus intravenous doses should be given over at least 15 seconds. Ketorolac Injection should not be used for epidural or spinal administration.

The time to onset of analgesic effect following both IV and IM administration is approximately 30 minutes, maximum analgesia occurs within one to two hours. Analgesia normally lasts for four to six hours.

Adults: The recommended initial dose of Ketorolac Injection is 10mg followed by 10 to 30mg every four to six hours as required. In the initial post-operative period, Ketorolac Injection may be given as often as every two hours if needed. The lowest effective dose should be given. A total daily dose of 90mg for non-elderly and 60mg for the elderly, patients with renal impairment and patients less than 50kg should not be exceeded. The maximum duration of treatment should not exceed two days. Opioid analgesics (e.g. morphine, pethidine) may be used concomitantly. When used with ketorolac, the daily dose of opioid is usually less than that normally required but opioid side effects should still be considered.

Patients receiving Ketorolac Injection and oral ketorolac should receive a total combined daily dose not exceeding 90mg (60mg for the elderly, patients with renal impairment and patients less than 50kg). The oral component should not exceed 40mg on the day the change of formulation is made. Patients should be converted to oral treatment as soon as possible.

Children: Ketorolac Injection is not recommended for use in children under 16 years of age.

Contra-Indications

- active or previous peptic ulcer. History of upper gastrointestinal bleeding or perforation, related to previous NSAID therapy
- suspected or confirmed cerebrovascular bleeding
- haemorrhagic diatheses, including coagulation disorders
- hypersensitivity to ketorolac trometamol or other NSAIDs and those patients in whom aspirin or other prostaglandin synthesis inhibitors induce allergic reactions
- the complete or partial syndrome of nasal polyps, angioedema or bronchospasm
- concurrent treatment with other NSAIDs including cylcooxygenase 2 specific inhibitors, oxpentifylline, probenecid or lithium salts
- hypovolaemia from any cause or dehydration
- moderate or severe renal impairment (serum creatinine> 160 micromol/l)
- a history of asthma

Driving and using machines

Ketorolac Injection may make you feel dizzy, drowsy or depressed, you may also get headaches, visual disturbances, vertigo or have difficulty sleeping. If you experience any of these you should not drive or operate machines.

Important information about some of the ingredients of Ketorolac Injection

This medicinal product contains 100mg of ethanol (alcohol) per dose, equivalent to 2ml beer or 1 ml wine per dose.

Harmful for those suffering from alcoholism.

To be taken into account in pregnant or breast feeding women, children and high-risk groups such as those with liver disease, or epilepsy.

Taking/using other medicines

Please note that these statements may apply to products taken some time ago or at some time in the future.

Please tell your doctor if you are taking, or have recently taken, any other medicine – even those not prescribed.

This is important because ketorolac could alter how other medicines work. These include medicines for blood clots (anti-coagulants, oxpentifilline), heart failure (frusemide, diuretics or cardiac glycosides such as digoxin), depression (lithium), high blood pressure (propranolol and other beta-blockers, ACE inhibitors), gout (probenecid) and psoriasis (methotrexate), arthritis (steroids), other non-steroidal anti-inflammatory drugs (such as aspirin), acute organ rejection (cyclosporin) or a drug, usually prescribed through hospitals, called mifepristone. Ketorolac should not be used for 8 - 12 days after taking mifepristone.

3. How should Ketorolac Injection be given and how much will I receive?

You will normally be given Ketorolac Injection whilst in hospital. A doctor or nurse will give the injection into a muscle or a vein.

The usual dose is 10mg initially followed by 10-30mg every 4 to 6 hours. The dose may be lowered if you are over 65 years of age, you have kidney problems or if you weigh less than 50kg.

The maximum duration of treatment should not be more than 2 days

If you have the impression that the effect of Ketorolac Injection is too strong or too weak, talk to your doctor.

4. Possible side effects

Like other medicines, Ketorolac Injection may cause undesirable effects in some patients. This should not alarm you as most patients are given ketorolac without experiencing problems.

The following effects have been reported:

- Sickness, indigestion, stomach pain or discomfort, vomiting blood, inflammation of the stomach, blood problems, bleeding, problems with the pancreas, stomach ulcer, diarrhoea, belching, constipation, wind or passing of black, tarry stools or blood.
- Anxiety, drowsiness, tiredness, dizziness, headache, sweating, fever, dry mouth, mouth ulcers, sore throat, agitation, nervousness, mental disturbances, mood changes, abnormal thinking and feelings, inability to concentrate, inability to sleep, convulsions, giddiness, hyperactivity, a mild form of meningitis, hallucinations, abnormal dreams, excessive thirst, alterations of vision, taste or hearing.
- muscle pain, numbness or tingling, muscle spasms or weakness.
- Kidney problems, high level of potassium or low levels of sodium in your blood, a change in the amount of urine passed or frequency in going to the toilet, blood in the urine, fluid retention, weight gain or kidney pain.
- Facial redness or paleness, bruising, anaemia, changes in the blood, low blood pressure, increased blood pressure, palpitations, chest pain or slow heart beat. Medicines such as Ketorolac may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke.
- difficulty in breathing or wheezes, severe allergic reactions. Hypersensitivity reactions can be very serious
- Swelling of skin (hives), itching, rash, skin lesions, flaky skin or spots, blisters on skin, severe skin reactions including ulceration and peeling, skin sensitivity to light; if this occurs you should contact your doctor immediately.
- bleeding from the site of the operation or bruising or a nose bleed.
- pain at the site of injection.
- very rarely, jaundice (yellowing of the skin and whites of the eyes) and inflammation of the liver have been reported.

If you are concerned about these or any other unwanted effects talk to your doctor.

5. Storing Ketorolac Injection

The hospital will store the medicines. Ketorolac Injection should not be stored above 30°C. It should be kept in the original container and protected from light. Keep out of reach and sight of children.

Use by date: Ketorolac Injection should not be used after the date on the carton.

This leaflet does not include all the information about this medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last approved in: March 2007

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- patients who have had operations with a high risk of haemorrhage or incomplete haemostasis
- patients on anti-coagulants including low dose heparin (2500 - 5000 units twelve hourly)
- during pregnancy, labour, delivery or lactation
- children under 16 years of age
- Ketorolac is contra-indicated as prophylactic analgesia before surgery intra-operatively.
- patients currently receiving aspirin

Interactions with other Medicinal Products and other Forms of Interaction

Ketorolac should not be used with other NSAIDs or in patients receiving aspirin because of the potential for additive side-effects.

Care should be taken when administering ketorolac with anti-coagulants since co-administration may cause an enhanced anti-coagulant effect.

Ketorolac may reduce the diuretic response to frusemide (approx. 20%) so particular care should be taken in patients with cardiac decompensation.

Ketorolac and other non-steroidal anti-inflammatory drugs can reduce the anti-hypertensive effect of beta-blockers and may increase the risk of renal impairment when administered concurrently with ACE inhibitors, particularly in volume depleted patients.

NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels when co-administered with cardiac glycosides. Care is advised when methotrexate is co-administered. Some prostaglandin synthesis inhibiting drugs may reduce the clearance of methotrexate, possibly enhancing its toxicity.

Probenecid should not be administered concurrently with ketorolac because of increases in ketorolac plasma level and half-life.

As with all NSAIDs caution is advised when cyclosporin is co-administered because of the increased risk of nephrotoxicity.

NSAIDs should not be used for 8-12 days after mifepristone. NSAIDs can reduce the effects of mifepristone.

As with all NSAIDs, caution should be taken when co-administering with cortico-steroids because of the increased risk of gastro-intestinal bleeding.

Patients taking quinolones may have an increased risk of developing convulsions.

Co-administration with diuretics can lead to a reduced diuretic effect, and increase the risk of nephrotoxicity of NSAIDs.

Because of an increased tendency to bleeding when oxpentifylline is administered concurrently, this combination should be avoided.

In patients receiving lithium there is a possible inhibition of renal lithium clearance, increased plasma lithium concentration and potential lithium toxicity. (See section 4.3 Contra-indications).

Incompatibilities

Ketorolac Injection should not be mixed in a small volume (e.g. in a syringe) with morphine sulphate, pethidine hydrochloride, promethazine hydrochloride or hydroxyzine hydrochloride, as precipitation of ketorolac will occur. Ketorolac Injection is compatible with normal saline, 5% dextrose, Ringer's, lactated Ringer's or Plasmacyte solutions. Compatibility of Ketorolac Injection with other drugs is unknown.

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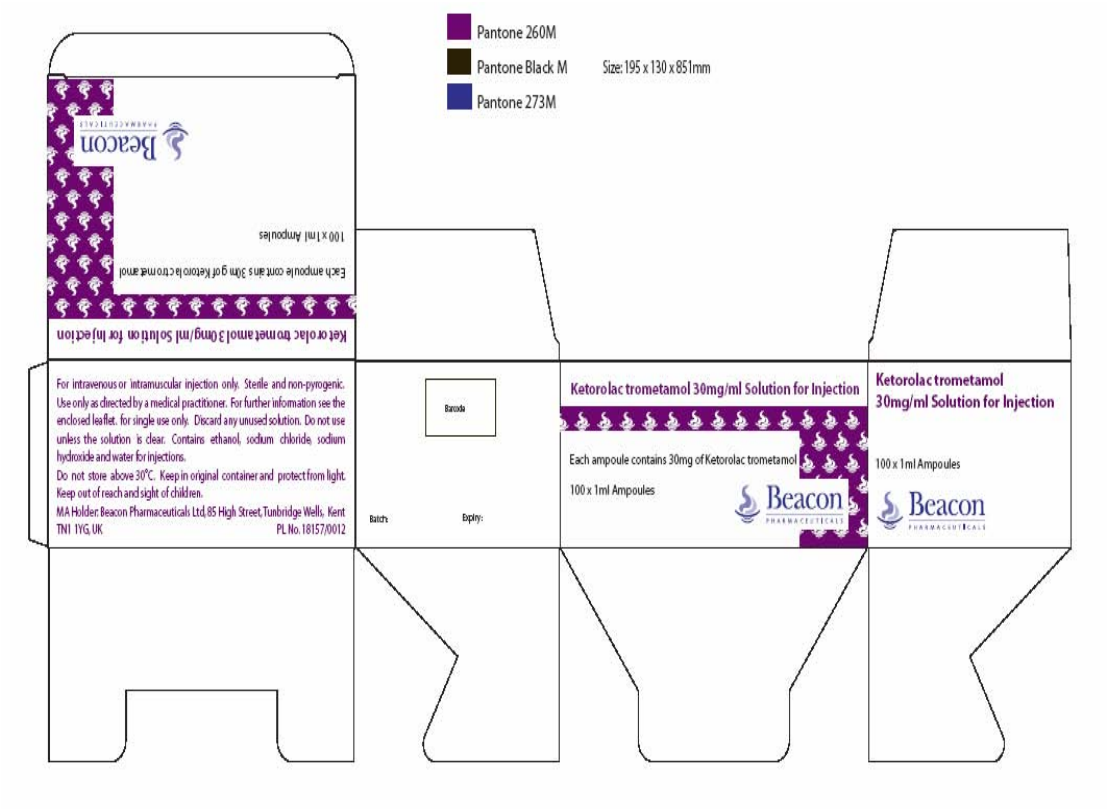
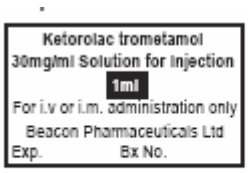

Pantone 260M
Pantone Black M
Pantone 273M
Size: 195 x 130 x 851mm
Beacon
Ketorolac trometamol 30mg/ml Solution for Injection
100 x 1ml Ampoules
Each ampoule contains 30mg of Ketorolac trometamol
100 x 1ml Ampoules
Ketorolac trometamol 30mg/ml Solution for Injection
100 x 1ml Ampoules
Beacon
For intravenous or intramuscular injection only. Sterile and non-pyrogenic. Use only as directed by a medical practitioner. For further information see the enclosed leaflet. for single use only. Discard any unused solution. Do not use unless the solution is clear. Contains ethanol, sodium chloride, sodium hydroxide and water for injections.
Do not store above 30°C. Keep in original container and protect from light. Keep out of reach and sight of children.
MA Holder: Beacon Pharmaceuticals Ltd, 85 High Street, Tunbridge Wells, Kent TN1 1YG, UK
PL No. 18157/0012
Batch:
Expiry: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30mg/ml Solution for Injection
1ml
For i.v or i.m. administration only
Beacon Pharmaceuticals Ltd
Exp.
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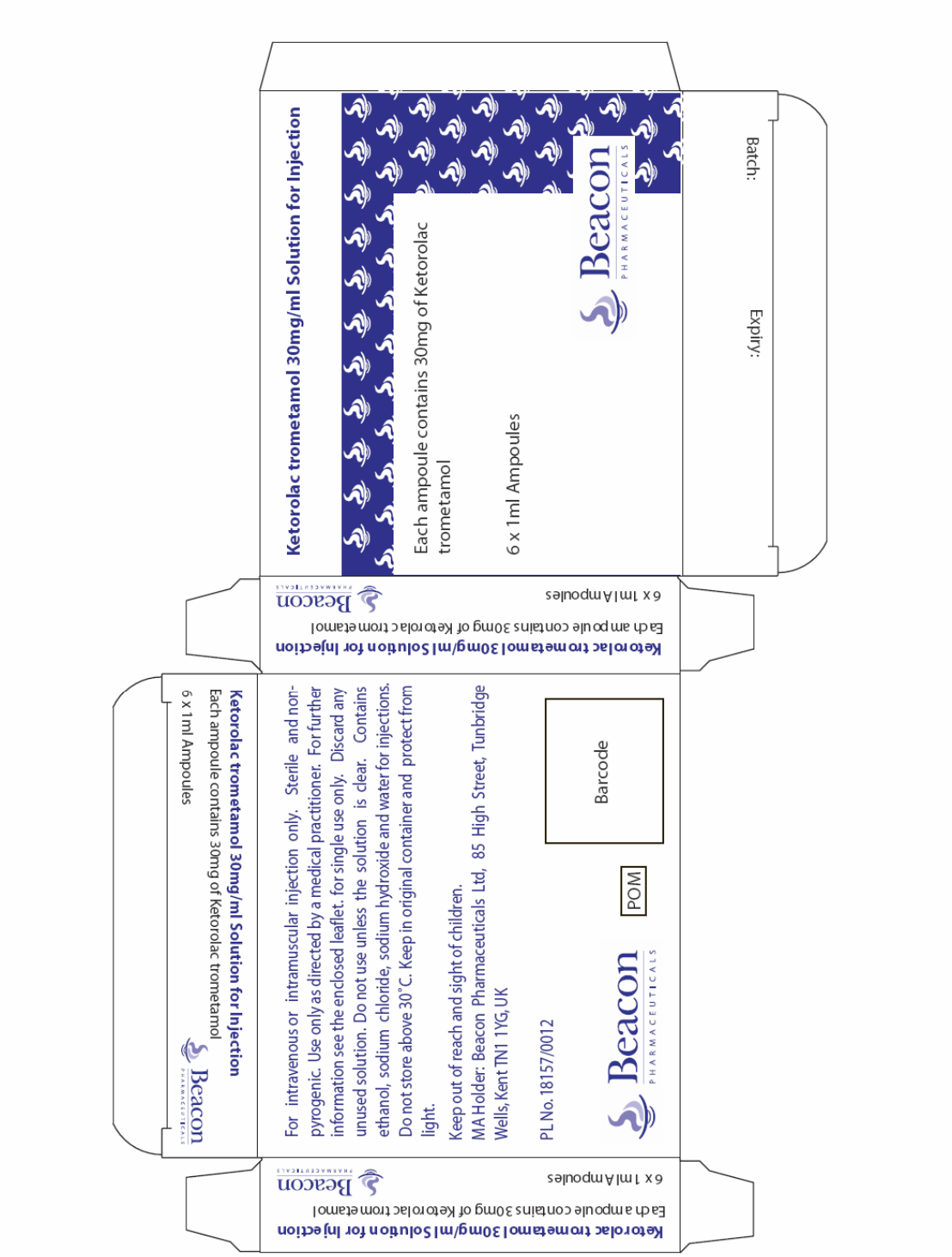

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