Bupivacaine Hydrochloride 1mg/ml and Fentanyl 2microgram/ml Solution for Injection/Infusion

PL 12064/0062

UKPAR

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BUPIVACAINE HYDROCHLORIDE 1MG/ML AND FENTANYL 2MICROGRAM/ML SOLUTION FOR INJECTION/INFUSION

PL 12064/0062

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for the medicinal product Bupivacaine 1mg/ml Injection and Fentanyl 2mcg/ml Solution for Injection/Infusion (product licence number: PL 12064/0062). This medicine is available only by prescription.

Bupivacaine 1mg/ml Injection and Fentanyl 2mcg/ml Solution for Injection/Infusion contains a mixture of two active ingredients: bupivacaine, which is a local anaesthetic (a medicine used to numb areas of your body in order to relieve pain), and fentanyl, which is used to treat pain. Bupivacaine 1mg/ml Injection and Fentanyl 2mcg/ml Solution for Injection/Infusion is a medicine that is used to treat pain during labour and after operations. It is given in hospital under supervision of an anaesthetist.

Bupivacaine 1mg/ml Injection and Fentanyl 2mcg/ml raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

BUPIVACAINE HYDROCHLORIDE 1MG/ML AND FENTANYL 2MICROGRAM/ML SOLUTION FOR INJECTION/INFUSION

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Bupivacaine 1mg/ml Injection and Fentanyl 2mcg/ml Solution for Injection/Infusion on 20 November 2009.

This is an abridged application made under Article 10a of EC Directive 2001/83, as amended. This application is for a new combination of known active ingredients (fentanyl 2 micrograms/ml and bupivacaine HCl 1mg/1ml) in an injection product.

Bupivacaine 1mg/ml Injection and Fentanyl 2mcg/ml Solution for Injection/Infusion is used via epidural infusion and/or bolus administration to treat pain in labour and the postoperative period.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Appropriate specifications in line with the Ph Eur monographs have been provided.

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

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

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

Full specifications are provided for the packaging used to store the bupivacaine and fentanyl, these are satisfactory.

Appropriate stability data have been generated supporting the retest periods.

DRUG PRODUCT

Description and Composition of the Drug Product

The product is an aqueous solution containing the active ingredients and the excipients sodium chloride, dilute hydrochloric acid and water for injections

All excipients are controlled in line with the relevant Ph. Eur. monograph. Appropriate justification for the inclusion of each excipient has been provided. Satisfactory certificates of analysis have been provided for all excipients.

The applicant has provided satisfactory certificates stating that neither the excipients nor the active substance contain substances of human or animal origin.

There were no novel excipients used and no overages.

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 product batches and 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 finished product is packed in 10ml clear Type I glass vials with a Type I rubber stopper and aluminium crimp seal. Vials are packed in cartons containing one or 10 vials.

Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. Stability results are considered acceptable to demonstrate the compatibility of the product with the proposed packaging.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years with the storage precautions “keep the container in the outer carton” is appropriate.

Product literature
All product literature (SPC, PIL and labelling) is satisfactory. The package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusions
A Marketing Authorisation may be granted for this application.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

BACKGROUND
Fentanyl is a potent synthetic opioid with short onset of action and moderate duration of action. Bupivacaine is an amide anaesthetic with a longer duration of action than other local anaesthetic agents. The product is used in epidural anaesthesia.

INDICATIONS
The indications for this product are satisfactory.

DOSE & DOSE SCHEDULE
The posology for this product is satisfactory.

TOXICOLOGY
Satisfactory

CLINICAL PHARMACOLOGY
Satisfactory

EFFICACY
Satisfactory

SAFETY
Satisfactory

EXPERT REPORTS
The expert report is satisfactory and references the key literature.

MEDICAL CONCLUSION
A Marketing Authorisation may be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Bupivacaine 1mg/ml Injection and Fentanyl 2mcg/ml Solution for Injection/Infusion 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.

PRECLINICAL

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

EFFICACY

The efficacy of bupivacaine and fentanyl is well established.
The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with bupivacaine and fentanyl. The risk benefit ration is, therefore, considered to be positive.

BUPIVACAINE HYDROCHLORIDE 1MG/ML AND FENTANYL 2MICROGRAM/ML SOLUTION FOR INJECTION/INFUSION

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 28 November 2000
2	Following assessment of the application the MHRA requested further information relating to the dossier on 28 February 2001 and 1 March 2001
3	The applicant responded to the MHRA's requests, providing further information on the dossier on 28 September 2001
4	Following assessment of the response the MHRA requested further information relating to the dossier on 22 November 2001
5	The applicant responded to the MHRA's requests, providing further information on the dossier on 28 March 2002 and 20 May 2002
6	Following assessment of the response the MHRA requested further information relating to the dossier on 20 May 2002
7	The applicant responded to the MHRA's requests, providing further information on the dossier on 7 October 2002
8	The application was discussed at the Committee of Safety of Medicines (CSM) on 24 November 2004 and 20 April 2006 and at the Committee for the Safety of Human Medicines (CHM) on 23 May 2008 and 16 July 2009
9	The applicant responded to the requests made by the committees on 1 May 2009 and 1 June 2009
10	The application was determined on 20 November 2009

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bupivacaine Hydrochloride 1mg/ml and Fentanyl 2microgram/ml Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre of solution for injection/infusion contains

Bupivacaine Hydrochloride 1mg/ml
Fentanyl (as Citrate) 2microgram/ml

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection/infusion
The sterile product is for epidural use

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bupivacaine hydrochloride 1mg/ml Injection and Fentanyl 2 microgram/ml Solution for Injection/Infusion is used via epidural infusion and / or bolus administration to treat pain in labour and the postoperative period.

4.2 Posology and method of administration

This injection should only be administered under the supervision of a suitably qualified anaesthetist.

After the administration of a test dose, Bupivacaine Hydrochloride 1mg/ml and Fentanyl 2microgram/ml Solution for Injection/Infusion has been administered using the following regimens:

Epidural infusion:
• Slow injection of a loading dose of 10 to 20 ml
• Infusion at 5-20 ml/h

Epidural intermittent boluses:
• Slow injection of a loading dose of 10 to 20 ml
• Top-ups of 3-20 ml repeated on demand

The dosage may vary from patient to patient and the rate may need to be varied from time to time, titrated to effect. Regimes for post-operative pain in particular may need to be varied according to intensity of pain and site of surgery.

To avoid overdose:
• Where conscious, maintain verbal contact with the patient throughout
• Record pulse and blood pressure
• In the case of labour, monitor foetal heart rate every 5 minutes for 20 minutes
• Monitoring of the patient's blood pressure should be continued every 30 minutes.
• Following commencement of an infusion, blood pressure should be monitored every 30 minutes, and height of sensory block every hour.

4.3 Contraindications

The use of Bupivacaine Hydrochloride 1mg/ml and Fentanyl 2 microgram/ml Solution for Injection/Infusion is contraindicated in case of:
• hypersensitivity to bupivicaine, fentanyl or to any of the excipients,
• acute respiratory depression,
• acute alcoholism,
• acute abdomen,
• raised intracranial pressure or head injury,
• phaeochromocytoma,
• concurrent administration of monoamine oxidase inhibitors (MAOI's) or within 2 weeks of their discontinuation,
• intravenous regional anaesthesia (Bier's block)
• hypovolaemia and complete heart block.

The general contraindications of epidural anaesthesia include:

• Active disease of the central nervous system such as meningitis, poliomyelitis, intracranial haemorrhage, sub-acute combined degeneration of the cord due to pernicious anaemia and cerebral and spinal tumours, tuberculosis of the spine.
• Pyogenic infection of the skin at or adjacent to the site of lumbar puncture.
• Cardiogenic or hypovolaemic shock.
• Coagulation disorders or ongoing anticoagulation treatment.

4.4 Special warnings and precautions for use

The utmost care should be taken to avoid an accidental intravascular injection.

Rapid onset of sensory or motor blockade with/without hypotension may indicate accidental intrathecal injection.

Ensure the availability of oxygen, artificial airways, IV fluids and suitable vasopressors (eg Ephedrine) and secure adequate venous access.

Caution should be used in patients with hypotension, hypothyroidism, asthma, decreased respiratory reserve, prostatic hypertrophy, convulsive disorders, shock and adrenocorticol insufficiency. A reduced dose may be needed in patients with hepatic impairment, renal impairment, the elderly and the debilitated.

Bupivacaine Hydrochloride should be administered with caution to patients with cardiovascular disease, hypertension or hyperthyroidism.

4.5 Interaction with other medicinal products and other forms of interaction

- Alcohol, antipsychotics such as droperidol, anxiolytics or hypnotics may enhance the sedative and hypotensive effects if administered at the same time.
- Cisapride, domperidone and metoclopramide may antagonise the gastrointestinal effects.
- Beta-blockers, especially propanolol, will increase the risk of bupivacaine toxicity.
- Antihypertensives, especially verapamil, may cause severe hypotension and bradycardia during epidural anaesthesia with bupivacaine.

Bupivacaine in the blood is a potent inhibitor of plasma cholinesterase, so would interfere with the measurement of that enzyme.

4.6 Pregnancy and lactation

Studies using *iv* fentanyl during labour detected fentanyl in breast milk, but at levels which were low enough to permit breast feeding. The use of Fentanyl by the epidural route permits lower doses (although the elimination half-life may be extended). The use of fentanyl epidurally during labour need not preclude initiation of breast feeding. The potential risk to the new-born should however be borne in mind

Bupivacaine enters the mother's milk, but in such small quantities that there is no risk of affecting the child at small therapeutic dose levels. There is no evidence of untoward effects in human pregnancy.

4.7 Effects on ability to drive and use machines

Where early discharge is envisaged, patients should be advised not to drive or operate machinery for 24 hours. A formal clinical test of motor power is advised.

4.8 Undesirable effects

It should be noted that the levels of each active component in this injection are below those typically used when administered singly. The risk of undesirable effects should therefore be lower, and their occurrence may be an indication of accidental intrathecal or other misrouted injection.

Adverse side effects associated with intravenous fentanyl citrate include nausea, vomiting, constipation, drowsiness, confusion, micturition difficulties, dry mouth, sweating, facial flushing, vertigo, bradycardia, palpitations, orthostatic hypotension, hypothermia, restlessness, changes of mood, hallucinations, miosis, raised intracranial pressure, muscle failure, rigidity, respiratory depression, convulsions, rabdomyolysis, dilation of pupils, hypoxia, pulmonary oedema.

Side effects of bupivacaine include confusion, respiratory depression and convulsions, hypotension and bradycardia, which may lead to cardiac arrest. Shivering may occur, but is infrequently troublesome.

4.9 Overdose

It should be noted that the levels of each active component in this injection are below those typically used when administered singly. The risks of overdose should therefore be lower, and its occurrence may be an indication of accidental intrathecal or other misrouted injection.

The symptoms of overdosage by **Fentanyl Citrate** are essentially an extension of the pharmacological effects. Respiratory depression may be reversed using naloxone in combination with other supportive measures such as mechanical ventilation. If respiratory depression is associated with muscular rigidity, then the use of suxamethonium has been successful in reversing the effects.

Bradycardia may be treated with atropine sulphate.

The symptoms of overdosage by **Bupivacaine Hydrochloride** are systemic toxicity if plasma concentrations become great enough for the drug to exert its membrane-stabilizing effect on the central nervous system and the myocardium. All local anaesthetics have very similar toxic effects. Initial features may include anxiety, tinnitus, circumoral numbness, a metallic taste in the mouth and irrational behaviour. Then there is a loss of consciousness and the patient may convulse and finally become apnoeic. Death may occur unless effective supportive therapy is instituted. The airways must be maintained and the lungs must be ventilated with oxygen. Convulsions should be controlled with small incremental doses of thiopentone (25-50mg) or diazepam (2.5-5mg) given intravenously.

With Bupivacaine, cardiac arrest may occur before the CNS symptoms, and treatment may be prolonged and difficult. Bretylium may be required.

In the event of hypotension, TURN the epidural infusion OFF, lie patient on his/her left hand side (if pregnant), elevate feet (DO NOT tip bed head down), rapidly administer 500ml Hartmanns solution or colloid intravenously, administer oxygen via face mask, administer ephedrine injection. Ephedrine injection should be administered by a qualified medical practitioner.

If the block rises above the desired level, reduce or discontinue the infusion as directed by a qualified anaesthetist.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Fentanyl Citrate

Fentanyl primarily affects the central nervous system and the gastrointestinal tract, and has the typical opioid actions of analgesia and respiratory depression. By the epidural route 100mcg has an onset of action of 4-6 min, a time to peak effect of 10-20 min, and a duration of action of 2-3 hours.

Fentanyl is a potent respiratory depressant and reduces brain stem respiratory responsiveness to carbon dioxide and peripheral chemoreceptor input during hypoxaemia. It exerts minimal effects on the circulation. There is a vagallymediated bradycardia and a slight fall in systemic vascular resistance. There is a reduction in metabolic activity following fentanyl, and hence in oxygen consumption.

Nausea and vomiting is due to stimulation of the chemoreceptor trigger zone. Cough suppression, pupillary constriction and itching of the nose occur.

Bupivacaine Hydrochloride

In common with other local anaesthetics, bupivacaine acts to block conduction in the nerves by decreasing or stopping the large transient increase in permeability of the cell membrane to sodium ions that follows depolarization of that membrane. The exact mechanism by which bupivacaine and the other local anaesthetics block conduction is thought to be because they bind to a specific receptor site within sodium channels.
Bupivacaine is roughly four times as potent as lignocaine, but the onset of action is a little slower. Bupivacaine has a longer duration of action and this also results in lower toxicity.

5.2 Pharmacokinetic properties

Fentanyl citrate

Fentanyl is highly lipophilic with an apparent octanol/water partition coefficient at pH 7.4 of 955 compared to 1.4 for morphine. After epidural administration the decay curve corresponds to a two-compartment model, with a rapid distribution half-life (t½α) of 2.2 min (*iv*= 8 min), and a slower elimination half-life (t½β) of 244min (*iv* = 89 min). Cmax = 0.81±1.13 ng/ml; Tmax = 1.00±1.33h; AUC = 1.17±0.88ng/ml; VD = 7.58l/kg.

Bupivacaine hydrochloride

Bupivacaine is rapidly absorbed from the site of injection, the rate of rise in plasma concentration and the peak plasma concentration depending on the particular local anaesthetic technique being used. There is also some interindividual variation, and peak systemic concentrations may occur between 5 and 30 minutes after administration. The addition of a vasoconstrictor will delay absorption and result in lower plasma concentrations. The liver is the main site of metabolism.
For an amide, bupivacaine has a longer elimination half life of 2.7 hours, a low plasma clearance rate of 0.58l/min and a small volume distribution (73 1). The greater risk of systemic toxicity implied by these figures is balanced by greater potency and duration of action, reducing the dose required.
Bupivacaine is about 95% bound to plasma proteins. Reported half-lives are from 1.5 to 5.5 hours in adults and about 8 hours in neonates. It is metabolised in the liver and is excreted in the urine principally as metabolites with only 5 to 6 % as unchanged drug.
Renal disease is unlikely to alter the kinetics of bupivacaine to any great extent, though there is evidence for a slight reduction in the elimination in old age. Severe liver disease would be expected to increase the half life of the drug, as bupivacaine is metabolised in the liver. Less than 10% of the dose is excreted unchanged in the urine.

5.3 Preclinical safety data

There are no pre-clinical safety data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Dilute Hydrochloric Acid
Water for Injections

6.2 Incompatibilities

This product is incompatible with methohexital, pentobarbital and thiopental.

6.3 Shelf life

2 Years

6.4 Special precautions for storage

Do not store above 25°C
Keep the container in the outer carton.

6.5 Nature and contents of container

10ml clear Type I glass vial with Type I rubber stopper and aluminium crimp seal.

Vials are packed in cartons. Cartons contain 1 or 10 vials.

6.6 Special precautions for disposal

Single use only. Discard any remaining solution in the appropriate manner.

7 MARKETING AUTHORISATION HOLDER

Aurum Pharmaceuticals Ltd
Bampton Road, Harold Hill
Romford, Essex
RM3 8UG

8 MARKETING AUTHORISATION NUMBER(S)

PL 12064/0062

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/11/2009

10 DATE OF REVISION OF THE TEXT

20/11/2009

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER D00499

Bupivacaine Hydrochloride 1mg/ml and Fentanyl 2microgram/ml Solution for Injection/Infusion

Bupivacaine Hydrochloride
Fentanyl (as citrate)

(Referred to as Bupivacaine and Fentanyl Injection in this leaflet)

Read all of this leaflet carefully before you use Bupivacaine and Fentanyl Injection.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or nurse.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

In this leaflet:

1. What Bupivacaine and Fentanyl Injection is and what it is used for

This medicine is a mixture of two active ingredients: Bupivacaine, which is a local anaesthetic, a medicine used to numb areas of your body in order to relieve pain and Fentanyl, which is used to treat pain.

Bupivacaine and Fentanyl Injection is a medicine that is used to treat pain during labour and after operations. It will be given to you in hospital under supervision of an anaesthetist.

2. Before having Bupivacaine and Fentanyl Solution

You should not be given Bupivacaine and Fentanyl Injection if you:
- are allergic to bupivacaine, fentanyl or any of the other ingredients listed in section 6 of this leaflet
- are currently having difficulty breathing
- suffer from alcoholism
- are suffering from severe stomach pain
- have suffered a head injury or have severe and undiagnosed headaches
- suffer from a tumour of the adrenal gland known as phaeochromocytoma
- are currently taking drugs used to treat depression known as monoamine oxidase inhibitors (MAOIs) or have taken them in the last 2 weeks
- have been given a type of local anaesthesia known as Biers block
- have been told you have a low blood volume in your body (hypovolaemia)
- have a heart problem known as complete heart block
- are suffering from a disease that affects the brain or the nerves in your spine such as meningitis, poliomyelitis, brain or spinal tumours, tuberculosis of the spine or bleeding in the brain
- are suffering from a blood disorder known as pernicious anaemia
- are suffering from a serious skin infection of your lower back that is producing pus
- are suffering from shock caused by a lack of blood or problems with your blood circulation. The symptoms of this include feeling weak, cold or pale skin, breathing quickly and feelings of anxiety
- have problems with your blood clotting or you are taking medicines to stop your blood clotting.

Special care will be taken with Bupivacaine and Fentanyl Injection. Tell your doctor if you suffer from:
- low or high blood pressure
- problems with your thyroid
- asthma or other breathing problems
- problems with your prostate
- a disorder that causes fits such as epilepsy
- problems with your adrenal glands
- liver or kidney problems
- heart disease.

Special care will be taken when this medicine is being given to the elderly and ill.

If any of the above apply to you or your child, please consult your doctor.

Taking other medicines
Please tell your doctor or nurse if you are taking or have recently taken any other medicines, including those obtained without prescription.

You **must not** be given Bupivacaine and Fentanyl Injection if you are taking:
- drugs used to treat severe depression, such as phenelzine or moclobemide, or if you have stopped taking them within the last 2 weeks. These drugs are known as Monoamine Oxidase Inhibitors (MAOI's).
- medicines used to stop your blood clotting (anticoagulants)

Tell your doctor if you are taking any of the following medicines that may interact with Bupivacaine and Fentanyl Injection:

- medicines used to treat mental disorders (antipsychotics) such as droperidol
- medicines used to help you to relax (anxiolytics) such as diazepam, buspirone and barbiturates
- medicines used to help you to sleep (hypnotics) such as temazepam, zolpidem and chloral hydrate
- medicines used to treat feeling or being sick and other stomach problems like heartburn and acid reflux, such as cisapride, domperidone and metoclopramide
- medicines used to treat high blood pressure (beta-blockers and calcium channel blockers) such as propranolol

If you have any doubts about whether this medicine should be given to you, consult your doctor or nurse.

Pregnancy & breast-feeding
Bupivacaine and Fentanyl Injection is thought to be safe for use during pregnancy and breast-feeding. However if you are pregnant, trying to become pregnant or breast-feeding you should ask your doctor for advice before taking any medicine.

Continued overleaf

Effects on the ability to drive and use machines
Bupivacaine and Fentanyl Injection may affect your ability to drive or operate machinery. If you are discharged from hospital soon after receiving this medicine and plan to resume these activities, ask your doctor when it will be safe to do so.

Having this medicine with food and drink
You should not drink alcohol during your treatment with Bupivacaine and Fentanyl Injection

3. How Bupivacaine and Fentanyl Injection is given

Bupivacaine and Fentanyl Injection will be given to you as an injection into your lower back (epidural). The injection will be given to you either as several single doses or as a continuous infusion (drip). In certain circumstances the doctor may give you a different dose to those stated here.

By infusion (drip)
The usual initial dose is a slow injection of 10-20ml, followed by a continuous dose of 5-20ml per hour if necessary.

By injection
The usual initial dose is a slow injection of 10-20ml, followed by further injections of 3-20ml if necessary.

If you are given too much Bupivacaine and Fentanyl Injection
As this medicine will be given to you whilst you are in hospital, it is unlikely that you will be given too little or too much, however, tell your doctor or nurse if you have any concerns.

4. Possible side effects

Like all medicines, Bupivacaine and Fentanyl Injection can cause side effects, although not everybody gets them.

If any of the following symptoms occur tell your doctor or nurse immediately. These are symptoms of a serious allergic reaction:
- sudden wheeziness and tightness of chest
- swelling of eyelids, face or lips
- skin lumps or hives
- skin rash (red spots), itchiness, fever
- collapse.

Other possible side effects include:
- feeling or being sick
- constipation
- drowsiness
- confusion
- feeling very cold, shivering
- difficulty passing urine
- dry mouth
- sweating
- facial flushing
- an unusually slow or irregular heartbeat
- a feeling of dizziness or spinning (vertigo)
- feeling faint on standing up from a seated position
- low blood pressure
- restlessness
- changes in mood
- seeing or hearing things that aren't real (hallucinations)
- pin-point pupils or unusually large pupils
- headaches
- muscle damage, weakness or stiffness
- slowed breathing
- fits
- lack of oxygen in the body (hypoxia), the symptoms of which include dizziness and feeling faint
- water on the lungs.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

5. Storing Bupivacaine and Fentanyl Injection

Keep out of the reach and sight of children.

You should not be given Bupivacaine and Fentanyl Injection after the expiry date which is printed on the carton and vial label. The doctor or nurse will check that the expiry date on the label has not been passed before administering the injection to you. The expiry date refers to the last day of that month.

Do not store above 25°C. Keep container in the outer carton.

6. Further Information

What Bupivacaine and Fentanyl Injection contains
The active substances are bupivacaine hydrochloride and fentanyl (as citrate).
The other ingredients are sodium chloride, dilute hydrochloric acid, water for injection.

What Bupivacaine and Fentanyl Injection looks like and contents of the pack
Bupivacaine and Fentanyl Injection is a clear, colourless solution supplied in a 10ml clear glass vial. Each vial contains 20 micrograms of fentanyl and 10mg of bupivacaine hydrochloride.

Marketing Authorisation Holder:
Aurum Pharmaceuticals Ltd.,
Bampton Road,
Harold Hill,
Romford, Essex.
RM3 8UG UK

Manufacturer:
Burton Hospital NHS Trust,
Belvedere Road,
Burton on Trent,
DE13 0RB,
United Kingdom.

If you would like any more information, or would like the leaflet in a different format e.g. large print, please contact Medical Information at the Marketing Authorisation Holder's address.
Product licence number: PL 12064/0062

Date of last revision: October 2009

AURUM

Bampton Road, Harold Hill, Romford
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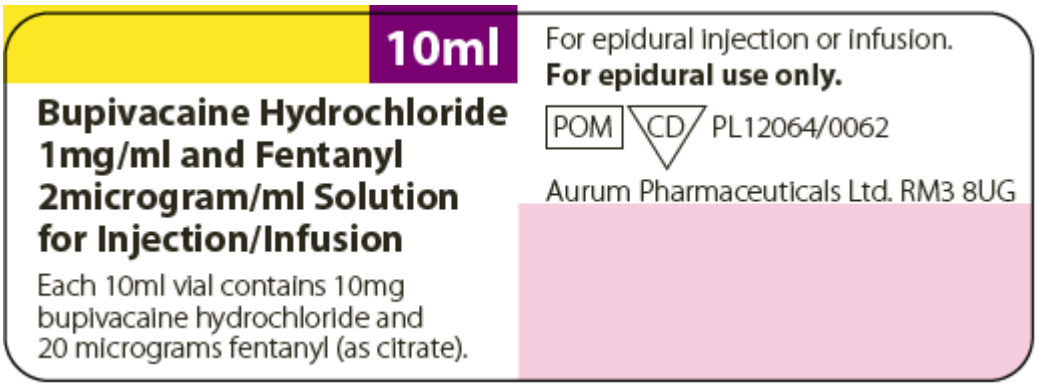
LABELLING


10ml
Bupivacaine Hydrochloride 1mg/ml and Fentanyl 2microgram/ml Solution for Injection/Infusion
Each 10ml vial contains 10mg bupivacaine hydrochloride and 20 micrograms fentanyl (as citrate).
For epidural injection or infusion.
For epidural use only.
POM
CD
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