

BEDFORDSHIRE AND LUTON JOINT PRESCRIBING COMMITTEE

SHARED CARE GUIDELINE FOR THE USE OF KETAMINE (oral and subcutaneous injection) FOR ANALGESIA IN ADULT PALLIATIVE CARE PATIENTS

PATIENT'S NAME:

PATIENT'S ADDRESS:

NHS NUMBER:

CONSULTANT'S NAME AND CONTACT DETAILS:

OTHER HEALTH PROFESSIONAL CONTACT DETAILS:

Background

Ketamine is the most potent NMDA-receptor channel blocker available for clinical use. The NMDA receptor channel complex is closely involved in the development of central sensitization of dorsal horn neurons which transmit pain signals. When the channels are unblocked as a result of prolonged excitation, neuronal hyperexcitability results causing hyperalgesia and allodynia and a reduction in opioid sensitivity.

A systematic review of ketamine in chronic cancer pain found that a number of studies supported its use but only in patients with severe pain that no longer responded to conventional pain therapies. They suggested it should be a third line analgesic after optimal opioid and co-analgesics have been tried¹. The Palliative Care Formulary gives the same conclusions that there are case reports, retrospective surveys or uncontrolled studies in cancer patients with refractory pain that have benefitted from ketamine as a third line medication when there has been lack of response to other analgesic options².

Historically, specialist palliative care patients with complex cancer pain have been prescribed ketamine by their hospice consultant. This prescription has then been carried on by their GP. However routes for on-going monitoring of the patient, or for obtaining further supplies of ketamine

have not always been clear. This Shared Care guideline is designed to provide GPs with further information on safe prescribing of ketamine and how to obtain specialist advice when the patient is discharged from the hospice to ensure current practice can be maintained in a safe manner.

Prescribing of ketamine (oral or subcutaneous)

The use of ketamine in palliative care for analgesia (orally or subcutaneously) is an unlicensed use lying outside its UK marketing authorisation. It has been established practice that GPs take over the prescribing of ketamine after the initial prescription by Specialist Palliative Care. This shared care guideline aims to continue this practice and more clearly define Specialist Palliative Care and GP responsibilities.

A) Specialist Palliative Care Physician responsibilities

Assessment and monitor

- Confirm diagnosis and indication for drug treatment.
- Assess risk of abuse potential by family members or others within the patient's home, by liaison with community staff such as GP and Community Macmillan Nurse as necessary.
- Discuss potential benefits and side-effects of treatment with patient.
- Inform the patient to keep ketamine in a safe container to prevent accidental use by others, especially children.
- Inform the patient to store ketamine in a cool place away from sunlight.
- Provide patient with Sue Ryder St John's Hospice (or other suitable leaflet) patient information leaflet on starting treatment.
- Discuss with GP whether further monitoring is required. For patients rapidly approaching end of life, no further monitoring may be necessary. For stable patients with a longer prognosis monthly BP checks and LFTs may be needed.
- Discuss with Community Specialist Palliative Care Nurse Specialist what further monitoring is required. This is likely to be checking for urinary and neuropsychiatric side effects on each patient visit.
- Arrange out-patient or domiciliary visit follow up from a Specialist Palliative Care Physician as required.
- Provide advice to the GP and Community Specialist Palliative Care Nurse Specialist on demand, via the team of consultants and middle grade doctors available at the hospice, and via the consultant on call service Out of Hours.
- Decide when to stop therapy or change the dose .

Prescribing arrangements

- Initiate prescribing of ketamine ensuring that the route of administration, frequency of administration, formulation and dose of ketamine are clearly stated on the prescription.
- Modify opioid dosage if appropriate and ensure the GP is notified of any changes made.
- Provide prescriptions until dose titration is completed.

- Check for possible drug interactions when initiating ketamine, prescribing any new medications or when stopping concurrent medications
- Check for cautions and contra-indications when initiating therapy.
- If prescribed subcutaneously use the Bedfordshire continuous subcutaneous infusion (CSCI) prescription chart on discharge from the hospice.

Communication

- Formally ask the GP to take over prescribing responsibility when clinically appropriate to do so.
- Provide GP with written details of the required prescription and monitoring requirements and a copy of the full Shared Care Guidelines.
- Ensure the dosage regimen, the route and frequency of administration are clearly explained to the GP and patient.
- Ensure that any modifications to opioid dosage is explained to the GP and explain to monitor for any signs of opioid toxicity.
- Explain any monitoring requirements to the patient.
- Provide patient with Sue Ryder St John's Hospice (or other suitable leaflet) patient information leaflet on starting treatment.
- Advise patient to inform their community pharmacist they are taking ketamine and to ask for repeat prescriptions with at least 3-4 working days notice to allow the pharmacist to have supplies delivered (NB: To ensure consistency of supply, it is better to try and give 10-14 days notice to the community pharmacist).
- Provide advice to the GP and Community Specialist Palliative Care Nurse Specialist on demand, via the team of consultants and middle grade doctors available at the hospice, and via the consultant on call service Out of Hours.
- Inform the patient to report any side effects to the GP, Community Specialist Palliative care Nurse Specialist or Specialist Palliative Care Physician, particularly headache, urinary symptoms, abdominal pain, confusion, hallucinations, delirium or nausea.

B) General Practitioner Responsibilities

As part of this shared care agreement, the GP agrees to take over the prescribing responsibility and monitoring responsibility (as indicated by the specialist) for ketamine.

General points:

- Monitor patient's overall health and well-being.
- Report any significant change in the patient's condition/loss of effectiveness of medication to either the Community Specialist Palliative Care Nurse Specialist or Palliative Care Physician.

- Ensure that the GP medical record is updated to reflect any dose changes to opioid medication that the Specialist may have made on initiation of ketamine.
- Monitor the patient for any side effects to ketamine and refer back to the Palliative Care Physician or Community Specialist Palliative Care Nurse Specialist should any side effects occur. Report side effects to the MHRA if appropriate.

Prescribing and monitoring

- Report any significant increase in blood pressure (if blood pressure monitoring has been requested) to either the Community Specialist Palliative Care Nurse Specialist or Palliative Care Physician.
- Report any significant change in LFTs (if LFT monitoring has been requested) to either the Community Specialist Palliative Care Nurse Specialist or Palliative Care Physician.
- Record the dosage instructions in the GP medical record.
- Prescribe ketamine on a FP10 as per the Palliative Care Physician's instructions.
- Ketamine is classed as a Schedule 2 CD (Controlled Drug), therefore all prescriptions must satisfy CD prescription requirements to be valid and include details of the dose, form, strength, directions for use and total quantity (in both words and figures).
- Ensure the route of administration, dosage, frequency and formulation of ketamine is clearly stated on the prescription.
- If prescribing by the subcutaneous route, please prescribe on a FP10 (to facilitate supplies from the community pharmacy) and in addition, prescribe on the Bedfordshire CSCI prescription chart for administration purposes.
- No changes should be made to the dose / route of administration without the advice of the Specialist; Discuss and agree any modifications to the dose or route of administration that may be required with a specialist (either the Palliative Care Physician or Community Specialist Palliative Care Nurse Specialist) prior to making any such changes NB: A dose modification is required if switching between po and CSCI and vice versa – contact Specialist team for advice.
- Ensure repeat prescriptions are authorised so that the Community Pharmacist has at least 3-4 working days in which to obtain supplies.
- Provide a maximum of 4 weeks supply at a time.
- Remind the patient to keep ketamine in a safe container to prevent accidental use by others, especially children.

Communication

- Ensure all relevant staff and patients are aware of shared care arrangements.
- Record any requested monitoring (monthly BP check, LFTs) in the patient record.
- Explain clearly the dose regimen to the patient.

- Inform the patient to contact the Palliative Care Hub, GP, Community Specialist Palliative Care Nurse Specialist or Palliative Care Physician if side effects occur, especially headache, urinary symptoms, abdominal pain, confusion, hallucinations or nausea.
- Discuss with either the Community Specialist Palliative Care Nurse Specialist or Palliative Care Physician if the patient experiences headache, urinary symptoms, abdominal pain, confusion, hallucinations, delirium or nausea.
- Contact the Palliative Care Physician if any changes in dose or route are considered, prior to making the change.

C) Patient's Responsibilities (applicable to carers if patient is unable to comply)

- Discuss potential benefits and side effects of treatment with their GP, Community Specialist Palliative Care Nurse Specialist or Palliative Care Physician and share any concerns they have in relation to their treatment.
- To report any side effects to their GP, Community Specialist Palliative Care Nurse Specialist or Palliative Care Physician. To report immediately any headache, urinary symptoms, abdominal pain, confusion, hallucinations, delirium or nausea.
- To inform their Community Pharmacist they are taking ketamine.
- To inform their GP, Community Specialist Palliative Care Nurse Specialist and Palliative Care Physician of all medicines (including OTC preparations) they are currently taking.
- To keep ketamine in a safe container to prevent accidental use by others, especially children.
- To store ketamine in a cool place away from sunlight.

BACK-UP ADVICE AND SUPPORT – CONTACT DETAILS

Bedfordshire Palliative Care Hub 24 hours advice line – 01767 641349

St John's Hospice – 01767 642410

For Keech Cottage Patients – contact Palliative Care Advice Line 08081807788 (freephone/ 24-hour).

References:

1. Zgaia et al. The role of ketamine in the treatment of chronic cancer pain. Clujul Med. 2015; 88(4): 457–461. www.ncbi.nlm.nih.gov/pmc/articles/PMC4689236/
2. Ketamine monograph. PCF 5 Palliative Care Formulary <https://www.palliativesdrugs.com/palliative-care-formulary.html>
3. BNFOne. <https://www.medicinescomplete.com/mc/bnf/current/DMD10637811000001103.htm?q=ketamine&t=search&ss=text&tot=11&p=6#DMD10637811000001103>
4. SPC for Ketalar 50mg/ml injection. <https://www.medicines.org.uk/emc/medicine/28465>

Ketamine in Palliative Care Summary Fact Sheet

The drug information regarding the use of ketamine as an analgesia in palliative care is derived from the National Palliative Care Formulary. Additional general information regarding ketamine, can also be accessed via the SpC (www.medicines.org.uk) and electronic BNF <https://bnf.nice.org.uk/>

Description of product and available preparations

Oral route

- Ketamine Oral Suspension 50mg/5ml (Drug Tariff Special (April 2018); Cost £122/200ml)
- Ketamine Oral Solution 50mg/5ml (Drug Tariff Special (April 2018); Cost £109/200ml)

The specific formulation of oral ketamine included in this guideline (see above) must be prescribed in order to ensure drug tariff price is paid.

Community pharmacists can obtain supplies of ketamine oral solution from the various specials manufacturers. It is available in many strengths and flavours from 'Specials' manufacturers e.g.

Cardinal Health (Martindale Pharmaceuticals Ltd) - Tel 0800 137627

The Specials Laboratory in Prudoe – Tel 0800 0828 4925

These companies usually keep limited stocks of some strengths, pack sizes and flavours, which are generally cheaper and have longer shelf-lives (e.g. up to 12 months vs. 3 months) than products that are made to order. Ketamine oral solution can usually be supplied within a period of about 3-4 working days. However to ensure continuity of supply in the event of any delay, the patient should be advised to obtain repeat prescriptions and take them to the community pharmacy that he/she uses 10 to 14 days before the next supply is needed.

Sue Ryder St John's Hospice uses a 50mg in 5ml peppermint flavoured oral solution from Cardinal Health (Martindale Pharmaceuticals Ltd), which currently costs £111.20 per 500ml plus a £10.00 carriage fee for each delivery. No patient details are required and the expiry of this solution is 1 year from the date of manufacture.

Subcutaneous route

Ketamine injection preparations available

- 10mg/ml x 20ml £4.22
- 100mg/ml x 10 ml £16.10
- 50mg/ml x 10ml £8.77

Ketamine injection is normally only supplied to hospitals, but arrangements can be made for it to be supplied to community pharmacies. 50mg/ml vials are usually used.

The following details should be faxed to the manufacturer (Pfizer) on 01310 651006.

- Pharmacy name and address
- Pharmacist's name
- GP's name
- Patient's name
- Dose of ketamine prescribed
- Quantity, strength and volume of ketamine vials required
- Name and branch of pharmaceutical wholesaler
- The pharmacy's account number with the wholesaler

N.B. Pfizer only distributes its products through Unichem.

Indications in Specialist Palliative Care

The use of ketamine is reserved to specialist palliative care patients who have failed to obtain relief from standard drug and non-drug therapies. It may be used for neuropathic, inflammatory, ischaemic limb and procedure-related pain unresponsive to standard treatments. The use of ketamine in palliative care for analgesia (orally or subcutaneously) is an unlicensed use and lies outside its UK marketing authorisation.

Dosage and administration

Oral route

- Initially 10-25mg tds
- If necessary titrated upwards in steps of 10-25mg up to 100mg qds. NB No changes should be made to the dose / route of administration without the advice of the Specialist

Continuous subcutaneous infusion (CSCI)

- Initially 1-2.5mg/kg/24 hours
- If necessary, titrate upwards by 50-100mg/24 hours until adequate pain relief. Usual maximum dose 500mg/24hrs
- No changes should be made to the dose / route of administration without the advice of the Specialist
- Dilute with sodium chloride 0.9% , For specific instructions of how to set up the syringe driver , refer to the local Standard Operating Procedure (SOP). (NB The type of syringe drivers use in the hospice may differ from those used in the Community setting).
- Use largest volume possible to avoid risk of skin irritation
- Check syringe driver daily for turbidity
- Change the infusion site daily to prevent skin necrosis. Dexamethasone 0.5mg - 1mg may be added to the infusion if irritation is a problem
- Do not mix with other medication without checking drug compatibility. Call Bedfordshire Palliative Care Hub if unsure for specialist advice
- Once the vials have been opened they must be discarded (single use only)

Contraindications

Any situation in which an increase in blood pressure or intracranial pressure would constitute a hazard.

Ketamine should be avoided in patients with:

- Raised intracranial pressure
- Severe systemic hypertension
- Raised intra-ocular pressure
- Recent history of epilepsy
- Recent history of psychosis.
- Severe cardiac disease

Cautions

Ketamine should be used with caution in patients with:

- History of psychiatric disorders
- Hypertension, heart failure, cardiac arrhythmia, ischaemic heart disease or stroke
- Hyperthyroidism
- Intracranial space occupying lesion
- Conditions causing increased upper airway secretions
- Severe hepatic impairment

Drug interactions

- **CYP3A4 inhibitors liver enzyme inhibitors**, such as clarithromycin, grapefruit juice, increase the plasma concentration of the active component of ketamine.
- **CYP3A4 liver enzyme inducers**, such as rifampicin and St John's wort, reduce the plasma concentration of the active component of ketamine. Other potent inducers of CYP3A4 and CYP2B6 may have similar effect.
- **Opioids** – there is an increased risk of opioid toxicity during initiation of ketamine. Ketamine should only initiated by a Specialist Palliative Care Physician experienced in its use.
- **Memantine** – Avoid – risk of increase CNS side effects
- Increase risk of hypotension if co-prescribed with other drugs that can cause hypotension
Increased risk of CNS depressant effects if co-prescribed with other drugs that can cause CNS depressant effects.

Side effects

Common or very common side effects (≥1/10):

Dose related neuropsychiatric effects: euphoria, dysphasia, blunted affect, psychomotor retardation, vivid dreams, nightmares, impaired attention and memory, illusions, hallucinations, altered body image, delirium, drowsiness, dizziness, diplopia, blurred vision, nystagmus, altered hearing, hypertension, tachycardia, hypersalivation, nausea and vomiting.

Neuropsychiatric effects commonly develop in the initiation phase of treatment. Midazolam or haloperidol are usually co-prescribed for patients receiving CSCI ketamine to reduce the risk of hallucinations. Effects are less common during oral titration. Transient effects can be alleviated by a benzodiazepine such as lorazepam.

CSCI use may cause pain and irritation at injection site.

Uncommon ($\geq 1/1000$ to $< 1/100$)

Arrhythmias, bradycardia, hypotension, laryngospasm, respiratory depression

Rare but important side effects ($\leq 1/1000$):

Urinary symptoms: frequency, urgency, urge incontinence, dysuria, haematuria and lower abdominal pain. May lead to interstitial cystitis.

Hepatobiliary: abnormal LFTs have developed with therapeutic ketamine use. Abdominal pain and common bile duct problems have been reported in ketamine abusers.

Monitoring

Monthly blood pressure, LFTs and check on urinary symptoms.

If patients develop urinary symptoms in the absence of other explanation e.g. UTI, discuss with Specialist Palliative Care Physician as ketamine may need to be stopped. Symptoms usually settle several weeks after stopping ketamine.

If patient develops abnormal LFTs in the absence of other explanation e.g. deteriorating liver metastases, discuss with Specialist Palliative Care Physician as ketamine may need to be stopped. Symptoms usually settle quickly after stopping ketamine.

**IF IN ANY DOUBT ABOUT ANY ASPECT OF PRESCRIBING KETAMINE AND/OR
MONITORING PLEASE CONTACT THE SPECIALIST PALLIATIVE CARE
CONSULTANT VIA BEDFORDSHIRE PALLIATIVE CARE HUB**

01767 641349

**For Keech Cottage Patients – contact Palliative Care Advice Line 08081807788
(freephone/ 24-hour).**

Guidance Sheet for Ketamine Syringe Drivers for District Nurses

Indications in Specialist Palliative Care

The use of ketamine is reserved for use in Specialist Palliative Care patients who have failed to obtain relief from standard drug and non-drug therapies. It may be used for neuropathic, inflammatory, ischaemic limb and procedure-related pain unresponsive to standard treatments.

Drug Information

For drug information, see the Ketamine in Palliative Care Summary Fact Sheet (page 6)

Syringe Driver Information

A ketamine syringe driver should only be started under guidance from a Specialist Palliative Care physician. Please note that the type of syringe driver used in the hospice setting may differ from the type used in Community – in the Community setting, district nurses should refer to the relevant Standard Operating Procedure (SOP) for details of how to set up a syringe driver.

Changes in doses of ketamine

No changes in dose of ketamine in the syringe driver should be made without consultation with the palliative care physician directing treatment.

KETAMINE PATIENT INFORMATION LEAFLET- FOR USE IN ADULTS IN THE PALLIATIVE CARE SETTING

You have been prescribed Ketamine. It is available in an oral liquid or injection.

What is Ketamine and what is it used for?

Ketamine is an anaesthetic medication, which in very small doses can be used to help control pain that has not responded to standard treatment. It is started on the advice of a specialist in pain control or palliative care.

Why have I been given Ketamine?

Ketamine is used to treat complex pain, often in combination with other painkillers like morphine. It works by blocking the pathway that transmits pain signals to the brain at the level of the spinal cord.

How do I take Ketamine?

Ketamine is usually started by the Palliative care team based at the hospital or hospice.

The team will decide the best way for you to take ketamine. It can be given orally three to four times a day. Ketamine injection is administered under the skin if you have difficulty swallowing or when a continuous dose is required to manage your pain. A portable battery operated pump administers the ketamine over a 24 hr period through a small needle placed under the skin. A district nurse will change the syringe of medicine each day.

Are there any side effects from taking ketamine?

Everyone reacts differently to medication. Some side effects of ketamine are listed below but you may not experience any of these. It is advisable to report any side effects to your doctor.

- Vivid dreams, nightmares, hallucinations and confusion. These symptoms can often be helped with the addition of other medications enabling you to continue using ketamine without experiencing these side effects.
- High blood pressure and fast pulse rate. The doctor will monitor your blood pressure and pulse rate when you start treatment and then as needed.
- Ketamine can cause skin irritation if given by continuous injection under the skin. Your nurse will check the skin daily for signs of redness or discomfort at the needle site.

Can I drive?

You should not drive after starting ketamine until you have had a discussion with your doctor regarding whether it is safe /advisable.

Can I drink alcohol when I am taking ketamine?

A small glass of wine, beer or sherry may help you feel better and improve your appetite. It is best to avoid taking more than this as you may become drowsy. Remember that alcohol will also affect your ability to drive or operate machinery.

What about travel abroad?

You can travel abroad, but the rules governing how much ketamine you can take with you vary according to the country you are visiting. Check with doctor as soon as possible.

Can I stop ketamine if my pain goes away?

If your pain disappears when taking ketamine, this may be due to the fact that it's doing its job. In this case, stopping ketamine suddenly may cause an increase in pain and other side effects. Some people find that their pain responds well to just a couple of weeks treatment. With ketamine. In this situation, your doctor may decide to stop ketamine, please discuss it with your doctor. so that a gradual reduction in your dose can be undertaken.

Can I take other medicines together with ketamine?

Certain medicines can affect the dose of ketamine that you require. Any doctor prescribing medicines for you should check that additional medications can be safely taken with ketamine. If you buy 'over the counter' medicines from a pharmacy always tell the pharmacist that you are on ketamine.

If the ketamine controls your pain well you may need a lower dose of your other pain killers. If you feel that you are sleepier than usual, feeling sick, or having bad dreams, please contact your doctor.

What do I do if I forget to take a regular dose of oral ketamine?

Take the dose as soon as you remember. Do not take a double dose to make up for the missed one. If you are sick within one hour of taking a dose of ketamine repeat the dose as soon as you feel better.

How do I get a new prescription of Ketamine?

If you are in the hospice, one of the hospice doctor will prescribe your ketamine: when you go home, they will make sure you have 14 days supply to take with you.

When you are at home your GP will prescribe the ketamine. To avoid running out of medication, please let your community pharmacist know in advance that you will be requesting supplies of ketamine on a prescription as it may take several days for the community pharmacist to obtain supplies.

If you have been started on ketamine at the hospital the team looking after you will provide you with supply of seven days of ketamine and subsequent prescriptions will need to be obtained from your GP.

Where should I keep my ketamine?

Ketamine should be stored out of reach of children, in a cool place away from sunlight. The medicine should be stored in a safe container to prevent accidental use by others, especially children.

Ketamine does not currently hold a product license for the treatment of pain. What does this mean?

All medicines need to be licensed before they can be used to treat patients. Ketamine is licensed for use as an anaesthetic but also has been used for the treatment of pain for many years. This is an 'off license' use but has been shown to be safe and effective at controlling pain.

Who should I phone if I need advice urgently about my ketamine?

Please contact Bedfordshire Palliative Care Hub who will discuss it with the palliative care team based at the hospice or hospital. They can contact the on call palliative care consultant for advice out of hours.

Written by: Patient Information Leaflet In-house Publication by St John's Hospice