Fentanyl

http://www.patient.co.uk/showdoc/30003222/

Fentanyl is used to treat severe pain

Symptoms of too high a dose of fentanyl include trouble breathing, tiredness, extreme sleepiness, inability to think or talk normally, feeling faint and confusion. If you experience these symptoms, contact your doctor straight away.

http://books.google.co.uk/books?id=0Bw2UJTC_uMC&pg=PA628&lpg=PA628&dq=trimethoprim+increase+creatinine&source=web&ots=W56mAuopTD&sig=IjtKv18TFuhZgPCVKx8S62ZcSLw&hl=en&sa=X&oi=book_result&resnum=3&ct=result#PPA306,M1

http://www.fda.gov/cder/foi/label/2005/19813s039lbl.pdf

Full Prescribing Information
FOR USE IN OPIOID-TOLERANT PATIENTS ONLY

DURAGESIC® contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (DURAGESIC®) may be a particular target for abuse and diversion.

DURAGESIC® is indicated for management of persistent, moderate to severe chronic pain that:
• requires continuous, around-the-clock opioid administration for an extended period of time, and
• cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids

DURAGESIC® should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to DURAGESIC□ 25 mcg/h. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could occur, DURAGESIC® (fentanyl transdermal system) is contraindicated:

• in patients who are not opioid-tolerant

• in the management of acute pain or in patients who require opioid analgesia for a short period of time

• in the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies)

• in the management of mild pain

• in the management of intermittent pain [e.g., use on an as needed basis (prn)]

(See CONTRAINDICATIONS for further information.)

Since the peak fentanyl levels occur between 24 and 72 hours of treatment, prescribers should be aware that serious or life threatening hypoventilation may occur, even in opioid-tolerant patients, during the initial application period.

http://www.drugabusehelp.com/drugs/fentanyl/

Effects:

Fentanyl's primary effect is on the central nervous system; its primary therapeutic effects are analgesia and sedation. Other effects of fentanyl may include mood changes, euphoria, dysphoria, or drowsiness. Fentanyl depresses the respiratory centers and the cough reflex and constricts the pupils. Nausea, vomiting, and postural syncope may also occur although more commonly in ambulatory patients.

Source: http://www.duragesic.com

Side Effects:

Typical side effects of Duragesic therapy include abdominal pain, anxiety, confusion, constipation, depression, diarrhea, dizziness, dry mouth, euphoria, hallucinations, headache, impaired or interrupted breathing, indigestion, itching, anorexia, nausea, agitation, shortness of breath, sleepiness, sweating, urinary retention, vomiting, and weakness.

Source: http://www.pdrhealth.com

Cautionary Notes:
The following contraindications can cause serious or life-threatening hypoventilation if Duragesic is used:

· For acute or post-operative pain
· For mild or intermittent pain responsive to PRN (take as needed) or non--opioid therapy
· In doses exceeding 25 µg/hour at the initiation of opioid therapy

General Caution:

*To ensure controlled drug delivery, do not cut or damage the Duragesic patch.
*Heat can increase the release of fentanyl from the Duragesic patch, increasing breathing difficulties and other side effects. Do not expose the patch to heating pads, electric blankets, heated water beds, heat lamps, saunas, hot tubs, or other external sources of heat. Alert your doctor if you develop a high fever (104 degrees Fahrenheit or more).
*Duragesic can impair your reactions. Do not drive or operate dangerous machinery until you know how this drug affects you.
*Duragesic's tendency to reduce respiration can be especially dangerous if your breathing is impaired by chronic pulmonary disease.
*Duragesic is not recommended for people with head injuries and other conditions that increase pressure on the brain.
*If you have an irregular heartbeat, Duragesic can make the problem worse.
*Use Duragesic with caution if you have kidney or liver disease.
*This medicine should be used with caution by patients with a known allergy to morphine, codeine, or acetaminophen products.
It is very important to check with your physician before combining Duragesic with the following:

*Antifungal medications such as Diflucan, Nizoral, and Sporanox
*HIV drugs classified as protease inhibitors, including Agenerase, Crixivan, Fortovase, Invirase, Kaletra, Norvir, and Viracept
*Macrolide antibiotics such as erythromycin, Biaxin, and Zithromax

Drugs that may decrease the effects of Duragesic:

*Carbamazepine (Tegretol)
*Phenytoin (Dilantin)
*Rifampin (Rifadin)

Fentanyl is a central nervous system depressant and intensifies the effects of alcohol. Do not drink alcohol while taking this medication.

When wearing a Duragesic patch, check with your doctor before taking any other central nervous system (CNS) depressant drugs. The combined effect can lead to difficulty breathing, hypotension, and possibly coma.

Drugs in this category include the following:

*Antipsychotic drugs such as Compazine, Mellaril, Stelazine, and Thorazine
*Muscle relaxants such as Flexeril, Robaxin, and Skelaxin
*Narcotic painkillers such as Demerol, Percodan, OxyContin, and Vicodin
*Sleep aids such as Ambien, Halcion, and Sonata
*Sleep-inducing antihistamines such as Benadryl and Phenergan
*Tranquilizers such as Ativan, Librium, Valium, and Xanax
*Alcoholic beverages

Overdosage:

Users are susceptible to an overdose if they take too much transdermal fentanyl, or combine it with excessive amounts of another narcotic. An overdose can cause severe breathing problems (breathing may even stop), unconsciousness, and death. Serious signs of an overdose include very slow breathing and drowsiness so severe the person is unresponsive. Other signs of an overdose include cold, clammy skin; low blood pressure; pinpoint pupils of eyes; and slow heartbeat. If this occurs, get emergency help right away.
Source: *http://www.mayoclinic.com*

http://www.drugs.com/drug-interactions/duragesic_d00233_chlorpromazine_d00064.html

duragesic and Chlorpromazine Interactions

Interaction(s) found:

chlorproMAZINE and fentanyl (Moderate Drug-Drug)

MONITOR: Central nervous system- and/or respiratory-depressant effects may be additively or synergistically increased in patients taking multiple drugs that cause these effects, especially in elderly or debilitated patients.

MANAGEMENT: During concomitant use of these drugs, patients should be monitored for potentially excessive or prolonged CNS and respiratory depression. Ambulatory patients should be counseled to avoid hazardous activities requiring complete mental alertness and motor coordination until they know how these agents affect them, and to notify their physician if they experience excessive or prolonged CNS effects that interfere with their normal activities.

http://www.drugs.com/drug-interactions/duragesic_d00233_amiloride_d00169.html

duragesic and Amiloride Interactions

Interaction(s) found:

amiloride and fentanyl (Moderate Drug-Drug)
MONITOR: Many psychotherapeutic and CNS-active agents (e.g., anxiolytics, sedatives, hypnotics, antidepressants, antipsychotics, opioids, alcohol, muscle relaxants) exhibit hypotensive effects, especially during initiation of therapy and dose escalation. Coadministration with antihypertensive agents, in particular vasodilators and alpha-blockers, may result in additive effects on blood pressure and orthostasis.

MANAGEMENT: Caution is advised during coadministration of these agents. Close monitoring for development of hypotension is recommended. Patients should be advised to avoid rising abruptly from a sitting or recumbent position and to notify their physician if they experience dizziness, lightheadedness, syncope, orthostasis, or tachycardia.

http://www.netce.com/coursecontent.php?courseid=345

The most potent opioids are hydromorphone (Dilaudid) and fentanyl; neither drug should be given to an opioid-naïve patient. Hydromorphone, which is four times as potent as morphine, is available in immediate-release form. An extended-release form of hydromorphone was approved by the FDA in 2004; however, sales and marketing of the drug were suspended by the manufacturer in 2005 because of the potential for severe side effects when taken with alcohol [99] . Fentanyl is the strongest opioid (approximately 80 to 100 times the potency of morphine and is available as a transdermal drug-delivery system (Duragesic) [245] . Because peak delivery does not occur until 12 hours, an alternate analgesic must also be given initially. Transdermal fentanyl is helpful for patients who are unable (or unwilling) to take an oral opioid [174] . Because of its potency, fentanyl must be used with extreme care, as deaths have been associated with its use. Physicians must emphasize to patients and their families the importance of following prescribing information closely, and members of the healthcare team should monitor the use of the drug.

http://www.ohsu.edu/medicine/residency/handouts/pharmpearls/Pain%20Management/MorphineToFentanylPatch.pdf

CONVERTING MORPHINE TO FENTANYL PATCH

As a rule, all published opioid equianalgesic ratios should be thought of as a general reference guide to help avoid

gross under or over dosing. Once chosen, the calculated dose is just a starting point for upward or downward dose
titration.

IV Morphine Sulfate (MS) Fentanyl Transdermal Patch
If patients require less than 80mg oral morphine or 30 mg IV per day then even a 25mcg/hr patch may be 'too strong'
and cause side effects.
Fentanyl patches **are not** very helpful with unstable pain. Again it is good practice to use four hourly morphine in
this situation until analgesic requirements are steady and then convert morphine to the equivalent patch

1) Convert to 24 hr oral Morphine dose
2) Adjust for incomplete cross-tolerance with a 33-50% dose reduction
3) Convert adjusted dose to Fentanyl Transdermal Patch dose by dividing by 3.6 (the conversion factor
from **mg oral MS** to **mcg/hr Fentanyl Patch**) or 90 mg po morphine=25 mcg/hr *Fentanyl*
Transdermal Patch.
4) Round to closest Fentanyl Patch dosage form (25, 50, 75, 100 mcg/hr)
5) Provide oral morphine for break-through-pain at 10% of 24 hr opioid total

Example: Patient is receiving 100 mg IV Morphine sulfate and is going home on a
Fentanyl Patch. What do you prescribe for the Fentanyl Patch dose?

1) Convert to 24 hr oral MS dose
100mg/d IV MS = x_____ x = 300mg/d oral MS
10mg/d IV MS 30mg/d oral MS

2) Adjust for cross-tolerance
300mg/d oral MS x 0.65† = 200mg/d oral MS
†Deriving a 35% dose reduction is equivalent to multiplying by 0.65.

3) Convert adjusted dose to Fentanyl Transdermal Patch dose
200mg/d oral MS = 55mcg/hr Fentanyl Patch
3.6

4) Round to closest Fentanyl Patch dosage form (25, 50, 75, 100)
55mcg/hr ***50mcg/hr Fentanyl Patch***††
††
Replace patch every 3 days

5) Provide oral morphine q2-4h for break-through-pain at 10% of 24 hr opioid total
200mg/d oral MS x 0.10 = ***20mg oral MS q2-4h prn breakthrough pain***

Patient is receiving a 50mcg/hr Fentanyl Transdermal Patch
GENERAL GUIDELINES:
From PCA to transdermal: Apply the patch and continue ½ basal rate for 12 hours. Same PCA dose

From 12 hrs sustained release p.o. to transdermal: *apply patch and give last p.o. dose (this is because the patch takes*
8-12 hrs to achieve sufficient levels in the blood for a noticeable effect) and oral morphine q2-4h for break-through-
pain.
From immediate release p.o. to transdermal: *apply the patch and continue to give p.o. for the next*
3 dose
From transdermal to 12 hrs sustained release p.o.: *remove the patch and give the first p.o. dose*
after 8 hrs
From transdermal to immediate release: *remove patch and give p.o .after 12 hrs*

Ali Olyaei PharmD, 2005
Important Note: This document is a guideline, and not a policy statement. Always use clinical judgment when making decisions for an individual

http://www.duragesic.com/duragesic/

DURAGESIC® (fentanyl transdermal system) CII contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (DURAGESIC®) may be a particular target for abuse and diversion.

DURAGESIC® is indicated for management of <u>persistent</u>, moderate to severe chronic pain that:

- **Requires continuous, around-the-clock opioid administration for an extended period of time, and**
- **Cannot be managed by other means such as nonsteroidal analgesics, opioid combination products, or immediate-release opioids**

DURAGESIC® should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to DURAGESIC® 25 mcg/hr. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral

hydromorphone daily or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could occur, DURAGESIC® is contraindicated:

- In patients who are not opioid-tolerant
- In the management of acute pain or in patients who require opioid analgesia for a short period of time
- In the management of postoperative pain, including use after outpatient or day surgeries (e.g., tonsillectomies)
- In the management of mild pain
- In the management of intermittent pain (e.g., use on an as needed basis [p.r.n.])

(See CONTRAINDICATIONS section of the full Prescribing Information for further information.)

Since the peak fentanyl levels occur between 24 and 72 hours of treatment, prescribers should be aware that serious or life-threatening hypoventilation may occur, even in opioid-tolerant patients, during the initial application period.

The concomitant use of DURAGESIC® with all cytochrome P450 3A4 inhibitors such as (ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amiodarone, amprenavir, aprepitant diltazem, erythrocin, fluconazole, fosamprenavir, grapefruit juice, and verapamil) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving DURAGESIC® and any CYP3A4 inhibitors should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted. (See CLINICAL PHARMACOLOGY-Drug Interactions, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections of the full Prescribing Information for further information.)

The safety of DURAGESIC® has not been established in children under 2 years of age. DURAGESIC® should be administered to children only if they are opioid-tolerant and 2 years of age or older. (See PRECAUTIONS - Pediatric Use section of the full Prescribing Information.)

DURAGESIC® is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. Overestimating the DURAGESIC® dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean elimination half-life of 17 hours of DURAGESIC®, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

DURAGESIC® can be abused in a manner similar to other opioid agonists, legal or illicit. This risk should be considered when administering, prescribing, or dispensing.

http://www.lindencentre.org.uk/symptom/symptfset.htm

indications for choosing alternatives to morphine

1. When dose limiting side effects prevent titration to effective analgesic doses.

2. When intolerable CNS side effects develop during continuous use (e.g. agitation, delirium, myoclonic jerks, hallucinations and in extreme cases hyperalgesia and allodynia), which are unresponsive to dose reduction, or when dose reduction leads to increased pain.

3. When the patient is unable to swallow, and parenteral or rectal routes are inappropriate in that individual.

If pain is uncontrolled / escalating.

Oral hydromorphone or oxycodone permit dose titration.

If pain is stable.

In patients with malabsorption, dysphagia, poor compliance, renal impairment or resistant moderate-to-severe constipation, fentanyl patches are indicated.

Although comments on use in renal impairment are made in the following sections, always seek specialist advice before use.

The following alternative strong opioids are not in order of preference. Selection depends on the profile of the individual drug and suitability of available presentations. Seek specialist palliative care advice.

Fentanyl/ patch (Durogesic)

Reminder: Mersey Palliative Care Audit group has recommended oral morphine as the first line strong opioid in all cases.

The fentanyl patch provides a transdermal strong opioid.

Fentanyl patches will not help if oral morphine has failed, unless there is an absorption problem, or adverse effects prevented adequate doses from being given. Absorption of oral morphine is not usually a problem with the rapid onset presentations.

Patients using these patches require a rapid onset oral morphine preparation for breakthrough pain.

The patches are suitable only when pain is stable, not if rapidly changing.

Fentanyl patch presentations: Durogesic 25 (releasing approx. 25 micrograms/hour for 72 hours), and Durogesic 50, 75 & 100.

See Table 5 for dose conversion scheme.

Table 5: Dose Conversion: "Durogesic" patches

Note: these are only approximate. Patients must be titrated and monitored.

In strong-opioid naive patients, start with the lowest strength patch if unable to titrate to analgesia with an alternative opioid.

Onset is gradual, so evaluate the initial effect only after the first 24 hours. Phase out previous analgesic therapy gradually during this time e.g. continue 4hrly oral morphine for about 6-12 hours, or apply patch at same time as the last 12 hourly MR morphine dose, or 12- 18 hours after the last once daily MR morphine.

Carry out dose adjustments in 72-hour steps of "25 micrograms/hour". Many patients need a higher strength patch after the first three days. Remember to adjust the individual rescue dose if this occurs. More than one patch may be used at a time for doses greater than 100 micrograms/hour (apply at the same time to avoid confusion). Vary the site to rest the skin.

If pain relief does not last three days, some local practitioners have found that occasionally, patients do better changing the patch every two days. However, others prefer to increase to the next patch strength and assess response, and only try changing every two days if pain is still poorly controlled. There has also been local experience in two patients who were admitted on 48hrly changes but were still not pain controlled; measurement of fentanyl levels on day 3 showed that levels had not dropped, and the patients responded to a change in opioid. In view of these different experiences and practices, if pain relief does not last for the full three days seek specialist palliative care advice. Sudden escalation of pain always warrants reassessment of the pain syndrome.

Opioid withdrawal symptoms (such as colic, diarrhoea, nausea, sweating and

restlessness) may occur for a few days on switching to the fentanyl patch, even though pain is relieved. Treat with rescue doses of oral morphine *(see previous advice on Rescue Doses under MR morphine section).*

At doses above 300 micrograms/hour, consider additional or alternative analgesia.

Fentanyl is an option in renal impairment because there are no active metabolites. Dose reduction depends on renal function. Seek specialist advice.

Changing from fentanyl patches to MR oral morphine

Remove the patch about 12 hours before the first dose of MR oral morphine, to give time for residual levels in the skin to drop. Make sure rapid-onset oral morphine in a sufficient rescue dose is prescribed and available to be given during this time, if required.

Fentanyl patches and subcutaneous diamorphine infusion

1. If the patient is dying, continue using fentanyl patches as before. Use subcutaneous diamorphine when required as rescue medication. If this is needed regularly over 24 hours, give it by subcutaneous infusion using a syringe driver, in addition to the patch.

2. If the patient is not dying and there is some reason to remove the patch and convert to a syringe driver:

. The conversion from the patch, to diamorphine by subcutaneous infusion over 24hours, requires an intermediate step of calculating the patch

equivalent in terms of oral morphine/24hours. However, if the publicised dose conversion scheme is applied when switching in the direction from the patch to oral morphine, this may result in a larger dose than is actually required, even if the lower end of the morphine range is selected. Individual titration is essential. **Seek specialist palliative care advice. The following points are only intended to indicate the general approach.**

- Using the conversion scheme, convert the fentanyl patch dose to the equivalent 24 hour oral morphine dose. Use the lower end (or less) of the suggested equivalent range, as advised by the palliative care specialist.
- Divide this oral morphine dose by three to give the equivalent diamorphine dose for subcutaneous infusion over 24 hours.
- Start the syringe driver 12-18 hours after removing the patch.
- Make sure appropriate breakthrough analgesia is prescribed and available for the period of patch removal and after the syringe driver is set up.

Prescribing fentanyl patches

In addition to the usual Controlled Drug prescribing requirements, this is an example of the specific *fentanyl* details required for the prescription:

Fentanyl patch 25 microgram per hour

Supply 10 (ten) patches

One patch to be applied every 72 hours

CHLORPROMAZINE

http://www.the-shipman-inquiry.org.uk/fr_page.asp?id=105

The proprietary name for chlorpromazine is Largactil. Chlorpromazine is an anti-psychotic or neuroleptic drug, which has been in use for more than 25 years. It can be used to manage agitated states in the elderly and, since it suppresses nausea and potentiates the effects of other centrally acting depressant drugs, it has been much used in the treatment of the pain of terminal illness. It exists in tablet, elixir and injectable forms.

Dr Grieve, one of Shipman's partners in Todmorden, confirmed to the Inquiry that the doctors there used injectable chlorpromazine in the treatment of terminally ill patients, such as Mrs Lily Crossley, and there are references also to its use by Shipman during the Hyde years.

n 1974 to 1976, ampoules of chlorpromazine for injection contained either 25mg in 1ml of solution or 50mg in either 2ml or 5ml of solution. The recommended dosage was 25 to 50mg, to be repeated every 6 to 8 hours. Smaller dosages would be appropriate in the case of small, elderly or frail patients. The March 2001 British National Formulary refers to ampoules containing 25mg chlorpromazine in 2ml of solution.

The solution is given by deep intramuscular injection, into either the buttock or upper arm. It has irritant properties which would make intravenous injection painful and, to all intents and purposes, impracticable. While a massive overdose of chlorpromazine might be capable of directly causing death (for example, by inducing fatal cardiac arrhythmia), such an overdose would involve the injection of a substantial volume of fluid and I do not think that Shipman would ever have chosen to kill a patient by this method.

On the other hand, a smaller overdose of chlorpromazine could have an indirect lethal effect in very much the same way as might be achieved by a sublethal dose of morphine or diamorphine. A dose of 100mg chlorpromazine is not a lethal dose, but could contribute to a patient's death. The mechanism would be by suppression of the respiration, or of the protective cough reflex, of a frail person, especially where that person already had a chest infection or history of chronic obstructive pulmonary disease. Depending on the circumstances of the individual and the dosage given, death might ensue by this indirect mechanism after anything between a small number of hours and several days. The patient would go into a deep sleep quite soon after the giving of the injection, a sleep from which he or she might well not wake if death followed as an indirect result of the injection.

Other drugs exerting a comparable depressant effect on the respiration or central nervous system would include the anxiolytics, hypnotics and some of the more sedating anti-depressants and anti-histamines.

http://emc.medicines.org.uk/emc/assets/c/html/DisplayDoc.asp?DocumentID=804

Largactil should be avoided in patients with liver or renal dysfunction, Parkinson's disease, hypothyroidism, cardiac failure, phaeochromocytoma, myasthenia gravis and prostate hypertrophy. It should be avoided in patients known to be hypersensitive to phenothiazines or with a history of narrow angle glaucoma or agranulocytosis. It should be used with caution in the elderly, particularly during very

hot or cold weather (risk of hyper-, hypothermia). The elderly are particularly susceptible to postural hypotension.

http://www.merseycare.nhs.uk/Library/Services/Clinical_Services/Pharmacy/MI%20e-bulletin%20_Issue%20%209.pdf

Chlorpromazine Injection [Largactil® Injection]

Chlorpromazine injection is still available on the market but is not recommended because it can cause significant problems, e.g. severe postural hypotension, serious cardiac arrhythmias and it has been associated with reports of sudden death. The oral route of administration should be used.

http://www.drugs.com/mtm/thorazine.html

What is chlorpromazine?

Chlorpromazine is an anti-psychotic medication in a group of drugs called phenothiazines (FEEN-oh-THYE-a-zeens). It works by changing the actions of chemicals in your brain.

Chlorpromazine is used to treat psychotic disorders such as schizophrenia or manic-depression, and severe behavioral problems in children. It is also used to treat nausea and vomiting, anxiety before surgery, chronic hiccups, acute intermittent porphyria, and symptoms of tetanus.

Chlorpromazine may also be used for other purposes not listed in this medication guide.

What is the most important information I should know about chlorpromazine?

Stop using this medication and call your doctor at once if you have twitching or uncontrollable movements of your eyes, lips, tongue, face, arms, or legs. These could be early signs of dangerous side effects. Chlorpromazine is not for use in psychotic conditions related to dementia. Chlorpromazine may cause heart failure, sudden death, or pneumonia in older adults with dementia-related conditions. Do not use chlorpromazine if you have brain damage, bone marrow depression, or are also using large amounts of alcohol or medicines that make you sleepy. Do not use if you are allergic to chlorpromazine or other phenothiazines.

Before you take chlorpromazine, tell your doctor if you have liver or kidney disease, heart disease or high blood pressure, glaucoma, severe breathing problems, past or present breast cancer, low levels of calcium in your blood, adrenal gland tumor, enlarged prostate or urination problems, a history of seizures, Parkinson's disease, or if you have ever had a serious side effect while using chlorpromazine or similar

medicines.

Before taking chlorpromazine, tell your doctor about all other medications you use.

What should I discuss with my healthcare provider before taking chlorpromazine?

Chlorpromazine is not for use in psychotic conditions related to dementia. Chlorpromazine may cause heart failure, sudden death, or pneumonia in older adults with dementia-related conditions. Do not use chlorpromazine if you have brain damage, bone marrow depression, or are also using large amounts of alcohol or medicines that make you sleepy. Do not use if you are allergic to chlorpromazine or other phenothiazines such as fluphenazine (Permitil), perphenazine (Trilafon), prochlorperazine (Compazine, Compro), promethazine (Adgan, Pentazine, Phenergan), thioridazine (Mellaril), or trifluoperazine (Stelazine).

If you have certain conditions, you may need a dose adjustment or special tests to safely use this medication. Before you take chlorpromazine, tell your doctor if you have:

- liver or kidney disease;
- heart disease or high blood pressure;
- severe asthma, emphysema, or other breathing problem;
- glaucoma;
- past or present breast cancer;
- low levels of calcium in your blood (hypocalcemia);
- adrenal gland tumor (pheochromocytoma);
- an enlarged prostate or urination problems;
- a history of seizures;
- Parkinson's disease; or
- if you have ever had a serious side effect while using chlorpromazine or any other phenothiazine.

Tell your doctor if you will be exposed to extreme heat or cold, or to insecticide poisons while you are taking chlorpromazine.

It is not known whether chlorpromazine will harm an unborn baby. Chlorpromazine may cause side effects in a newborn if the mother takes the medication during pregnancy. Do not take this medication without first talking to your doctor if you are pregnant. Tell your doctor if you become pregnant while taking chlorpromazine.

Chlorpromazine can pass into breast milk and may harm a nursing baby. Do not use this medication without telling your doctor if you are breast-feeding a baby.

Talk with your doctor before giving this medication to a child who has been ill with a fever or flu symptoms.

Older adults may be more likely to have side effects from this medication.

Trimethoprim

About Trimethoprim

This belongs to the group of medicines known as *antibiotics.*

Trimethoprim is used to treat bacterial infections of the chest and urinary tract by killing or stopping the growth of the bacteria responsible.

Trimethoprim is available in tablet and liquid form.

It is also sometimes known as: *Monotrim; Trimopan*. You may notice the use of any of these names on the packaging of your medicine.

Before Taking Trimethoprim

Before taking any of this medicine make sure your doctor or pharmacist knows:

- if you are pregnant, trying for a baby or breast-feeding
- if you suffer from kidney problems
- if you suffer from a blood disorder or porphyria
- if you have ever had an allergic reaction to this or **any** other medicine

if you are taking **any** other medicines, including those available to buy without a prescription, herbal or complementary medicines

http://www.bmj.com/cgi/content/full/308/6926/454/b

DRUG POINTS:Hyperkalaemia and non-oliguric renal failure associated with trimethoprim

G W Smith, S B Cohen

Fazakerley Hospital, Liverpool L9 7AL.

Hyperkalaemia and non-oliguric renal failure associated with trimethoprim

Drs G W Smith and S B Cohen (Fazakerley Hospital, Liverpool L9 7AL) write: A 79 year old woman was admitted with urinary frequency and suprapubic pain. Her usual treatment was mesalazine, diphenoxylate, prednisolone, cimetidine, and diclofenac for Crohn's disease and osteoarthritis. Trimethoprim 200 mg twice daily was started to treat a urinary tract infection.

On admission her serum urea and electrolyte concentrations were normal. Four days later they were deranged: potassium concentration was 7.0 mmol/l, urea concentration 16.0 mmol/l, serum creatinine concentration 225 µmol/l. Arterial blood gases showed mild metabolic acidosis. An electrocardiogram appeared normal. All

drugs were stopped and standard measures taken to lower serum potassium concentration. Trimethoprim was replaced by ampicillin in reduced dose. Urine output was 1.5 1/day and kidneys were of normal size on ultrasonography. Seventy two hours later potassium concentration was 4.3 mmol/l, urea concentration 8.5 mmol/l, and serum creatinine concentration 85 µmol/l. Mesalazine and diphenoxylate were not given again, and she was discharged taking prednisolone and diclofenac. Her renal function remains normal.

Renal failure is not a recognised side effect of trimethoprim, although manufacturers advise caution when treating elderly people and people with impaired renal function. Our patient developed hyperkalaemia with non-oliguric renal failure shortly after starting trimethoprim. After stopping the drug and treating the hyperkalaemia the results of serum biochemistry returned to normal.

Renal failure has been reported with trimethoprim in combination with sulphamethoxazole (cotrimoxazole). Trimethoprim can also reversibly increase serum creatinine concentration and reduce creatinine clearance without decreasing glomerular filtration rate both in people with normal renal function and in those with renal allografts.[1,2] Trimethoprim alone can cause an important but reversible increase in serum creatinine concentration in acute uncomplicated cystitis and in chronic renal failure.[3,4] The mechanism is probably competitive inhibition of tubular secretion of creatinine and does not signify a deterioration in renal function. Non -steroidal inflammatory drugs including diclofenac can cause both renal failure and hyperkalaemia, but in this case timing strongly implicated trimethoprim. Indeed, renal function remained stable when diclofenac was given again.

Three cases of renal failure and one of deterioration in renal function associated with trimethoprim have been reported to the Committee on Safety of Medicines (personal communication).

http://books.google.co.uk/books?id=0Bw2UJTC_uMC&pg=PA628&lpg=PA628&dq=trimethoprim+increase+creatinine&source=web&ots=W56mAuopTD&sig=IjtKv18TFuhZgPCVKx8S62ZcSLw&hl=en&sa=X&oi=book_result&resnum=3&ct=result#PPA167,M1

Potassium-sparing diuretics (amiloride) increased risk of hyperkalemia

http://www.kidney.org/professionals/KLS/GFR.cfm#18

18) What factors affect creatinine secretion?

Some medications, including trimethoprim, cimetidine and some older cephalosporins, inhibit tubular secretion of creatinine, thereby decreasing creatinine clearance and increasing serum creatinine without a change in GFR.

http://www.patient.co.uk/showdoc/30002970/

Thioridazine

About Thioridazine

This belongs to the group of medicines known as *neuroleptics*.

Thioridazine is used to treat schizophrenia.

Thioridazine is effective in helping symptoms such as hearing voices, loss of energy, thought disturbances and difficulties communicating with others as well as other symptoms of schizophrenia.

Thioridazine is available in tablet and oral liquid form.

It is also sometimes known as: *Melleril*. You may notice the use of any of these names on the packaging of your medicine.

Before taking Thioridazine

Before taking Thioridazine make sure your doctor or pharmacist knows:

- if you are pregnant, trying for a baby or breast-feeding
- if you suffer from **any** heart problems or anyone in your immediate family has suffered from heart problems
- if you suffer from kidney, liver or breathing problems
- if you suffer from Parkinson's disease or *myasthenia gravis* (a muscle weakening disease),
- if you suffer from *epilepsy*, *porphyria* (a blood disorder), *phaeochromocytoma* (a growth on the adrenal glands), an under active thyroid gland or prostate problems
- if you suffer from glaucoma
- if you have ever had an allergic reaction to this or **any** other medicine
- if you are taking **any** other medicines, including those available to buy without a prescription, herbal and complementary medicines

How to take Thioridazine

- Take Thioridazine exactly as directed by you doctor.
- Always read the manufacturer's information leaflet, if possible before beginning treatment.
- Try to take Thioridazine at the same times each day to avoid missing any doses.
- You may have to take Thioridazine for several weeks before you begin to feel better.
- **Do not** stop taking Thioridazine without speaking to your doctor first. Stopping this medicine suddenly is likely to cause problems such as sickness, diarrhoea and dizziness.
- Never take more than the prescribed dose. If you suspect that you or someone else has taken an overdose of Thioridazine contact your doctor or go to the accident and emergency department of your local hospital at once. Try to

take the container with you, even if it is empty.

- This medicine is for you. Never give it to others even if their condition appears to be the same as yours.

Getting the most from your treatment

- Before taking any 'over-the-counter' medicines, check with your pharmacist which medicines are safe for you to take alongside Thioridazine.
- Keep your regular appointments with your doctor so that your progress can be checked. Your doctor will probably want to carry out an *Electrocardiograph* (ECG) - an electrical check of the heart - during your treatment.
- Thioridazine may cause drowsiness, blurred vision or dizziness. Make sure you know how Thioridazine affects you before driving, operating machinery, or doing other jobs that could be dangerous if you were not fully alert or able to see well.
- Try to avoid drinking alcohol whilst you are taking Thioridazine. Alcohol will increase any feelings of drowsiness. If you do drink alcohol, drink only a little and be aware of its effects on you.
- Before having any surgery, including dental or emergency treatment, tell the doctor, dentist or surgeon that you are taking Thioridazine.
- Dizziness, light-headedness or fainting may occur, especially when you get up from a lying or sitting position. Getting up slowly may help. If the problem continues or gets worse then speak with your doctor.
- Thioridazine may cause you to sweat less, causing your body temperature to increase. Take extra care not to become overheated during exercise or hot weather.
- Thioridazine may cause some people's skin to become more sensitive to the sun. Avoid strong sunlight and sun beds whilst taking Thioridazine and use a sun block higher than factor 15.
- Thioridazine can cause dryness of the mouth. If you experience this try sucking sugar-free sweets, pieces of ice or chewing sugar-free gum. If a dry mouth becomes too troublesome, discuss the problem with your doctor or pharmacist.

Can Thioridazine cause problems?

Along with their useful effects all medicines can cause unwanted side effects. These usually improve as your body adjusts to the new medicine. Speak with your doctor or pharmacist if any of the following side effects become troublesome.

Drowsiness, dizziness, confusion, headaches, shakiness and muscle stiffness, trouble sleeping, dry mouth, blurred vision, feeling or being sick, diarrhoea, constipation, loss of appetite, difficulty passing water, irregular menstrual periods, sexual problems, skin rashes, unintentional movements, feeling slow, agitation, a *fever* (high temperature) or uncontrollable movements of the tongue, face and jaw.

IMPORTANT: If you experience a fast/fluttering heartbeat, breathlessness, fainting or pains in the chest contact your doctor **immediately.**

IMPORTANT: If you experience 'flu like' symptoms such as stiffness, high temperature, abnormal paleness, leaking bladder and a racing heartbeat contact your doctor or go to the accident and emergency department of your local hospital **immediately.**

IMPORTANT: If you have problems with your eyesight such as blurring, everything having a brownish colouring or problems seeing at night, speak with your doctor **as soon as possible.**

If you experience any other worrying symptoms, which you think may be due to this medicine, discuss them with your doctor or pharmacist.

How to store Thioridazine

- Keep out of the reach of children.
- Store in a cool, dry place, away from direct light and heat.
- Do not keep any out of date or unwanted medicines. Discard them safely out of the reach of children or take them to your pharmacist who will dispose of them for you.

www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019553&RevisionSelectionMethod=LatestReleased

4.3 Contra-indications

Thioridazine is contra-indicated in patients with:

- Uncorrected hypokalaemia or hypomagnesaemia
- Comatose states, dementia and severe depression of the CNS.

4.4 Special Warnings and Precautions for Use.

It is advisable to avoid the use of thioridazine in patients with other risk factors known to predict for or aggravate arrhythmia, for example, those who have clinically significant heart disease (cardiomyopathy, congestive cardiac failure, ischaemic heart disease), a family history of sudden death, patients with electrolyte disturbances (as seen in patients taking potassium-wasting diuretics or in association with the administration of insulin in acute settings or in patients with persistent vomiting and/or chronic diarrhoea or renal failure), altered nutritional states and cerebrovascular accidents. (See Section 4.3: Contra-indications).

Before commencing treatment with thioridazine, baseline ECG should be performed and serum calcium, magnesium and potassium levels measured and corrected in all patients. Patients with a QTc interval greater than 450 msec in males and greater than 470 msec in females should not receive thioridazine. ECG should be monitored before each dose increase, a week following the maximum therapeutic dose being reached and at 6 monthly intervals.

Neuroleptic Malignant Syndrome (NMS): This syndrome has been reported in very rare cases in association with thioridazine. NMS is a potentially fatal disorder characterized by muscular rigidity, hyperthermia, altered consciousness and autonomic dysfunction (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

In cases where NMS develops and in patients with unexplained high fever

without additional clinical manifestations of NMS, thioridazine must be discontinued.

4.5 Interactions with Other Medicaments and Other Forms of Interaction
Pharmacokinetic interactions
Cytochrome P450 2D6 metabolism: Thioridazine is metabolised by P450 2D6 and is itself an inhibitor of this drug metabolising enzyme. The plasma concentrations and the effects of thioridazine may therefore be increased and prolonged by drugs that are either the substrates and/or inhibitors of this P450 isoform, possibly resulting in severe hypotension, cardiac arrhythmias or CNS side effect. Examples of drugs which are substrates or inhibitors of cytochrome P450 2D6 include anti-arrhythmics, certain antidepressants including SSRIs, and tricyclics, certain antipsychotics, ß-blockers, protease inhibitors, opiates, and ecstasy (MDMA). This list is not exhaustive.

This list would include: Chlopromazine and temazapan

Other side effects:

Even in low dosage, in susceptible (especially non-psychotic) individuals, thioridazine may cause feelings of being mentally dulled or slowed down, nausea, dizziness, headache or paradoxical effects of excitement, agitation or insomnia. Confusional states or epileptic fits can occur.

http://www.patient.co.uk/reference/Antipsychotics.htm

Neuroleptic Malignant Syndrome
The triad of:3

- Rigidity
- Hyperthermia
- Autonomic instability e.g. hypertension, tachycardia and sweating

Often associated with fluctuating conscious level and a rise in creatinine kinase (usually in the thousands). Develops over 24 -72 hours and is potentially fatal.□

□**Management:**

- Urgent admission
- Stop antipsychotic
- Supportive therapy for fever and dehydration and nutrition
- Dopamine agonists have been used to accelerate reversal e.g. bromocriptine (but hypotension limits its use)
- Dantrolene has also been used (inhibits calcium release)
- Usually lasts 5 - 7 days, may be longer with depot preparations

Once patient recovered can initiate a new antipsychotic (probably best under specialist supervision), but must start at very low doses and be very cautious for recurrence of neuroleptic malignant syndrome.

http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1305729&blobtype=pdf

Thioridazine is not more effective than placebo or other neuroleptic drugs for improving the behavioral, global dinical, or cognitive states of elderly patients with dementia. Thioridazine reduced anxiety only when compared with placebo or diazepam and led to worsened behavioral scores and increased dizziness when compared with chlormethiazole.

http://www.umm.edu/altmed/drugs/midazolam-087200.htm#Warnings/Precautions

Midazolam

Warnings/Precautions

May cause severe respiratory depression, respiratory arrest, or apnea. Use with extreme caution, particularly in noncritical care settings. Appropriate resuscitative equipment and qualified personnel must be available for administration and monitoring. Initial dosing must be cautiously titrated and individualized, particularly in elderly or debilitated patients, patients with hepatic impairment (including alcoholics), or in renal impairment, particularly if other CNS depressants (including opiates) are used concurrently. Initial doses in elderly or debilitated patients should not exceed 2.5 mg. Use with caution in patients with respiratory disease or impaired gag reflex. Use during upper airway procedures may increase risk of hypoventilation. Prolonged responses have been noted following extended administration by continuous infusion (possibly due to metabolite accumulation) or in the presence of drugs which inhibit midazolam metabolism.