

Prescribing and Clinical Effectiveness Bulletin

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USE OF UNLICENSED PHARMACEUTICAL 'SPECIALS'

What are pharmaceutical 'specials'?

A pharmaceutical 'special' as defined by law is a medicine made to satisfy an individual patient need. Most 'specials' are oral liquids made to order for adult patients unable to take tablets or capsules; other types of specials include oral liquids made for children and specially formulated ointments, creams and ophthalmic preparations.

Specials are unlicensed medicines made in pharmacies or, more commonly, in specialised manufacturing units. **Because of low production volumes, specials tend to be very expensive, typically costing over £100 for one bottle.** They may have short shelf lives (e.g. 7 days) and may need refrigerated storage.

Why has prescribing of 'specials' become an issue?

Prescribing expenditure on 'specials' in Lincolnshire primary care is in excess of £1.9M p.a.; in the last 2 years, it has increased from approximately £100,000 per month to in excess of £150,000 per month. This appears to be driven by an increase in the cost of specials, rather than an increase in the volume of use.

Specials manufacturers can set any price for these products with a large variation in cost for the same items depending on the supplier and the method of procurement (see example box below).

Example: Omeprazole liquid special 20mg in 5ml

In the 4 months from January – April 2010 NHS Lincolnshire spent in excess of £22K on 82 items of omeprazole liquid special 20mg in 5ml. The item size ranged from 60ml to 300ml. The price charged to the PCT ranged from £0.39 to £4.96 per ml with a mean cost of £1.67 per ml. The highest price paid for one prescription of this 'special' was £743.46 for 150ml! While recognising that some individuals may need to be treated with omeprazole 20mg in 5ml as a 'special' product, there are a number of licensed alternatives that might be suitable for use in some patients (e.g. omeprazole (MUPs) dispersible tablets 10 and 20mg, lansoprazole orodispersible tablets 15mg and 30mg, ranitidine syrup SF 75mg in 5ml and ranitidine effervescent tablets 150mg).

Recent EPACT monitoring for January to April 2010 reveals one prescription for a liquid special which cost in excess of £13,000!

What are the implications of 'specials' being unlicensed?

With the exception of pharmacies, special medicines should be manufactured by a supplier who has a specials manufacturing license. This means that the facilities must meet a minimum standard. It does not mean that the product is licensed in any way or that it will meet the same quality standards as a licensed alternative. The amount of patient information provided with 'specials' varies significantly as does the level of stability testing. There is rarely a common recipe for a special followed uniformly by different manufacturers; as a result, the same medicine is likely to be formulated differently depending on the manufacturer. There are anecdotal cases of harm associated with differences in formulations (e.g. poor suspension of clobazam resulting in seizures due to inadequate dosing).

When writing a prescription for a 'special', it is difficult for a prescriber to have reassurance on the level of the quality of the product. Prescribers of unlicensed products are responsible for their use (unless the product is faulty) and are professionally accountable for their judgement in so doing. In the case of adverse events, prescribers may be called upon to justify their actions.

What are the alternatives to using 'specials'?

Alternatives include:

- 1. Using a licensed alternative of the same medicine (e.g. a liquid preparation or a soluble tablet or powders/granules for suspension).**
- 2. Using an alternative medicine from the same class in a formulation more convenient for the patient (e.g. licensed fluoxetine 20mg in 5ml oral solution rather than an unlicensed special of an alternative SSRI).**
- 3. Using a licensed medicine in an unlicensed way (e.g. crushing or dispersing tablets).**
- 4. Using a medicine that is unlicensed in the UK but is licensed in another country.**

Medico-legally, all of these alternatives are associated with a lower risk than prescribing an unlicensed special. There is considerable evidence based on custom and practice that some medicines can be administered in an unlicensed manner without compromising the effectiveness of the medicine. To support prescribers an appendix to this bulletin contains information on commonly prescribed specials and alternative preparations that *may* be suitable for consideration.

Prescribers are reminded that not all preparations are suitable for crushing or dispersing e.g. enteric coated, modified release, cytotoxic, antibiotic and hormonal drugs should not usually be crushed. Similarly sublingual or buccal tablets should not usually be crushed as this might reduce their bioavailability. Chewable tablets should not be crushed or dispersed unless there is specific information to the contrary because some chewable preparations are designed so that a proportion of the drug is absorbed in the mouth (e.g. Tegretol Chewtabs).

Care staff in nursing or residential care may only administer medicines in an unlicensed manner on the specific instructions of the prescriber; to facilitate this a written direction must be documented in the patient's care plan.

Monitoring of prescribing data reveals that it is relatively common for an unlicensed special to be prescribed even where a licensed alternative is available.

Example: Levothyroxine oral liquid

Despite the fact that levothyroxine is available as a licensed oral liquid in a range of different strengths, there have been a number of prescriptions for liquid levothyroxine specials in the last quarter. This is probably a consequence of the difficulty distinguishing licensed liquid preparations from 'specials' on some GP clinical systems. SystmOne identifies specials with icons for 'special order products' and 'unlicensed products' and attaches a note with 'cost warning' to these products. EMIS systems do not currently highlight special order products.

PACEF Recommendations:

- (1) Wherever a licensed preparation is available, it should be used in preference to a special-order product.
- (2) If there is no suitable licensed preparation, consider using a licensed medicine in an unlicensed manner, for example by crushing tablets or opening capsules. Where this is not possible, consider switching to a different agent in the same class.
- (3) If none of these options are viable, consider using a 'special' as a last resort.
- (4) Patients (or their carers) receiving an unlicensed medicine should be informed and their consent obtained.
- (5) Prescribers should ensure that the continued prescription of a 'special' is reviewed and justified for the individual patient.
- (6) Prescriptions for liquid specials should always be given in 'milligrams' rather than 'mls' to avoid confusion – there may be a number of different strengths available.
- (7) The Prescribing and Medicines Management Team are currently working with individual practices to help to identify inappropriate prescribing of 'specials' and to recommend appropriate alternatives. If you have any queries about a particular special or need advice on possible alternatives in a particular situation do not hesitate to contact your local prescribing adviser.

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Appendix: Alternatives to Special Order products

The following alternatives are suggestions and may be inappropriate for some patients (e.g. young children requiring small doses and those who are unable to manipulate medicines). It will not be possible to always avoid using a special.

If a tablet is crushed or dispersed in water, or a capsule opened, clear instructions should be given. In most cases the product becomes 'unlicensed' but the use of a licensed product in an unlicensed way is probably associated with a lower risk than using an unlicensed special.

Any manipulation of tablets or capsules should be done immediately before administration. Dispersal of tablets in water may take several minutes. Unless there are specific instructions to the contrary when dispersing tablets this should be done in a small volume of water (≈ 10 mls), using a medicine administration pot or egg cup. Do not use boiling water to try to encourage dispersal of tablets as this might degrade the drug. Crushed tablets may be mixed with a teaspoon of cold food to mask the taste and for ease of swallowing.

Care staff may only crush or disperse tablets or open capsules on the instruction of the prescriber. A written direction must be documented in the patient's care plan.

'Special order' product & average cost per item	Possible alternatives & approximate cost for 28 days
Allopurinol 100mg or 300mg / 5ml liquid special (£220)	Tablets may be crushed. Allopurinol is insoluble in water but tablets will disperse if shaken in ≈ 10 mls water to produce a milky suspension (£2)
Amiodarone 200mg / 5ml liquid special (£250)	Tablets may be crushed; taste is very bitter. Mix with jam if taken orally (£3).
Amisulpiride 25mg / 5ml liquid special (£155)	A licensed solution (100mg/ml) is available (Solian) and comes with a dosing pipette allowing 50mg (0.5ml) to be accurately measured (£30)
Amitriptyline HCl liquid special 10mg in 5ml (£50)	A licensed solution containing 25mg in 5ml or 50mg in 5ml is available (£20). Consider the use of 12.5mg (2.5ml) using an oral syringe.
Amlodipine 5mg or 10mg / 5ml liquid special (£160)	Tablets may be crushed. They readily disperse in water (£2)
Atorvastatin liquid specials (£230)	Tablets may be crushed. Tablets will disperse slowly in ≈ 10 mls water to produce a fine milky suspension (£25). Light sensitive; do not delay administration.
Azathioprine 25mg or 50mg or 125mg in 5ml (£135)	Cytotoxic – do not crush. Tablets are usually film coated and will disperse in ≈ 10 mls water within 5 minutes to give a yellow milky dispersion (£10).
Bendrofluazide 2.5mg / 5ml liquid special (£130)	Tablets may be crushed or dispersed in water to produce a milky suspension (£1).
Bisoprolol fumarate 2.5mg or 5mg or 7.5mg in 5ml (£120)	Some brands are film coated but may be crushed. Some patient information leaflets may advise against crushing or chewing presumably because of the film coating. They disperse in water to produce a fine suspension (£10).
Captopril 25mg / 5ml liquid special (£140)	Tablets (12.5mg, 25mg & 50mg) can be crushed or will disperse readily in water (£2). Use of a liquid special may be required for accurate administration of paediatric doses.

'Special order' product & average cost per item	Possible alternatives & approximate cost for 28 days
Carbimazole 5mg or 10mg in 5ml (£150)	Tablets can be crushed (the active drug is contained within the central core of the tablet; the coloured compression coat is inert). Tablets will disperse in water only with vigorous shaking to produce a fine dispersion (£12).
Chloral hydrate liquid special 200mg / 5ml (chloral elixir, paediatric) or 500mg / 5ml (chloral mixture) (£110)	A licensed elixir is available (Welldorm) containing 143.3mg/5ml (£10)
Clobazam liquid special, 10mg / 5ml (£215)	Tablets (10mg) can be crushed or dispersed in water (£5).
Clonazepam 2.5mg /ml, 2mg /5ml and 500mcg / 5ml liquid special (£165)	Tablets (500 mcg and 2mg tablets) can be crushed or will disperse in water within 5 minutes to produce a coarse dispersion (£5)
Co-careldopa liquid special 25mg/100mg in 5ml liquid special (£150)	Consider changing to co-beneldopa dispersible tablets, (co-beneldopa 25/100, Madopar Dispersible tablets 125 or co-beneldopa 12.5/50, Madopar Dispersible 62.5). Non-MR Sinemet tablets (co-careldopa) disperse readily in ≈ 10mls water. Take care to administer the whole dose; there is a tendency for settlement to the bottom of the container or syringe.
Co-dydramol liquid special 10/500 in 5ml (£230)	Consider use of co-codamol 8/500 dispersible tablets (high sodium content). Licensed liquid preparations of dihydrocodeine (10mg in 5ml) and paracetamol are available.
Dantrolene sodium liquid special 25mg / 5ml (£160)	Open capsules (25mg) and mix contents with orange juice (to maintain acidity). Take immediately (£20).
Diazepam oral solution 2.5mg / 5ml or 10mg / 5ml (£45)	Licensed solution contains 2mg / 5ml or 5mg / 5ml (£10)
Diltiazem HCl liquid special 60mg / 5ml (£155)	Consider whether amlodipine tablets can be used in place of diltiazem. 60mg MR tablets designed for dosing three times a day may be crushed although this is likely to affect the pharmacokinetics, it is unlikely to cause adverse effects (£3). Slozem capsules (once daily) may be opened and the pellets taken with soft food without crushing. Pellets may block smaller sized tubes.
Diltiazem 2% cream (£120)	Anoheal brand of diltiazem 2% cream is lower cost. It is unlicensed, available directly from SLA Pharm 01923 681001, 2 day order to delivery schedule & 18 month shelf life (£50).
Dipyridamole liquid special 100mg or 200mg in 5ml (£266)	Licensed liquid preparation contains 50mg in 5ml (£40 for 150mls). For stroke prevention, open MR capsules and mix granules with yoghurt or similar cold food. Do not crush granules. Granules may block tubes (£10).
Doxazosin mesilate 1mg / 5ml, 2mg / 5ml & 4mg / 5ml (£220)	Non-MR tablets can be crushed or they can be dispersed in ≈ 10ml water to give a coarse dispersion (£2).
Enalapril 5mg in 5ml liquid special (£195)	Tablets can be crushed or dispersed in water to create a fine suspension (£2).

'Special order' product & average cost per item	Possible alternatives & approximate cost for 28 days
Ferrous sulphate liquid special 60mg in 5ml (£130)	Licensed iron preparations available e.g. Fersamel syrup (ferrous fumarate 140mg (45mg iron) / 5ml (if for tube administration dilute with an equal volume of water to reduce viscosity). Ironorm Drops (ferrous sulphate 125mg (25mg iron) /ml, etc.
Folic acid liquid special 5mg/5ml (£100)	Licensed preparation contains 2.5mg / 5ml (£10)
Gabapentin liquid special 250mg or 500mg or 600mg in 5ml (£330)	Capsules can be opened (100mg, 300mg or 400mg) and contents dissolved in water and taken immediately (£10). 100mg caps are fiddly due to small size.
Gliclazide 40 or 80mg in 5ml (£175)	Non-MR tablets can be crushed (£4)
Glyceryl trinitrate ointment 0.2% (£165)	Glyceryl trinitrate ointment 0.4% (Rectogesic) is licensed (£35)
Hydrocortisone 10mg in 5ml (£125)	10mg or 20mg tablets can be crushed and mixed with food. They will disintegrate readily in water. Hydrocortisone 10mg tablets are scored (£45).
Isosorbide mononitrate liquid special 20mg in 5ml (£195)	Non-MR tablets can be crushed (£2).
Levothyroxine liquid specials (£105)	Licensed solutions are available (25mcg, 50mcg and 100mcg in 5ml £50). Tablets can be crushed or dispersed in water (£3).
Lisinopril liquid special (£100)	Tablets can be dispersed in water to give a fine dispersion or they can be crushed and taken with food (£2).
Lorazepam liquid special (£145)	1mg and 2.5mg tablets can be crushed or dispersed in water. Tablets can also be administered sublingually (£10)
Magnesium glycerophosphate tablets 97.2mg (£40 for 50 tabs)	Magnaphate 4mmol tablets (4mmols equal to 97.2mg of magnesium and 1g of magnesium glycerophosphate; tabs may be chewed or swallowed whole & are scored so they can be broken into quarters. Available from Arjun products). (£20 for 50 tabs).
Meloxicam liquid special (£220)	Tablets are film coated but will disperse in water to give a clear suspension with a virtually neutral taste (£2). Suppositories are available (£10).
Metformin liquid special (500mg in 5ml) (£75)	500mg or 1g sachets are available as a licensed product (Glucophage). This is the lowest cost option for patients with swallowing difficulties (Note: sachets should be taken in 150ml water) or a licensed oral liquid 500mg in 5ml is available, £62 for 100ml.
Methyldopa liquid special 250mg in 5ml (£105)	Tablets can be crushed and dispersed in water for oral administration; unsuitable for tube administration because the tablet coating may not dissolve and may block the tube (£10)
Midazolam liquid special 10mg / ml (buccal or oromucosal) (£190)	Midazolam buccal liquid 10mg/ml x 4 doses (5ml) (Epistatus) is an unlicensed product that has been approved in Lincolnshire for the emergency treatment of status epilepticus after specialist initiation. Prescribing by brand name (Epistatus) may reduce costs (approximately £65 inc. carriage, if purchased direct from Special Products Ltd; the cost via a wholesaler may be greater). Epistatus has a long shelf-life and its stability is unaffected after opening.

'Special order' product & average cost per item	Possible alternatives & approximate cost for 28 days
Omeprazole liquid special 10mg or 20mg in 5ml (£270)	MUPS dispersible tablets disintegrate to give a dispersion of small granules (may block fine bore feeding tubes <8Fr). Do not crush or chew dispersible tablets (£12). Omeprazole capsules may be opened and sprinkled on food or jam but the granules must not be crushed (£2) Consider lansoprazole orodispersible tablets as a possible alternative.
Ondansetron liquid special 4mg in 5ml (£55)	A licensed ondansetron syrup SF 4mg/5ml is available (contains sorbitol) (£35). Zofran Melt (oral lyophilisates) can be allowed to disperse on the tongue and swallowed (£35). Plain tablets will disperse slowly in water (£23)
Paracetamol liquid special 500mg in 5ml (£85)	Use paracetamol dispersible tablets or paracetamol 250mg/5ml suspension.
Phenytoin liquid special 90mg in 5ml (£85)	Licensed phenytoin liquid contains 30mg / 5ml (£5)
Pregabalin 75mg in 5ml liquid special (£175)	Capsules can be opened and contents mixed with water or food (unpleasant taste) (£65)
Quetiapine liquid special (£280)	Non-MR tablets can be crushed and mixed into soft food. Bitter taste, yoghurt is the best vehicle (£34 – £170)
Ramipril liquid specials (£150)	Tablets disperse within 2 – 5minutes in water to give a fine dispersion which settles quickly but may be flushed down an 8Fr NG tube. Ramipril capsules can be opened and mixed with food or water (£2)
Riluzole liquid special 50mg in 5ml (£900)	The tablets are film coated but can be crushed and mixed with water or food. Use within 15 minutes (£280)
Rosuvastatin liquid specials (£370)	The tablets are film coated and will disperse in water within 5 minutes to give a pale pink, milky dispersion that flushes down an 8Fr NG tube without blockage (£30)
Sertraline liquid special 50mg in 5ml (£190)	Film coated tablets that are difficult to disperse or crush. Consider changing to an alternative SSRI available as a liquid preparation (e.g. citalopram 40mg/ml oral drops £18, or fluoxetine 20mg in 5ml, £5)
Sildenafil liquid special 25mg/5ml (£475)	Tablets can be crushed and dispersed in water or mixed with food. Use of a liquid special may be required for accurate administration of paediatric doses (£20).
Simvastatin liquid specials 20mg or 40mg in 5ml (£230)	Simvastatin tablets slowly disperse in water or may be crushed. Licensed preparations of simvastatin liquid are now available from Rosemont containing 20mg in 5ml (£100 for 150mls) and 40mg in 5mls (£150 for 150mls)
Sodium bicarbonate liquid special 420mg/5ml (8.4%) (£55 for 100mls)	SodiBic 1mmol/ml (8.4%, 420mg/5ml) oral solution, preservative free from Arjun Products (£15 for 100mls).
Spironolactone liquid specials 25mg or 50mg in 5ml (£140)	Tablets can be crushed and will disperse in water (£3).
Terbinafine 250mg in 5ml liquid special (£650)	Tablets can be crushed and will disperse in water (£5).
Tolterodine liquid special 1mg or 2mg in 5ml (£265)	Non-MR tablets are film coated and can be crushed and mixed with water or food. They will disperse in water but tolterodine is relatively insoluble (£30).
Venlafaxine liquid special 37.5mg or 75mg in 5ml (£130)	Non-MR venlafaxine tablets may be crushed and taken with food. They will disperse slowly in water, but may require shaking (particularly 75mg tablet) (£5).

'Special order' product & average cost per item	Possible alternatives & approximate cost for 28 days
Warfarin liquid special (£145)	Tablets may be crushed and taken with food. Most brands of tablets will disperse in water within 5 minutes if shaken (£2).
Zopiclone liquid special (£160)	Do not crush zopiclone tablets (they are difficult to crush, taste very bitter and the bioavailability may be affected). Consider temazepam oral liquid 10mg in 5ml (£30 - 300mls)

References

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Pharmacy Department, Medicines Information, Royal Cornwall Hospitals. Guidance on the administration of drugs via enteral feeding tubes, February 2009.

NHS Lincolnshire PACE Bulletin 2009; 3(2): 2. Buccal Midazolam

Prices of specials are average prices paid by NHS Lincolnshire from EPACT data Q1 10 – 11.

Prices of other drugs are approximations given for comparative purposes only, taken from Drug Tariff October 2010 and Chemist & Druggist accessed 15th October 2010.