

# NEWSLETTER

Supporting the Derbyshire Health Community

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## JAPC Update

The Joint Area Prescribing Committee (JAPC) is a countywide group covering Derbyshire County PCT and Derby City PCT. It provides recommendations on drugs and medicines management issues.

RED drugs are those where prescribing responsibility lies with a hospital consultant or a specialist. AMBER drugs are those that are initiated within a hospital/specialist setting but are suitable for shared care with a GP under a shared care agreement. GREEN drugs are regarded as suitable for primary care prescribing. BROWN drugs are those that JAPC does not recommend for use, except in exceptional circumstances, due to lack of data on safety, effectiveness, and/or cost-effectiveness.

The most recent updates are in the table below; the full list is available at

<http://www.derbyshirecountypct.nhs.uk/guidelines/default.asp>

The guidelines, formulary chapters, newsletters, etc can now be found via this link.

Drug	Date considered	Decision
Bicalutamide 50mg/150mg tabs	April 2009	AMBER (with Derby hospitals)
Melatonin	April 2009	AMBER
U500 Humulin R insulin	April 2009	RED
Fentanyl patch/tablet/lozenge	March 2009	GREEN (third-line use only)
Fluticasone furoate nasal spray (Avamys)	March 2009	BROWN
Ranolazine	March 2009	BROWN
Tadalafil 2.5mg and 5mg tablets (Cialis once-a-day)	March 2009	BROWN
Targinact (oxycodone + naloxone)	March 2009	BROWN
NuvaRing	March 2009	RED
Lacosamide	February 2009	RED
Ropinirole XL	February 2009	GREEN (only on consultant recommendation)

## NuvaRing

NuvaRing is a new form of contraceptive. It is a flexible, transparent ring made of EVA and contains the estrogen ethinylestradiol and the progestogen etonogestrel. It is inserted in the vagina and has once-a-month administration. The monthly cost is £9.

JAPC has designated NuvaRing as a RED drug, only for use by the Contraceptive and Sexual Health Service. It will be reserved for when other methods of contraception have proved unacceptable. The agreed criteria are:

- Malabsorption, bowel disease or eating disorders causing vomiting
- Intermittent antibiotic use e.g. cystic fibrosis, severe asthma, severe acne
- Lactose intolerance
- Mild hepatic disease
- Systemic disease requiring lowest hormonal dose e.g. diabetes
- Nausea with COCs
- Severe needle phobia with injectables or implant
- Inability to swallow pills
- Menstrual cycle control on OCs
- Compliance problems with pills, e.g. abortion on pill, recurrent missed pills, chaotic teenage lifestyle, shift workers and cabin crew

### **Fish oil supplements for behavioural problems**

JAPC has been asked for a decision on whether it is appropriate to prescribe fish oil supplements for behavioural problems. The North West Medicines Information Centre have produced two reports, A: 'Fish oil supplements – is there evidence that they improve concentration and behaviour in children?' and B: 'Fish oil supplements in dyslexia – is there evidence of benefit?'

#### **Summary from A:**

- A deficiency in essential omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) may affect children's behaviour and concentration but more robust data are necessary to confirm this.
- There is limited evidence that supplementation with omega-3 and omega-6 PUFAs may improve behaviour and concentration in children with behavioural and/or learning problems. The evidence is insufficient to support the routine use of these supplements in the management of children with attention-deficit hyperactivity disorder (ADHD).
- There is no credible evidence that PUFA supplementation improves concentration and academic performance in children without behavioural problems. Studies claiming to investigate such outcomes are of poor design, have no control group, and add little more than anecdote to the evidence base.
- There are no published dose-finding studies or head-to-head comparisons of different PUFA supplements. Consequently the ideal dose for supplementation is unknown, as is whether there are any meaningful differences between the available preparations.
- Fatty acid supplements are not NHS blacklisted at present but, as they are classed as food supplements rather than licensed medicinal products, prescribing may be open to challenge.

#### **Summary from B:**

- There is some evidence that a deficiency in essential omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) is involved in the aetiology of dyslexia in males (a correlation has yet to be found in females).
- There is little published literature to support the efficacy and safety of PUFA supplementation using fish oils in dyslexia. Available studies have examined the effect of fish oil supplements in children with a broad range of neurodevelopmental disorders, including dyslexia. There is very limited evidence that supplementation may produce a clinical improvement in some cases, but larger randomised controlled trials are required to confirm this.
- The only trials involving adults with dyslexia assessed the effect of PUFA supplements on dark adaptation, not reading or spelling ability.
- The *eye q* supplement was used in the largest study, the Oxford-Durham trial, but there are no published dose-finding studies or head-to-head comparisons of different PUFA supplements. Consequently the ideal dose for supplementation is unknown, as is whether there are any meaningful differences between the available preparations.
- There are few reports of adverse effects associated with fatty acid supplements in published trials. However, fish oils can cause gastrointestinal disturbances. Increases in bleeding time and adverse effects on the metabolic control of patients with non-insulin dependent diabetes mellitus may also occur.
- As the published trials have only been of a maximum of 6 months duration, it is not yet possible to draw conclusions about the long-term safety and efficacy of fish oil supplements. Further long-term studies specifically investigating the effect of fish oil supplements in dyslexia are required.

**JAPC has concluded that there is insufficient evidence to support fish oil supplements. Products such as Eflex and Eye-Q should not be prescribed as they are food supplements and not licensed drugs.**

**Insulin analogues**

JAPC has reviewed the evidence for the effectiveness and cost-effectiveness of insulin analogues compared with conventional insulins. There are two Cochrane reviews<sup>1,2</sup> and two papers from the Canadian Agency for Drugs and Technologies in Health, one on effectiveness<sup>3</sup> and one on cost-effectiveness<sup>4</sup>.

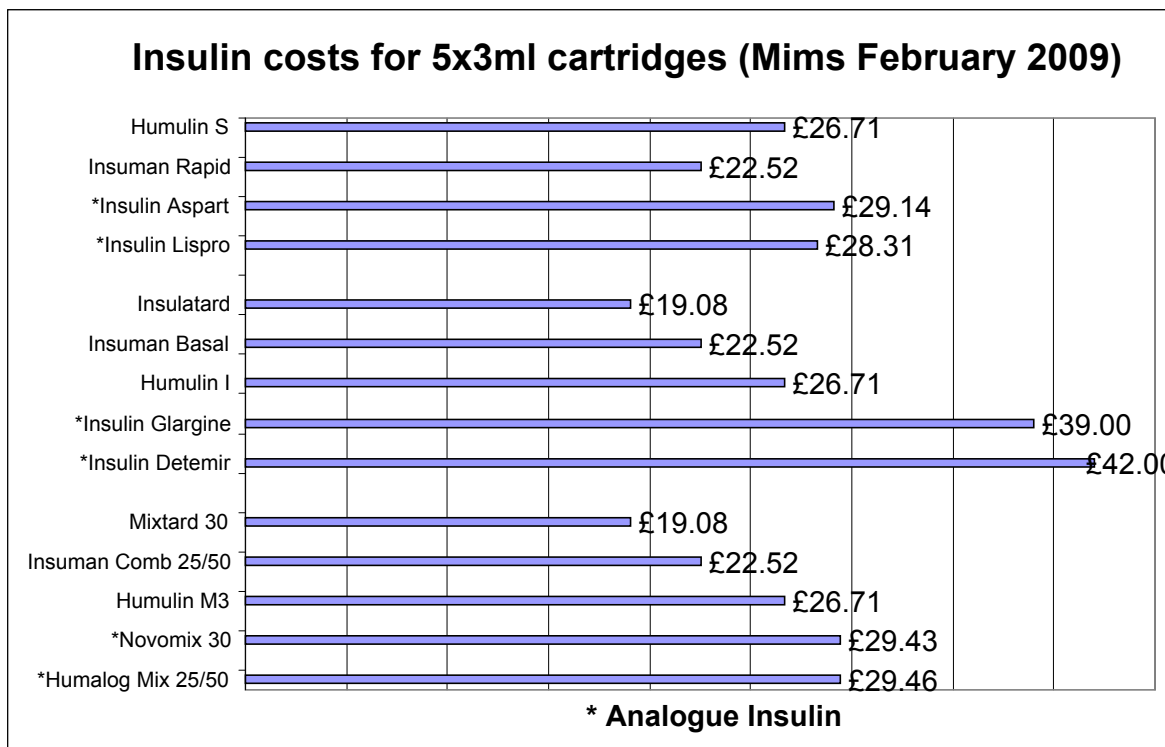
The Cochrane review of long-acting insulin analogues versus NPH (isophane) insulin for type 2 diabetes<sup>1</sup> concludes “if at all only a minor clinical benefit of treatment with long-acting insulin analogues for patients with diabetes mellitus type 2 treated with ‘basal’ insulin regarding symptomatic nocturnal hypoglycaemic events. Until long-term efficacy and safety data are available, we suggest a cautious approach to therapy with insulin glargine or detemir”.

The Canadian Health Technology Assessment on effectiveness and safety<sup>3</sup> concluded that insulin analogues offer little clinical advantage over older, conventional insulins in terms of glycaemic control or reduced hypoglycaemia for the management of patients with type 1, type 2 or gestational diabetes. The cost-effectiveness analysis<sup>4</sup> concludes that routine use of insulin analogues, especially long-acting analogues in type 2 diabetes, is unlikely to represent efficient use of finite health care resources.

From the editorial<sup>5</sup> that accompanies the Canadian reviews:

- The improved glycaemic control, reduced risk of hypoglycemia and improved quality of life achieved with insulin analogues versus conventional insulins are at best minor and of clinically debateable relevance.
- Insulin analogues should be reserved for use in selected patients, such as those with nocturnal hypoglycemia.
- Efforts should be focused on offering structured educational programs to help patients manage their diabetes and improve glycaemic control.

Despite an increase in prescribing of the more expensive insulin analogues, there is still no strong evidence that they result in large improvements in HbA<sub>1c</sub> compared with conventional insulins. In the absence of long-term safety data the wide-spread use of insulin analogues cannot be supported. **JAPC has concluded that insulin analogues are overused in Derbyshire and should be used less. The only indication for their use in type 2 diabetes is if the patient is suffering from symptomatic nocturnal hypoglycaemia on conventional insulins.**



1. Cochrane Database of Systematic Reviews, Issue 1, 2009 DOI:10.1002/14651858.CD005613.pub3.
2. Cochrane Database of Systematic Reviews, Issue 1, 2009 DOI:10.1002/14651858.CD006297.pub2
3. CMAJ 2009; 180:385-97
4. CMAJ 2009; 180:400-7
5. CMAJ 2009; 180:369-70

## **Drug Safety Update**

This can be found at [www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/index.htm](http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/index.htm)

Here are some key points from the March issue.

### **Methylphenidate:** *updated guidance on safe and effective use in ADHD*

The benefits of methylphenidate continue to outweigh the risks when used to treat ADHD in children aged 6 years or older and adolescents. Treatment must be under the supervision of a specialist in childhood behavioural disorders. Patients should be monitored during treatment, which should be interrupted at least once a year to determine whether continuation is needed.

#### **Key safety information and advice for healthcare professionals:**

##### *Contraindications – methylphenidate should not be used in patients with:*

- Diagnosis or history of severe depression, anorexia nervosa or anorexic disorders, suicidal tendencies, psychotic symptoms, mania, schizophrenia, severe mood disorders, or psychopathic or borderline personality disorder
- Diagnosis or history of severe and episodic (type 1) bipolar (affective) disorder that is not well-controlled.
- Pre-existing cerebrovascular disorders – eg, cerebral aneurysm and vascular abnormalities, including vasculitis or stroke.
- Unless specialist cardiac advice has been obtained: in pre-existing cardiovascular disorders, including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias, and dysfunction of cardiac ion channels.

##### *Pretreatment screening*

- Before prescribing, the patient's baseline cardiovascular status, including blood pressure and heart rate, should be assessed.

### **Atomoxetine:** *risk of psychotic or manic symptoms*

Atomoxetine is associated with treatment-emergent psychotic or manic symptoms in children and adolescents without a history of such disorders. If such symptoms occur, consideration should be given to a possible causal role of atomoxetine and discontinuation of treatment.

#### **Advice for healthcare professionals:**

- At normal doses, atomoxetine can be associated with treatment-emergent psychotic or manic symptoms (eg, hallucinations, delusional thinking, mania, or agitation) in children and adolescents without a history of psychotic illness or mania.
- If such symptoms occur, consideration should be given to a possible causal role of atomoxetine and discontinuation of treatment.
- It remains possible that atomoxetine might exacerbate pre-existing psychotic or manic symptoms.

### **Exenatide (Byetta ▼):** *risk of severe pancreatitis and renal failure*

Suspected adverse reaction reports of necrotising and haemorrhagic pancreatitis have been received in association with exenatide. Some of these reports had a fatal outcome. If pancreatitis is diagnosed, exenatide should be permanently discontinued. Reports of renal impairment, including acute renal failure and worsened

chronic renal failure have also been received. Exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment.

Advice for healthcare professionals:

- There have been reports of necrotising and haemorrhagic pancreatitis with exenatide, some of which were fatal.
- If pancreatitis is suspected, treatment with exenatide should be suspended immediately; if pancreatitis is diagnosed, exenatide should be permanently discontinued.
- Diagnosed pancreatitis with an unexpectedly prolonged course, haemodynamic instability, fever, failure of medical therapy, or presence of fluid collections on CT suggest possible necrosis.
- Exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 ml/min).

**Bisphosphonates:** *atypical stress fractures*

Atypical stress fractures of the proximal femoral shaft have been reported in patients treated long-term with alendronic acid. Patients who develop stress fractures should discontinue alendronic acid and receive no further bisphosphonate treatment unless the benefits for the individual clearly outweigh the risk of harm. An increased risk of atypical stress fractures with other bisphosphonates cannot be excluded.

Information and advice for healthcare professionals:

Alendronic acid

- Atypical stress fractures (also known as insufficiency fractures) of the proximal femoral shaft have been reported in patients treated long-term with alendronic acid (in most cases, time to onset ranged from 18 months to 10 years).
- Fractures occurred after minimal or no trauma, and some patients experienced thigh pain weeks to months before presenting with a completed femoral fracture. Fractures were frequently bilateral; therefore the contralateral femur should be examined in patients treated with alendronic acid who have a femoral shaft fracture. Poor healing of these fractures was also reported.
- Patients who develop atypical stress fractures should discontinue alendronic acid and receive no further bisphosphonate treatment unless the benefits of continued treatment are thought to clearly outweigh the risks to the individual.
- Product information for alendronic acid will be updated to include a warning about atypical stress fractures.

All other bisphosphonates

- Limited data are available for the other bisphosphonates in support of a causal association with atypical stress fractures. This might reflect their lower usage and the limited long-term data that exist for other bisphosphonates.
- The possibility that other bisphosphonates may be associated with an increased risk of atypical stress fractures cannot be excluded.
- The risk of atypical stress fractures with all bisphosphonates will be kept under close review, including consideration of further epidemiological research and further information will be issued for healthcare professionals when available.

**Cialis Once-A-Day**

Oral tadalafil (Cialis) 10mg and 20mg has been available for several years for the treatment of erectile dysfunction and is intended to be taken prior to anticipated sexual activity. It is not recommended for continuous daily use.

Recently Lilly have launched Cialis Once-A-Day (tadalafil 2.5mg and 5mg) which is designed to be taken as a daily regimen in men who have responded to the on-demand regimen, and who may have intercourse more than once a week.

The Department of Health's (DH) guidance on treatment for impotence (HSC1999/148) recommends in paragraph 5 that one treatment per week will be appropriate for most patients being treated for erectile dysfunction.

However, the guidance also states that, "If the GP in exercising his clinical judgement considers that more than one treatment a week is appropriate he should prescribe that amount on the NHS." This guidance is only appropriate to those men who are listed as eligible to receive the treatment on the NHS.

In response to queries about Cialis Once-A-Day the DH state that, in exercising their clinical judgement, GPs may consider this suitable for a small number of patients. This suggests a very limited use for a more expensive product.

Cialis 10mg and 20mg cost £24.99 for a 4-tab pack (recommended quantity per month) and £49.77 for an 8-tab pack. Cialis Once-A-Day costs £54.99 for a 28-day pack. **JAPC has designated Cialis Once-A-Day as BROWN** as it is less cost effective than current standard therapy and does not meet with DH guidance on appropriate dosing.

### **Sensible HbA<sub>1c</sub> targets**

NICE clinical guideline 66 on the management of type 2 diabetes says that when setting a target HbA<sub>1c</sub> the person with diabetes should be involved in the decision about their individual target level. As readers will be aware, three important studies, ACCORD, ADVANCE and VADT have provided further evidence that tight glycaemic control does not provide substantial benefit and may increase the risk of adverse outcomes.

In September 2008, after reviewing ACCORD and ADVANCE, JAPC concluded that the QoF target of HbA<sub>1c</sub> ≤7.5% was reasonable but chasing the NICE target of ≤6.5% was not advised and may cause harm.

From April, the HbA<sub>1c</sub> QoF target in one of the diabetes indicators is changing from a target of ≤7.5% to a target of ≤7%. Why? As a recent BMJ editorial<sup>1</sup> states, reducing HbA<sub>1c</sub> below 7% is not supported by evidence and may even be harmful. The authors go on to say that the new QoF target encourages an outdated strategy and it should be withdrawn before it wastes resources and possibly harms patients. They add that patient preference should play a strong role in the strategy that is pursued.

In the spirit of concordance, if the pros and cons of tight glycaemic control were explained to patients, how many would say 'yes please'? The optimal glycaemic target is unknown but is there really anything actually wrong with 7% - 8% if symptoms of hyperglycaemia are controlled? The important, evidence-based intervention is to maximise the use of metformin. A QoF target that meets the essential criteria of effective, cost-effective, and affordable would have been: percentage of those with type 2 diabetes taking metformin.

1. BMJ 2009; 338:b800

### **Metformin SR**

Metformin SR is recommended by JAPC for those patients who are intolerant of standard-release metformin, even after slow dose titration. It should be tried before switching to an alternative hypoglycaemic agent.

A new strength of metformin SR of 1000mg tablet has been added to the range. It compliments the existing 500mg and 750mg tablets. Prescribing 750mg or 1000mg tablets is less costly than using 500mg for the equivalent dose.

### **Antipsychotics: use in dementia**

Safety concerns over the use of both typical and atypical antipsychotics in elderly patients with dementia have been well documented. In 2004, the CSM advised that the atypical antipsychotics, olanzapine and risperidone, should not be used for treatment of behavioural symptoms of dementia due to evidence of an increased risk of stroke in elderly patients with such symptoms. More recently, in November 2008, the EMEA published a report which concluded that typical antipsychotics are also likely to be associated with increased mortality when used in elderly patients with dementia.

It is now thought that all antipsychotics, regardless of their type, are associated with an increased risk of serious adverse reactions.

A new cohort study suggests that both typical and atypical antipsychotic drugs increase the risk of sudden cardiac death<sup>1</sup>. The risk was approximately twice that of patients in the general population.

The MHRA has issued advice on the use of antipsychotics in elderly people with dementia<sup>2</sup>. They state that there is a clear increased risk of stroke and a small increased risk of death when typical or atypical antipsychotics are used in elderly people with dementia.

#### *Use of antipsychotics in dementia*

Only one antipsychotic, risperidone (Risperdal ▼), is licensed for treatment of dementia-related behavioural disturbances: and then only specifically for short-term (up to 6 weeks') treatment of persistent aggression in Alzheimer's dementia unresponsive to non-pharmacological approaches and where there is a risk of harm to the patient or others. Elderly people with dementia are at risk from specific serious and life-threatening side-effects when treated with antipsychotics.

#### *Risk of stroke*

In 2004 the Committee on Safety of Medicines (the predecessor to the Commission on Human Medicines) advised of a clear increase in the risk of stroke with the use of the atypical antipsychotics risperidone ▼ or olanzapine in elderly people with dementia (approximately three-times increased risk compared with placebo), and that the magnitude of risk outweighed any likely benefit of treating dementia-related behavioural problems with these drugs. A year later a Europe-wide review concluded that this risk could not be excluded for other antipsychotics (atypical or typical), and the product information for all antipsychotics was updated to include a class warning.

#### *Increased mortality*

In 2005 an analysis of 17 placebo-controlled trials found that atypical antipsychotics are associated with increased mortality when used in elderly people with dementia (about 1-2% increased risk compared with no treatment). For risperidone, there is an additional increase in the risk when coprescribed with furosemide.

Subsequently in November 2008, a European assessment of published observational data concluded that a similar increased risk of death could not be excluded for the typical (conventional) antipsychotics.

#### *About risperidone ▼*

In the case of persistent aggression in moderate to severe Alzheimer's disease, where the patient puts themselves or others at risk of harm, short-term treatment with risperidone may be indicated if the behaviour has not responded to non-pharmacological means. A new analysis of three randomised control trials conducted in behavioural problems in the elderly showed a clear benefit for the short-term use of risperidone when aggression only was considered. The balance of risks and benefits for risperidone use to treat behavioural disturbances in dementia is only considered to be positive within its narrow licensed indication: ie, short-term use for persistent aggression in Alzheimer's-type dementia.

#### *Advice for healthcare professionals:*

- There is a clear increased risk of stroke and a small increased risk of death when antipsychotics (typical or atypical) are used in elderly people with dementia.
- The balance of risks and benefits associated with risperidone treatment should be carefully assessed for every patient, taking into consideration the known increased mortality rate associated with antipsychotic treatment in the elderly. Prescribers should carefully consider the risk of cerebrovascular events before treating with risperidone any patient who has a previous history of stroke or transient ischaemic attack. Consideration should also be given to other risk factors for cerebrovascular disease including hypertension, diabetes, smoking, and atrial fibrillation.

#### *Risperidone: new Black Triangle (▼) status*

The Black Triangle Scheme identifies medicines whose safety profiles are monitored intensively by MHRA and CHM. Risperidone ▼ has been added to the list of black triangle medicines after the granting of the new narrow

indication in Alzheimer's dementia as outlined above. Healthcare professionals are asked to please report via the Yellow Card Scheme all suspected side-effects to risperidone ▼ that occur when it is used to treat elderly people with dementia. You do not have to be certain of causality – if in doubt, please report.

1. N Engl J Med 2009; 360:225-35
2. Drug Safety Update; 2(8), March 2009

### **OTC cough and cold medicines in young children**

In the absence of robust evidence for their effectiveness and the risk of harm, the MHRA has warned against the use of many commonly used over-the-counter cough and cold medicines for children under six years of age. Supply of these medicines for children aged 6–12 years is restricted to pharmacies.

Parents and carers should no longer give over-the-counter (OTC) cough and cold medicines containing certain ingredients (see below) to children less than six years of age. They should follow advice to relieve symptoms as outlined in the Department of Health's 2007 guidance '[Birth to Five](#)'. For 6 to 12 year olds, these medicines will continue to be available but will only be sold in pharmacies, with clearer advice on the packaging.

OTC cough and cold medicines containing the following active ingredients are affected by the advice:

- antitussives: dextromethorphan and pholcodine
- expectorants: guaifenesin and ipecacuanha
- nasal decongestants: ephedrine, oxymetazoline, phenylephrine, pseudoephedrine and xylometazoline
- antihistamines: brompheniramine, chlorphenamine, diphenhydramine, doxylamine, promethazine and triprolidine.

A list of [branded products affected](#) are available on the MHRA website. These have details of:

- the products parents can still use to treat coughs and colds in children under 6 years of age ('List 1');
- the products which already only have dosages for children aged 6 years and over ('List 2'); and
- the products which currently have doses for children aged under 6 and are changing their labelling to remove these doses. These can still be used to treat children over 6 years old ('List 3')

A list of combination products that will be phased out from the market for use in children under 12 years is also available on the MHRA website.

The MHRA review did not identify the safety issues of the kind which prompted their action in the under-2s in March 2008. However, the review found no robust evidence for their effectiveness but recognised that they can cause side effects, such as allergic reactions, effects on sleep or hallucinations.

The MHRA suggest that certain cough and cold medicines should **not** be used at all in children under the age of 6 years. They go on to advise that they should not be used first-line in children aged 6–12 years but, if they are, this should be for no more than five days. For children aged over 6 years, the MHRA considered that the risk from these ingredients is reduced because: they suffer from cough and cold less frequently and consequently require medicines less often; with increased age and size, they tolerate the medicines better; and they can say if the medicine is working. For these reasons, cold and cough medicines containing the above ingredients will still be available for these older children, but only through pharmacies.

Although these medicines will still be available in their current packaging, they will eventually have strengthened warnings on labels, and all liquid cough and cold medicines (including those for adults) will be supplied in child resistant containers. The MHRA recognised that some combinations of ingredients are illogical (such as cough suppressants and expectorants) and medicines containing these combinations will be phased out.