All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

National Prescribing Indicators 2015–2016

February 2015

This report has been prepared by a multiprofessional collaborative group, with support from the All Wales Prescribing Advisory Group (AWPAG) and the All Wales Therapeutics and Toxicology Centre (AWTTC), and has subsequently been endorsed by the All Wales Medicines Strategy Group (AWMSG).

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INTRODUCTION

Prescribing indicators are used to compare the way in which different prescribers and organisations use a particular medicine or group of medicines. Prescribing indicators should be evidence-based, clear, easily understood and allow health boards, practices and prescribers to compare current practice against an agreed standard of quality. Ideally they should be validated by a group of experts, and should recommend the direction that prescribing should move, even if it is not possible to specify an exact value that represents 'good practice'. They should usually be standardised to allow comparison between health boards or practices serving different size populations. Weighting can also consider the age and demographics of the population.

In October 2003, the All Wales Medicines Strategy Group (AWMSG) agreed that National Prescribing Indicators (NPIs) were useful tools to promote rational prescribing across NHS Wales. It was agreed that NPIs should address efficiency as well as quality and that targets should be challenging, but achievable, and applicable at practice level.

Traditionally, NPIs have been set to compare prescribing in primary care, as accurate prescribing data are available, and standardised targets can be set. However, the principles and evidence base supporting the NPIs are applicable to both primary and secondary care. Although it is not currently possible to set targets for NPIs in secondary care, ongoing comparative monitoring is undertaken and reported to identify differences in prescribing practice.

Method used to review and update NPIs
An NPI Task and Finish Group of the All Wales Prescribing Advisory Group (AWPAG) was established to review the 2014–2015 NPIs, to ensure they were still valid and reflected best practice.

Prior to the NPI Task and Finish Group meeting, Health Board Chief Pharmacists, their medicines management teams, Medicines and Therapeutics Committees and Assistant Medical Directors were asked to complete a short feedback form to review the continued relevance of the 2014–2015 NPIs, whether any of the Local Comparators should be considered as new NPIs and other priority areas that may be appropriate to monitor as an NPI. This information then fed into the discussions of the NPI Task and Finish Group.

The proposed NPIs for 2015–2016, accompanied by the supporting evidence, were presented to AWPAG for their comment. The NPIs for 2015–2016 were also distributed for wider consultation prior to their endorsement by AWMSG.

Key changes:

- Two new NPIs: Proton pump inhibitors (PPIs) and inhaled corticosteroids (ICS).
- Three NPIs to be removed: Antidepressants, insulin and total opioid analgesics, of which antidepressants and insulin will continue to be monitored as Local Comparators.
- Three NPIs to have new measures: co-amoxiclav, cephalosporins, and fluoroquinolones.

Measures

- Where possible, measures used should be accessible to all medicines management teams through CASPA.net.
- The average daily quantity (ADQ) and specific therapeutic group age–sex related prescribing unit (STAR-PU) measurements are used for certain indicators instead of the defined daily dose (DDD) measurement and prescribing unit (PU) weighting, despite not being available on CASPA.net, in

order to benchmark with the 'Quality, innovation, productivity and prevention' (QIPP) comparators in England. These data are available on a quarterly basis through the NHS Wales Shared Services Partnership: Primary Care Services.
- Yellow Card Centre (YCC) Wales will monitor yellow card reporting by general practitioners, providing feedback at health board and practice level.

Targets

Targets should be challenging but achievable, and based on the principle of encouraging all health boards, local cluster groups and practices to achieve prescribing rates in the best quartile. The target is therefore not an absolute value and can be achieved if there is movement towards the threshold set.

- The threshold is based on prescribing data for all general practices in Wales.
- For each NPI, the threshold will normally be set at the 75th percentile, (i.e. the prescribing rate of the best performing 25% of practices) for the quarter ending 31 December 2014. However, a threshold may be retained from a previous year if considered appropriate by the NPI Task and Finish Group.
- The target may be to achieve movement to the highest prescribing quartile or the lowest prescribing quartile depending on the aim of the NPI.
- One NPI has been included without a target – total antibiotic prescribing. Seasonal variation prevents a target being set based on prescribing in any one particular quarter; however, year on year prescribing will be monitored, aiming for a reduction in prescribing.
- One NPI has been included using alternative monitoring methods – yellow card reporting. This will be monitored by YCC Wales, who will provide data to the Welsh Analytical Prescribing Support Unit (WAPSU) and individual health board Chief Pharmacists on a quarterly basis.
- Targets are not currently set for the NPIs in secondary care, as it is not possible to weight the prescribing data. However, where appropriate and relevant, monitoring of prescribing will be undertaken to ensure the principle and evidence base supporting the NPI is considered and implemented in all settings.

Table 1 details the NPIs for 2015–2016, with the evidence and supporting prescribing messages within the text that follows. Data to support the proposed NPIs for 2015–2016 are contained within Appendix 1.

Please note:
The NPIs constitute guidance only, and this document, either in isolation or as part of wider policy, is not associated with any financial incentive scheme, and does not offer any medical practice and/or practitioner any financial incentive to prescribe a specific named medicine.

Implementation of the recommended NPIs does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. This is supported by the prudent healthcare agenda which encourages the creation of a prescribing partnership where the process of prescribing, dispensing and administering medicines puts the patient at its centre and encourages shared decision making[1].

Table 1. Proposed AWMSG NPIs 2015–2016

Indicator	BNF chapter	Unit of measure	Target for 2015–2016
Proton pump inhibitors (PPIs)	1.3.5	PPI DDDs per 1,000 PUs	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
Lipid-modifying drugs	2.12	LAC statin items as a percentage of all statin, ezetimibe and simvastatin/ezetimibe combination prescribing	Maintain performance levels within the upper quartile, or show an increase towards the quartile above (threshold to remain as for 2013–2014 NPI)
Inhaled corticosteroids (ICS)	3.2	Low strength ICS items as a percentage of all ICS prescribing	Maintain performance levels within the upper quartile, or show an increase towards the quartile above
Hypnotics and anxiolytics	4.1	Hypnotic and anxiolytic ADQs per 1,000 STAR-PUs	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
Opioid analgesics	4.7.2	Morphine items as a percentage of strong opioid prescribing	Maintain performance levels within the upper quartile, or show an increase towards the quartile above
	4.7.2	Tramadol DDDs per 1,000 patients	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
Antibiotics	5.1	Total antibacterial items per 1,000 STAR-PUs	No performance target set; aim for reduction in prescribing year on year, measuring quarter to December only
	5.1.1	Co-amoxiclav items per 1,000 patients Co-amoxiclav items as a percentage of total antibacterial items	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
	5.1.2	Cephalosporin items per 1,000 patients Cephalosporin items as a percentage of total antibacterial items	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
	5.1.12	Fluoroquinolone items per 1,000 patients Fluoroquinolone items as a percentage of total antibacterial items	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
Non-steroidal anti-inflammatory drugs (NSAIDs)	10.1.1	NSAID ADQs per 1,000 STAR-PUs	Maintain performance levels within the lower quartile, or show a reduction towards the quartile below
	10.1.1	Ibuprofen and naproxen items as a percentage of NSAID prescribing	Maintain performance levels within the upper quartile, or show an increase towards the quartile above
Yellow cards		Number of yellow cards submitted per practice and per health board	Target for GP practice – GPs to submit one yellow card per 2,000 practice population. Target for each health board – submit yellow cards in excess of one per 2,000 health board population.

ADQ = average daily quantity; DDD = defined daily dose; LAC = low acquisition cost; PU = prescribing unit; STAR-PU = specific therapeutic group age–sex related prescribing unit

1.0 PROTON PUMP INHIBITORS

***Purpose*:** To ensure appropriate use of PPIs.

Unit of measure: PPI DDDs per 1,000 PUs.

Target for 2015–2016: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

Background and evidence

PPIs are licensed and prescribed for a range of indications including uninvestigated dyspepsia, gastro-oesophageal reflux disease, peptic ulcer and non-ulcer (or functional) dyspepsia, eradication of *Helicobacter pylori* (in combination with antibiotics), controlling excessive acid secretion in Zollinger–Ellison syndrome, and the prevention and treatment of non-steroidal anti-inflammatory drug (NSAID)-associated ulcers[2,3]. In addition, they are used for a number of unlicensed indications (more common in hospital settings), including the reduction of re-bleeding episodes after treatment of severe peptic ulcer bleeding, prophylaxis of acid aspiration during general anaesthesia and stress ulcer prophylaxis[3].

PPI use (measured in DDDs) is continuing to increase across Wales at a rate of 6% per year[4]. In the financial year 2013–2014, over 4 million prescriptions for PPIs were dispensed in Wales[4]. Assuming each patient received 13 (28-day) prescriptions during the year, 311,000 patients (9.8% of the population) received PPIs[4]. This is probably an underestimate of the number receiving PPIs, as many patients will take these medicines as required and would therefore not receive 13 prescriptions in the course of a year[4]. It has been suggested that the reduction in cost, with patent expiry, has led to more liberal usage of PPIs for a wide variety of upper gastrointestinal (GI) symptoms[5]. Additionally, recommendations on the importance of gastroprotection, particularly for patients on combinations of high-risk medicines, e.g. NSAIDs for the treatment of osteoarthritis[6] and rheumatoid arthritis (RA)[7], have contributed to increased PPI use. It is recommended that all patients are reviewed and stepped down from treatment doses where appropriate[8,9].

Although PPIs are generally well tolerated, there is emerging evidence that some serious adverse effects may be linked with long-term PPI use. These include fractures of the hip, wrist and spine (frequency ≥ 1/1,000 to < 1/100)[10], *Clostridium difficile* infection and hospital- or community-acquired pneumonia[11]. Medicines and Healthcare Products Regulatory Agency (MHRA) advice issued in April 2012 stated that "There is recent epidemiological evidence of an increased risk of fracture with long-term use of PPIs. Patients at risk of osteoporosis should be treated according to current clinical guidelines to ensure they have an adequate intake of vitamin D and calcium"[12]. Further advice in the same issue of Drug Safety Update warned of the risk of hypomagnesaemia following long-term use of PPIs[13]. A review of case reports found that hypomagnesaemia occurred most commonly after one year of PPI treatment, and presented with fatigue, tetany, delirium, convulsions, dizziness, and ventricular arrhythmia[13].

Long-term PPI use has also been linked to rebound hypersecretion[11]. NICE confirms this, and states that "This may exacerbate symptoms once PPI therapy is discontinued although this is a theoretical concern as there are no data that support acid rebound as a clinical problem in patients"[2].

Useful resources

- AWMSG (2013) All Wales PPI and Dyspepsia Resource Pack.
- AWMSG (2014) Polypharmacy: Guidance for Prescribing in Frail Adults.

2.0 LIPID-MODIFYING DRUGS

***Purpose*:** Ensure appropriate prescribing of lipid-modifying drugs with the lowest acquisition cost (LAC) in line with NICE guidance.

Unit of measure: LAC statin items (simvastatin, pravastatin and atorvastatin) as a percentage of all statin, ezetimibe and simvastatin/ezetimibe combination prescribing.

Target for 2015–2016: Maintain performance levels within the upper quartile, or show an increase towards the quartile above (threshold to remain as for 2013–2014 NPI).

Background and evidence

The use of LAC statins is promoted through the Department of Health 'Better Care, Better Value' (BCBV) indicators[14]. The BCBV indicators are not targets, but are intended to provide useful comparative information to help NHS organisations to decide where and how to improve performance. There are still savings to be made by some NHS organisations through the use of LAC statins.

NICE issued Clinical Guideline (CG) 181 in July 2014, which updates the guidance relating to lipid modification in adults both with and without diabetes. The guidance recommends the use of atorvastatin 20 mg for the primary prevention of cardiovascular disease to people, with or without type 2 diabetes, who have a 10% or greater 10-year risk of developing cardiovascular disease[15]. Atorvastatin 20 mg is also recommended for primary prevention in patients with type 1 diabetes in specific circumstances[15]. Atorvastatin 80 mg is recommended for patients with established cardiovascular disease*. Lower doses should be used if there are potential drug interactions, if the patient is at high risk of adverse effects, or if patient preference is for a lower dose[15].

NICE CG181 reviewed the evidence around rosuvastatin and, whilst meta-analysis indicates that the effectiveness of atorvastatin 80 mg and rosuvastatin 40 mg in reducing low density lipoprotein (LDL) cholesterol are similar[16], there was no evidence to suggest rosuvastatin 10 mg, 20 mg or 40 mg would be more effective than atorvastatin 80 mg in reducing cardiovascular events[15]. Therefore, in the absence of trial evidence of greater effectiveness, the guideline development group were unable to recommend the use of rosuvastatin[15].

NICE guidance recommends that if patients are unable to tolerate a high-intensity statin (atorvastatin 20 mg or higher), a reduction in dose, or switching to a lower intensity statin may be appropriate[15].

Muscle-related problems are the most frequently reported side effects of statins. The following statin side effect incidences have been estimated based on randomised trial data, cohort studies, published case reports and spontaneous reports:

- Mild muscle pain: 190 cases per 100,000 patient years
- Myopathy: 5 cases per 100,000 patient years
- Rhabdomyolysis: 1.6 cases per 100,000 patient years[17]

The risk of myopathy is increased with all statins and is known to be dose dependent. Myopathy risk also increases when certain medicines are used together with statins,

*NICE CG181: At the time of publication (July 2014), atorvastatin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented[15].

either because both medicines can cause myopathy or because the second medicine increases the blood plasma concentration of the statin dose[17].

The MHRA recommends reduced maximum doses for atorvastatin in combination with specific medicines. The maximum dose of atorvastatin in conjunction with itraconazole is 40 mg, with clarithromycin is 20 mg[18] and with ciclosporin, and tipranavir combined with ritonavir, is 10 mg[19]. The maximum daily dose of simvastatin in conjunction with lomitapide is 40 mg; with amiodarone, amlodipine, diltiazem, ranolazine or verapamil is 20 mg; and with bezafibrate or ciprofibrate is 10 mg[19].

NICE CG71 on the management of familial hypercholesterolaemia (FH) recommends using the maximum licensed or tolerated dose of statins, plus ezetimibe if necessary, to try to achieve at least 50% reduction in LDL cholesterol from baseline[20]. However, if a patient cannot tolerate or does not wish to take such intensive treatment, one cohort study suggested that the prognosis for patients with FH may be improved substantially when standard doses of 'less intensive' statins were introduced, and, when other risk factors e.g. hypertension and smoking were addressed, risk of coronary heart disease may be reduced to that of the general population[21].

NICE Technology Appraisal (TA) 132 recommends ezetimibe as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia, in the following circumstances:

- where statins are contraindicated or not tolerated;
- in conjunction with a statin where serum total or LDL cholesterol is not appropriately controlled by initial statin therapy (after appropriate dose titration or because dose titration is limited by intolerance), and when consideration is being given to changing the initial statin therapy to an alternative statin[22].

Evidence for efficacy of ezetimibe is based largely on surrogate outcomes (i.e. cholesterol lowering). It is not known whether the reduction in cholesterol achieved with ezetimibe in clinical trials translates into reduced cardiovascular mortality or morbidity[23]. There is currently no evidence to indicate that ezetimibe, alone or added to a statin, reduces the risk of cardiovascular disease or mortality.

Useful resources

- NICE (2014) CG181: Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease.
- NICE (2014) Cardiovascular disease prevention overview – includes section on lipid modification therapy.
- NICE (2014) CG181: Lipid modification: patient decision aid.
- NICE (2008) CG71: Identification and management of familial hypercholesterolaemia.
- NICE (2007) TA132: Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia.

3.0 INHALED CORTICOSTEROIDS

Purpose: To encourage the routine review of ICS in people with asthma, particularly those on high doses, encouraging step down of the dose when clinically appropriate.

Unit of measure: Low strength ICS* items as a percentage of all ICS prescribing.

Target for 2015–2016: Maintain performance levels within upper quartile, or show an increase towards the quartile above.

*Low strength ICS: Any inhaler device which when used at the usual dose provides a daily dose of ICS < 800 mcg of beclometasone or equivalent (see Appendix 2 for the specific basket of medicines to be monitored, in this document referred to as a user-defined group [UDG]).

Background and evidence

This NPI focuses on use of ICS in asthma; however, prescribing data obtained from CASPA do not differentiate between the indications for ICS, namely asthma and chronic obstructive pulmonary disease (COPD). QOF data from 2013–2014 show that the prevalence of asthma in Wales is 6.9%, and the prevalence of COPD is 2.2%[24]. Low dose (< 800 mcg of beclometasone or equivalent) combination ICS therapy and ICS monotherapy are not licensed for use in COPD. The limited place of ICS in the management of COPD and the prevalence data therefore suggest that the majority of ICS prescribed in Wales should be for the management of asthma.

The *British guideline on the management of asthma* advocates a stepwise approach for the treatment of asthma[25]. ICS are the first-choice regular preventer therapy for adults and children with asthma for achieving overall treatment goals. ICS should be considered for patients (adults and children, aged 5 years and older) with any of the following asthma-related features: exacerbations of asthma in the last two years, using inhaled beta-2 agonists three times a week or more, symptomatic three times a week or more, waking one night a week[25]. To minimise side effects from ICS in people with asthma, the *British guideline on the management of asthma* recommends that the dose of ICS should be titrated to the lowest dose at which effective control of asthma is maintained[25]. They recommend that dose reduction should be considered every 3 months, decreasing the dose by approximately 25–50% each time[25].

ICS are the first choice preventer drug; however, a proportion of patients may not be adequately controlled on an ICS, and additional preventer therapy may be appropriate. There is no exact dose of ICS at which it can be deemed appropriate to add on another therapy[25]. A meta-analysis studying the dose-response relation of fluticasone propionate in adolescents and adults with asthma suggests that most of the therapeutic benefit is achieved with a total daily dose of 100–250 mcg[26]; a second meta-analysis supports this, suggesting that most therapeutic benefit is achieved with a total daily dose of 200 mcg fluticasone propionate, with minimal further clinical benefit achieved with higher doses[27].

There are safety issues relating to the use of high doses of ICS in asthma. Unpleasant local side effects, including oral candidiasis and dysphonia, can occur with ICS at standard doses, but are more common with higher doses. Potentially serious systemic side effects, such as adrenal suppression, growth failure, decrease in bone mineral density, cataracts and glaucoma, may be associated with ICS particularly at high doses (above 800 micrograms beclometasone or equivalent per day in adults and above 400 micrograms beclometasone or equivalent per day in children)[25,28]. The MHRA advises that in addition to these known systemic side effects, the prolonged use of high

doses of ICS carries the risk of a range of psychological or behavioural effects (e.g., psychomotor hyperactivity, sleep disorders, anxiety, depression and aggression)[29]. The Committee on Safety of Medicines (CSM) has issued warnings about the use of high-dose ICS, particularly in children and in relation to fluticasone propionate[30].

NICE recommends that ICS should only be considered in combination with a long-acting beta-2 agonist (LABA) in patients with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators[31]. NICE recommends an ICS and LABA as an option for maintenance therapy in patients with severe COPD (FEV_1 < 50% predicted)[31]. In patients with mild to moderate COPD (FEV_1 > 50% predicted) this combination may be considered if the patient has persistent breathlessness or exacerbations despite treatment with a LABA[31].

ICS have been associated with increased risk of pneumonia, but the magnitude of risk and how this varies among different ICS remains unclear[32]. A review of clinical trials suggested that budesonide and fluticasone (fluticasone furoate and fluticasone propionate), delivered alone or in combination with a long-acting beta-2 agonist, are associated with increased risk of serious adverse pneumonia events, but neither significantly affected mortality compared with controls[32]. The review concluded, however, that these safety concerns should be balanced with established randomised evidence of efficacy regarding exacerbations and quality of life[32].

In Wales, over 1.6 million prescriptions were dispensed in primary care for ICS in the financial year to March 2014, costing NHS Wales £54.9 million. This group of medicines accounts for the highest spend in primary care in Wales; of those 1.6 million prescriptions, 44% were for high-strength (i.e. providing a daily dose of ICS equivalent to beclometasone ≥ 800 mcg) combination inhalers[4].

Useful resources

SIGN (2014) SIGN: British guideline on the management of asthma.
NICE (2010) CG101: Chronic obstructive pulmonary disease

4.0 HYPNOTICS AND ANXIOLYTICS

***Purpose*:** Reduce inappropriate prescribing of hypnotics and anxiolytics.

Unit of measure: Hypnotic and anxiolytic ADQs per 1,000 STAR-PUs (UDG).

Target for 2015–2016: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

UDG: chlordiazepoxide, diazepam, flurazepam, loprazolam, lorazepam, lormetazepam, nitrazepam, oxazepam, temazepam, zaleplon, zolpidem, zopiclone

Background and evidence

There has been concern with regard to the high level of anxiolytic and hypnotic prescribing within NHS Wales. Some prescribing may be inappropriate and contribute to the problem of physical and psychological dependence, and/or may be responsible for masking underlying depression. In 1988, advice from the CSM recommended that benzodiazepines should be used for no more than two to four weeks for insomnia and anxiety, only if it is severe, disabling, or subjecting the individual to extreme distress[33]. The National Service Framework (NSF) for Mental Health stated that by 2001 all health authorities should have systems in place to monitor and review prescribing rates of benzodiazepines within the local clinical audit programme[34]. Key action point 33 in the revised Adult Mental Health NSF and Action Plan for Wales states that "healthcare organisations are to ensure that patients and service users are provided with effective treatment and care that conforms to the NICE TAs and interventional procedures and the recommendations of AWMSG and is also based on nationally agreed best practice guidelines as defined in NSFs, NICE CGs, national plans and agreed national guidance on service delivery"[35]. The performance target set was that by March 2007, local health boards/NHS trusts should have undertaken a systematic review of NICE guidelines and TAs, and developed a local incremental implementation plan[35].

The substance misuse strategy of the Welsh Government (*Working together to reduce harm*) calls for the reduction of inappropriately prescribed benzodiazepines[36].

More recently the long-term use of benzodiazepine hypnotics and anxiolytics has been associated with an increased risk of Alzheimer's disease. An observational study in Canada showed that the risk of Alzheimer's disease was increased by 43–51% among those who had used benzodiazepines in the past. Risk increased with increased exposure and when long-acting benzodiazepines were used[37].

Benzodiazepine hypnotics and anxiolytics significantly increase risk of falls[38]. Falls risk assessment tools advise reviewing benzodiazepines in patients at high risk of falling[39].

The prescribing volume of hypnotics and anxiolytics (UDG) in Wales has declined over recent years. In the financial year 2013–2014, the number of items dispensed was 1,482,234 compared to 1,515,667 in 2012–2013: a reduction of 2.2% (total quantity of tablets reduced by 4.4% from 43,040,735 to 41,145,680 for the same period)[4]. However, there is a large variation in prescribing rates of these medicines across health boards and between GP practices, and prescribing in Wales is still high in comparison to England, with six out of seven health boards in Wales within the highest prescribing quartile when compared to clinical commissioning groups (CCGs) in England.

Useful resources

- Welsh Medicines Partnership (2011) Educational Pack: Material to Support Appropriate Prescribing of Hypnotics and Anxiolytics across Wales.
- AWMSG (2014) Polypharmacy: Guidance for Prescribing in Frail Adults.

5.0 OPIOID ANALGESICS

***Purpose*:** Encourage the appropriate prescribing of opioid analgesics.

1. *Unit of measure:* Morphine items as a percentage of strong opioid prescribing (UDG).

Target for 2015–2016: Maintain performance levels within upper quartile, or show an increase towards the quartile above.

UDG: Buprenorphine, dipipanone, fentanyl, hydromorphone, morphine, oxycodone, pentazocine, pethidine, tapentadol* (excluding injection formulations and buprenorphine preparations prescribed for the management of opioid dependence[19]).

*Note that, as of August 2014, tapentadol modified-release (Palexia® SR) is the only formulation of tapentadol that has been recommended by AWMSG and ratified by the Minister for Health and Social Services for use within NHS Wales[40].

2. Unit of measure: Tramadol DDDs per 1,000 patients.

Target for 2015–2016: Maintain performance levels within lower quartile, or show a reduction towards the quartile below.

Background and evidence

Morphine

Opioids have a well established role in the management of acute pain following trauma (including surgery), and in the management of pain associated with terminal illness.

Opioids are increasingly being used in chronic non-cancer pain management, with a number of potential reasons for this, including new preparations and formulations of opioids, changes in patient expectation, medical practice and societal attitudes[41]. There is evidence from clinical trials that opioids can be effective, in the short and medium term, in providing symptomatic improvement in a variety of non-cancer pain conditions[42]. However, the safety and efficacy of opioids in the long term is uncertain as is the propensity for these drugs to cause problems of tolerance, dependence and addiction. The benefits of opioid treatment for the patient must be balanced against the burdens of long-term use, as therapy for persistent pain may need to be continued for months or years[42].

The World Health Organisation (WHO) has developed a three-step 'ladder' for cancer pain. Although developed and validated only for the treatment of cancer pain, the WHO analgesic ladder is widely used to guide basic treatment of acute and chronic pain[41]:

- Step 1. Non-opioid analgesic (e.g. paracetamol, NSAID)
- Step 2. Opioid for mild to moderate pain (e.g. codeine) with or without a non-opioid analgesic
- Step 3. Opioid for moderate to severe pain (e.g. morphine) with or without a non-opioid analgesic[43]

The SIGN guideline for the management of chronic pain suggests that careful assessment and diagnosis is key to initiating appropriate pharmacotherapy and that regular scheduled re-assessment of pain relief and pharmacotherapy is required. Its guideline includes pathways for assessing and managing care and a pathway for using strong opioids in patients with chronic pain[41]. The British Pain Society recommends starting with a low dose and titrating according to analgesia and side-effects. They also

recommend that doses greater than 180 mg morphine daily (or equivalent) require specialist advice, whilst requests for dose increases should be evaluated carefully[42].

NICE CG140 recommends oral modified-release morphine as the first-line maintenance treatment for patients with advanced and progressive disease who require strong opioids[44]. Morphine remains the most valuable opioid analgesic for severe pain. It is the standard against which other opioid analgesics are compared[19]. The majority of patients tolerate oral morphine well[45]. Where possible, modified-release opioids administered at regular intervals should be used in the management of patients with persistent pain. Use of more flexible dosing regimens using immediate-release preparations (alone or in combination with modified-release preparations) may be justified in some circumstances[42].

The efficacy and safety of morphine is established in clinical practice. There is a lack of evidence from high-quality comparative trials that other opioids have advantages in terms of either efficacy or side effects that would make them preferable to morphine for first-line use in cancer pain. Familiarity with the use of morphine by most practitioners is an additional consideration for patient safety[45].

Eighty percent of patients taking opioids will experience at least one adverse effect[42]. These should be discussed with the patient before treatment begins. The most common adverse effects are constipation, nausea, somnolence, itching, dizziness and vomiting. Tolerance to some side effects usually occurs within the first few days of treatment; pruritus and constipation tend to persist. Adverse effects should be managed actively with anti-emetics, antihistamines and laxatives as appropriate[42].

The clinical response to morphine is highly variable as the systemic bioavailability of morphine by the oral route is poor, with wide variation between individuals. However, with individual dose titration, a satisfactory level of analgesia can usually be achieved[45]. A significant minority of patients are unable to tolerate morphine, mainly due to adverse side effects.

NICE CG140 states that transdermal patch formulations should not routinely be used as first-line maintenance treatment in palliative care. It does, however, state that they can be considered in patients for whom oral opioids are not suitable and analgesic requirements are stable[44]. The MHRA reports several instances of unintentional overdose of fentanyl due to dosing errors, accidental exposure and exposure of the patch to a heat source[46]. Fentanyl is a potent opioid analgesic and should be used only in patients who have previously tolerated opioids[46].

The Welsh average for morphine items as a percentage of strong opioid items prescribed (UDG) for the quarter to March 2014 was 52.74% compared to 46.3% the previous year[4].

Tramadol

Tramadol is licensed for the treatment of moderate to severe pain and is classed as a strong opioid. Tramadol produces analgesia by two mechanisms: an opioid effect and an enhancement of the serotonergic and adrenergic pathways[19]. It has fewer of the typical opioid side effects, e.g. less respiratory depression and constipation, but psychiatric reactions have been reported.

Tramadol accounts for an increasing number of deaths and reports to the National Poisons Information Service[47]. It is subject to abuse and dependence and there are concerns with regard to interactions. Deaths related to the misuse of tramadol in England and Wales increased from 83 in 2008 to 220 in 2013[48]. In June 2014, tramadol was placed within Schedule III to the Misuse of Drugs Regulations but with exemptions from safe custody.

Dizziness and nausea are the most commonly reported adverse effects of tramadol. Headache, somnolence, vomiting, constipation, dry mouth, fatigue and sweating are other common side effects[49]. Hallucinations, confusion and convulsions, as well as rare cases of dependence and withdrawal, have been reported with tramadol at therapeutic doses[50].

To minimise the risk of convulsions, the CSM recommended that patients with a history of epilepsy take tramadol only if there are compelling reasons to do so[50]. In addition, tramadol should be used with caution in patients taking concomitant medicines that can lower the seizure threshold, such as tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs)[50]. The use of tramadol is contra-indicated in uncontrolled epilepsy and in patients receiving, or who have recently discontinued (within the previous two weeks) monoamine oxidase inhibitors.

This NPI seeks to ensure the appropriate use and review of tramadol, minimising the potential for misuse.

The NPI does not measure the prescribing of Tramacet® (tramadol/paracetamol combination) as there are no DDDs available. Tramacet® is a non-formulary item in all health boards in Wales and prescribing accounts for 1.9% of all tramadol prescribed. Health boards may wish to identify high prescribers of this combination product to review alongside this NPI.

Useful resources

- National Patient Safety Agency (2008) Reducing dosing errors with opioid medicines.
- MHRA Opioids Learning Module – aimed at helping healthcare professionals to reduce the risks associated with opioid prescribing.
- WHO Pain Relief Ladder.
- NICE (2012) CG140: Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults.
- SIGN (2013) SIGN 136. Management of chronic pain
- AWMSG (2013) Tramadol Educational Resource Materials.
- AWMSG (2012) Patient Information Leaflet: Opioids in Palliative Care.

6.0 ANTIBIOTICS

***Purpose*:** The development of NPIs for antibiotic prescribing supports one of the key elements of the Welsh Antimicrobial Resistance Programme: to inform, support and promote the prudent use of antimicrobials[51].

Total items
Unit of measure:
Total antibacterial items per 1,000 STAR-PUs.

Target for 2015–2016:
No performance target set. Aim for reduction in prescribing year on year, measuring quarter to December only.

Co-amoxiclav
Units of measure:
Co-amoxiclav items per 1,000 patients.
Co-amoxiclav items as a percentage of total antibacterial items.

Target for 2015–2016:
Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

Cephalosporins
Units of measure:
Cephalosporin items per 1,000 patients.
Cephalosporin items as a percentage of total antibacterial items.

Target for 2015–2016:
Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

Fluoroquinolones
Units of measure:
Fluoroquinolone items per 1,000 patients.
Fluoroquinolone items as a percentage of total antibacterial items.

Target for 2015–2016:
Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

Notes
The above NPIs only cover antibacterials that appear in Chapter 5 (Infections) of the British National Formulary (BNF)[19].

Comparative trends for all the antibiotic NPIs should be interpreted with caution, with particular respect to seasonal variation.

Background and evidence
Total antibacterial items
The Public Health Wales report *Antimicrobial Resistance and Usage in Wales (2005–2011)* presents the different prescribing and antimicrobial resistance (AMR) patterns across Wales[52]. The report shows that AMR in Wales has increased over the seven years reported for some of the major pathogens. In some cases there is considerable variability in resistance rates between different hospitals and health boards in Wales,

suggesting an opportunity to reduce antibiotic use in some areas[52]. For the year April 2013–March 2014, primary care prescribing rates varied from 704 to 843 items per 1,000 patients across Welsh health boards[4].

The *UK Five Year Antimicrobial Resistance Strategy 2013–2018* was published in September 2013[53]. This has been developed collaboratively with the UK devolved administrations and will provide surveillance and a coordinated plan of action needed to address this issue. The overarching goal of the strategy is to slow the development and spread of AMR. It focuses activities around three strategic aims:

- improve the knowledge and understanding of AMR,
- conserve and steward the effectiveness of existing treatments,
- stimulate the development of new antibiotics, diagnostics and novel therapies.

The Welsh Government set new targets in 2014 for reducing *C. difficile* and methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia healthcare-associated infections. To achieve the national target, each of the health boards is required to reduce rates to no more than 31 per 100,000 population for *C. difficile* cases, and 2.6 per 100,000 population for MRSA bacteraemias[54].

Public health guidance states "Use simple generic antibiotics if possible. Avoid broad spectrum antibiotics (e.g. co-amoxiclav, quinolones and cephalosporins) when narrow spectrum antibiotics remain effective, as they increase risk of *C. difficile*, MRSA and resistant urinary tract infections"[55]. Broad-spectrum antibiotics need to be reserved to treat resistant disease, and should generally be used only when narrow-spectrum and less expensive antibiotics are ineffective. The guidance advises when it may be appropriate to consider a broad-spectrum antibiotic[55].

The principal risk factor for *C. difficile*-associated disease is prior antimicrobial therapy, especially with broad-spectrum antibiotics. Some antibiotics appear to have a much higher propensity to cause disease than others. The use of co-amoxiclav is associated with a moderate risk of *C. difficile* infection, whilst second- and third-generation cephalosporins and fluoroquinolones are associated with a high risk of *C. difficile* infection[56].

NICE is currently developing a guideline on antimicrobial stewardship (publication expected 2015) and a public health guideline, *Antimicrobial resistance – changing risk-related behaviours*, is due for publication in March 2016.

Co-amoxiclav

Co-amoxiclav is a broad-spectrum penicillin with activity against beta-lactamase-producing organisms such as *S. aureus* and *Escherichia coli*. In 1997, the CSM (now the MHRA) issued guidance which limited the indications for co-amoxiclav due to an increased risk of cholestatic jaundice compared with other antibacterial agents[57].

Cephalosporins

The cephalosporins are broad-spectrum antibiotics, which are used for the treatment of septicaemia, pneumonia, meningitis, biliary-tract infections, peritonitis and urinary tract infections[19] mainly in secondary care settings. Cephalosporins are not listed as first-line treatments in the public health report *Management of infection guidance for primary care for consultation and local adaption*[55].

Fluoroquinolones

The prescribing of fluoroquinolones in general practice remains a concern due to increasing resistance (e.g. quinolone-resistant *Neisseria gonorrhoeae*, *E. coli* and other Enterobacteriaceae). They are recommended first-line only in limited situations (e.g. acute pyelonephritis or acute prostatitis)[55].

Useful resources

- AWMSG (2013) CEPP National Audit: Focus on Antibiotic Prescribing.
- Welsh Medicines Resource Centre (WeMeReC) (2012) Bulletin: Appropriate antibiotic use – whose responsibility?
- Royal College of General Practitioners. TARGET Antibiotics toolkit.

7.0 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Purpose: Ensure that the risks associated with NSAIDs are minimised by appropriate choice and use.

1. Unit of measure: NSAID ADQs per 1,000 STAR-PUs.

Target for 2015–2016: Maintain performance levels within the lower quartile, or show a reduction towards the quartile below.

2. Unit of measure: Ibuprofen and naproxen items as a percentage of NSAID prescribing.

Target for 2015–2016: Maintain performance levels within the upper quartile, or show an increase towards the quartile above.

Background and evidence

There is overwhelming evidence to reduce prescribing of NSAIDs, especially in the elderly, due to the risk of GI, cardiovascular and renal complications[58–61]. The MHRA recommends that people should use the lowest effective dose, for the shortest duration necessary to control symptoms, in order to minimise adverse effects[62].

All oral NSAIDs/COX-2 inhibitors have analgesic effects of a similar magnitude but vary in their potential GI, liver and cardio-renal toxicity; therefore, when choosing the agent and dose, it is important to take into account individual patient risk factors, including age[6,7].

NICE CGs recommend that if a person with osteoarthritis/RA needs to take low-dose aspirin, healthcare professionals should consider other analgesics before substituting or adding an NSAID or COX-2 inhibitor[6,7]. Gastroprotection, with a PPI, is recommended particularly for patients on NSAIDs with osteoarthritis or RA (in people over 45 years). Ibuprofen and selective COX-2 inhibitors are associated with the lowest GI risk, but serious and fatal GI reactions have nevertheless been reported[58]. Co-prescription of SSRIs may be associated with a similar increase in the risk of GI complications as low-dose aspirin[63].

The MHRA has issued warnings on the increased risk of renal failure and thrombotic events associated with the use of NSAIDs[59–61]. COX-2 inhibitors, diclofenac 150 mg and ibuprofen 2.4 g daily are associated with an increased risk of thrombotic events[19]. NSAIDs are contraindicated in severe heart failure and should only be prescribed for patients with signs of heart failure when considered essential[64]. A 2011 systematic review concluded that naproxen and low-dose ibuprofen (≤ 1,200 mg daily) appear least harmful in respect of cardiovascular toxicity[65].

In June 2013, the MHRA issued advice confirming that diclofenac should not be used in patients with serious underlying heart conditions such as heart failure, heart disease, circulatory problems or previous heart attack or stroke[66]. This followed a review of the safety of NSAIDs conducted by the European Medicines Agency, which concluded that the cardiovascular risk associated with diclofenac was similar to that of selective COX-2 inhibitors[67].

Acute kidney injury (AKI) is seen in 13–18% of all patients admitted to hospital and is increasingly being seen in primary care particularly in older people. NSAIDs are nephrotoxic and can cause AKI particularly in people with other risk factors e.g. heart failure, diabetes, liver disease and dehydration[68]. NSAIDs in combination with diuretics

and angiotensin converting enzyme inhibitors or angiotensin receptor blockers are associated with an increased risk of AKI[69].

NICE CG182 highlights that in patients with chronic kidney disease (CKD), the chronic use of NSAIDs may be associated with progression and acute use is associated with a reversible decrease in glomerular filtration rate. It recommends exercising caution when treating people with CKD with NSAIDs over prolonged periods of time[70].

Prescribing should be based on the safety profiles of individual NSAIDs or selective COX-2 inhibitors and on individual patient risk profiles (e.g. GI and cardiovascular). If an NSAID is needed, the preferred choices are ibuprofen (1,200 mg per day or less) or naproxen (1,000 mg per day or less).

Useful resources

- AWMSG (2010) CEPP All Wales Audit: Towards appropriate NSAID prescribing 2010–2012.
- NPC (2007) MeReC Extra Issue: Cardiovascular and GI safety of NSAIDs.

8.0 YELLOW CARDS

***Purpose*:** Increase the number of yellow cards submitted by GPs in Wales.

***Unit of measure*:** Number of yellow cards submitted per practice and per health board.

***Target for 2015–2016*:** Target for GP practice – GPs to submit one yellow card per 2,000 practice population. Target for each health board – submit yellow cards in excess of one per 2,000 health board population.

Background and evidence

Adverse drug reactions (ADRs) are a significant clinical problem, increasing morbidity and mortality. ADRs are attributed to 6.5% of hospital admissions in adults and 2.1% in children[71,72].

The Yellow Card Scheme is vital in helping the MHRA monitor the safety of medicines and vaccines that are on the market. YCC Wales is one of five regional ADR monitoring centres, acting on behalf of the MHRA.

Prior to April 2013, the number of reports from GPs across Wales had been in decline for several years. In April 2013, yellow card reporting was included as a CEPP Local Comparator and in April 2014 it became an NPI. Data obtained from YCC Wales show that the number of ADRs reported to the MHRA in Wales increased by 81% in 2013–2014 (from 649 reports in 2012–2013 to 1,177 reports in 2013–2014). This is the highest number of reports for the last six years.

In May 2013, YCC Wales worked in collaboration with WeMeReC to produce a pharmacovigilance module that was completed by 411 GPs. This resulted in an increase in the number of yellow cards received from GPs in Wales from 116 (in 2012–2013) to 271 (in 2013–2014), a rise of 134%.

It is anticipated that the inclusion of yellow card reporting as an NPI for 2015–2016 will further increase reporting rates amongst GPs.

Useful resources

- MHRA website
- Yellow Card website
- WeMeReC (2013) Pharmacovigilance
- YCC Wales website
- British Medical Journal Learning (2012) Pharmacovigilance – identifying and reporting adverse drug reactions module.

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GLOSSARY

ADQ: The average daily quantity (ADQ) is a measure of prescribing volume based upon prescribing behaviour in England. It represents the assumed average maintenance dose per day for a medicine used for its main indication in adults. ADQ is not a recommended dose but an analytical unit to compare prescribing activity.

DDD: The defined daily dose (DDD) developed by the World Health Organisation is a unit of measurement whereby each medicine is assigned a value within its recognised dosage range. The value is the assumed average maintenance dose per day for a medicine when used for its main indication in adults. A medicine can have different DDDs depending on the route of administration.

PU: Prescribing units (PUs) were adopted to take account of the greater need of elderly patients for medication in reporting prescribing performance in primary care. Patients aged 65 years and over are counted as three prescribing units; patients under 65 years and temporary residents are counted as one.

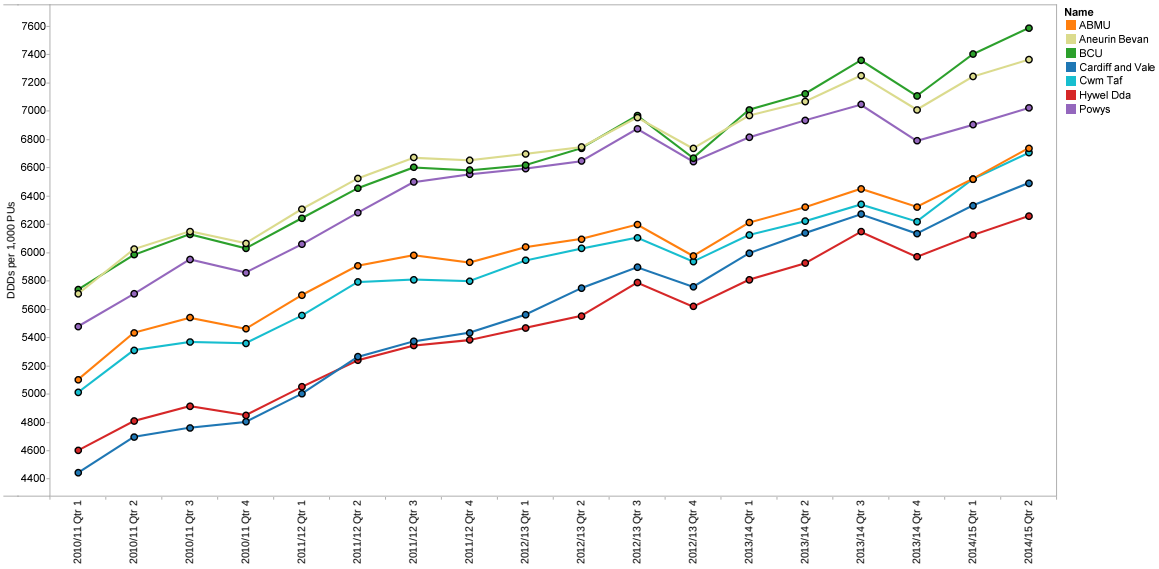
STAR-PU: Specific therapeutic group age–sex related prescribing units (STAR-PUs) are designed to measure prescribing weighted for age and sex of patients. There are differences in the age and sex of patients for whom medicines in specific therapeutic groups are usually prescribed. To make such comparisons, STAR-PUs have been developed based on costs of prescribing items within therapeutic groups.

APPENDIX 1. NHS WALES HEALTH BOARDS PERFORMANCE AND COMPARISON WITH ENGLISH CCGS AGAINST THE PROPOSED 2015–2016 NPIS

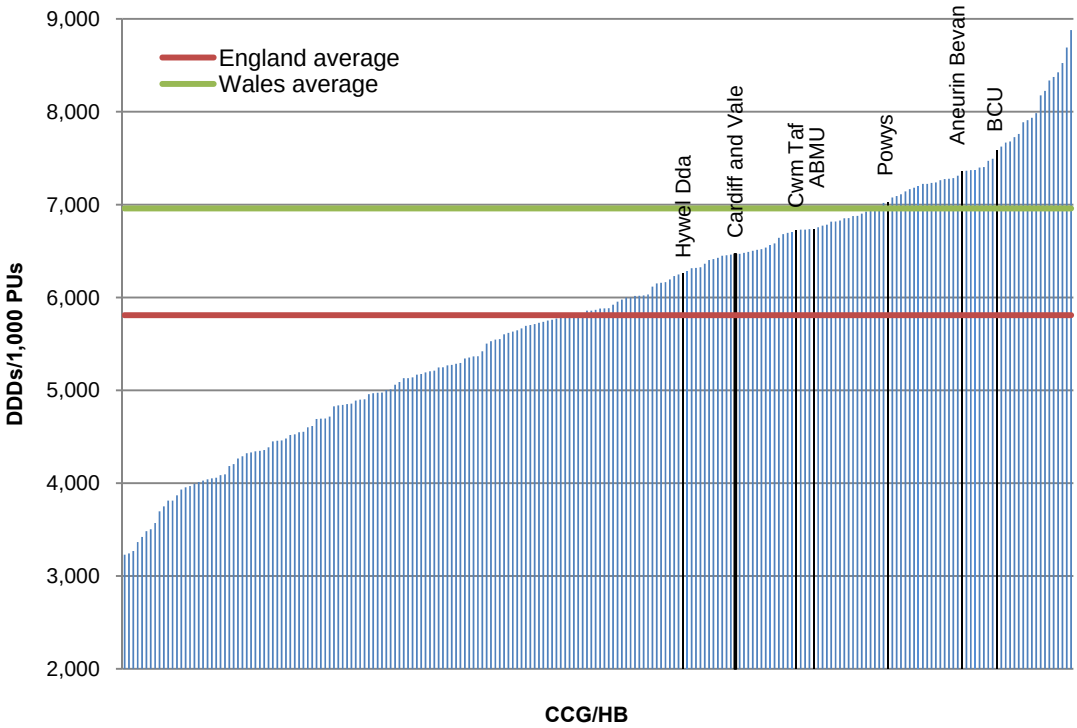
Data for each NPI are presented in two ways: a line graph/bar chart showing the trend in prescribing for each health board and a bar chart comparing prescribing of each health board with that of each CCG in England. The black bars represent the seven health boards in Wales; the blue bars represent the 211 CCGs in England.

1.0 PROTON PUMP INHIBITORS

Trend in PPI DDDs per 1,000 PUs to quarter ending September 2014

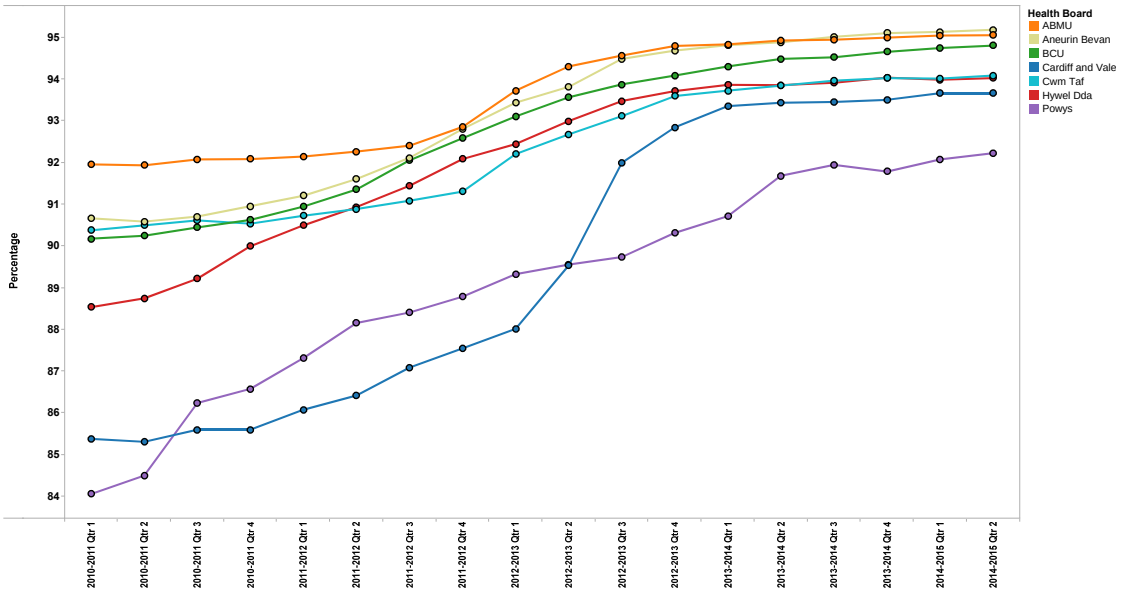


PPI DDDs per 1,000 PUs – Quarter ending September 2014

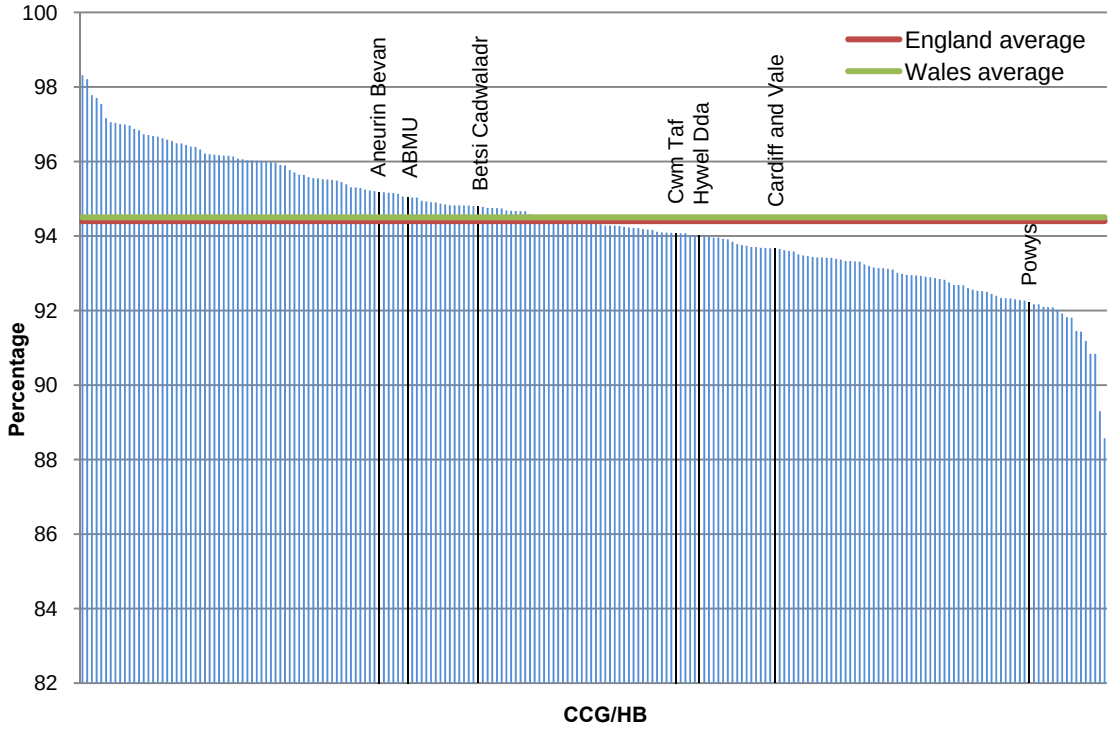


2.0 LIPID-MODIFYING DRUGS

Trend in LAC statin prescribing as a percentage of all statin, ezetimibe and simvastatin/ezetimibe combination prescribing to quarter ending September 2014

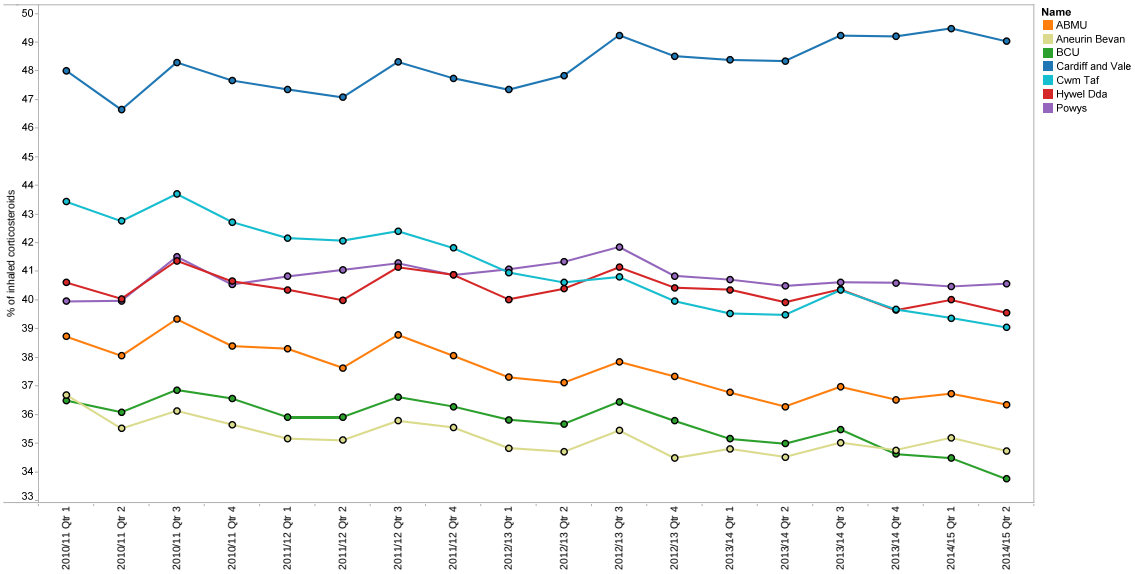


LAC statin items as a percentage of all statin, ezetimibe and simvastatin/ezetimibe combination prescribing – Quarter ending September 2014

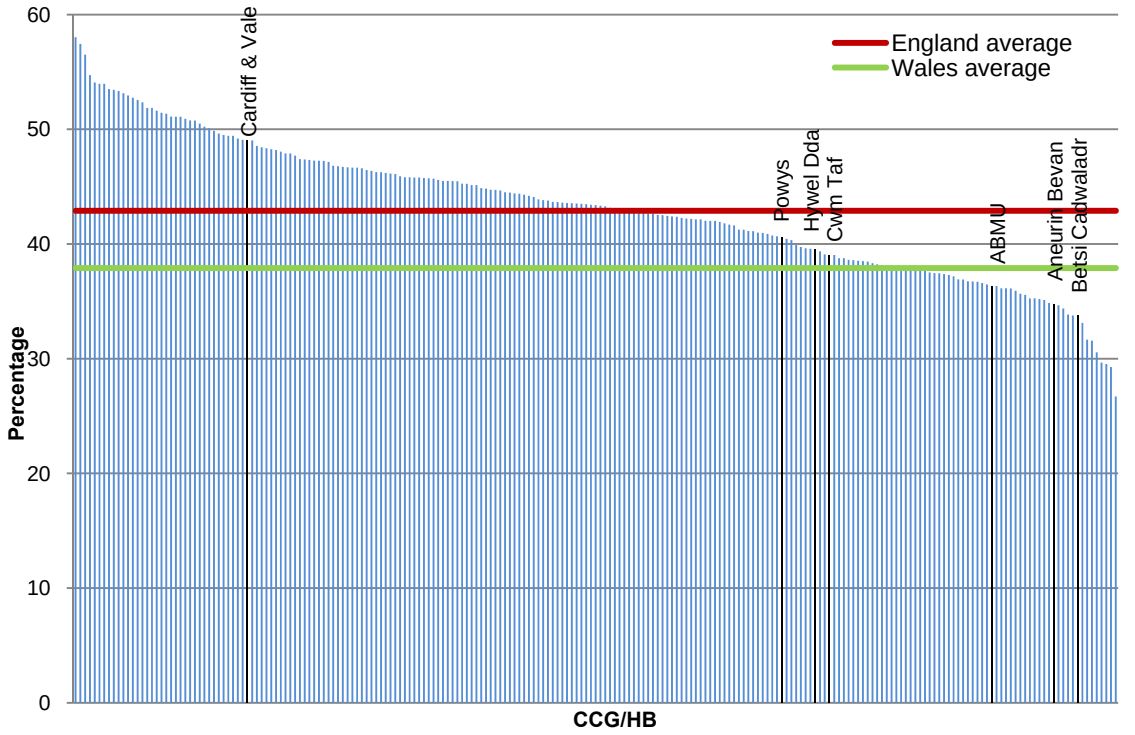


3.0 INHALED CORTICOSTEROIDS

Trend in low strength ICS as a percentage of all ICS prescribing to quarter ending September 2014

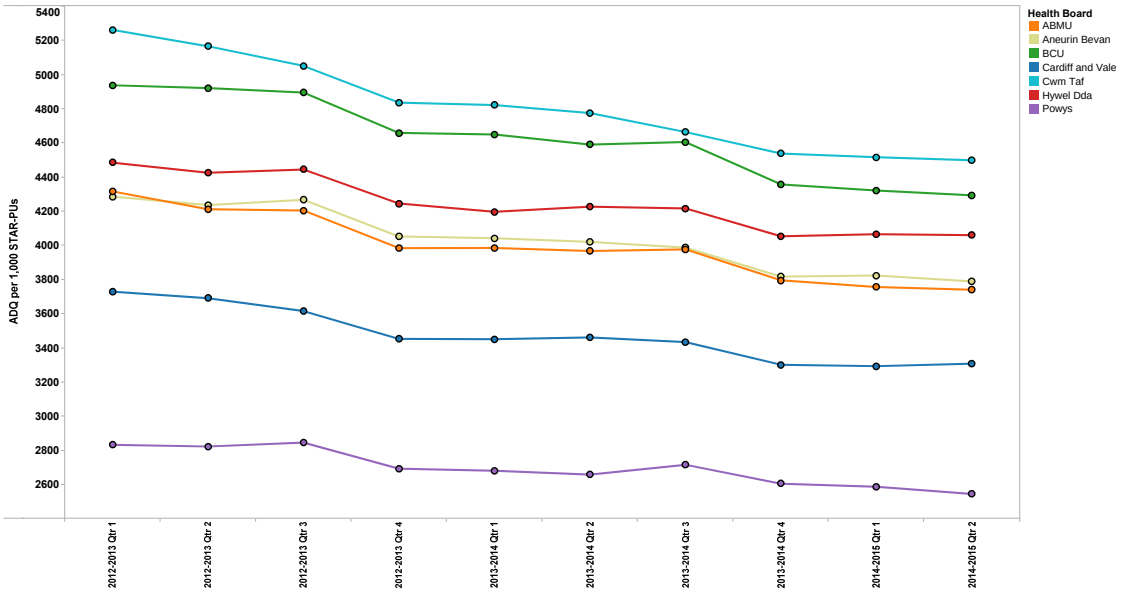


Low strength ICS items as a percentage of all ICS prescribing – Quarter ending September 2014

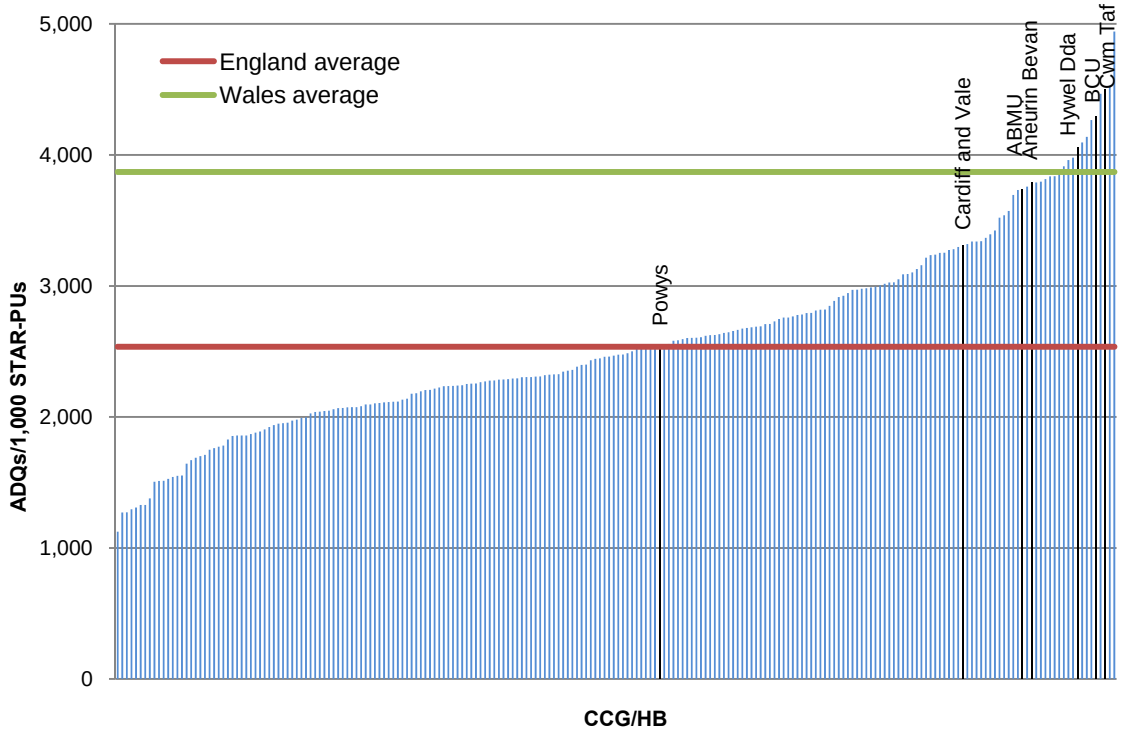


4.0 HYPNOTICS AND ANXIOLYTICS

Trend in hypnotic and anxiolytic prescribing (ADQs per 1,000 STAR-PUs (13)† (2012–2013 UDG) to quarter ending September 2014



Hypnotics and anxiolytics ADQs per 1,000 STAR-PUs (13) (2012–2013 UDG) Quarter ending September 2014

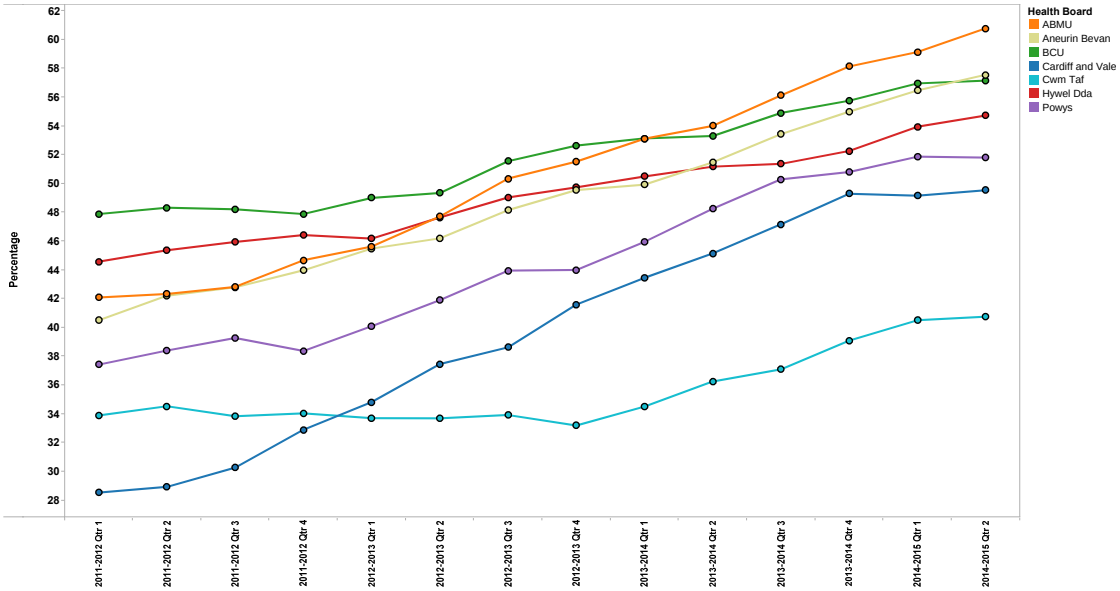


† STAR-PU weightings have been revised by the Health and Social Care Information Centre. STAR-PU (09) weightings have been updated to the STAR-PU (13) versions. These measures are routinely being used in data reported from April 2014. The data used in this document have been retrospectively calculated to provide comparisons dating back to April 2013.

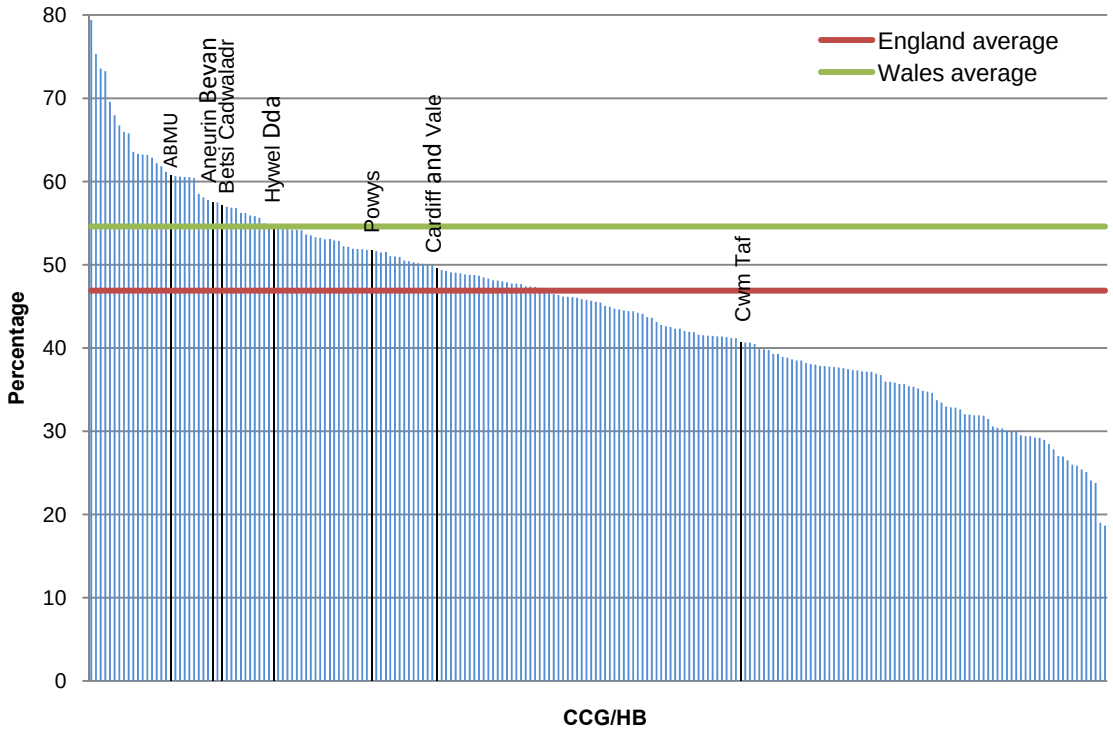
5.0 OPIOID ANALGESICS

5.1 Morphine

Trend in morphine prescribing as a percentage of strong opioid prescribing (2013–2014 UDG) to quarter ending September 2014

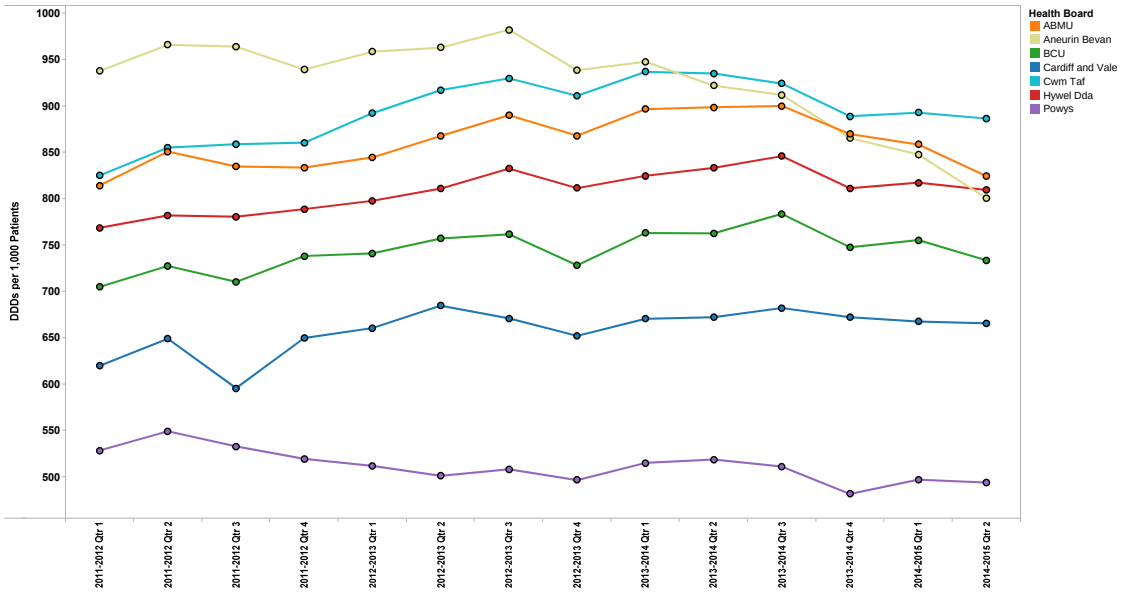


Morphine items as a percentage of strong opioid prescribing (2013–2014 UDG) Quarter ending September 2014

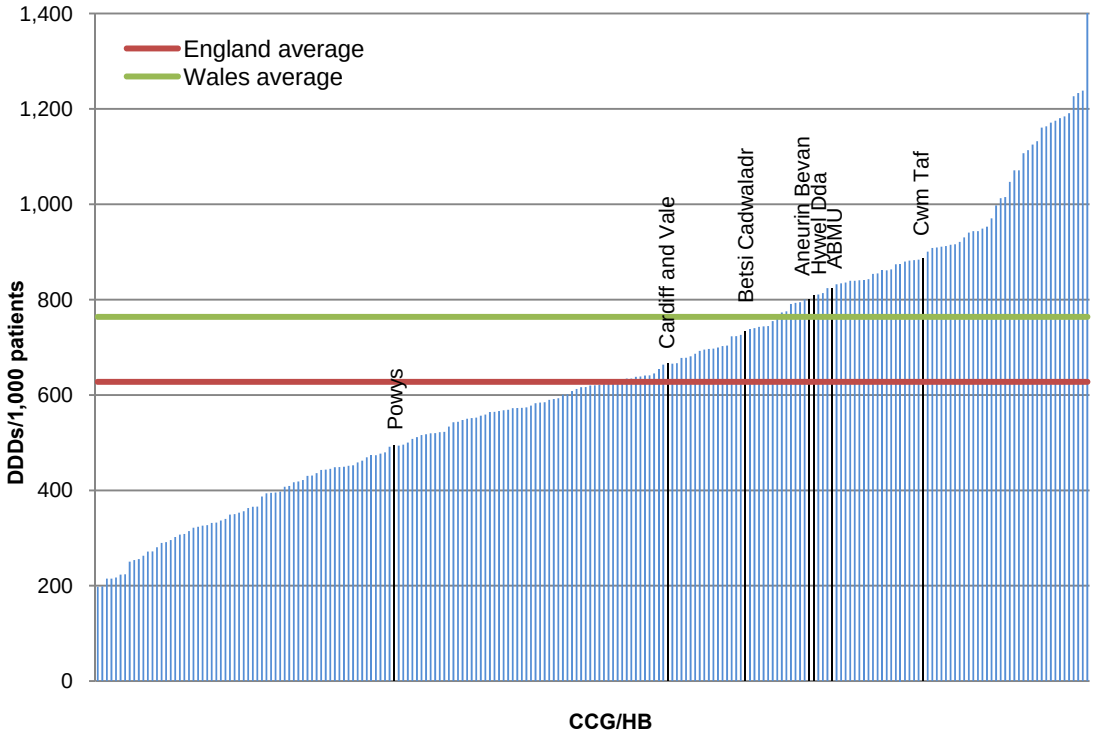


5.2 Tramadol

Trend in tramadol prescribing (DDDs per 1,000 patients) to quarter ending September 2014



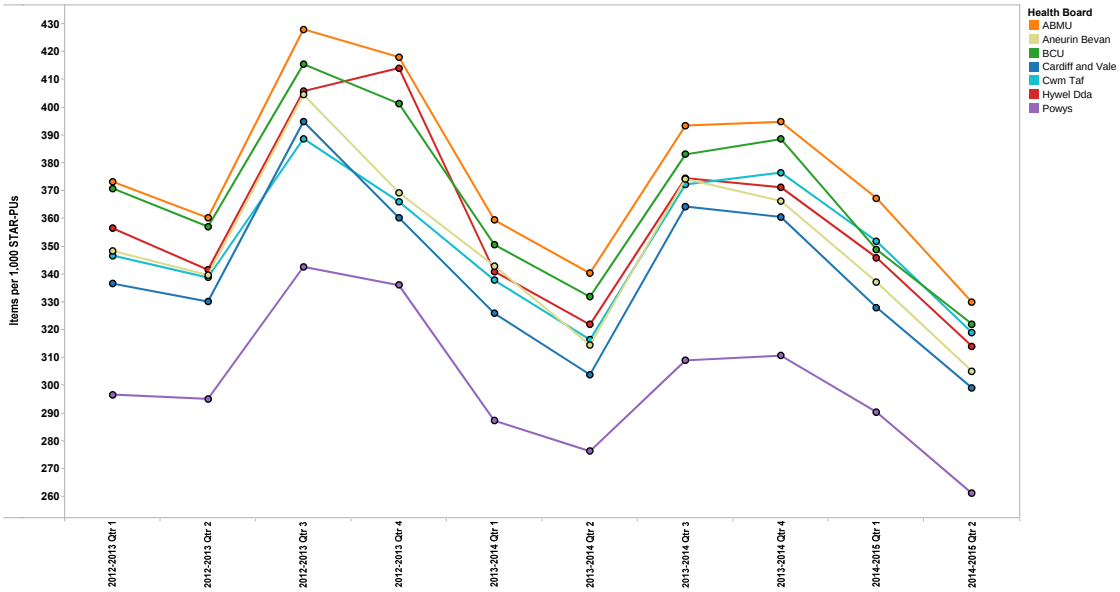
Tramadol DDDs per 1,000 patients – Quarter ending September 2014



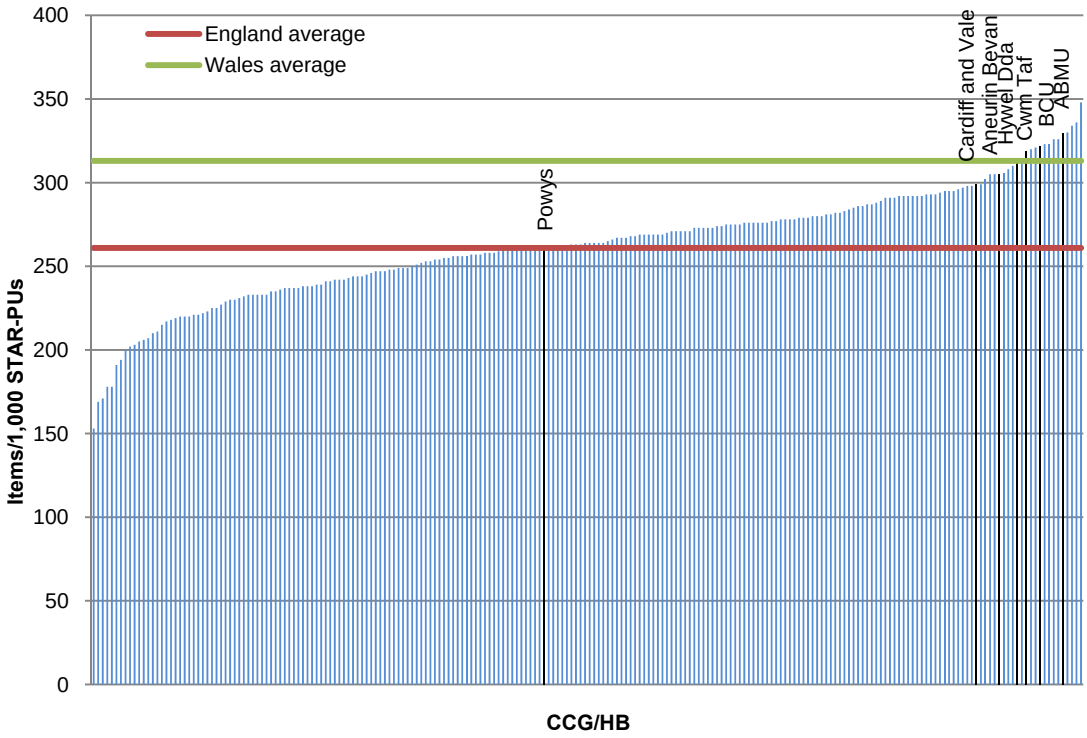
6.0 ANTIBIOTICS

6.1 Total antibiotics

Trend in total antibacterial prescribing (items per 1,000 STAR-PUs [13]) to quarter ending September 2014

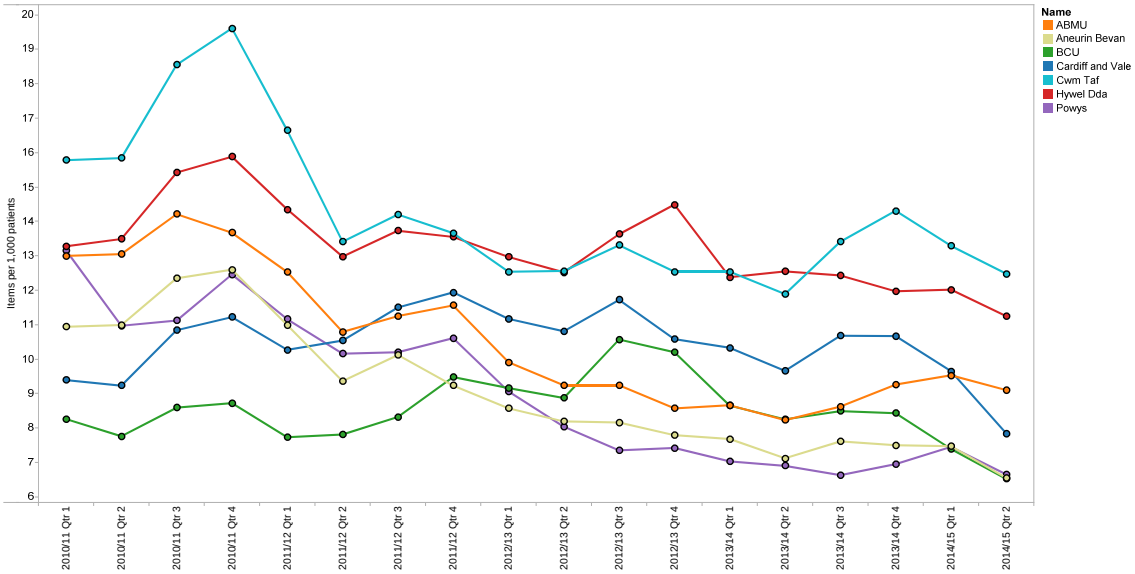


Total antibacterial items per 1,000 STAR-PUs (13) – Quarter ending September 2014

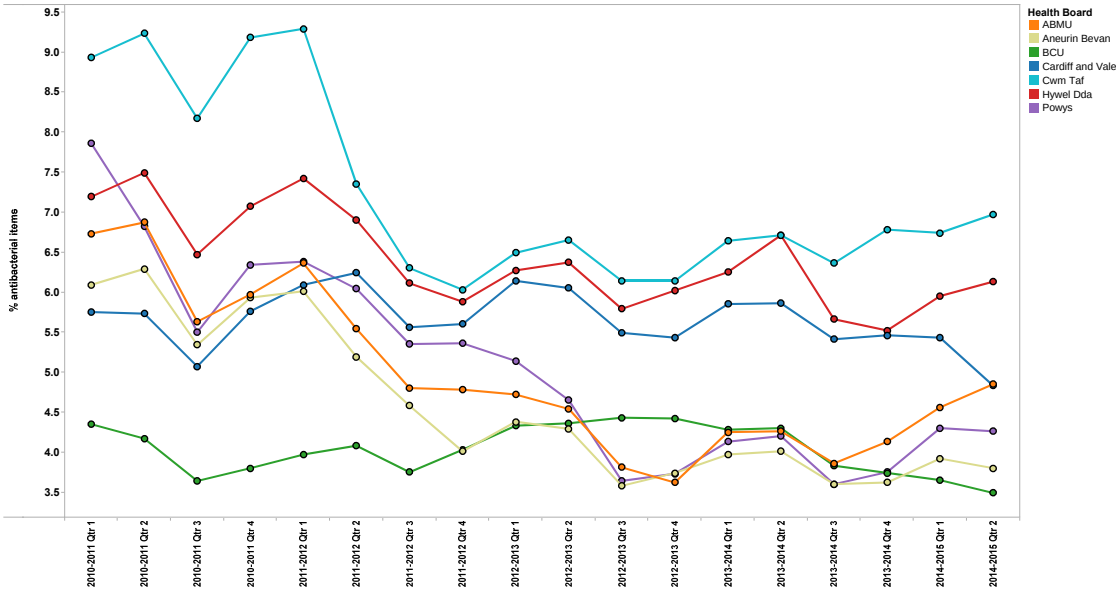


6.2 Co-amoxiclav

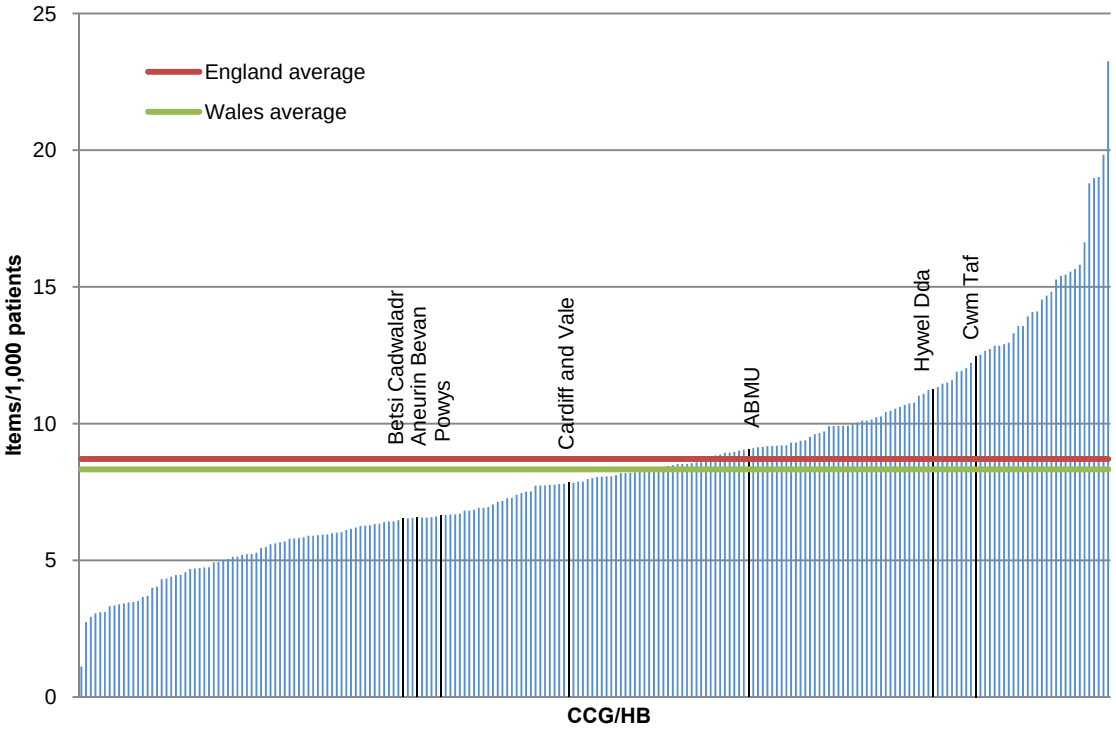
Trend in co-amoxiclav items per 1,000 patients to quarter ending September 2014



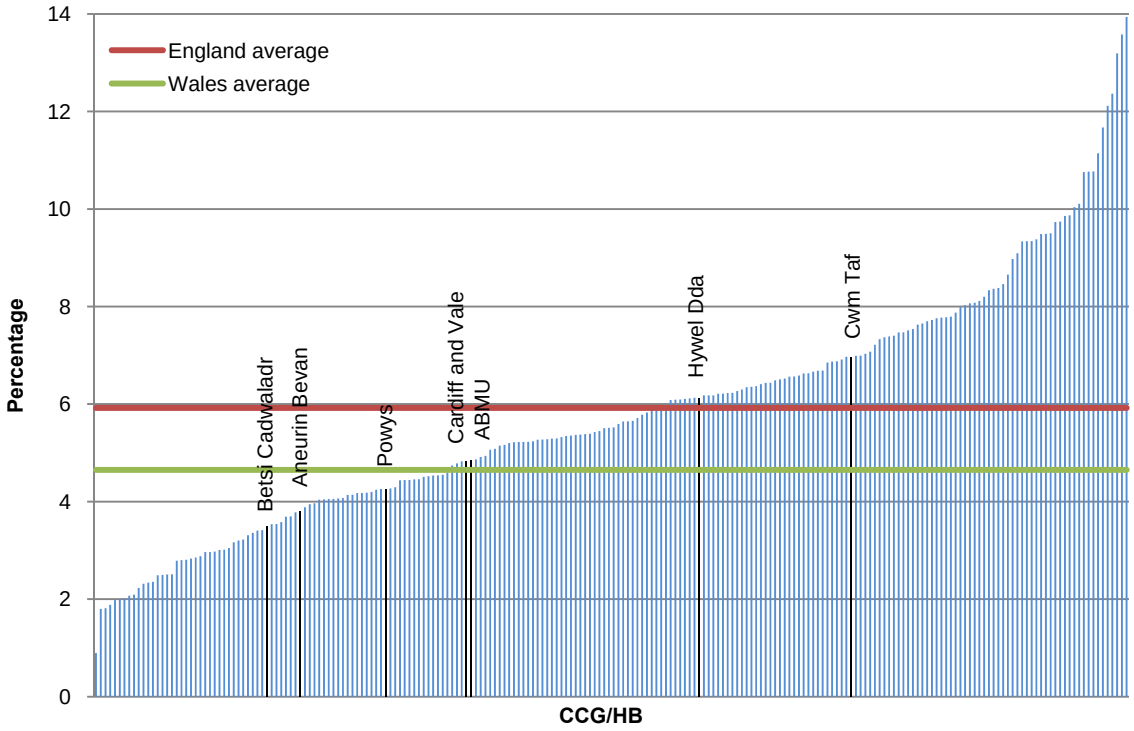
Trend in co-amoxiclav prescribing as a percentage of total antibacterial items to quarter to September 2014



Co-amoxiclav items per 1,000 patients – Quarter ending September 2014

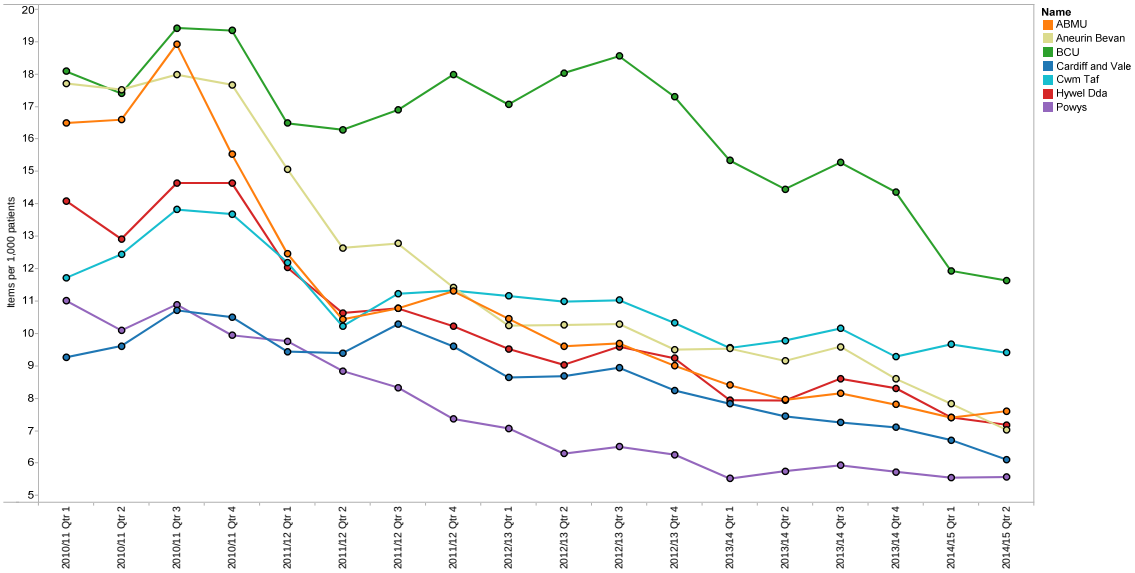


Co-amoxiclav prescribing as a percentage of total antibacterial items – Quarter ending September 2014

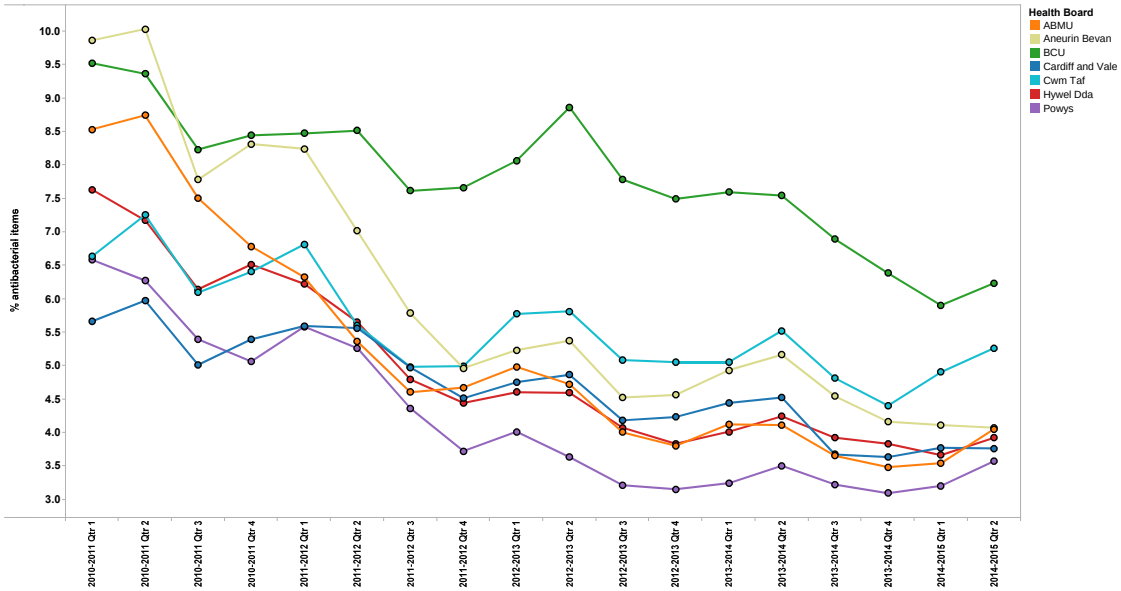


6.3 Cephalosporins

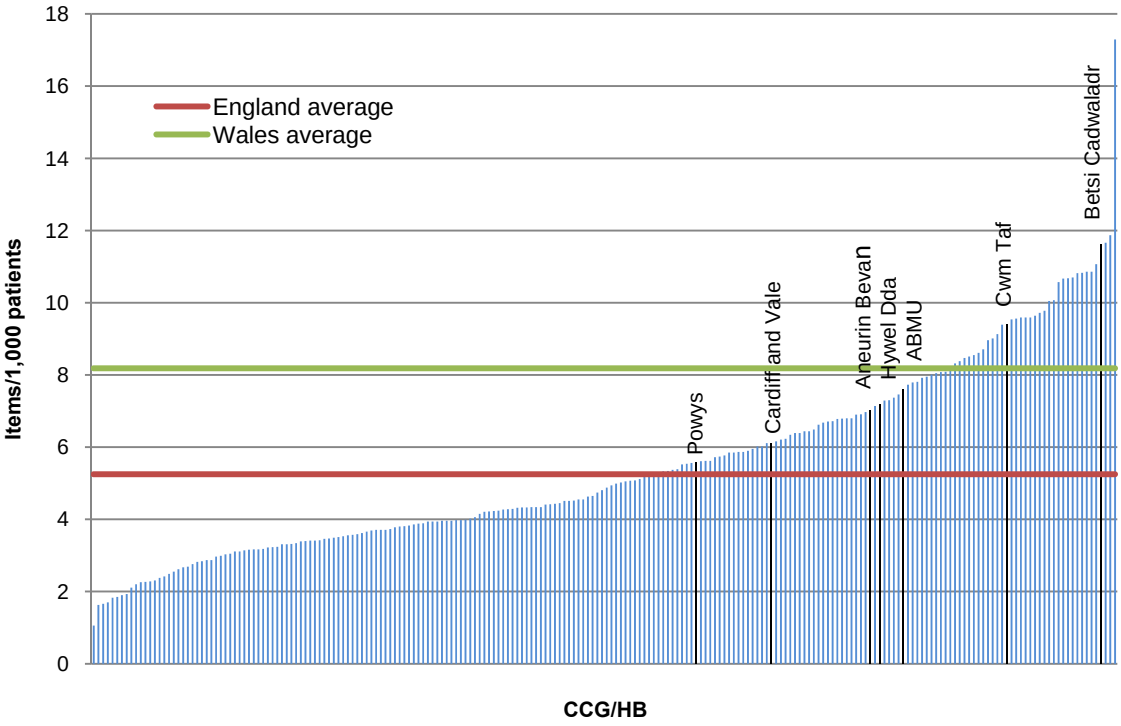
Trend in cephalosporin items per 1,000 patients to quarter ending September 2014



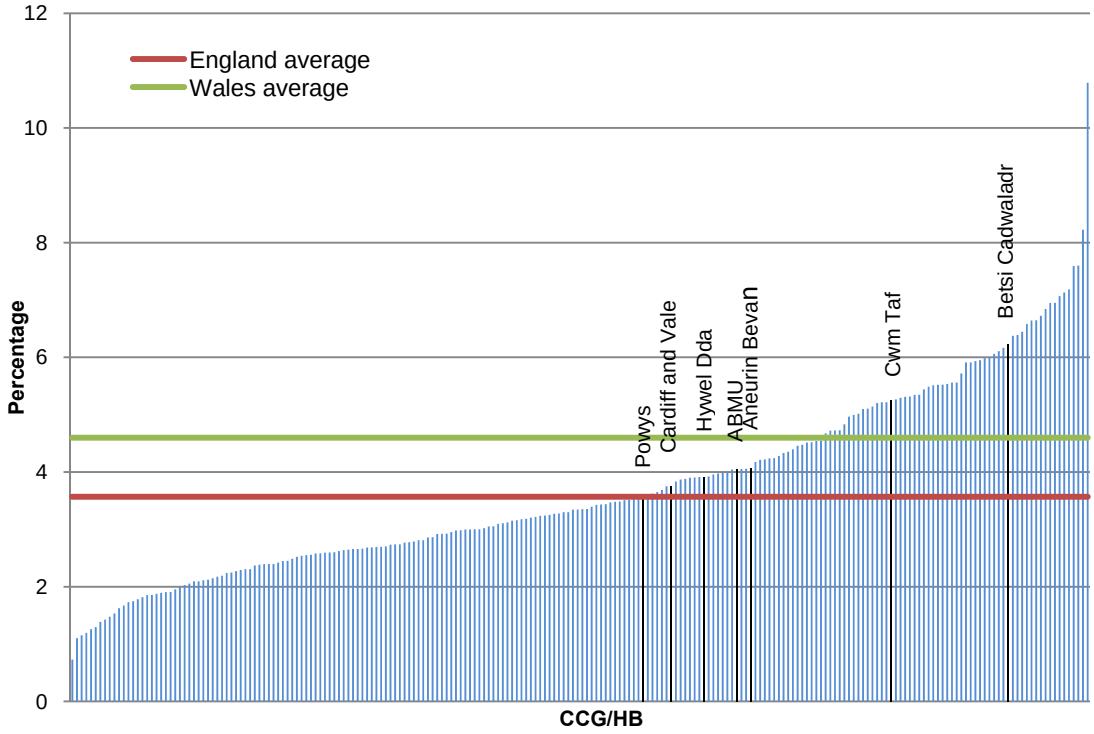
Trend in cephalosporin prescribing as a percentage of total antibacterial items to quarter September 2014



Cephalosporin items per 1,000 patients – Quarter ending September 2014

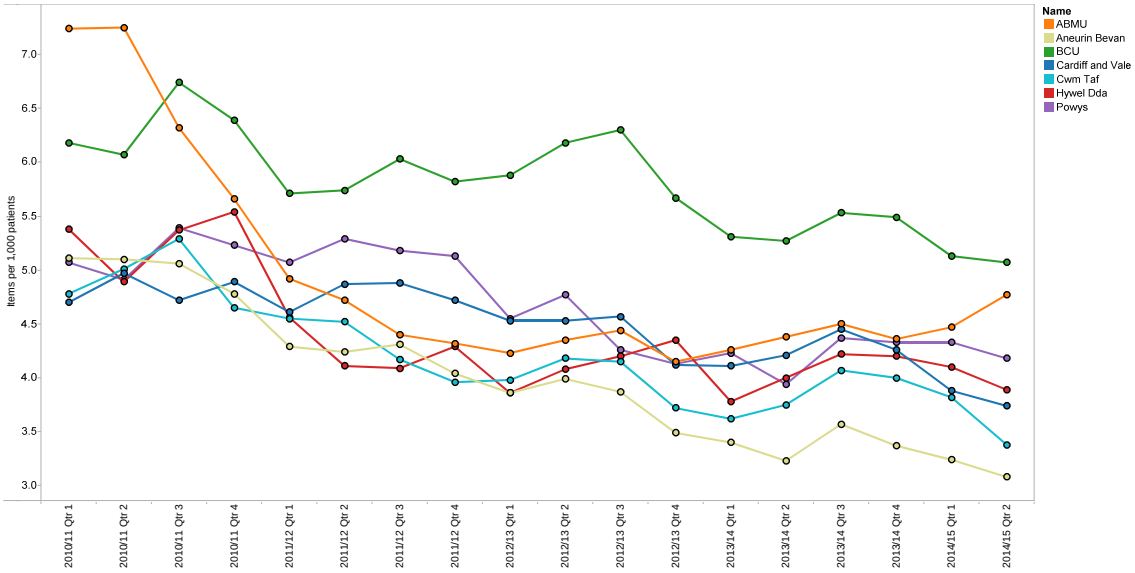


Cephalosporin prescribing as a percentage of total antibacterial items – Quarter ending September 2014

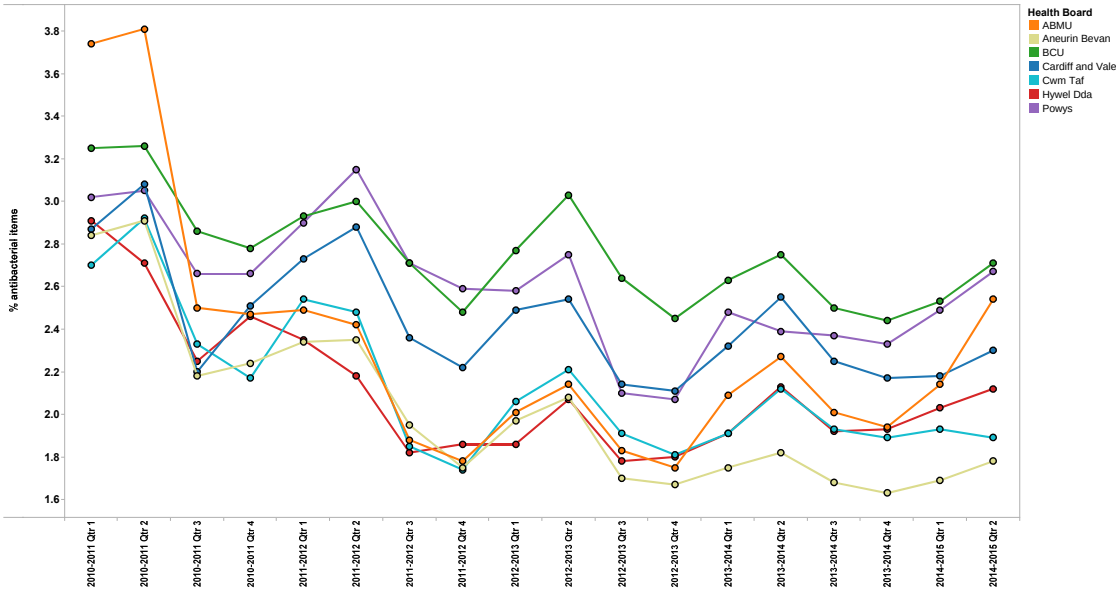


6.4 Fluoroquinolones

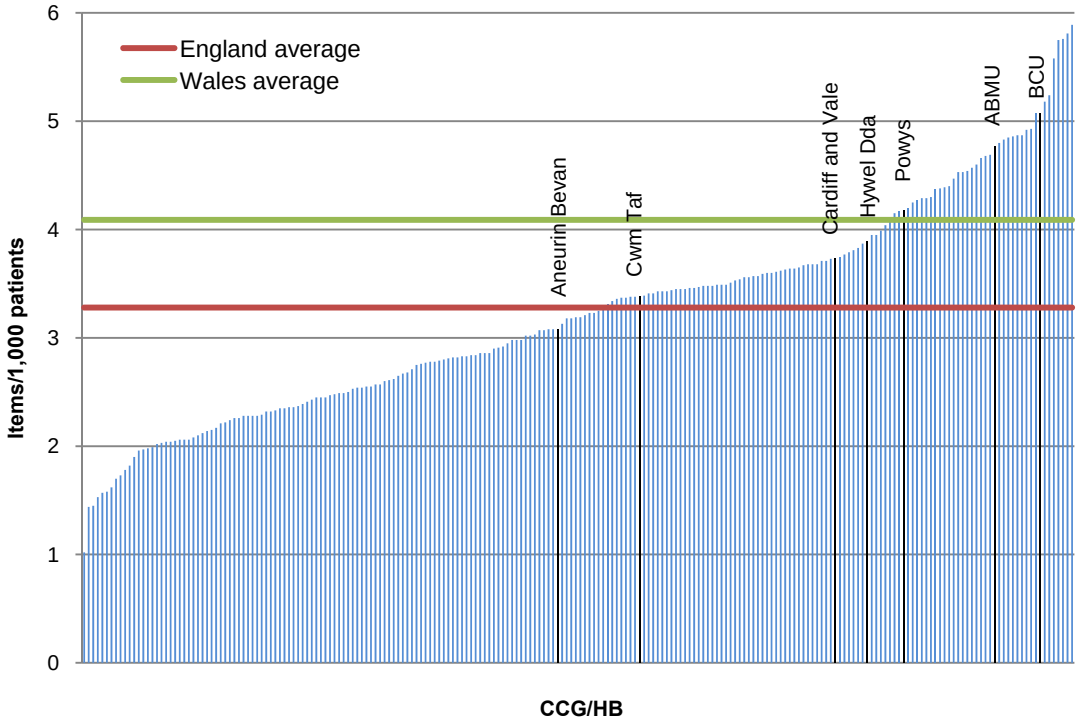
Trend in fluoroquinolone items per 1,000 patients to quarter ending September 2014



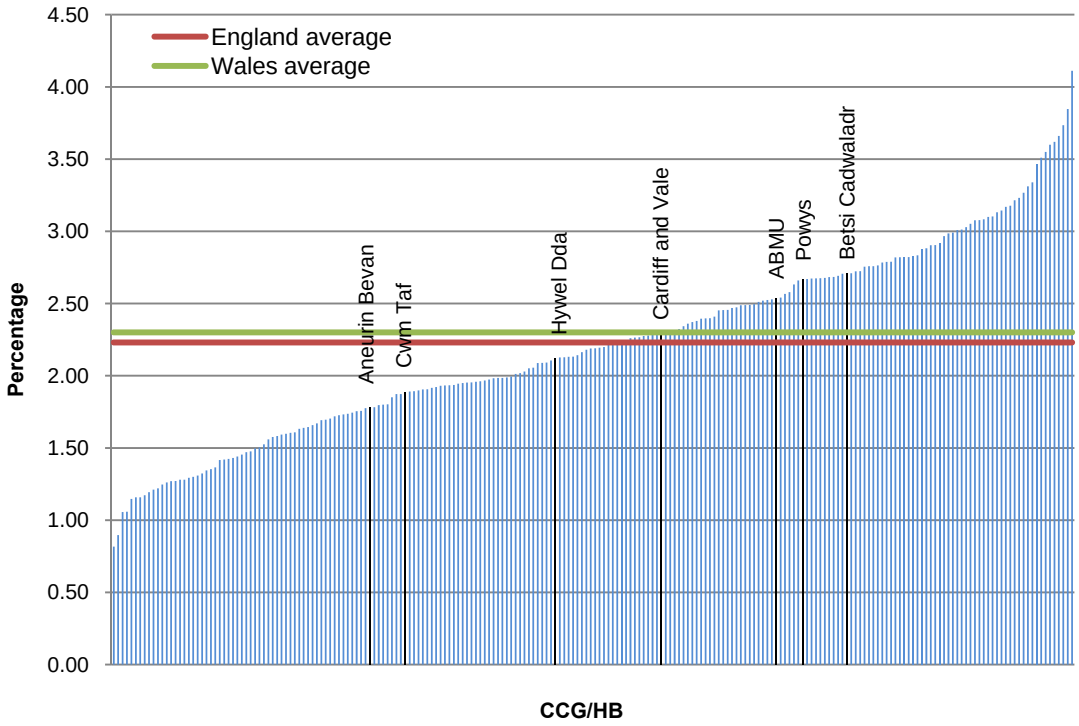
Trend in fluoroquinolone prescribing as a percentage of total antibacterial items to quarter ending September 2014



Fluoroquinolone items per 1,000 patients – Quarter ending September 2014



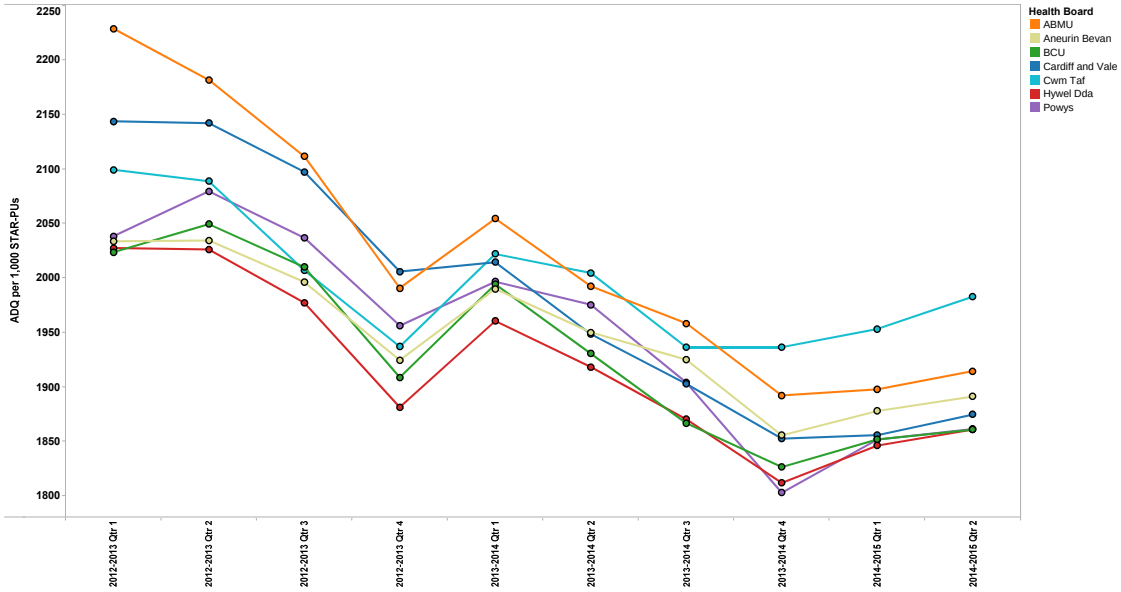
Fluoroquinolone prescribing as a percentage of total antibacterial items – Quarter ending September 2014



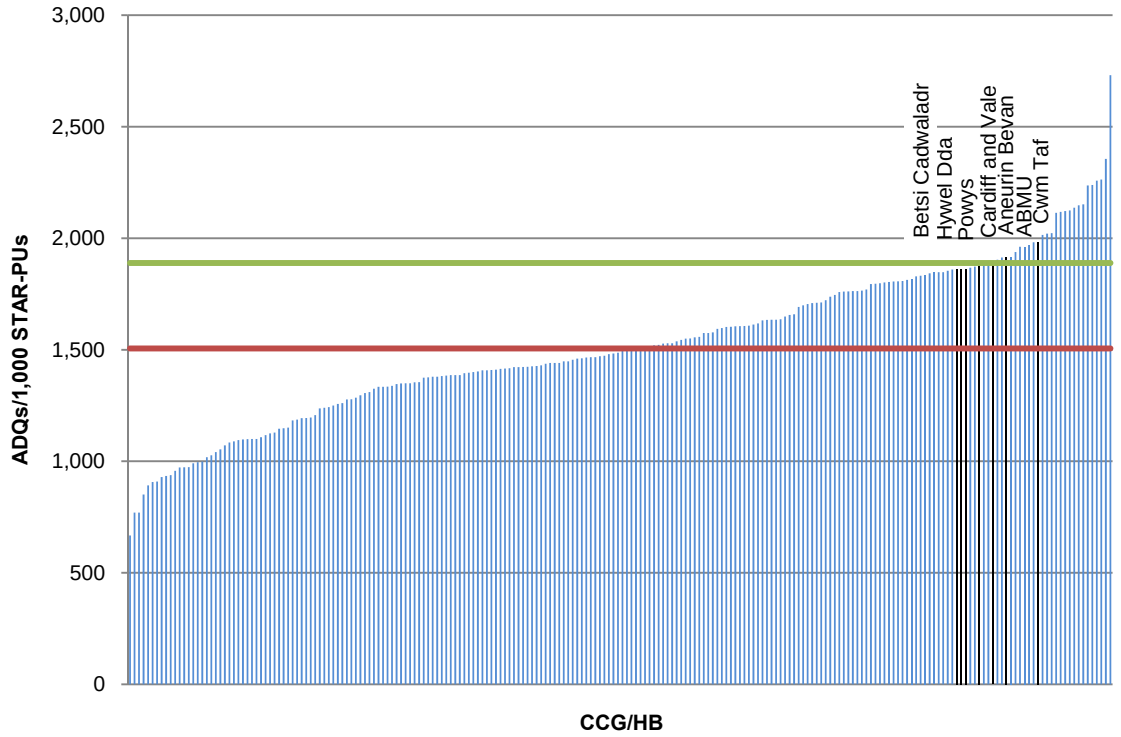
7.0 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

7.1 Total NSAIDS

Trend in NSAID prescribing (ADQs per 1,000 STAR-PUs (13)) to quarter ending September 2014

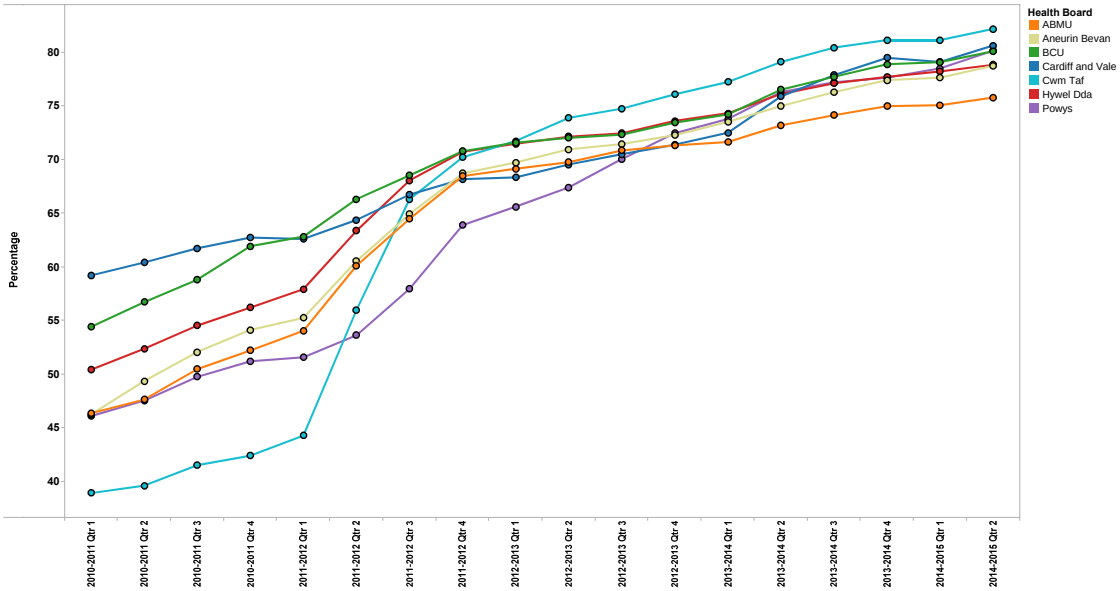


NSAID ADQs per 1,000 STAR-PUs (13) – Quarter ending September 2014

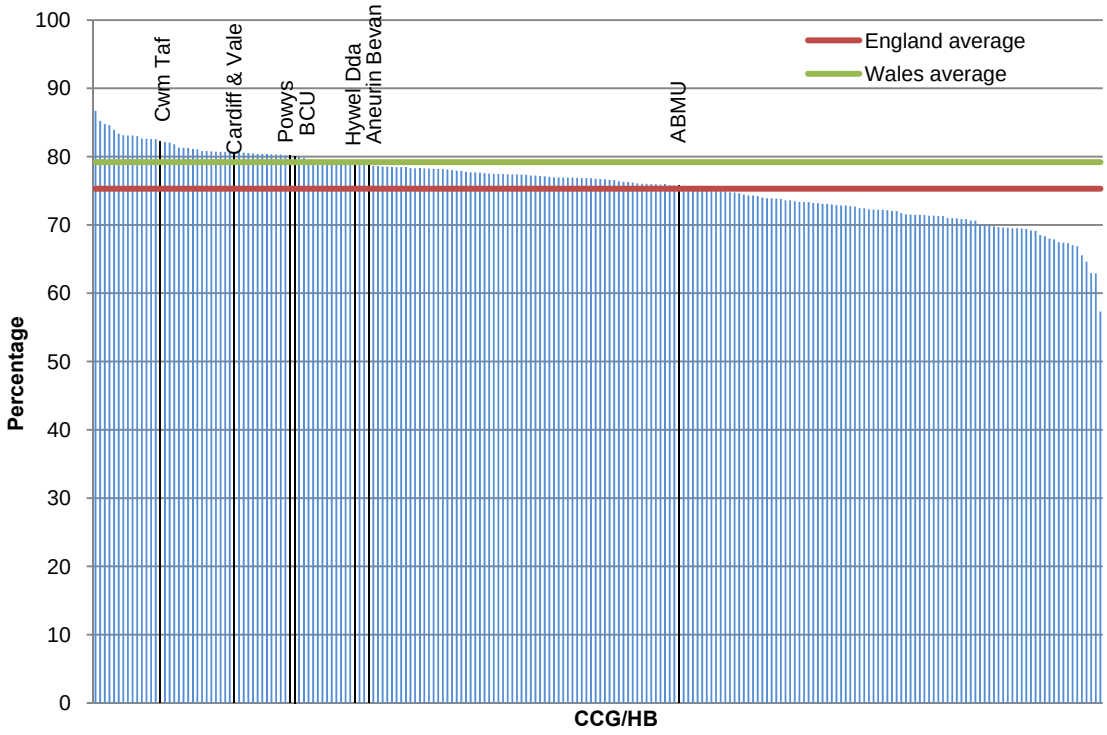


7.2 Ibuprofen and naproxen

Trend in ibuprofen and naproxen items as a percentage of NSAID prescribing to quarter ending September 2014

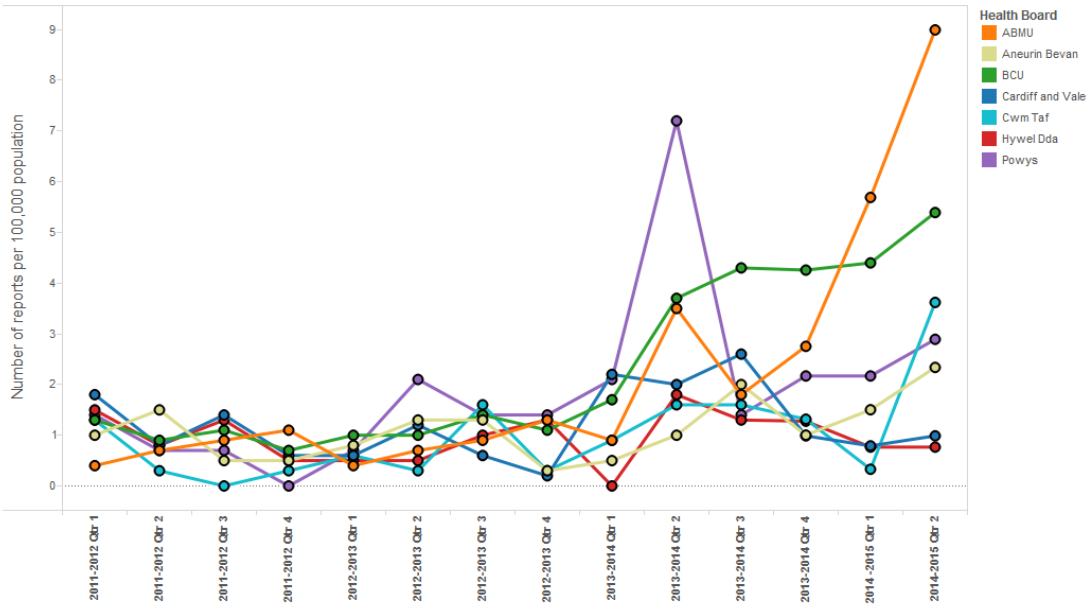


Ibuprofen and naproxen items as a percentage of NSAID prescribing Quarter ending September 2014



8.0 YELLOW CARDS

Trend in yellow card reporting to quarter ending September 2014



APPENDIX 2. USER-DEFINED GROUP OF LOW-STRENGTH ICS

The list below is the user-defined group being monitored as low-strength ICS, i.e. any inhaler device, which when used at the usual dose provides < 800 mcg of beclometasone or equivalent.

BNF name	BNF code
Beclomet Diprop_Inha 50mcg (200d)	0302000C0AAAAAA
Beclomet Diprop_Inha 100mcg (200d)	0302000C0AAABAB
Beclomet Diprop_Inha B/a 50mcg (200 D)	0302000C0AAASAS
Beclomet Diprop_Inha B/a 100mcg (200 D)	0302000C0AAATAT
Beclomet Diprop_Inha 50mcg (200 D) Cff	0302000C0AABEBE
Beclomet Diprop_Inha 100mcg (200 D) Cff	0302000C0AABFBF
Beclomet Diprop_Inha B/a 50mcg(200 D)cff	0302000C0AABGBG
Beclomet Diprop_Inha B/a100mcg(200 D)cff	0302000C0AABHBH
Beclomet Diprop_Pdr For Inh 100mcg(200 D	0302000C0AABJBJ
Beclomet Diprop_Inha B/a 100mcg (100 D)	0302000C0AABQBQ
Beclomet Diprop_Inha B/a 200mcg (100 D)	0302000C0AABRBR
Beclazone 100 E-Breathe_Inha 100mcg(200d	0302000C0BFAEAT
Asmabec Clickhaler_D/p Inh 50mcg (200 D)	0302000C0BIADBI
Asmabec Clickhaler_D/p Inh 100mcg (200d)	0302000C0BIAEBJ
Qvar 50_Inha 50mcg (200 D)	0302000C0BJAABE
Qvar 50_Autohaler 50mcg (200 D)	0302000C0BJACBG
Qvar 50 E-Breathe_Inha 50mcg (200 D)	0302000C0BJAEBG
Pulvinal Beclomet_Inha 200mcg (100 D)	0302000C0BLAABM
Pulvinal Beclomet_Inha 100mcg (100 D)	0302000C0BLABBN
Clenil Modulite_Inha 50mcg (200d)	0302000C0BPAABE
Clenil Modulite_Inha 100mcg (200d)	0302000C0BPABBF
Budesonide_Pdr For Inh 200mcg (100 D)	0302000K0AAAGAG
Budesonide_Pdr For Inh 100mcg (200 D)	0302000K0AAAKAK
Gppe Pdr For Inhb/a_Symbicort 100/6(120d	0302000K0AAALAL
Gppe Pdr For Inhb/a_Symbicort 200/6(120d	0302000K0AAAMAM
Budesonide_Pdr For Inh 200mcg (100d)+dev	0302000K0AAAVAV
Budesonide_Pdr For Inh 200mcg (100d) Ref	0302000K0AAAWAW
Budesonide_Pdr For Inh 200mcg (200 D)	0302000K0AAAXAX
Pulmicort_Turbohaler 200mcg (100 D)	0302000K0BBAHAG
Pulmicort_Turbohaler 100mcg (200 D)	0302000K0BBAKAK
Symbicort_Turbohaler 100mcg/6mcg (120 D)	0302000K0BDAAAL
Symbicort_Turbohaler 200mcg/6mcg (120 D)	0302000K0BDABAM
Easyhaler_Budesonide 100mcg (200 D)	0302000K0BGAAAK
Easyhaler_Budesonide 200mcg (200 D)	0302000K0BGABAX
Duoresp Spiromax_Inh 160mcg/4.5mcg(120d)	0302000K0BHAAAM
Fluticasone Prop_Pdr For Inh 50mcg (60d)	0302000N0AAARAR
Fluticasone Prop_Pdr For Inh 100mcg(60d)	0302000N0AAASAS
Gppe Pdr For Inh_Seretide 100 (60 D)	0302000N0AAAXAX
Gppe Inha_Seretide 50 Evohaler (120d)cff	0302000N0AABEBE
Fluticasone Prop_Inha 50mcg (120 D) Cff	0302000N0AABHBH
Fluticasone/formoterol_Inh 50/5mcg 120 D	0302000N0AABLBL
Flixotide_Accuhaler 50mcg (60 D)	0302000N0BBARAR
Flixotide_Accuhaler 100mcg (60 D)	0302000N0BBASAS
Flixotide_Evohaler 50mcg (120 D)	0302000N0BBBBBH
Seretide 100_Accuhaler 100mcg/50mcg(60d)	0302000N0BCAAAX
Seretide 50_Evohaler 50mcg/25mcg (120 D)	0302000N0BCADBE
Flutiform_Inha 50/5mcg (120 D)	0302000N0BDACBL
Mometasone Fur_Pdr For Inh 200mcg (30 D)	0302000R0AAAAAA
Mometasone Fur_Pdr For Inh 200mcg (60 D)	0302000R0AAABAB

Asmanex Twisthaler_D/p Inh 200mcg (30 D)	0302000R0BBAAAA
Asmanex Twisthaler_D/p Inh 200mcg (60 D)	0302000R0BBABAB
Ciclesonide_Inh 80mcg (120 D) Cff	0302000U0AAAAAA
Alvesco 80_Inh 80mcg (120 D) Cff	0302000U0BBAAAA