Ruxolitinib **oral** *Jakavi* Novartis	***Indication:*** Myelofibrosis (MF), chronic idiopathic, and MF due to polycythaemia vera or essential thrombocythaemia.	***Current status:*** Approved in EU Aug 2012. Launched in US – see prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** Ruxolitinib due Jun 2013. ***Reviews:*** LCNDG Jul 2012, NHSC Aug 2010.
Target population: The UK incidence of myelofibrosis is 0.5-1.5 per 100,000 people. Overall median survival is 5 years. ***Sector:*** Secondary care.		***Implications:*** Stem-cell transplant is the only potentially curative treatment but is often unsuitable. Unlicensed palliative treatment options used for splenomegaly include hydroxycarbamide, interferon alfa and thalidomide. ***Financial:*** Ruxolitinib could replace current unlicensed and comparatively less expensive therapeutic options but may delay need for surgical treatment. US cost is about $6,800/month. ***PbR:*** Tariff excluded.		
Pharmacology: Janus kinase-1 and 2 inhibitor. First in a new drug class for myelofibrosis. ***Efficacy:*** In the published PIII COMFORT-I trial (n=309), response rates for the primary outcome of ≥35% reduction in spleen volume were 42% and 0.7% at 24 weeks in the ruxolitinib and placebo groups, respectively (p<0.001). In the published PIII COMFORT-II trial (n=219), response rates were 32% and 0% at 24 weeks, and 29% and 0% at 48 weeks, in patients given ruxolitinib or best available therapy, respectively (all p<0.001). ***Safety:*** Common adverse effects include thrombocytopenia, anaemia, diarrhoea and peripheral oedema.				
Alemtuzumab **injection** *Lemtrada* Genzyme	***Indication:*** Multiple sclerosis (MS), relapsing remitting disease (RRMS).	***Current status:*** Filed in EU Jun 2012.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** Multiple sclerosis (update due TBC), Fingolimod, Natalizumab, Beta interferon & glatiramer. ***Reviews:*** NHSC Dec 2010.
Target population: Around 100,000 people in the UK have MS and 40% have RRMS (67 per 100,000 people). Around 2,500 new cases are diagnosed each year, 80% of which are RRMS. There were 28,430 hospital admissions for MS in 2010/11. ***Sector:*** Secondary care.		***Implications:*** This is a new class of drug for MS and as a single annual treatment it may be attractive. ***Financial:*** Cost of the *MabCampath* brand of alemtuzumab was about £1,300 for a 5 day course. This is no longer available as the company intends to focus on *Lemtrada* for MS whilst supplying *MabCampath* on a named patient basis for non-MS indications. The cost of *Lemtrada* is likely to be in line with that of other MS treatments. ***PbR:*** Likely tariff excluded.		
Pharmacology: Monoclonal CD52 antibody given by i.v. infusion daily for 5 consecutive days as a first annual treatment course, and as a 3 day course in the second year. An ongoing study will help define a subsequent treatment regimen. ***Efficacy:*** Two PIII studies, CARE-MS 1 in 581 patients with early, active RRMS who had received no prior therapy, and CARE MS II in 840 patients who had relapsed on prior therapy, compared alemtuzumab to high dose s.c. interferon beta-1a. Both studies met the co-primary outcome of reducing relapse rate at 2 years (a 55% and 49% reduction vs. interferon, respectively, p<0.0001). CARE-MS II also met the co-primary outcome of sustained accumulation of disability at 2 years (42% risk reduction vs. interferon, p=0.0084), but CARE-MS I did not. ***Safety:*** See emc.medicines.org.uk.				
Laquinimod **oral** Teva	***Indication:*** Multiple sclerosis (MS), relapsing remitting disease (RRMS).	***Current status:*** Filed in EU Jul 2012. Further studies needed to support US licensing.	***Predicted UK launch:*** 2013	***National guidance:*** As for alemtuzumab above. ***Reviews:*** NHSC Aug 2011.
Target population: As for alemtuzumab above. ***Sector:*** Secondary care initiated.		***Implications:*** Around 30% of patients are treated with injectable agents, mainly beta-interferon. Oral options may increase the proportion treated. ***Financial:*** Beta-interferon costs up to £10,500/year. The cost of fingolimod, the only licensed oral preparation for RRMS is about £19,500/year, although there is a PAS in place. There may be price competition as more oral agents become available. ***PbR:*** Likely tariff excluded.		
Pharmacology: SAIK compound, an immune defence regulator. ***Efficacy:*** In the 2-year PIII ALLEGRO study (n=1,106), laquinimod reduced the annualised relapse rate (ARR) by 23% (p=0.0024), disability progression by 36% (p<0.02) and progression of brain atrophy by 33% (p<0.0001) vs. placebo. In the PIII BRAVO study, laquinimod did not reduce the ARR vs. placebo whereas beta-interferon did. ***Safety:*** Adverse events include headaches, nasopharyngitis and back pain. Increases in liver enzymes are reported.				

Dimethyl fumarate **oral** *Panaclar* Biogen Idec	***Indication:*** Multiple sclerosis (MS), relapsing remitting disease (RRMS).	***Current status:*** Filed in EU May 2012.	***Predicted UK launch:*** 2013	***National guidance:*** As for alemtuzumab above. ***Reviews:*** NHSC Dec 2011.
Target population: As for alemtuzumab above. ***Sector:*** Secondary care initiated.		***Implications:*** As for laquinimod above. ***Financial:*** As for laquinimod above. ***PbR:*** Likely tariff excluded.		

Pharmacology: A derivative of fumaric acid with dual immunosuppressive and cytoprotective actions.

Efficacy: Two PIII studies, DEFINE (n=1,237) and CONFIRM (n=1,232), evaluated dimethyl fumarate 240mg 2-3 times a day. In DEFINE, the proportion of patients relapsing over 2 years vs. placebo was reduced by 49% and 50%, respectively ($p<0.0001$ for both doses), and by 34% and 45% ($p<0.003$ and $p<0.0001$, respectively) in CONFIRM. In the glatiramer arm in CONFIRM, 29% fewer patients relapsed ($p<0.01$ vs. placebo). Across the 2 studies, dimethyl fumarate was associated with a reduction in annualised relapse rate of between 44-53% vs. placebo ($p<0.0001$), and a reduction in risk of disability progression of 21-34%. In a published PIIb study, dimethyl fumarate 240mg 3 times daily was associated with 69% fewer new gadolinium enhancing lesions than placebo (1.4 vs. 4.5, $p<0.0001$).

Safety: Flushing and gastrointestinal effects are the most frequent adverse events.

Teriflunomide **oral** *Aubagio* Sanofi	***Indication:*** Multiple sclerosis (MS), relapsing-remitting disease (RRMS) - monotherapy	***Current status:*** Filed in EU Feb 2012.	***Predicted UK launch:*** 2013	***National guidance:*** As for alemtuzumab above and **NICE:** Teriflunomide -proposed appraisal. ***Reviews:*** NHSC Aug 2011.
Target population: As for alemtuzumab above. ***Sector:*** Secondary care initiated.		***Implications:*** As for dimethyl fumarate above. ***Financial:*** As for dimethyl fumarate above. ***PbR:*** Likely tariff excluded.		

Pharmacology: The active metabolite of leflunomide, teriflunomide is a dehydrogenase inhibitor.

Efficacy: In the published 2-year PIII TEMSO study (n=1,088), the annualised relapse rate (ARR) was 0.37 for patients on either 7mg or 14mg terflunomide daily vs. 0.54 in those on placebo, equating to a relative risk reduction of around 31% ($p<0.001$). Terflunomide was superior to placebo in a key secondary outcome, time to disability progression, only at the 14mg dose. In the TOWER study (n=1,169), patients in the 14mg teriflunomide group had a 36.3% reduction in the primary outcome of ARR vs. placebo ($p<0.0001$) and a 31.5% reduction in the risk of 12-week sustained accumulation of disability (SAD), $p=0.04$ vs. placebo. Although the reduction in ARR in the 7mg group reached statistical significance vs. placebo, the 12-week SAD did not. In the PIII TENERE trial, the risk of treatment failure (primary outcome, defined as a confirmed relapse, or discontinuation of treatment for any reason) was similar among the 324 patients randomised to teriflunomide 7mg or 14mg or to beta-interferon (48.6%, 37.8% and 42.3%, respectively).

Safety: Headache, diarrhoea, hair thinning and rises in liver enzymes have been reported.

BNF 9. Nutrition and blood

Ferumoxytol **injection** *Rienso* Takeda	***Indication:*** Anaemia in chronic kidney disease (CKD).	***Current status:*** Approved in EU Jul 2012.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** Anaemia in CKD. **SIGN:** CKD ***Reviews:*** NHSC Feb 2011.
Target population: The UK prevalence of stage 3-5 kidney failure is about 8.5% (8,500 per 100,000 people). Ferumoxytol may be used when oral iron is ineffective, not tolerated or contraindicated. ***Sector:*** Secondary care.		***Implications:*** Currently available i.v. options involve several outpatient visits and for some, lengthy infusions. Ferumoxytol is given by slow injection and requires only 1 or 2 doses. ***Financial:*** Ferumoxytol is likely to be competitively priced with the more expensive i.v. iron preparations. A reduced number of outpatient visits for administration will help offset costs. ***PbR:*** In tariff.		

Pharmacology: Iron oxide semi-synthetic nanoparticle with a polyglucose sorbitol carboxymethylether coating formulated with mannitol. It is given by slow i.v. injection for 1 or 2 doses only.

Efficacy: Pooled data from PIII trials (437, 424 and a published trial) involving a total of 885 patients who received 2 doses of ferumoxytol or oral iron 200mg/day for 3 weeks showed that the primary outcome, the mean increase in haemoglobin (Hb) from baseline at day 35, was greater in the ferumoxytol group than the oral iron group (1.03 vs. 0.42 g/dL, $p<0.0001$). In a PII study (n=162), the Hb increase at week 5 was comparable in patients receiving ferumoxytol or iron sucrose, but more patients on ferumoxytol (50% vs. 42%) achieved ≥1g/dL increase in Hb.

Safety: Serious and life-threatening adverse reactions have occurred, monitoring is recommended for at least 30 minutes after administration. See prescribing data.

Peginesatide **injection** *Omontys (US)* Takeda	***Indication:*** Anaemia due to chronic kidney disease (CKD) in adults on dialysis.	***Current status:*** Filed in EU Feb 2012. Launched in US - see prescribing data.	***Predicted UK launch:*** 2013	***National guidance:*** As for ferumoxytol above. ***Reviews:*** NHSC Jun 2012.
Target population: The UK prevalence of stage 3-5 kidney failure is about 8,500 per 100,000 people; about 80 per 100,000 are on dialysis. ***Sector:*** Secondary care.		***Implications:*** Peginesatide is given less frequently (once a month) than available treatment options, reducing the need for outpatient appointments for those on peritoneal dialysis. It may be suitable for homecare delivery. ***Financial:*** The price may be competitive as recombinant technology is not required for manufacture. ***PbR:*** In tariff.		
Pharmacology: a PEGylated synthetic erythropoiesis stimulating agent (ESA) mimetic given by monthly i.v or s.c. injection. ***Efficacy:*** In open-label PIII studies, EMERALD 1 and EMERALD 2 (>1,600 patients in total), once-monthly peginesatide was non-inferior to continued treatment with epoetin alpha or beta, given 1-3 times weekly, in maintaining haemoglobin (Hb) within the range 10 -12 g/dL during weeks 29 and 36 (primary outcome). The proportion who maintained Hb within range between weeks 29 and 52 was similar between groups, as was the need for blood transfusions. ***Safety:*** In patients on dialysis, the rate of adverse cardiovascular events in the peginesatide and epoetin groups was similar (22.8% vs. 24.4%). The rate was higher with peginesatide in patients not on dialysis. The company must conduct extra studies to further assess safety as a requirement of US approval. The studies are due to report in 2018 and 2019.				
Eltrombopag **oral** *Revolade* GlaxoSmith-Kline	***Indication:*** Thrombocytopenia (TCP) associated with hepatitis C (HepC).	***Current status:*** Filed in EU May 2012.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** TCP- eltrombopag. **SIGN:** Management of hepatitis C. ***Reviews:*** None.
Target population: About 250,000 people in the UK are infected with hepatitis C (400 per 100,000). In a systematic review of 27 studies, the prevalence of HepC associated TCP was 0.16- 45.4%. More than half of the studies reported a TCP prevalence of ≥ 24%. ***Sector:*** Secondary care initiated.		***Implications:*** Thrombocytopenia may interfere with diagnostic procedures, such as liver biopsy, because of bleeding risk, and can exclude patients from effective antiviral treatment jeopardising the chances of achieving sustained virologic response (SVR). ***Financial:*** For a 28 day course, eltrombopag costs £770 for 25mg/day or £1,540 for 50mg/day. ***PbR:*** Tariff excluded.		
Pharmacology: Thrombopoietin receptor agonist given orally in doses (25 to 100mg daily) determined by platelet count. ***Efficacy:*** Two PIII studies, ENABLE 1 (n=716) and ENABLE 2 (n=805) treated patients with HepC associated TCP with open-label eltrombopag for 9 weeks. Those patients who achieved a platelet count that enabled antiviral therapy to be started were randomised to continued eltrombopag or placebo, plus peginterferon alfa and ribavirin for 24 or 48 weeks depending on genotype. The primary outcome was the proportion of patients who achieved SVR 24 weeks after antiviral therapy had finished. SVR was achieved by 23% vs. 14% in the eltrombopag and placebo groups, respectively (p=0.0064) in ENABLE 1 and 19% vs.13% (p=0.02) in ENABLE 2. ENABLE ALL is an ongoing open-label study enrolling 340 subjects from ENABLE 1and 2, who discontinued from these studies due to thrombocytopenia. ***Safety:*** See emc.medicines.org.uk. In ENABLE 1 and 2, events consistent with worsening of liver function were reported in 13-15% of eltrombopag patients and in 8% of placebo patients. The ocular safety of eltrombopag is being investigated in the long-term observational LENS study in patients treated in PII or PIII trials for any indication.				

Tofacitinib **oral** Pfizer	***Indication:*** Rheumatoid arthritis (RA) in patients with moderate-to-severe disease unresponsive to DMARDs.	***Current status:*** Filed in EU Nov 2011. Recommended for approval in US May 2012 but further data review requested Aug 2012.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** *RA:* clinical guideline, commissioning guides (RA, biologicals), quality standard due Jun 2013. Tofacitinib due Sep 2013, Tocilizumab, Golimumab, Certolizumab, Adalimumab, etanercept and infliximab. **SIGN:** Early RA. ***Reviews:*** None.

Target population: NICE suggest the benchmark rate for the number of people with RA eligible for and receiving biologic drugs is 86 per 100,000 adults per year. ***Sector:*** Secondary care.	***Implications:*** Oral tofacitinib will compete with i.v. or s.c. therapies and be more attractive. There may be potential for homecare delivery. ***Financial:*** The average annual cost of a biological is about £9,500 per patient but competition is reducing this. In 2007-8, the cost of biologic drugs for RA was £0.8 to £3.5 million per acute trust. Funding, staff and outpatient facilities may limit use of second-line agents. PASs are in place for golimumab and tocilizumab use in RA. ***PbR:*** Tariff excluded.

Pharmacology: Janus kinase (JAK) 3 inhibitor.

Efficacy: The ORAL PIII programme evaluating tofacitinib, at doses of 5mg and 10mg twice daily, is ongoing. In ORAL Scan (n=797, all on methotrexate) tofacitinib 10mg improved ACR20 response rates and DAS28.4 scores at 6 months (both $p<0.001$ vs. placebo) and delayed progression of structural damage ($p<0.05$). Two year data are due in 2012. In the published ORAL Standard study (n=717), the primary outcome of ACR20 at 6 months was achieved by 28.3% of patients on placebo, by 51.5% and 52.6% patients on tofacitinib 5mg and 10mg, respectively and by 47.2% of patients on adalimumab twice monthly. All patients were on background methotrexate. This study was not designed to show comparative efficacy with adalimumab. ORAL sync (n=792) assessed patient reported outcomes at 3 months. Tofacitinib in combination with disease modifying agents, improved scores for patient global assessment of disease activity, pain, physical function, health-related quality of life (HRQoL), fatigue and sleep ($p\leq0.05$ for both doses vs. placebo). All primary outcomes were met in ORAL Step (n=400) in which tofacitinib was evaluated in patients on methotrexate who had an inadequate response to TNF inhibitors. The published ORAL Solo study (n=610) compared tofacitinib vs. placebo as monotherapy in moderate-to-severe RA. Two of three primary outcomes were met (ARC20 response rate and physical function).

Safety: Potential risks include higher rates of cancers and serious infections.

Canakinumab **injection** *Ilaris* Novartis	***Indication:*** Gout - acute flares and reduction in frequency of subsequent attacks.	***Current status:*** Filed in EU Dec 2010. Not recommended in US due to safety concerns.	***Predicted UK licence extension:*** 2013	***National guidance:*** **NICE:** Canakinumab appraisal suspended due to non submission. ***Reviews:*** NHSC May 2010.

Target population: Prevalence of gout is 1.4%, increasing to 7.3% in men >65 years. About 72% have at least one flare annually. ***Sector:*** Secondary care.	***Implications:*** Current management of acute gout flares includes colchicine and/or a NSAID. Canakinumab could be used as an alternative to corticosteroids for second-line therapy. ***Financial:*** Cost of *Ilaris* is £9,928 per 150mg dose. ***PbR:*** Tariff excluded.

Pharmacology: Interleukin-1 beta inhibitor, given as a single s.c. injection.

Efficacy: In 12-week PIII studies (β-RELIEVED AND β-RELIEVED-II, n>450) s.c. canakinumab 150mg was more effective than i.m. triamcinolone 40mg. Mean pain intensity, measured by a visual analogue scale at 72 hours (primary outcome), was 11.4mm and 9.8mm lower in the canakinumab groups, respectively, $p<0.01$ for both studies. The risk of a new gouty attack within 3 months (secondary outcome) was reduced with canakinumab by 55% in β-RELIEVED (40 vs. 21) and 68% in β-RELIEVED II (42 vs. 15), $p<0.01$ for both studies.

Safety: See emc.medicines.org.uk.

Pegloticase **injection** *Krystexxa* Savient	***Indication:*** Gout prophylaxis - second-line in patients refractory to conventional urate lowering drug therapy or when these are unsuitable.	***Current status:*** Filed in EU May 2011. Launched in US - see prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** Pegloticase due May 2013, Febuxostat. **SMC:** Febuxostat Feb 2010. ***Reviews:*** NHSC Dec 2010.
Target population: The prevalence of gout is 1.4%, increasing to 7.3% in men >65 years. Urate lowering drugs may be used in up to 61% of people. The number refractory to conventional therapy is uncertain. ***Sector:*** Secondary care.		***Implications:*** An option for refractory patients, likely to be used after failure of allopurinol and febuxostat, or for patients unsuitable for these. Currently no licensed alternative options exist. ***Financial:*** It is likely to be expensive, and has outpatient service implications for administration of an i.v. infusion. ***PbR:*** Likely tariff excluded.		
Pharmacology: A polyethylene glycol conjugate of recombinant uricase given by a 2-hour i.v. infusion every 2 weeks. ***Efficacy:*** The published PIII GOUT1 and 2 studies (n=225) randomised patients to pegloticase 8mg bi-weekly or monthly, or placebo, for 6 months. The primary outcome, plasma uric acid <6.0mg/dL 80% of the time at 3 and 6 months, was met in GOUT1 by 47% of patients (2 weekly, p<0.001) and 20% (4 weekly, p<0.05) and in GOUT2 by 38% (p=0.001) and 49% (p<0.001), respectively. ***Safety:*** Anaphylaxis and infusion reactions are reported and premedication with antihistamines and corticosteroids is advised in US prescribing data. Exacerbation of heart failure has been reported. Long term safety data are available.				
Strontium ranelate **oral sachet** *Protelos* Servier	***Indication:*** Osteoarthritis (OA).	***Current status:*** PIII.	***Predicted UK licence extension:*** Uncertain.	***National guidance:*** **NICE:** OA (update due Jan 2014). ***Reviews:*** NHSC Apr 2011.
Target population: By the age of 65, at least 50% of people have some degree of joint OA. About 10% of people over 65 have a major disability due to OA. ***Sector:*** Primary care.		***Implications:*** An add-on therapy for patients who require disease modifying therapy and of benefit for those with osteoporosis and OA. ***Financial:*** An additional cost; currently *Protelos* is about £30/month. ***PbR:*** In tariff.		
Pharmacology: Dual acting agent that stimulates bone formation and reduces resorption. ***Efficacy:*** In a PIII study (n=1,683), after a median follow-up of 29.8 months, strontium ranelate 1g and 2g/day was associated with smaller decreases in joint space width (-0.230mm and -0.270mm, respectively), vs. -0.370mm in the placebo group (p<0.001 and p<0.05, respectively). A PIII study in patients with knee OA has been completed and another 3-year PIII study assessed progression of knee articular damage in men and women is ongoing. A published post-hoc analysis of the SOTI and TROPOS studies assessed strontium ranelate vs. placebo in delaying clinical and structural progression of OA in a subgroup of 1,105 postmenopausal women with osteoporosis. Of the patients with worsening overall spinal OA score, 9.9% were in the strontium ranelate group vs. 17.1% on placebo (p=0.0005). ***Safety:*** See emc.medicines.org.uk.				

BNF 11. Eye

Fluocinolone acetonide **intravitreal implant** *Iluvien* Alimera Sciences	***Indication:*** Diabetic macular oedema (DMO) - second-line.	***Current status:*** Approved in UK May 2012. See prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** Fluocinolone due Nov 12, Ranibizumab in DMO. ***Reviews:*** LNDG Feb 2011.
Target population: Up to 10% of patients with diabetes develop DMO. In older patients, prevalence is 3-8% within 3 years of type 2 diabetes diagnosis. ***Sector:*** Secondary care.		***Implications:*** Frequency of use differs between available treatment options which may have service implications. This implant will treat for up to 3 years with one injection. ***Financial:*** Could be similar to dexamethasone implant (£870). ***PbR:*** Tariff excluded.		
Pharmacology: Corticosteroid. The intravitreal implant provides sustained therapy for 24 -36 months. ***Efficacy:*** In the PIII FAME study (n=956), at 2 years, an improvement of ≥15 letters of vision was seen in 28.7%, 28.6% and 16.2% treated with fluocinolone acetonide 0.2mcg/day, 0.5mcg/day and sham, respectively (p=0.002 for both vs. sham). ***Safety:*** Intraocular pressure increases ≥30mmHg were seen in 16.3% (0.2mcg) and 21.6% (0.5mcg) of patients. 2.1% and 5.1%, respectively, required a trabeculectomy to reduce pressure. It is unclear whether the insert can be removed to manage adverse effects.				

Ocriplasmin **intravitreal injection** *Clerezo* Alcon	***Indication:*** Symptomatic vitreomacular adhesion (VMA), including macular hole.	***Current status:*** Filed in EU Oct 2011.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** Ocriplasmin – proposed appraisal. ***Reviews:*** NHSC Sep 2011.
Target population: VMA occurs when vitreous gel adheres to the retina due to partial posterior vitreous detachment (PVD); a normal physiologic process in at least 75% of those aged >65 years, but also has other causes e.g. trauma. In the UK, macular holes occur in about 6,200 people each year. ***Sector:*** Secondary care.	***Implications:*** Currently treated with vitrectomy, ocriplasmin will be a non-surgical treatment for PVD. ***Financial:*** Likely to be expensive. ***PbR:*** Tariff excluded.			
Pharmacology: Truncated form of plasmin which dissolves protein structures in the eye that link the vitreous to the retina, given by intravitreous injection. ***Efficacy:*** In the TG-MV-006 study (n=326) a single injection of ocriplasmin was compared with placebo. The primary outcome of resolution of VMA at 1 month was met by 27.7% of ocriplasmin group vs. 13.2% receiving placebo (p=0.003, NNT=7). At least a 10 letter improvement in visual acuity (VA) was achieved by 25.5% vs. 11.3%, respectively (p<0.005). Of the patients with full thickness macular hole (FTMH), 45.6% of the 52 treated with ocriplasmin vs. 15.6% of the 32 receiving placebo had closure of the FTMH at 6 months (p=0.005). In the similarly designed TG-MV-007 study (n=326) the primary outcome was met by 25.3% vs. 6.2% of the ocriplasmin and placebo groups, respectively (p=0.001, NNT=5). At least a 10 letter improvement in VA was achieved by 22% vs. 11.1%, respectively (p<0.05). FTMH closure at 28 days was achieved in 36.7% of the 49 patients treated with ocriplasmin vs. 6.7% of 15 treated with placebo, p<0.03. ***Safety:*** Most commonly reported side effects were vitreous floaters, eye pain and photopsia. No increase in the rate of retinal tear or detachment was seen with ocriplasmin vs. placebo.				
Aflibercept **intravitreal injection** *Eylea* Bayer	***Indication:*** Wet age related macular degeneration (AMD).	***Current status:*** Filed in EU Jun 2011. Launched in US – see prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** Ranibizumab and pegaptanib, Photodynamic therapy, Aflibercept due Aug 13. ***Reviews:*** NETAG Mar 2012, NHSC Dec 2010, LNDG due TBC.
Target population: Estimates of the incidence of AMD range from 0.088% to 0.2% (88-200 per 100,000 people). ***Sector:*** Secondary care.	***Implications:*** Another option for AMD but may be given less frequently. ***Financial:*** Likely to be competitive with other options. ***PbR:*** Tariff excluded.			
Pharmacology: A vascular endothelial growth factor and placental growth factor inhibitor given monthly for 3 months then every 2 months. ***Efficacy:*** The 52-week PIII VIEW1 (n=1,217) and VIEW2 (n=1,240) studies assessed aflibercept (AFL) 0.5mg or 2mg given monthly, or 2mg every 2 months vs. ranibizumab (RAN) 0.5mg monthly in maintaining vision. In both studies, ≥94% of patients in all groups achieved the primary outcome of maintained vision (losing <15 letters). In VIEW1, the mean visual acuity improvement vs. baseline for AFL 2mg monthly was a gain of 10.9 letters vs. 8.1 for RAN (p<0.01). All other doses in VIEW1 and all groups in VIEW 2 were not statistically different demonstrating aflibercept is non-inferior to ranibizumab. ***Safety:*** Ocular adverse events include conjunctival and retinal haemorrhage and vitreous floaters.				
Aflibercept **intravitreal injection** *Eylea* Bayer	***Indication:*** Retinal vein occlusion (RVO).	***Current status:*** PIII with plans to file in EU in 2012.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** Dexamethasone, Ranibizumab due TBC. ***Reviews:*** NHSC May 2011.
Target population: Data from population studies suggest there are 520 new cases per million of RVO per year, typically occurring in patients >50 years of age. ***Sector:*** Secondary care.	***Implications:*** A new treatment option that will compete with ranibizumab injection and dexamethasone implant. ***Financial:*** Likely to be competitive with current options. ***PbR:*** Tariff excluded.			
Pharmacology: A vascular endothelial growth factor inhibitor and placental growth factor inhibitor given monthly. ***Efficacy:*** In the 6-month PIII GALILEO study (n=177), 60.2% on aflibercept 2mg monthly and 22.1% on sham treatment, gained ≥15 letters of vision from baseline (p<0.0001). The mean number of letters gained was 18 vs. 3.3, respectively (p<0.0001). In the PIII COPERNICUS (n=189), at 6 months, ≥15 letters were gained by 56.1% on aflibercept vs. 12.3% on placebo (p<0.0001). Those on aflibercept gained a mean of 17.3 letters vs. a mean loss of 4 letters with placebo, p<0.001. ***Safety:*** The most frequent adverse events were eye pain, conjunctival haemorrhage and elevated intraocular pressure.				

BNF 13. Skin

Ingenol mebutate **gel** *Picato* LEO Pharma	***Indication:*** Actinic keratosis (AK) - first-line.	***Current status:*** Filed in EU Nov 2011. Launched in US - see prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** None for topical therapy. ***Reviews:*** NHSC Dec 10.
Target population: In 2000 a published study estimated the prevalence of AK in a Merseyside population as 16% in men and 6% in women. ***Sector:*** Primary care.		***Implications:*** Ingenol is an alternative to existing options but has a shorter duration of treatment; 2-3 days only vs. several weeks treatment for other topical options. This could make it attractive. ***Financial:*** Likely to be competitive. ***PbR:*** Likely in tariff.		
Pharmacology: Protein kinase C inhibitor and stimulator of apoptosis in cancer cells. It is applied daily for 2 to 3 days. ***Efficacy:*** Pooled data from four PIII studies have been published. In 2 trials (n=547) ingenol mebutate 0.015% or placebo was applied daily to the face and scalp for 3 days; the primary outcome of complete clearance at 57 days was achieved by 42.2% vs. 3.7% patients, respectively (p<0.001, NNT=3). In the other 2 trials (n=458), after 2 days application of ingenol mebutate 0.05% or placebo to the trunk and extremities complete clearance at 57 days was achieved by 34.1% vs. 4.7%, respectively (p<0.001, NNT=3). ***Safety:*** Severe application site reactions can occur.				
Afamelanotide **implant** *Scenesse* Clinuvel pharma-ceuticals	***Indication:*** Erythropoietic protoporphyria (EPP).	***Current status:*** Filed in EU Feb 2012 with orphan status. Launched in Italy (2010) and Switzerland (2012).	***Predicted UK launch:*** 2013	***National guidance:*** None relevant. ***Reviews:*** No recent reviews.
Target population: EPP affects < 2 per 100,000 people in the EU. Protoporphyrin accumulates in the skin and causes severe photosensitivity with sun exposure leading to burning, erythema and pain. ***Sector:*** Secondary or tertiary care.		***Implications:*** There are no other specific EPP treatments. Options include staying indoors, sunblocking clothes and sunscreen. ***Financial:*** Likely to be expensive and will be a new cost pressure. ***PbR:*** Tariff excluded.		
Pharmacology: Synthetic analogue of alpha-melanocyte-stimulating hormone which induces the synthesis of melanin. Given as a controlled release dissolvable s.c implant. ***Efficacy:*** In the PIII CUV029 study 74 patients received afamelanotide or placebo once every 60 days, over nine months. Afamelanotide was associated with fewer phototoxic reactions measured by visual analogue scale (primary outcome; p=0.044) and a lower total median pain score (secondary outcome; 6.0 vs. 17.5, p=0.035). In the 12-month PIII CUV017 crossover trial 91 patients received afamelanotide or placebo implants every 2 months for a total of 6 implants (3 implants each of active and placebo drug). Afamelanotide reduced the total number of days on which patients experienced pain (p<0.003) and all individual daily pain scores were lower vs. placebo (p<0.002).				

Table 2. Drugs in Prescribing Outlook 2011 - development delayed

Generic and *trade* name	Company	Indication and reason for delay.
Afatinib **oral** *Tomtovok*	Boehringer Ingelheim	Non-small cell lung cancer, advanced relapsed. The PIII Lux-Lung 1 trial did not achieve its primary outcome.
Bortezomib **injection** *Velcade*	Janssen-Cilag	Non-Hodgkin's lymphoma (NHL), relapsed/ refractory follicular disease. EU application withdrawn because the EU licensing authority considered data did not support a positive benefit-risk balance. See EMA Q&A.
Brivanib alaninate **oral**	Bristol-Myers Squibb	Hepatocellular carcinoma (HCC), advanced. Two PIII trials (BRISK-FL and BRISK-PS) did not achieve their primary outcomes.
Ecallantide **injection** *Kalbitor*	Dyax	Hereditary angioedema (HAE). EU application withdrawn. The company stated they were unable to provide sufficient information to address the outstanding clinical issues identified during the evaluation of their application. See EMA Q&A.
Lapatinib **oral** *Tyverb*	GlaxoSmith-Kline	Breast cancer, metastatic – first-line in HER2-positive disease combined with paclitaxel. EU application withdrawn. The licensing authority stated the lack of an active-controlled trial with trastuzumab plus paclitaxel hampers the assessment of the benefit-risk balance in this indication. See EMA Q&A.
Lenalidomide oral *Revlimid*	Celgene	Multiple myeloma – maintenance after induction drug therapy or stem cell transplant. EU application withdrawn as the EU authority decided more data was required to allow a clear decision on benefit-risk balance to be reached. See EMA Q&A.
Nintedanib (formerly intedanib) **oral** *Vargatef*	Boehringer Ingelheim	Non-small cell lung cancer (NSCLC) advanced – second-line. PIII trials not due to complete until late 2013, therefore nintedanib is unlikely to be available before late 2014.
Pralatrexate **injection** *Folotyn*	Mundipharma	Peripheral T-cell lymphoma - relapsed or refractory. EU negative opinion has been issued. Initially, and in a re-examination of data, the licensing authority was concerned that data did not allow assessment compared with any other treatment or placebo and concluded there was insufficient evidence to establish the benefits of treatment. See EMA Q&A.
Romidepsin **injection** *Istodax*	Celgene	Peripheral T-cell lymphoma (PTCL) - second-line. EU negative opinion has been issued. It was considered there was insufficient evidence on the benefits and that the balance of its benefits and risks could not be established. See EMA Q&A.
Telavancin **injection** *Vibativ*	Theravance	Pneumonia known or suspected to be caused by methicillin-resistant *S. aureus*. An EU licence was granted in Sep 2011. However, the agreement between Astellas and Theravance for the licensing, development and commercialisation of telavancin was terminated in Jan 2012. Theravance are considering options.
Telavancin **injection** *Vibativ*	Theravance	Skin and soft tissue infections. The EU licensing authority concluded that, although telavancin is effective, due to safety concerns, the benefits do not outweigh the risks. See EMA Q&A.
Tesamorelin **injection** *Egrifta*	Ferrer	Abdominal fat reduction in HIV-associated lipodystrophy. EU application withdrawn by the company as the EU authorities considered data provided did not show a positive benefit-risk balance. See EMA Q&A.

Table 3. Recent UK drug launches or licence extensions (Aug 2011 to Aug 2012)

Generic and *brand* name. Company.	Indication and relevant guidance. Full prescribing information can be found on the electronic medicines compendium at emc.medicines.org.uk via *brand* name link.
BNF 1. Gastrointestinal system	
Adalimumab *Humira - SmPC* AbbVie	***Licence extension:*** Treatment of moderate to severe active ulcerative colitis (UC) in adults. ***Guidance:*** **NICE:** Adalimumab due TBC, UC due Jun 2013. **SMC:** Not approved. ***Reviews:*** LNDG Jul 2012.
Infliximab *Remicade - SmPC* MSD	***Licence extension:*** Treatment of severe active ulcerative colitis in patients aged 6-17 years. ***Guidance:*** **NICE:** UC due Jun 2013. **AWMSG:** Not endorsed. ***Reviews:*** LNDG Dec 2011, NHSC Sep 2011.
BNF 2. Cardiovascular system	
Alteplase *Actilyse - SmPC* Boehringer Ingelheim	***Licence extension:*** Treatment of acute ischaemic stroke started within 4.5 hours after onset of stroke symptoms. ***Guidance:*** **NICE:** Stroke pathway. **SMC:** Approved. ***Reviews:*** None.
Apixaban *Eliquis - SmPC* Pfizer	***Licensed indication:*** Prevention of venous thromboembolic events in adults who have undergone elective hip or knee replacement surgery. ***Guidance:*** **NICE:** VTE pathway. **SMC:** Approved. ***Reviews:*** None.
Argatroban *Exembol - SmPC* Mitsubishi Pharma Europe	***Licensed indication:*** Anticoagulation in adults with heparin-induced thrombocytopenia type II. ***Guidance:*** **SMC:** Due Nov 2012. ***Reviews:*** None.
Azilsartan *Edarbi - SmPC* Takeda	***Licensed indication:*** Treatment of hypertension. ***Guidance:*** **NICE:** Hypertension pathway. **SMC:** Not approved. **AWMSG:** Not endorsed. ***Reviews:*** LNDG due TBC.
Eplerenone *Inspra - SmPC* Pfizer	***Licence extension:*** Reduce risk of cardiovascular mortality and morbidity in adults with chronic heart failure and left ventricular systolic dysfunction after a recent myocardial infarction. ***Guidance:*** **NICE:** Chronic heart failure pathway. **SMC:** Approved. ***Reviews:*** NPC/UKMi Jul 2011, NPC Jan 2011.
Ivabradine *Procoralan - SmPC* Servier	***Licence extension:*** Treatment of chronic heart failure. ***Guidance:*** **NICE:** Chronic heart failure pathway. **SMC:** Due Oct 2012. ***Reviews:*** NPC/UKMi Mar 2011.
Olmesartan/ amlodipine/ hydrochlorothiazide *Sevikar HCT - SmPC* Daiichi Sankyo	***Licensed indication:*** Treatment of hypertension. ***Guidance:*** **NICE:** Hypertension pathway. **SMC:** Approved. ***Reviews:*** None.
Rivaroxaban *Xarelto - SmPC* Bayer	***Licence extension:*** Prevention of stroke and systemic embolism in atrial fibrillation. ***Guidance:*** **NICE:** Stroke pathway. **SMC:** Approved. **MTRAC:** Jan 2012. ***Reviews:*** LNDG Jan 2012, NYRDTC Jan 2012, NPC Oct 2011.
Rivaroxaban *Xarelto - SmPC* Bayer	***Licence extension:*** Treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism following acute DVT in adults. ***Guidance:*** **NICE:** VTE pathway. **SMC:** Approved. ***Reviews:*** NYRDTC Feb 2012. NPC Feb 2011.
BNF 3. Respiratory system	
C1 inhibitor *Cinryze - SmPC* ViroPharma	***Licensed indication:*** Treatment and prevention of angioedema in hereditary angioedema. ***Guidance:*** None. ***Reviews:*** LNDG Jun 2012.

Table 3. Recent UK drug launches or licence extensions (Aug 2011 to Aug 2012)

Generic and *brand* name. Company.	Indication and relevant guidance. Full prescribing information can be found on the electronic medicines compendium at emc.medicines.org.uk via *brand* name link.
Conestat alfa *Ruconest - SmPC* Swedish Orphan Biovitrum	***Licensed indication:*** Treatment of acute angioedema in hereditary angioedema due to C1 esterase inhibitor deficiency. ***Guidance:*** **SMC:** Not approved. ***Reviews:*** LNDG Jun 2012.
Mannitol *Bronchitol - SmPC* Pharmaxis	***Licensed indication:*** Treatment of cystic fibrosis in adults aged 18 years and above. ***Guidance:*** **NICE:** Mannitol due Nov 2012. ***Reviews:*** None.
BNF 4. Central nervous system	
Asenapine *Sycrest - SmPC* Lundbeck	***Licensed indication:*** Treatment of moderate to severe manic episodes associated with bipolar I disorder. ***Guidance:*** **NICE:** Bipolar disorder, update due TBC. **SMC:** Not approved. ***Reviews:*** NYRDTC Mar 2012.
Midazolam *Buccolam - SmPC* ViroPharma	***Licensed indication:*** Treatment of prolonged, acute, convulsive seizures in patients aged 3 months to 17 years. ***Guidance:*** **NICE:** Epilepsy pathway. **SMC:** Approved. **AWMSG:** Recommended. ***Reviews:*** None.
Zonisamide *Zonegran - SmPC* Eisai	***Licence extension:*** Monotherapy to treat partial seizures in newly diagnosed epilepsy. ***Guidance:*** **NICE:** Epilepsy pathway. ***Reviews:*** NHSC Apr 2011.
BNF 5. Infections	
Fidaxomicin *Dificlir - SmPC* Astellas	***Licensed indication:*** Treatment of *Clostridium difficile* infection in adults. ***Guidance:*** **SMC:** Approved. ***Reviews:*** LNDG Jun 2012, NICE evidence summary Jun 2012, NHSC Dec 2010.
Rifaximin *Xifaxanta - SmPC* Norgine	***Licensed indication:*** Treatment of travellers' diarrhoea. ***Guidance:*** **SMC:** Not approved. **AWMSG:** Recommended. ***Reviews:*** UKMi due TBC.
Rilpivirine *Edurant - SmPC* Janssen-Cilag	***Licensed indication:*** Treatment of HIV-1 infection in treatment-naïve adults. ***Guidance:*** **SMC:** Approved. **AWMSG:** Recommended. ***Reviews:*** LNDG Mar 2012.
Rilpivirine/ emtricitabine/ tenofovir *Eviplera - SmPC* Gilead	***Licensed indication:*** Treatment of HIV-1 infection in treatment-naïve adults. ***Guidance:*** **SMC:** Approved. **AWMSG:** Recommended. ***Reviews:*** LNDG Mar 2012.
Telaprevir *Incivo - SmPC* Janssen-Cilag	***Licensed indication:*** Treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease. ***Guidance:*** **NICE:** Telaprevir. **SMC:** Approved treatment-naïve, experienced. ***Reviews:*** NYRDTC Dec 2011, LNDG Dec 2011, NPC Oct 2011, Sep 2011.
Tobramycin *TOBI podhaler - SmPC* Novartis	***Licensed indication:*** *Pseudomonas aeruginosa* pulmonary infection in adults and children aged 6 years and older with cystic fibrosis. ***Guidance:*** **NICE:** Tobramycin due Mar 2013. **SMC:** Approved. ***Reviews:*** None.
BNF 6. Endocrine system	
Exenatide *Byetta - SmPC* Eli Lilly	***Licence extension:*** Treatment of type 2 diabetes mellitus in combination with basal insulin. ***Guidance:*** **NICE:** Diabetes pathway. **SMC:** Approved. **AWMSG:** Not endorsed. ***Reviews:*** NHSC Aug 2011.

Table 3. Recent UK drug launches or licence extensions (Aug 2011 to Aug 2012)	
Generic and *brand* name. Company.	Indication and relevant guidance. Full prescribing information can be found on the electronic medicines compendium at emc.medicines.org.uk via *brand* name link.
Linagliptin *Trajenta - SmPC* Boehringer Ingelheim	***Licensed indication:*** Treatment of type 2 diabetes mellitus in adults. ***Guidance:*** **NICE:** Diabetes pathway. **SMC:** Restricted use. **AWMSG:** Not recommended. ***Reviews:*** NYRDTC Mar 2012.
Saxagliptin *Onglyza - SmPC* Bristol-Myers Squibb-AstraZeneca	***Licence extension:*** Treatment of type 2 diabetes mellitus in combination with insulin. ***Guidance:*** **NICE:** Diabetes pathway. **SMC:** Not approved. **AWMSG:** Recommended. ***Reviews:*** None.
Vildagliptin *Galvus - SmPC* Novartis	***Licence extension:*** As monotherapy for the treatment of type 2 diabetes mellitus. ***Guidance:*** **NICE:** Diabetes pathway. **SMC:** Due TBC. ***Reviews:*** None.
BNF 7. Obstetrics, gynaecology, and urinary-tract disorders	
Ulipristal *Esmya - SmPC* Preglem UK	***Licensed indication:*** Pre-operative treatment of symptoms of uterine fibroids. ***Guidance:*** **NICE:** Ultrasound, Embolisation, Laser ablation. **AWMSG:** Not endorsed. ***Reviews:*** LNDG May 2012.
BNF 8. Malignant disease and immunosuppression	
Abiraterone *Zytiga - SmPC* Janssen-Cilag	***Licensed indication:*** Treatment of metastatic castration-resistant prostate cancer in men whose disease has progressed on or after a docetaxel-based chemotherapy regimen. ***Guidance:*** **NICE:** Prostate cancer pathway. **SMC:** Restricted use. **AWMSG:** Recommended. ***Reviews:*** LCNDG Sep 2011, NYRDTC Feb 2011.
Belatacept *Nulojix - SmPC* Bristol-Myers Squibb	***Licensed indication:*** Prophylaxis of renal transplant rejection. ***Guidance:*** **NICE:** Belatacept due TBC. **SMC:** Not approved. **AWMSG:** Not recommended. ***Reviews:*** None.
Belimumab *Benlysta - SmPC* GlaxoSmithKline	***Licensed indication:*** Treatment of autoantibody-positive systemic lupus erythematosus. ***Guidance:*** **NICE:** Belimumab due May 2012. **SMC:** Not approved. ***Reviews:*** NYRDTC Apr 2012, LNDG Oct 2011.
Bevacizumab *Avastin - SmPC* Roche	***Licence extension:*** First-line treatment of advanced ovarian, fallopian tube or primary peritoneal cancer. ***Guidance:*** **NICE:** Ovarian cancer pathway. **SMC:** Due Oct 2012. ***Reviews:*** LCNDG Mar 2012.
Erlotinib *Tarceva - SmPC* Roche	***Licence extension:*** First-line treatment of locally advanced or metastatic non-small cell lung cancer with EGFR-positive mutations. ***Guidance:*** **NICE:** Lung cancer pathway. **SMC:** Approved. ***Reviews:*** LCNDG Jan 2012, NHSC Aug 2010.
Everolimus *Afinitor - SmPC* Novartis	***Licence extension:*** Treatment of unresectable or metastatic pancreatic neuroendocrine tumours. ***Guidance:*** **SMC:** Approved. **AWMSG:** Recommended. ***Reviews:*** LCNDG Sep 2011.
Everolimus *Votubia - SmPC* Novartis	***Licensed indication:*** Treatment of tuberous sclerosis complex-associated subependymal giant cell astrocytoma in patients aged 3 years and older. ***Guidance:*** **SMC:** Not approved. **AWMSG:** Not endorsed. ***Reviews:*** None.
Everolimus *Afinitor - SmPC* Novartis	***Licence extension:*** Treatment of hormone receptor-positive, HER2 negative advanced breast cancer. ***Guidance:*** **NICE:** Breast cancer pathway. ***Reviews:*** NHSC Apr 2011.

Table 3. Recent UK drug launches or licence extensions (Aug 2011 to Aug 2012)

Generic and *brand* name. Company.	Indication and relevant guidance. Full prescribing information can be found on the electronic medicines compendium at emc.medicines.org.uk via *brand* name link.
Interferon beta-1a *Rebif - SmPC* Merck Serono	***Licence extension:*** Treatment of patients with multiple sclerosis with a single demyelinating event and an active inflammatory process. ***Guidance:*** **NICE:** Multiple sclerosis. **AWMSG:** Not endorsed. ***Reviews:*** None.
Mercaptopurine suspension *Xalupurine.* Nova Laboratories	***Licensed indication:*** Acute lymphoblastic leukaemia. ***Guidance:*** **NICE:** Haemato-oncology. **SMC:** Approved. ***Reviews:*** None.
Panitumumab *Vectibix - SmPC* Amgen	***Licence extension:*** First and second-line treatment of KRAS metastatic colorectal cancer. ***Guidance:*** **NICE:** Colorectal cancer pathway. **SMC:** Not approved . ***Reviews:*** LCNDG May 2012.
Pazopanib *Votrient - SmPC* GlaxoSmithKline	***Licensed indication:*** Treatment of advanced soft tissue sarcoma (STS). ***Guidance:*** **NICE:** STS- trabectedin, Sarcoma. **SMC:** Due Dec 2012. ***Reviews:*** NHSC Dec 2010.
Tegafur/ gimeracil/ oteracil *Teysuno - SmPC* Nordic Pharma	***Licensed indication:*** Treatment of adults with advanced gastric cancer. ***Guidance:*** **SMC:** Due Sep 2012. **AWMSG:** Not endorsed. ***Reviews:*** None.
Trastuzumab *Herceptin - SmPC* Roche	***Licence extension:*** Treatment of HER2 positive early breast cancer in combination with neoadjuvant chemotherapy, followed by adjuvant trastuzumab, for locally advanced disease. ***Guidance:*** **NICE:** Breast cancer pathway. ***Reviews:*** NHSC Aug 2010.
Vandetanib *Caprelsa - SmPC* AstraZeneca	***Licensed indication:*** Treatment of medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. ***Guidance:*** **SMC:** Not approved. **AWMSG:** Not endorsed. ***Reviews:*** NYRDTC Feb 2011.
Vemurafenib *Zelboraf - SmPC* Roche	***Licensed indication:*** Treatment of BRAF V600-positive unresectable/ metastatic melanoma. ***Guidance:*** **NICE:** Vemurafenib due Oct 2012. **SMC:** Due Sep 2012. ***Reviews:*** LCNDG Apr 2012, Mar 2012, NHSC Aug 2010.
BNF 9. Nutrition and blood	
Eculizumab *Soliris - SmPC* Alexion	***Licence extension:*** Treatment of atypical haemolytic uremic syndrome. ***Guidance:*** **SMC:** Not approved. **AWMSG:** Not endorsed. ***Reviews:*** NHSC Aug 2011, RDTC Jul 2012.
Methylthioninium chloride *Proveblue - SmPC* Provepharm	***Licensed indication:*** Acute symptomatic treatment of methaemoglobinaemia. ***Guidance:*** **AWMSG:** Not endorsed. ***Reviews:*** None.
Colecalciferol *Fultium-D3 - SmPC* Internis	***Licensed indication:*** Prevention and treatment of vitamin D deficiency and as an adjunct to the treatment of osteoporosis in patients with or at risk of vitamin D insufficiency. ***Guidance:*** **SMC:** Due Sep 2012. ***Reviews:*** None.
BNF 10. Musculoskeletal and joint diseases	
Adalimumab *Humira - SmPC* AbbVie	***Licence extension:*** Treatment of adults with severe axial spondyloarthritis. ***Guidance:*** None. ***Reviews:*** NHSC May 2011.

Table 3. Recent UK drug launches or licence extensions (Aug 2011 to Aug 2012)	
Generic and *brand* name. Company.	Indication and relevant guidance. Full prescribing information can be found on the electronic medicines compendium at emc.medicines.org.uk via *brand* name link.
Fampridine *Fampyra - SmPC* Biogen Idec	***Licensed indication:*** Improvement of walking in adults with multiple sclerosis. ***Guidance:*** **NICE:** Multiple sclerosis. **SMC:** Not approved. **AWMSG:** Not endorsed. **MTRAC:** May 2012. **NETAG:** Mar 2012. ***Reviews:*** RDTC Sep 2011, LNDG Aug 2011, NPC Aug 2010.
Golimumab *Simponi - SmPC* MSD	***Licence extension:*** Reduction in the rate of peripheral joint damage in psoriatic arthritis. ***Guidance:*** **NICE:** Golimumab. **SMC:** Approved. ***Reviews:*** None.
Strontium ranelate *Protelos - SmPC* Servier	***Licence extension:*** Treatment of osteoporosis in men at increased risk of fracture. ***Guidance:*** None relevant. ***Reviews:*** None.
BNF 14. Vaccines	
Herpes zoster vaccine *Zostavax - SmPC* SanofiPasteur MSD	***Licensed indication:*** Prevention of herpes zoster and post-herpetic neuralgia in adults aged 50 years or older. ***Guidance:*** None. ***Reviews:*** None.
Influenza vaccine intranasal *Fluenz - SmPC* AstraZeneca	***Licensed indication:*** Influenza prophylaxis in children aged between 2 and 18 years. ***Guidance:*** None. ***Reviews:*** None.
Meningococcal vaccine *Nimenrix - SmPC* GlaxoSmithKline	***Licensed indication:*** Immunisation of patients aged ≥12 months against *Neisseria meningitidis* (group A, C, W-135 and Y) meningococcal disease. ***Guidance:*** None. ***Reviews:*** None.
BNF 15. Anaesthesia	
Dexmedetomidine *Dexdor - SmPC* Orion Pharma	***Licensed indication:*** Sedation of adults in intensive care requiring a sedation level not deeper than arousal in response to verbal stimulation. ***Guidance:*** **SMC:** Approved. **AWMSG:** Recommended. ***Reviews:*** None.

Patent expiries 2012 - 2014

Generic medicines have a significant impact on prescribing budgets and can offset, to some extent, costs associated with the introduction of new medicines. Generic products can be marketed once the patent on the original product has expired although manufacturers may apply for a Supplementary Protection Certificate (SPC) to extend the effective patent life by up to 5 years (5½ years if it includes a Paediatric Investigation Plan). Expiry dates below take account of SPCs. The table highlights those drugs where there is a greater potential for the availability of a generic/biosimilar product. In addition, the table indicates where a licence for a generic/biosimilar product is in the latter stages of the EU licensing process or is already available in the EU. However, it does not follow that the generic/biosimilar product will be available in the UK as patent issues may differ between countries.

*** Drugs which have the greatest potential for generic/biosimilar preparations becoming available.**

 # Drugs where generic/biosimilar products are in later stages of EU licensing or are licensed in EU

♦ Patent extended by 6 months (paediatric extension)

Expiry date	Drug
2012	
Jan	Latanoprost ♦
	Galantamine #
Feb	Donepezil HCl #
	Mometasone furoate#
	Tolcapone
	Eptifibatide
Mar	Zolmitriptan #
	Naratriptan #
	Lepirudin
	Quetiapine fumarate #
Apr	Eprosartan mesylate
	Candesartan #
	Cidofovir
May	Atorvastatin calcium lactate #♦
Jul	Bemiparin
	Carmustine
	Rivastigmine hydrogen tartrate #
	Dipyridamole plus Aspirin
Aug	Irbesartan #
Sep	Tolterodine tartrate #
	Ramipril plus felodipine
Nov	Indinavir
	Rabeprazole #
	Entacapone
Dec	Desogestrel

Expiry date	Drug
2013	
Feb	Montelukast ♦
	Fosphenytoin sodium
	Ganirelix
	Dorzolamide plus timolol #
	Zidovudine plus lamivudine
Apr	Basiliximab
May	Nelarabine
	Tirofiban
	Zoledronic acid ♦#
Jun	Capecitabine #
	Nevirapine ♦#
	Sildenafil #
Jul	Etonogestrel
Aug	Raloxifene HCl #
	Rizatriptan ♦#
	Clopidogrel hydrogen sulphate ♦
Oct	Irbesartan plus hydrochlorothiazide
Nov	Efavirenz
	Rituximab *
Dec	Telmisartan #

Expiry date	Drug
2014	
Feb	Alemtuzumab
	Temoporfin
	Zanamivir *
Mar	Somatropin (synthetic hGH)
Apr	Memantine HCl
May	Anakinra
	Escitalopram oxalate
Jun	Abacavir
	Hydroxyethyl starch
	Moxifloxacin
	Ulipristal acetate *
Jul	Trastuzumab
	Verteporfin
Aug	Infliximab *
	Palivizumab
Sep	Cetuximab *
	Rosiglitazone
Oct	Aripiprazole *
	Nelfinavir mesylate
	Paliperidone
Nov	Insulin glargine
	Icatibant acetate
Dec	Almotriptan
	Bevacizumab
	Brinzolamide *
	Omalizumab

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UKMi

AZILSARTAN MEDOXOMIL PRIMARY CARE BRIEFING

This Primary Care Briefing has been produced to inform healthcare professionals in primary care of the new angiotensin II receptor blocker (ARB), azilsartan medoxomil (Edarbi® ▼).

Azilsartan medoxomil

- Azilsartan medoxomil ('azilsartan') is the eighth ARB to be launched in the UK.[1] It is licensed for the treatment of essential hypertension in adults.[2] The recommended starting dose is 40mg once daily (20mg once daily in those ≥75 years who are at risk of hypotension), increasing to 80mg OD if necessary. Near-maximal antihypertensive effect is seen at 2 weeks, with maximal effects at 4 weeks.[2]
- No dose adjustment is required in patients with mild or moderate renal impairment. Azilsartan should be used with caution in patients with severe renal impairment or end-stage renal disease, and in those with severe hepatic impairment due to lack of data.[2] Close monitoring of patients with mild to moderate hepatic impairment is recommended and a starting dose of 20mg OD should be used.[2] There are no data for the use of azilsartan in patients with congestive heart failure.[2]
- Peak plasma concentrations of azilsartan are reached within 1.5 to 3 hours post-dose. The elimination half-life is 11 hours.[2]

Current guidelines

NICE Guidance for the treatment of hypertension are [3]:

Age	Step 1	Step 2	Step 3
≤55 years	ACE inhibitor or low-cost ARB	Add calcium channel blocker	Add thiazide-like diuretic, e.g. bendroflumethiazide, indapamide
≥55 years OR black person of African/Caribbean family origin	Calcium channel blocker	Add ACEI or low-cost ARB	

Candesartan, losartan and valsartan are currently available as lower cost generic ARBs in the UK.[4]

Place in therapy

- Azilsartan is structurally related to candesartan but it is more lipophilic, which potentially increases its oral bioavailability.[5] It appears to be an overwhelmingly selective angiotensin receptor (AT1) antagonist, with greater potency and, because it takes longer to dissociate from the site of action, it has a longer-lasting pharmacologic effect compared with other ARBs.[5]
- Takeda suggest that azilsartan may be a useful treatment option to enhance blood pressure lowering for patients in whom dual antihypertensive therapy with a generic ACEI or ARB, plus either a calcium channel blocker (CCB) or diuretic has not reduced blood pressure to the desired level, before trying triple antihypertensive therapy. This is not in line with NICE guidance. In most cases the addition of azilsartan may be a more expensive option than the addition of a calcium channel blocker (CCB) or diuretic, noting the recent availability of generic ARBs in the UK (see Table 2). Patient adherence to and tolerability of a multiple-drug treatment regimen may need to be taken into consideration.
- However, bear in mind that none of the studies have compared azilsartan monotherapy with an ARB/ACEI plus CCB, as per NICE guidance.

Benefits of blood pressure lowering

- There are no cardiovascular outcome data for azilsartan. However the benefits of lowering blood pressure have been studied. A specified absolute BP reduction from any point on the BP distribution produces a constant proportional reduction in cardiovascular risk. For a reduction of 5mmHg in diastolic BP (DBP), cohort studies indicate that the risk of stroke is reduced by 34% and the risk of ischaemic heart disease by 21%, at 60-65 years. These proportional effects are similar at different ages.[6] Systolic (SBP) and diastolic BP are highly correlated and the results are similar whichever is used. The risk of a stroke or heart disease decreases as blood pressure is reduced, but there is no lower threshold.[6]
- The benefits of antihypertensive treatment on cardiovascular morbidity are thought to be mainly due to blood pressure lowering effects per se, independent of the drug class used. A recent meta-analysis of 20 cardiovascular morbidity-mortality trials (n=158,998) evaluated the impact of renin-angiotensin-aldosterone-system inhibitors (RAAS inhibitors which comprise of ARBs and ACE inhibitors) on all-cause and cardiovascular mortality.[7] The trials included were those with compared ACEI or ARB treatment with a control (placebo, active or usual care). Analysis was stratified according to ACEI (n=76,615) or ARB (n=82,383) treatment. The overall analysis included 677,005 patient years and 15,061 deaths.
    - In the 20 trials grouped together, treatment with a RAAS inhibitor was associated with a statistically significant 5% reduction in all-cause mortality and a significant 7% reduction in cardiovascular mortality.
    - ACEI treatment was associated with a 10% reduction in all-cause mortality (mortality incidence rate: 20.4 vs. 24.2 deaths per 1000 patient-years) (7 trials, HR 0.90, 95% CI: 0.84-0.97, p=0.004 compared with control).

- No significant reduction in mortality was demonstrated with ARB therapy (IR: 21.4 vs. 22.0 deaths per 1000 patient-years) (13 trials, HR 0.99, 95% CI: 0.94-1.04, p=0.683 compared with control).
- No difference in cardiovascular mortality was seen between ACEI and ARBs.
- There are limitations to the review: different definitions of hypertension were used in the trials, doses of the active and control drugs varied, target BP levels differed and follow-up times were different.

Phase III clinical studies with azilsartan (table 2)[8-14]

- The surrogate endpoint, change in 24 hour ambulatory blood pressure monitoring (ABPM), was used in most studies as the primary endpoint. This provides a good insight into blood pressure (BP) changes during everyday activities and is recommended for the evaluation of new antihypertensive drugs, but there are insufficient data to accept it as the sole basis for efficacy in an approval process.[15]
- Maximum licensed doses of the comparators (olmesartan, valsartan and ramipril) were used.
- All treatments lowered SBP and DBP but none of the studies were long enough to evaluate any differences between treatment groups in the reduction in clinical endpoints, i.e. morbidity and mortality.
- Azilsartan was shown to lower SBP and DBP to a greater degree than maximum doses of olmesartan, valsartan and ramipril and the differences were statistically significant for azilsartan 80mg vs. comparator.
- When used as monotherapy, the greatest difference in the primary endpoint was between azilsartan 80mg and ramipril 10mg (-9mmHg). Differences in the primary endpoints between azilsartan and other ARB monotherapies ranged from -0.4 to -4.3 mmHg.
- Response rates (SBP<140mHg and/or reduction of ≥20mmHg) were generally higher in patients treated with azilsartan.
- When azilsartan was used in combination with amlodipine or with chlorthalidone, blood pressure was lowered to a greater extent than amlodipine or chlorthalidone monotherapy, as would be expected.
- The combination of azilsartan plus chlorthalidone resulted in greater blood pressure reductions than olmesartan plus hydrochlorothiazide. Hydrochlorothiazide has traditionally been the thiazide used in combination products. Chlorthalidone has a longer half-life and can lower BP more effectively, which may partly account for these results.[16]
- The mean age of patients in the studies was over 55 years of age; according to NICE guidance treatment would be initiated with a calcium channel blocker.
- Exclusion criteria included secondary hypertension, seated DBP >114mmHg, advanced renal disease, major CV events within 6 months of enrolment, poorly controlled diabetes and hepatic abnormalities.

In summary: Responder rates (SBP <140mmHg and/or reduction of ≥20mmHg) were higher in the azilsartan groups (50-59%) compared with ramipril (33.8%), valsartan (47-49%) and olmesartan (49-53%) but note that none of the studies evaluated the BP lowering effects of azilsartan vs. ACEI/ARB plus CCB. The use of azilsartan in place of dual therapy prior to using triple therapy cannot be evaluated from the available clinical trials.

Cost

Note that this is a selection of antihypertensives, based on those used in the trials above, other generic ARBs and commonly used diuretics.

Table 1: Cost of selected antihypertensive drugs				**Examples of combinations, cost/year**		
Drug	**Max daily dose**[1]	**Cost per month**[1;17]	**Cost / year**	**+ amlodipine**	**+ amlodipine + bendroflumethiazide**	**+ amlodipine + indapamide**
Azilsartan (Edarbi®)	40-80mg OD	28x40mg: £16.80 28x80mg: £19.95	£218.40 – £259.35		-	
Candesartan*	32mg OD	28x32mg: £16.13	£209.69	£222.95	£233.22	£239.46
Losartan	100mg OD	28x100mg: £2.07	£26.91	£40.17	£50.44	£56.68
Olmesartan (Olmetec®)	40mg OD	28x40mg: £17.50	£227.50	£240.76	£251.03	£257.27
Valsartan	320mg OD	2x28x160mg: £10.34	£134.42	£147.68	£157.95	£164.19
Ramipril (capsules)	10mg OD	28x10mg: £1.43	£18.59	£31.85	£42.012	£48.36
Bendroflumethiazide	5mg OD	28x5mg: £0.79	£10.27	-	-	
Indapamide	2.5mg OD	28x2.5mg: £1.27	£16.51	-	-	
Amlodipine	10mg OD	28x10mg: £1.02	£13.26	-	-	
*candesartan came off patent in May 2012, further price reductions are anticipated; therefore a greater price differential between candesartan azilsartan expected.						

Table 2. Phase III randomised, double-blind, controlled trials evaluating the efficacy of azilsartan

<table>
<tr><th>Ref</th><th>No. of patients
Inclusion criteria</th><th>Dose, titration, power calculation</th><th>Results : Primary endpoint</th><th>Results: other parameters (BP measured in mmHg)</th></tr>
<tr><td>Bakris[8]</td><td>1275 pts (mean age 58) with sitting trough clinic SBP ≥150 to ≤180mmHg and 24-hour mean SBP ≥130 to ≤170mmHg.

Exclusions: history of major CV events, secondary hypertension, severe renal impairment, renal artery stenosis, type 1 or poorly controlled type 2 diabetes, hepatic abnormalities and raised serum potassium (K^+) levels.</td><td>Placebo
AZL 20mg, 40mg or 80mg OD
OLM 40mg OD

90% power to detect a difference of 5.5mmHg between AZL and placebo and a 4mmHg difference between AZL and OLM.</td><td>Mean change in 24-hour mean SBP (mmHg) by ABPM at week 6 (difference vs. OLM)

<table><tr><th>Placebo</th><th>AZL 20mg</th><th>AZL 40mg</th><th>AZL80mg</th><th>OLM 40mg</th></tr><tr><td>-1.4</td><td>-12.2* (0.4)</td><td>-13.5* (-0.9)</td><td>-14.6* (-2)</td><td>-12.6*</td></tr><tr><td>-</td><td>p=NS†</td><td>p=NS†</td><td>p=0.038†</td><td>-</td></tr></table>*p<0.001 vs. placebo; †p vs. olmesartan</td><td>• Early morning SBP at week 6 demonstrated trend towards greater reduction with AZL80mg (-12.2) than with OLM40mg (-9.9, p=0.054).

<table><tr><th>Changes in BP</th><th>AZL 20mg</th><th>AZL 40mg</th><th>AZL80mg</th><th>OLM 40mg</th></tr><tr><td>Clinic SBP</td><td>-14.3</td><td>-14.5</td><td>-17.6†</td><td>-14.9</td></tr><tr><td>24-hr mean DBP*</td><td>-6.8</td><td>-7.7</td><td>-7.9</td><td>-7.0</td></tr><tr><td>Clinic DBP*</td><td>-7.0</td><td>-7.1</td><td>-8.6†</td><td>-7.1</td></tr><tr><td>Responder rates</td><td>48%</td><td>50%</td><td>57%</td><td>53%</td></tr></table>* placebo subtracted †p=0.04 vs. OLM
• Adverse events (AEs) were similar to those observed in placebo group.</td></tr>
<tr><td>Sica[11]</td><td>984 pts (mean age 57) with clinic SBP ≥ 150 to ≤180mmHg and 24-hour mean SBP ≥130 to ≤170mmHg.
75% Caucasian, remainder were native American or Asian origin.
Exclusion criteria: secondary hypertension, renal dysfunction, major CV events within 6 months, type 1 or poorly controlled type 2 diabetes, raised serum K^+levels.</td><td>Forced titration after 2 weeks
AZL 20mg titrated to 40mg or 80mg OD
VAL 80mg titrated to 320mg OD

90% power to demonstrate non-inferiority between AZL and VAL on primary endpoint.</td><td>Mean change in 24 hour SBP (mmHg) by ABPM at week 24 (difference from VAL)

<table><tr><th>AZL 40mg:</th><th>AZL 80mg</th><th>VAL 320mg</th></tr><tr><td>-14.9* (-3.6)</td><td>-15.3* (-4)</td><td>-11.3</td></tr></table>*p<0.001 vs. VAL

• Mean decreases in ABPM tended to be smaller during 16-24 hour interval than during 1-15 hour interval in all groups.</td><td>• Changes in hourly SBP were lower at all time-points with AZL 40mg and 80mg than VAL 320mg.
• Adverse events incidences were lower in AZL groups (~65%) than in the VAL group (59.2%).

<table><tr><th>Changes in BP*</th><th>AZL 40mg</th><th>AZL 80mg</th><th>VAL 320mg</th></tr><tr><td>24-hr mean DBP</td><td>-2.16†</td><td>-2.69†</td><td>-</td></tr><tr><td>Clinic DBP</td><td>-2.52†</td><td>-2.76†</td><td>-</td></tr><tr><td>Responder rates</td><td>56% p=0.016</td><td>59%, p=0.002</td><td>47%</td></tr></table>* relative to valsartan (actual values not stated) †p≤0.001</td></tr>
<tr><td>Bonner[13]</td><td>884 pts (mean age 57) with clinic SBP 150-180mmHg.

Exclusion criteria not stated.- Conference abstract only.</td><td>Forced titration after 2 weeks
AZL 20mg OD titrated to 40mg or 80mg
RAM 2.5mg OD titrated to 10mg OD</td><td>Mean change in trough sitting clinic SBP (mmHg) at week 24 (difference from RAM)

<table><tr><th>AZL 40mg</th><th>AZL 80mg</th><th>RAM 10mg</th></tr><tr><td>-20.6* (-8.4)</td><td>-21.2* (-9)</td><td>-12.2</td></tr></table>* p<0.001 vs. RAM</td><td><table><tr><th></th><th>AZL 40mg</th><th>AZL 80mg</th><th>RAM 10mg</th></tr><tr><td>24-hour ambulatory</td><td>-12.7, p<0.001</td><td>-12.3, p<0.002</td><td>-7.8</td></tr><tr><td>Response rates</td><td>54%, p<0.001</td><td>53.6%, p<0.001</td><td>33.8%</td></tr></table>P value vs. RAM
• Discontinuation due to AEs was less frequent with AZL40mg and 80mg than with RAM 10mg. (2.4%, 3.1% and 4.8%), as was cough (1%, 1.4%, 8.2%)</td></tr>
<tr><td>Weber[14]</td><td>562 pts (mean age 58) with stage 2 hypertension (clinic SBP ≥160mmHg). Mean age 58 yrs.

Exclusion criteria not stated – conference abstract only.</td><td>Placebo
AZL 40mg or 80mg OD
All received amlodipine 5mg OD</td><td>Mean change in 24-hour mean SBP (mmHg) by ABPM at week 6 (difference from placebo + amlodipine)

<table><tr><th>Placebo + AML</th><th>AZL 40mg +AML</th><th>AZL 80mg + AML</th></tr><tr><td>-13.6</td><td>-24.8* (-11.2)</td><td>-24.5* (-10.9)</td></tr></table>*p<0.001 vs. placebo. All received amlodipine</td><td><table><tr><th>Change</th><th>Placebo</th><th>AZL 40mg</th><th>AZL 80mg</th></tr><tr><td>Clinic SBP</td><td>-15.9</td><td>-27.0*</td><td>-25.5*</td></tr><tr><td>Mean 24-hour DBP</td><td>-7.8</td><td>-15.3*</td><td>-15.4*</td></tr><tr><td>Clinic DBP</td><td>-7.1</td><td>-12.0*</td><td>-12.7*</td></tr><tr><td>Response rates</td><td>43%</td><td>66%</td><td>69%</td></tr></table>*p<0.001 vs. placebo. All received amlodipine.
• Peripheral oedema occurred in 4.9% (n=9) taking placebo + AML vs. 2.1% (n=4) taking AZL + AML.</td></tr>
</table>

AML: amlodipine AZL: azilsartan CLD: chlorthalidone HCZ: hydrochlorothiazide OLM: olmesartan RAM: ramipril VAL: valsartan

ABPM: ambulatory blood pressure monitoring SBP: systolic blood pressure DBP: diastolic blood pressure Responder = reduction in SBP to <140mmHg and/or reduction of ≥20mmHg