tariff exists. This list includes high-cost drugs for which a separate means of payment has to be established. The latest high cost drugs list for 2012/13 is available via this link (tab 17 for a detailed list of drugs currently excluded from tariff). In *Prescribing Outlook* an 'educated guess' as to the potential tariff positioning of each new medicine is made.

Patents

Availability of generic medicines allows significant savings to be made in the NHS. In previous years, *Prescribing Outlook* has listed those branded medicines whose patents are due to expire in the near future and made an 'educated guess' as to which have the potential for generic competition. This year, medicines for which generic product licence applications are currently in progress in the EU are also listed. This will help organisations plan for their introduction.

Please direct comments on *Prescribing Outlook – New Medicines* to the editor: Helen Davis, North West Medicines Information Centre, Pharmacy Practice Unit. helen.davis@lrippu.nhs.uk.

Other UKMi horizon scanning resources

Prescribing Outlook – National Developments estimates the impact on clinical practice and prescribing budgets of national guidance, mainly that issued by NICE. It is intended to inform discussions between commissioners and providers, and highlight issues around implementation of guidance. Access is via www.nelm.nhs.uk >evidence>horizon-scanning (registration required).

Prescribing Outlook – Cost Calculator is an Excel spreadsheet tool to facilitate estimates of potential prescribing changes for a local population. Access is via www.nelm.nhs.uk >evidence>horizon-scanning (registration required).

Please direct comments on *Prescribing Outlook – National Developments* and the *Cost Calculator* to: Devika Sennik or David Erskine, London and South East Medicines Information Centre, Guy's and St. Thomas' NHS Foundation Trust. devika.sennik@gstt.nhs.uk, david.erskine@gstt.nhs.uk

New Drugs Online (NDO) database includes information on medicines in clinical development from phase II trials to product launch and includes links to evaluated information on medicines up to one year post launch. This database is maintained by UKMi and forms the basis of the content of *Prescribing Outlook – New Medicines*. This dynamic horizon scanning tool is updated daily and can be used to produce reports based on a number of criteria including possible launch date, stage of clinical development or pharmaceutical company. Access is via www.nelm.nhs.uk and requires individual registration. From NeLM, click on 'Evidence' then 'Horizon scanning'. A hyperlink will take you to the registration page. Access is free and available to all with an NHS email address. Limited access is also freely available to non-NHS users via NHS Evidence (www.evidence.nhs.uk). To find an NDO entry, search NHS Evidence using the relevant medicine name and access from the Sources section in the left hand column.

Please direct comments and enquiries on *New Drugs Online* to: Alexandra Denby, London Medicines Information Service-Northwick Park, Northwick Park & St Mark's Hospitals. nwlh-tr.medinfo@nhs.net

Horizon scanning and new medicines support materials are available via NeLM www.nelm.nhs.uk

The information in these resources is the best available at the time of publication but is subject to significant change with time.

Abbreviations

AWMSG	All Wales Medicines Strategy Group
BNF	British National Formulary
DH	Department of Health
EMA	European Medicines Agency
EU	European Union
HR	Hazard ratio
i.m.	Intramuscular
i.v.	Intravenous
L(C)NDG	London (Cancer) New Drugs Group
MPC	Medicines Prescribing Centre (formerly NPC)
MTRAC	Midland Therapeutic Review & Advisory Committee
NDO	New Drugs Online
NeLM	National electronic Library for Medicines
NETAG	North East Treatment Advisory Group
NHSC	NIHR National Horizon Scanning Centre
NICE	National Institute for Health and Clinical Excellence
NNT	Number needed to treat
NPC	National Prescribing Centre (now the Medicines and Prescribing Centre – MPC)
NYRDTC	Northern and Yorkshire Regional Drug & Therapeutics Centre
PAS	Patient Access Scheme
PbR	Payment by Results
PFS	Progression free survival
s.c.	Subcutaneous
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
TBC	To be confirmed
UKMi	United Kingdom Medicines Information
US	United States

Key

Generic name and formulation

Brand name.

Company.

Medicines are listed by BNF category and hyperlinked to the relevant public pages of the NDO database which is updated daily.

The ***company*** that holds the marketing rights in the EU is listed together with a co-promoter company if relevant.

Indication

The ***indication*** for the product.

The closer the drug is to launch the more specific this can be.

Current status

PIII – in phase three trials.

Filed – licence application has been submitted.

Recommended for approval – opinion of the advisory committee of the licensing authority suggests the medicine should be approved. In the EU full approval is likely within three months of a positive recommendation. Relevant hyperlinks to the EMA website are included.

Approved – the licensing authority has granted a licence. The company will determine the launch date. Hyperlinks to relevant documents with prescribing information are included.

Launched – the medicine is marketed. If launched elsewhere in the world, but not the UK, hyperlinks to relevant prescribing data are included for information.

Orphan – If a medicine has a designated orphan status in the EU this is indicated (see page 6 for definitions).

Predicted UK launch or licence extension.

An informed estimate based on knowledge of processes and timescales involved in licensing systems.

It is easier to predict when a product will be available once it is has entered the licensing process as known time frames apply. However, once a licence has been granted the company decides when and where to launch the product.

National guidance: Relevant publications/ pathways are listed *(funding source)*.

NICE - National Institute for Health and Clinical Excellence: www.nice.org.uk *(DH)*.

SIGN - Scottish Intercollegiate Guidelines Network. www.sign.ac.uk *(NHS Scotland)*.

SMC - Scottish Medicines Consortium. www.scottishmedicines.org.uk *(NHS Scotland)*.

AWMSG - All Wales Medicines Strategy Group. www.wales.nhs.uk/awmsg *(NHS)*.

Reviews: Independent national reviews and regional guidance that is easily accessible to all NHS sectors published between 2010 and 2012 are included.

NHSC - NIHR Horizon Scanning Centre. www.nhsc-healthhorizons.org.uk. *(National Institute for Health Research-NIHR)*.

NPC - National Prescribing Centre (now the Medicines and Prescribing Centre) *(NICE)*. www.npc.co.uk. (Legacy site for reviews prior to May 2012).

UKMi - United Kingdom Medicines Information. www.nelm.nhs.uk *(NHS)*.

L(C)NDG – London (Cancer) New Drugs Groups www.nelm.nhs.uk *(NHS organisations in Greater London region)*.

MTRAC - Midlands Therapeutics Review & Advisory Committee. www.mtrac.co.uk. *(Primary Care NHS organisations in the Midlands region)*.

NETAG - North East Treatment Advisory Group. www.netag.nhs.uk. *(sub-group of the North East Specialised Commissioning Group)*.

NYRDTC –Northern and Yorkshire Regional Drug & Therapeutics Centre. www.nyrdtc.nhs.uk. *(NHS organisations in the North of England)*.

Target population: Data on prevalence (number with the disease) and incidence (number of new cases each year) are based on a 100,000 population if possible.

Sector: An indication of which sector in the NHS the medicine is likely to impact, at least initially, in terms of service provision.

Implications: Factors highlighted include patient options, monitoring or testing requirements and service implications related to medicine delivery.

Financial implications: Cost implications are based on a number of assumptions such as target population, whether the medicine is added to existing therapy or is a competitor in areas where budgets are established. Factors that are difficult to quantify include likely uptake of the medicine within the target population.

Financial impact refers to the effect on the NHS as a whole; local factors must be taken into account by individual organisations.

For launched products, costs are taken from the latest published NHS costs, or, for generic prices, from the Drug Tariff. Where a patient access scheme (PAS) may apply this is indicated. Unless otherwise stated costs do not include VAT.

Payment by Results **(PbR):** The actual or anticipated tariff position.

Pharmacology: Therapeutic class and/or mode of action together with administration details if appropriate.

Efficacy: Contains information on key studies with a link to trial details, especially when relevant for licence application. Primary outcome data and patient rather than disease orientated outcomes are preferentially included where available. Hyperlinks to published studies are included.

Safety: For medicines already marketed for other indications a link to the product information is included. For new medicines, information is included where it is thought adverse effects reported to date may influence licensing requirements e.g. increased monitoring or where they differ significantly from those associated with current treatments.

Summary of predicted launch dates

This list summarises the ***earliest*** predicted UK launch date for pipeline drugs listed in **Table 1 – Pipeline drugs.** Refer to the index for a full list of generic and proprietary names. *Indicates which drugs have been assigned orphan status in the EU (see next page for more details).

BNF	Drug	Indication	Page
	Late 2012		
1	Teduglutide*	Short bowel syndrome	10
1	Linaclotide	Irritable bowel syndrome	10
2	Rivaroxaban	Pulmonary embolism treatment and prevention of recurrent venous thromboembolism	11
2	Apixaban	Stroke prevention in atrial fibrillation	12
2	Clevidipine	Hypertension -perioperative	14
2	Defibrotide*	Hepatic veno-occlusive disease	14
2	Mipomersen	Hypercholesterolaemia-familial	15
3	Ivacaftor*	Cystic fibrosis	15
3	Glycopyrronium bromide	Chronic obstructive pulmonary disease	16
3	Aclidinium	Chronic obstructive pulmonary disease	16
4	Lisdex-amfetamine dimesylate	Attention-deficit hyperactivity disorder	18
4	Tafamidis meglumine*	Familial amyloid poly-neuropathy	20
5	Ceftaroline	Community acquired pneumonia and complicated skin and soft tissue infections.	20
6	Dapagliflozin	Type 2 diabetes mellitus	22
6	Insulin degludec	Type 1 and 2 diabetes mellitus	24
6	Hydrocortisone	Adrenal insufficiency	25
6	Pasireotide	Cushing's disease.	25
7	Mirabegron	Overactive bladder	26
7	Botulinum A toxin	Urinary incontinence	27
8	Crizotinib	Non-small cell lung cancer	28
8	Pertuzumab	Breast cancer	30
8	Lapatinib	Breast cancer	30
8	Aflibercept	Colorectal cancer	32
8	Axitinib*	Renal cell carcinoma	33
8	Bevacizumab	Ovarian cancer	35
8	Pixantrone	Non-Hodgkin's lymphoma	39
8	Brentuximab*	Hodgkin's lymphoma	39
8	Brentuximab*	Anaplastic large cell lymphoma	40
8	Bortezomib	Multiple myeloma	40
8	Bosutinib*	Chronic myeloid leukaemia	41
8	Decitabine*	Acute myeloid leukaemia	42
8	Rituximab	Vasculitis	42
8	Ruxolitinib	Myelofibrosis	43
9	Ferumoxytol	Anaemia in renal disease	44
9	Eltrombopag	Thrombocytopenia - hepatitis C associated	45
10	Tofacitinib	Rheumatoid arthritis	46
10	Pegloticase	Gout prophylaxis	47
11	Fluocinolone acetonide	Diabetic macular oedema	47
11	Aflibercept	Age related macular degeneration	48
13	Ingenol mebutate	Actinic keratosis	49
	2013		
1	Golimumab	Ulcerative colitis	10
2	Dabigatran	Venous thromboembolism treatment.	11
2	Apixaban	Venous thromboembolism treatment.	11
2	Dabigatran	Long-term secondary prevention of venous thromboembolism	12
2	Apixaban	Venous thromboembolism prevention in medically ill patients.	12
2	Rivaroxaban	Secondary prevention of atherosclerotic events in acute coronary syndrome	13
2	Prasugrel	Acute coronary syndrome	13
2	Imatinib	Pulmonary hypertension	14
2	Lomitapide*	Hypercholesterolaemia-familial	15
3	Indacaterol + glycopyrrolate	Chronic obstructive pulmonary disease	17
3	Pirfenidone*	Idiopathic pulmonary fibrosis	17
4	Loxapine	Schizophrenia and bipolar disorder	17
4	Phentermine/ topiramate	Obesity.	18
4	Liraglutide	Obesity.	18
4	Lorcaserin	Obesity.	19
4	Nalfurafine*	Dialysis-related pruritus.	19
4	Nalmefene	Alcohol dependence.	19
5	Elvitegravir, cobicistat, emtricitabine, tenofovir	HIV Infection.	21

BNF	Drug	Indication	Page
5	Cobicistat	HIV infection (booster).	21
6	Canagliflozin	Type 2 diabetes mellitus.	22
6	Alogliptin	Type 2 diabetes mellitus.	23
6	Lixisenatide	Type 2 diabetes mellitus.	23
6	Insulin degludec / insulin aspart	Type 1 and 2 diabetes mellitus.	24
6	Pasireotide*	Acromegaly.	25
7	Botulinum A toxin	Overactive bladder	26
7	Collagenase	Peyronie's disease	27
8	Sorafenib	Thyroid cancer	28
8	Cabozantinib	Thyroid cancer	28
8	Afatinib	Non-small cell lung cancer	29
8	Amrubicin*	Small cell lung cancer	29
8	Trastuzumab/ hyaluronidase	Breast cancer	29
8	Trastuzumab emtansine	Breast cancer	31
8	Doxorubicin heat-sensitive*	Hepatocellular carcinoma	32
8	Regorafenib	Colorectal cancer	32
8	Tivozanib*	Renal cell carcinoma	33
8	Abiraterone	Prostate cancer	34
8	Enzalutamide	Prostate cancer	34
8	Radium-223	Prostate cancer	35
8	Sipuleucel-T	Prostate cancer	35
8	Farletuzumab*	Ovarian cancer	36
8	Paclitaxel*	Ovarian cancer	36
8	Pazopanib	Ovarian cancer	36
8	Vintafolide*	Ovarian cancer	37
8	Vismodegib	Basal cell carcinoma	37
8	Dabrafenib	Malignant melanoma	38
8	Rituximab	Non-Hodgkin's lymphoma	38
8	Bendamustine	Non-Hodgkin's lymphoma	38
8	B cell lymphoma vaccine	Non-Hodgkin's lymphoma	39
8	Pomalidomide*	Multiple myeloma	41
8	Ponatinib	Chronic myeloid leukaemia and acute lymphoblastic leukaemia	42
8	Alemtuzumab	Multiple sclerosis	43
8	Laquinimod	Multiple sclerosis	43
8	Dimethyl fumarate	Multiple sclerosis	44
8	Teriflunomide	Multiple sclerosis	44
9	Peginesatide	Anaemia due to renal disease	45
10	Canakinumab	Gout - acute flares	46
11	Ocriplasmin	Vitreomacular adhesion	48
11	Aflibercept	Retinal vein occlusion	48
13	Afamelanotide*	Erythropoietic protoporphyria	49
		2014	
8	Everolimus	Breast cancer	30
8	Regorafenib	Gastrointestinal stromal tumours	31
8	Axitinib*	Renal cell carcinoma	33
		Uncertain	
2	Vorapaxar	Atherosclerosis, prevention of cardiovascular events.	13
3	Ataluren*	Cystic fibrosis	16
7	Dapoxetine	Premature ejaculation	27
8	Tertomotide*	Pancreatic cancer	31
8	Apaziquone	Bladder cancer	34
8	Ridaforolimus*	Bone and soft tissue sarcoma	37
8	Bortezomib	Multiple myeloma	40
8	Carfilzomib	Multiple myeloma	41
9	Strontium ranelate	Osteoarthritis	47

*Indicates which drugs have been assigned orphan status in the EU. To qualify for orphan designation, a medicine must meet one of these criteria:

- It is intended for a life-threatening or chronically debilitating condition affecting no more than 5 in 10,000 (50 in 100,000) people in the EU;
- It is intended for a life-threatening, seriously debilitating or serious and chronic condition and without incentives it is unlikely that the revenue after marketing would cover the investment in its development.

In both cases, there must also be either no satisfactory method of diagnosis, prevention or treatment of the condition concerned authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition. Manufacturers of drugs that have received orphan designation benefit from incentives to support development of medicines to treat rare diseases.

The US definition of an orphan drug is different. It is defined as a rare disease occurring in less than 200,000 individuals. Assuming a US population of about 311 million this translates to a prevalence of about 65 in 100,000.

The definition of an ultra orphan condition used by NICE is a UK prevalence of less than 1 in 50,000.

Highlights

The drugs listed below have been selected from table 1 (drugs not yet marketed) as warranting special consideration due to their expected overall NHS impact taking account of financial implications, service provisions, place in therapy and target population. Such data are limited so the list is for guidance only and will not take account of local factors or perspective which will vary by sector, geography and speciality. You may also want to refer to table 3 (recently launched drugs) to identify those requiring active management locally.

Drug	Indication	Reasons for highlighting
Rivaroxaban and **Dabigatran** and **Apixaban** *pages 11,12*	Venous thrombo-embolism (VTE).	VTE treatment and long term secondary prevention. Estimates of the incidence of VTE vary. In England in 2010-11 there were just under 69,000 finished consultant episodes with a diagnosis of VTE (~132 per 100,000 people). The risk of recurrence is up to 25%. Newer drugs eliminate the need for monitoring but reversing the anticoagulant effect is difficult. A licence for long-term secondary prevention may increase the number of people on anticoagulants. Competition will influence price but they are considerably more expensive than current options of low molecular weight heparin and warfarin.
Defibrotide *page 14*	Hepatic veno-occlusive disease (VOD).	In haematopoietic stem-cell transplant (HSCT) VOD is a leading cause of morbidity and mortality. Supportive care is the current treatment option. Defibrotide will be the first specific therapy for VOD and will be used for prevention and treatment. It is llikely to be expensive; based on a dose of 25mg/kg/day, current named patient cost is around £1,000 per day.
Lomitapide and **Mipomersen** *page 15*	Hypercholes-terolaemia, familial (FH).	Lomitapide will be an option for patients with homozygous FH (that affects about one in a million people) who have an inadequate response to current therapy. Mipomersen will also be an option in these patients and in those with severe heterozygous FH that affects around 200 per 100,000 people. These treatment options are likely to be expensive but may reduce the requirement for LDL apheresis. Lomitapride has the advantage of being an oral formulation vs. mipomersen which is injectable.
Ivacaftor *page 15*	Cystic fibrosis (CF).	UK prevalence of CF is over 8,500 (14 per 100,000). Ivacaftor will be used in patients with a G551D mutation in the CF transmembrane conductance regulator (CFTR) gene, possession of which is associated with more severe disease and occurs in 5.7% of patientswith CF in the UK. This is the first drug to target the underlying cause of CF. US cost of ivacaftor is about $294,000/year.
Pirfenidone *page 17*	Idiopathic pulmonary fibrosis (IPF).	IPF is a group of diseases that cause interstitial lung damage and loss of lung elasticity. The incidence and prevalence is 7-16 and 7-20 per 100,000 people, respectively, and increasing. Current symptomatic treatment includes N-acetyl cysteine and lung transplantation. Pirfenidone is the first treatment specifically for IPF and likely to be expensive.
Nalmefene *page 19*	Alcohol dependence.	In England, alcohol dependence affects around 4% of people aged 16-65 years. 290 prescription items per 100,000 people were dispensed for alcohol dependency in England in 2010. Unlike existing drug therapies, nalmefene is used 'as-needed' and does not require complete abstinence. This will make it attractive especially for 'binge' drinking and as a new treatment option nalmefene could be expensive.
Insulin degludec/ insulin aspart *page 24*	Type 1 and type 2 diabetes mellitus.	In 2011 the UK prevalence of diabetes was 4.45% (about 2.9 million people). It is thought a further 850,000 are undiagnosed. The prevalence is projected to increase to 5 million people by 2025. About 90% of patients with diabetes have type 2 disease. The total cost of insulin rose from £156 to £359 million between 2000 and 2009, a 130% increase. Spending on analogue insulin increased from 66% of total insulin cost in 2005, to 85% in 2009. Insulin degludec could be more expensive than insulin glargine. Further licensed insulin analogues may introduce more competition but combination use of analogues is likely to increase.

Crizotinib *page 28*	Non-small cell lung cancer (NSCLC), advanced.	Second-line treatment in ALK-positive patients. The UK incidence of advanced NSCLC is 40 per 100,000 people; 25% are able to have first-line therapy; of these 20-40% may be eligible for second-line therapy. 3-13% of patients have ALK fusion genes and will respond poorly to current therapies. Crizotinib may be used in place of current therapies (docetaxel, pemetrexed, erlotinib) in selected patients but is likely to be expensive and as first in class will attract interest. ALK testing is necessary. Cost in US is $9,600 per month. Median duration of treatment in studies was 5-8 months.
Pertuzumab *page 30*	Breast cancer (BC), metastatic.	First-line treatment in HER2-positive patients. The UK incidence of BC is about 78 per 100,000 people; HER2-positive disease accounts for up to 25%. About 40% of women develop metastatic disease; 20% of these are HER2-positive (6 per 100,000), which has a worse prognosis. Pertuzumab is likely to be used as add on to standard therapy.
Regorafenib *page 32*	Colorectal cancer (CRC), metastatic.	Third- or fourth-line treatment. CRC is the third most common cancer in the UK, with a crude incidence of 67 per 100,000 people. 20-55% of patients present with metastatic disease. Management is mainly palliative with a combination of surgery and chemo/radiotherapy for symptom control. For patients with no further treatment options, regorafenib may delay disease progression and improve quality of life. Cost is unknown but will be additive to other therapies.
Abiraterone acetate and **Sipuleucel-T** *pages 34,35*	Prostate cancer (PC), metastatic castration-resistant.	First-line treatment; abiraterone is currently licensed for second-line treatment. In the UK, the incidence of PC is 134 per 100,000 people, 55% - 65% develop metastatic disease and all eventually become resistant to standard hormonal therapy (castration-resistant). Abiraterone will delay the need for chemotherapy. Based on current prices, 30 weeks' treatment with abiraterone is £20,510 vs. £7,200 for 10 cycles of docetaxel, excluding added costs of i.v. administration (based on a body surface area of $1.7m^2$). Sipuleucel-T will compete with abiraterone buts its use is complicated by the fact leukapheresis is necessary. Cost in the US is $93,000 for 3 doses.
Pazopanib and **Vintafolide** *Pages 36,37*	Ovarian cancer (OC).	Maintenance treatment after first-line chemotherapy. The UK incidence of OC is 21 per 100,000 people. 75% have advanced disease and up to 80% respond to first-line platinum chemotherapy; of these 55-75% relapse within 2 years. Pazopanib will be used in addition to current therapies but may delay need for second-line chemotherapy. Monthly cost of pazopanib 800mg daily is £2,200. Vintafolide will be used in platinum-resistant, folate receptor (FR)-positive disease which involves use of a radiopharmaceutical diagnostic test to identify FR-positive tumours. 90% of patients have FR-positive tumours; most eventually relapse and develop platinum-resistant disease. Vintafolide will be used in addition to doxorubicin in patients with a poor prognosis and few options. It is likely to be expensive.
Vismodegib *page 37*	Basal cell carcinoma (BCC).	Treatment of locally advanced or metastatic disease.The incidence of BCC is underestimated but is likely to be about 100 per 100,000 people. Metastases occur rarely (in ≤0.5% of cases) but treatment options are limited and prognosis depends on site of spread. Vismodegib is an option for first and second-line use in advanced disease, where surgery or radiotherapy is inappropriate. It will be used in patients with no other therapeutic options and continued until disease progression. US cost is about $7,500/month and average duration of treatment is 10 months.
Pixantrone *page 39*	Non-Hodgkin's lymphoma (NHL).	Monotherapy for relapsed or refractory aggressive disease. About 55-60% of people with NHL have aggressive disease (10-12 per 100,000 people). 50-60% can be cured with combination chemotherapy. Pixantrone will be an option for patients resistant/ intolerant to standard therapies, those who have exceeded their lifetime limit of anthracyclines, and those unsuitable for stem cell transplantation. It is likely to be expensive.
Ruxolitinib *page 43*	Myelofibrosis (MF).	Chronic idiopathic disease and MF secondary to polycythaemia vera or essential thrombocythaemia.The UK incidence of MF is 0.5-1.5 per 100,000 people. 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. Ruxolitinib could replace current unlicensed and less expensive options but may delay need for surgical treatment. US cost is about $6,800/month.

Alemtuzumab and **Laquinimod** and **Dimethyl fumarate** and **Teriflunomide** *pages 43, 44*	Multiple sclerosis (MS)	Relapsing remitting disease (RRMS). Around 100,000 people in the UK have MS and 40% have RRMS (67 per 100,000 people). Alemtuzumab is a new class of drug for MS and as a single annual injectable treatment it may be attractive. Cost of the *MabCampath* brand of alemtuzumab was about £1,300 for a 5 day course. However, 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. Around 30% of patients with RRMS are treated with injectable agents, mainly beta-interferon. Oral preparations will improve convenience and may increase the proportion treated. 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.
Eltrombopag *page 45*	Thrombocyto -penia (TCP) associated with hepatitis C (HepC).	About 250,000 people in the UK are infected with hepatitis C (417 per 100,000); estimates of the prevalence of HepC associated TCP ranges from 0.16- 45.4%. Thrombocytopenia may interfere with diagnostic procedures, such as liver biopsy, and may exclude patients from effective antiviral treatment jeopardising the chances of achieving sustained virologic response. For a 28 day course, eltrombopag costs £770 for 25mg/day or £1,540 for 50mg/day.
Tofacitinib *page 46*	Rheumatoid arthritis (RA).	Moderate-to-severe disease unresponsive to DMARDs. 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. The average cost of a biological is about £9,500 per patient per year but competition is reducing this. In 2007-8, 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. Oral tofacitinib will compete with i.v. or s.c. therapies and be more attractive.
Strontium ranelate *page 47*	Osteoarthriti s treatment (OA).	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. Strontium will be an add-on therapy for patients who require disease modifying therapy and will be an additional benefit for those with osteoporosis and OA. Current cost of *Protelos* is about £30/month.

Table 1. Pipeline drugs

BNF 1. Gastrointestinal system

Golimumab injection *Simponi* MSD	***Indication:*** Ulcerative colitis (UC), moderate to severe – second-line.	***Current status:*** Filed in EU Jul 2012.	***Predicted UK licence extension:*** 2013	***National guidance:*** **NICE:** Infliximab - UC subacute manifestations, acute exacerbations. ***Reviews:*** NHSC Sep 2011.
Target population: The incidence and prevalence of UC in England and Wales is about 10-20 and 220-270 per 100,000 people, respectively. The majority present with moderate to severe disease. ***Sector:*** Secondary care.		***Implications:*** Golimumab will be a second-line option with the advantage of s.c. administration vs. i.v. administration for infliximab. However, monthly administration is required vs. every 6-8 weeks for infliximab. ***Financial:*** As a further treatment option it will be additional to current costs. ***PbR:*** Tariff excluded.		
Pharmacology: Anti-TNF monoclonal antibody given by once monthly by s.c. injection. ***Efficacy:*** In the PIII PURSUIT study, 774 patients with moderate to severely active UC who had failed to respond to, or could not tolerate conventional agents, received induction treatment with golimumab (either 200mg or 400mg at week 0 and 100mg or 200mg at week 2) or placebo. The primary outcome of clinical response (defined as Mayo score of ≥30% and 3 points vs. baseline score, with a decrease in rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1) at week 6 was met by 51.8%, 55% and 29.7% of patients, respectively, p<0.0001. The results of this study and those from the ongoing PURSUIT-maintenance study (n=1,350) form the basis of licence applications. ***Safety:*** See emc.medicines.org.uk.				
Teduglutide injection *Revestive* Takeda	***Indication:*** Short bowel syndrome (SBS).	***Current status:*** Recommended for approval in EU Jun 2012 with orphan status.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** Nutrition support in adults: clinical guideline, quality standard due Nov 2012 (draft). ***Reviews:*** No recent reviews.
Target population: UK incidence of SBS (a group of diseases) is about 2 per million people. ***Sector:*** Severe intestinal failure treatment is a specialised service.		***Implications:*** Teduglutide would be the first drug specifically licensed for SBS, the most common indication for home parenteral nutrition (PN). It may reduce PN volume requirements. ***Financial:*** Likely to be expensive and additive to current options. ***PbR:*** Tariff excluded.		
Pharmacology: Glucagon-like peptide-2 (GLP-2) analogue given by daily s.c. injection. ***Efficacy:*** In a published PIII study (n=83), the primary outcome, a reduction in PN of ≥20% from baseline to weeks 16−24, was achieved by 46% of patients on teduglutide 0.05mg/kg vs. 6% on placebo (p=0.007, NNT=3) and by 25% on teduglutide 0.1mg/kg (p=0.16 vs. placebo). In the 24-week PIII STEPS study (n=86) the primary outcome (reduction in PN of ≥20% from baseline at weeks 20 and 24 was achieved by 63% of patients on teduglutide 0.05mg/kg vs. 30% on placebo (p=0.002, NNT=3). There were also improvements in the secondary outcome of reduction from baseline in weekly parenteral nutrition volume at 24 weeks; 4.4L with teduglutide vs. 2.3L placebo (p≤0.001). Patients from this study (n=76) were enrolled in the 24-month extension study, STEPS2. At 12-months, 91% of 37 patients on teduglutide showed a 20-100% reduction in PN volume from baseline. Three patients became independent of PN, whilst 24% were able to reduce the number of infusion days per week by 3 or more after 12 months of treatment. Data at 24-months have not yet been reported. ***Safety:*** Adverse effects include abdominal and gastrointestinal effects, injection site reactions.				
Linaclotide oral *Constella* Almirall	***Indication:*** Irritable bowel syndrome with constipation (IBS-C).	***Current status:*** Filed in EU Sep 2011.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** IBS. ***Reviews:*** None
Target population: Prevalence of IBS is about 10-15% but only a third visit their GP. About one third have IBS-C. ***Sector:*** Primary care.		***Implications:*** As first in a new class of drugs and with potential for use in a large number of patients there is likely to be interest in linaclotide. ***Financial:*** Likely to be more expensive than existing therapies for IBS-C. ***PbR:*** Likely in tariff.		
Pharmacology: Oral guanylate cyclase C-agonist given once daily. ***Efficacy:*** Pooled data from two (1 and 2) PIII trials in over 1,600 patients show linaclotide is associated with a higher response rate than placebo. In the larger trial (n=804) 12.7% of patients on linaclotide vs. 3% on placebo (p<0.0001, NNT=10) had, in the same week, ≥30% reduction in abdominal pain, at least 3 complete spontaneous bowel movements(CSBM), and an increase of one or more CSBMs. These criteria had to be met for at least 9 weeks of the 12-week treatment period for a patient to be considered a responder. ***Safety***: Most commonly reported side effects are diarrhoea, flatulence and abdominal pain.				

BNF 2. Cardiovascular system

Rivaroxaban **oral** *Xarelto* Bayer	***Indication:*** Treatment of pulmonary embolism (PE) and prevention of recurrent venous thromboembolism (VTE).	***Current status:*** Filed in EU Apr 2012. Filed in US May 2012 with priority review.	***Predicted UK licence extension:*** 2012	***National guidance:*** **NICE:** VTE pathway, quality standard due Apr 2013, Anticoagulation commissioning guide, Rivaroxaban - VTE (treatment of deep vein thrombosis and long term secondary prevention) due Jul 2012, Rivaroxaban for PE treatment due Sep 2013, Dabigatran for VTE treatment due TBC. **SIGN:** VTE. ***Reviews:*** None.

Target population: Estimates of the incidence of VTE vary. In England in 2010-11 there were just under 69,000 finished consultant episodes with a diagnosis of VTE (~132 per 100,000 people). There were ~40,000 finished consultant episodes for PE in England in 2010-11 (~77 per 100,000 people). The risk of recurrence is up to 25%. ***Sector:*** Initiated in secondary care.	***Implications:*** Newer drugs eliminate the need for monitoring but reversing the anticoagulant effect is difficult. A licence for long-term secondary prevention may increase the number of people on anticoagulants. Differences in dosing frequency may be important for compliance. Competition will influence pricing strategies. ***Financial:*** Based on current prices, cost for 28 days of maintenance treatment is about £59 for rivaroxaban (20mg daily), £70 for dabigatran (150mg twice daily), £106 for apixaban (5mg twice daily) and £2 for a warfarin regimen (excluding monitoring costs and initial cost of low molecular weight heparin). ***PbR:*** In tariff.

Pharmacology: Factor Xa inhibitor.

Efficacy: A published open-label PIII trial (n=4,832) compared rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) with standard care (enoxaparin and warfarin) in patients with acute, symptomatic PE with or without DVT. Rivaroxaban was found to be non-inferior to standard care for the prevention of the primary outcome of recurrent PE or DVT (2.1% vs. 1.8%, p=0.003 for non-inferiority).

Safety: See emc.medicines.org.uk.

Dabigatran **oral** *Pradaxa* Boehringer Ingelheim	***Indication:*** Venous thromboembolism (VTE) treatment.	***Current status:*** PIII.	***Predicted UK licence extension:*** 2013	***National guidance:*** As for rivaroxaban above. ***Reviews:*** None.

Target population: As for rivaroxaban above. ***Sector:*** Secondary care initiated.	***Implications:*** As for rivaroxaban above. ***Financial:*** As for rivaroxaban above. ***PbR:*** In tariff.

Pharmacology: Direct thrombin inhibitor.

Efficacy: The published RE-COVER study (n=2,539) evaluated whether dabigatran (150mg twice daily) was non-inferior to warfarin (INR 2.0-3.0) for treatment of acute symptomatic VTE. The primary outcome was a composite of recurrent symptomatic VTE and deaths related to VTE, which was confirmed in 2.4% of patients on dabigatran and 2.1% of patients on warfarin (p<0.001 for non-inferiority). Major bleeding did not differ between the groups at 1.6% vs. 1.9%, respectively.

Safety: See emc.medicines.org.uk.

Apixaban **oral** *Eliquis* Pfizer	***Indication:*** Venous thromboembolism (VTE) treatment.	***Current status:*** PIII.	***Predicted UK licence extension:*** 2013	***National guidance:*** As for rivaroxaban above. ***Reviews:*** None.

Target population: As for rivaroxaban above. ***Sector:*** Secondary care initiated.	***Implications:*** As for rivaroxaban above. ***Financial:*** As for rivaroxaban above. ***PbR:*** In tariff.

Pharmacology: Factor Xa inhibitor.

Efficacy: Two PIII trials are ongoing. AMPLIFY aims to recruit 4,816 patients with acute VTE to compare apixaban (10mg twice daily for one week followed by 5mg twice daily for 6 months) with enoxaparin and warfarin. AMPLIFY-EXT will compare apixaban (2.5mg or 5mg twice daily for 12 months) with placebo in previously treated patients.

Safety: See emc.medicines.org.uk.

Dabigatran **oral** *Pradaxa* Boehringer Ingelheim	***Indication:*** Long-term secondary prevention of venous thromboembolism (VTE).	***Current status:*** PIII	***Predicted UK licence extension:*** 2013	***National guidance:*** **NICE:** VTE pathway, VTE prevention quality standard, Anticoagulation commissioning guide. **SIGN:** VTE. ***Reviews:*** NHSC Apr 2010.
Target population: As for rivaroxaban above. ***Sector:*** Secondary care initiated		***Implications:*** As for rivaroxaban above. ***Financial:*** As for rivaroxaban above. ***PbR:*** In tariff.		
Pharmacology: Direct thrombin inhibitor. ***Efficacy:*** Two trials are completed but not fully published. RE-MEDY (n=2,856) compared dabigatran and warfarin given for 18 months for the long-term treatment and secondary prevention of VTE successfully treated with a standard anticoagulant for 3-6 months. Recurrent VTE occurred in 1.8% of patients on dabigatran vs. 1.3% on warfarin (HR 1.44, p=0.03 for non-inferiority). In RE-SONATE in 1,343 patients with symptomatic VTE who completed 6-18 months of treatment, recurrent VTE occurred in 0.4% on dabigatran vs. 5.6% on placebo (HR 0.08, p<0.0001). ***Safety:*** In RE-MEDY fewer patients on dabigatran vs. warfarin had major bleeds (HR 0.52) but in RE-COVER there was no difference. See emc.medicines.org.uk.				
Apixaban **oral** *Eliquis* Pfizer	***Indication:*** Venous thromboembolism (VTE) prevention in medically ill patients.	***Current status:*** PIII.	***Predicted UK licence extension:*** 2013	***National guidance:*** **NICE:** As for dabigatran for VTE prevention above, Apixaban (acute medical illness) due TBC. **SIGN:** VTE. ***Reviews:*** No recent reviews.
Target population: As for rivaroxaban above. The risk of pulmonary embolism (PE) in the absence of prophylaxis is about 1% in acutely ill medical patients. ***Sector:*** Secondary care.		***Implications:*** Apixaban will compete with low molecular weight heparins, rivaroxaban and dabigatran. ***Financial:*** Currently more expensive than other treatment options but competition will influence pricing strategies. ***PbR:*** In tariff.		
Pharmacology: Factor Xa inhibitor. ***Efficacy:*** In the published PIII ADOPT trial (n=6,528), acutely medically ill hospitalised patients with risk factors for VTE were randomised to apixaban (2.5mg twice daily for 30 days), or enoxaparin (40mg once daily for 6 -14 days). The primary outcome, a composite of VTE and death related to VTE occurred in 2.71% of the apixaban group and 3.06% of the enoxaparin group (p=0.44). ***Safety:*** See emc.medicines.org.uk.				
Apixaban **oral** *Eliquis* Pfizer	***Indication:*** Stroke prevention in atrial fibrillation (AF).	***Current status:*** Filed in EU in late 2011.	***Predicted UK licence extension:*** 2012	***National guidance:*** **NICE:** AF, Anticoagulation commissioning guide, Dabigatran, Rivaroxaban, Apixaban due Apr 2013. ***Reviews:*** NPC Nov 2011, NHSC Aug 2010, LNDG due TBC, NYRDTC due TBC.
Target population: The prevalence of AF is about 1,400 per 100,000 people. More than 20% of strokes are attributed to AF. NICE estimates about 47% of people with AF currently receive anticoagulant therapy, with an additional 30% eligible, but not receiving therapy. ***Sector:*** Primary care.		***Implications:*** Apixaban will compete with dabigatran and rivaroxaban and may increase uptake of newer anticoagulants. There will be an impact on anticoagulant service commissioning. There is no requirement for monitoring of newer anticoagulant drugs but reversing the anticoagulant effect is difficult. This may have implications for at risk patients. ***Financial:*** Considerably more costly than warfarin, even when the cost of monitoring is taken into account. Currently more expensive than either rivaroxaban or dabigatran. ***PbR:*** In tariff.		
Pharmacology: Factor Xa inhibitor. ***Efficacy:*** The published AVERROES trial compared apixaban with aspirin in 5,599 patients with AF who were at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable. The rate of stroke or systemic embolism (primary outcome) was 1.6% per year for apixaban vs. 3.7% for aspirin (HR 0.45, p<0.001). In the published ARISTOTLE trial, comparing apixaban with warfarin (INR 2-3) in 18,201 patients with AF and at least one additional risk factor for stroke, apixaban was shown to be non-inferior on the combined outcome of stroke and systemic embolism; 1.27% per year for apixaban vs. 1.60% for warfarin (HR 0.79, p<0.001). ***Safety:*** See emc.medicines.org.uk.				

Prasugrel **oral** *Efient* Eli Lilly	***Indication:*** Acute coronary syndrome (ACS), medical management.	***Current status:*** PIII in EU with plans to file in 2012.	***Predicted UK licence extension:*** 2013	***National guidance:*** **NICE:** ACS: Ticagrelor , Prasugrel with percutaneous coronary intervention, Unstable angina (UA) and NSTEMI. **SIGN:** ACS ***Reviews:*** NHSC Sep 2011.
Target population: ACS encompasses a spectrum of disease from UA to myocardial infaction (MI). In England during 2010/11, there were 58,571 hospital admissions for UA and 92,067 for MI. ***Sector:*** Initiated in secondary care.		***Implications:*** Prasugrel may have a faster onset of action with a more consistent platelet response than alternatives, but increased bleeding may limit its use. ***Financial:*** Cost for prasugrel ~ £620 per year vs. £710 for ticagrelor and £30 for clopidogrel. ***PbR:*** In tariff.		
Pharmacology: Antiplatelet - P2Y12 adenosine diphosphate receptor antagonist. ***Efficacy:*** The recently completed TRILOGY ACS trial (n=10,300) compared prasugrel and clopidogrel, both plus aspirin, in ACS patients with UA/NSTEMI who were medically managed. The primary outcome was reduction in risk of the composite outcome of first occurrence of cardiovascular death, myocardial infarction or stroke. Results have not yet been published. ***Safety:*** See emc.medicines.org.uk.				
Rivaroxaban **oral** *Xarelto* Bayer	***Indication:*** Secondary prevention of atherosclerotic events in acute coronary syndrome (ACS).	***Current status:*** Filed in EU Dec 2011.	***Predicted UK licence extension:*** 2013	***National guidance:*** As for prasugrel above and **NICE:** Secondary prevention post MI. ***Reviews:*** NPC Mar 2012, NHSC Apr 2011.
Target population: As for prasugrel above. ***Sector:*** Initiated in secondary care.		***Implications:*** Likely to be given in addition to aspirin and a thienopyridine. ***Financial:*** Cost will be in addition to existing therapy. ***PbR:*** In tariff.		
Pharmacology: Factor Xa inhibitor. ***Efficacy:*** A published PIII trial (n=15,526) compared rivaroxaban with placebo in patients hospitalised with ACS, who were also receiving aspirin and a thienopyridine (clopidogrel or ticlodipine). The 2-year event rate for the primary outcome, a composite of death from cardiovascular (CV) causes, myocardial infarction or stroke, was reduced in patients on rivaroxaban 2.5mg or 5mg twice daily vs. placebo (8.9% vs.10.7%, respectively, HR 0.84, p=0.008). Rivaroxaban 2.5mg reduced CV death rate (p=0.002) and death from any cause (p=0.002); a survival benefit was not seen with 5mg. See NPC rapid review. ***Safety:*** See emc.medicines.org.uk.				
Vorapaxar **oral** MSD	***Indication:*** Atherosclerosis, secondary prevention of cardiovascular (CV) events.	***Current status:*** PIII.	***Predicted UK launch:*** Uncertain.	***National guidance:*** **NICE:** Myocardial infarction (MI) - secondary prevention. ***Reviews:*** NHSC Aug 2010.
Target population: In England in 2007-08, 18% of all patients registered with a GP had a history of coronary heart disease, hypertension or stroke. ***Sector:*** Initiated in secondary care.		***Implications:*** Likely to be added to existing therapies but the increase in bleeding associated with vorapaxar could make it difficult to establish a place in therapy. ***Financial:*** Likely to be more expensive than generic aspirin and clopidogrel. ***PbR:*** Likely in tariff.		
Pharmacology: Thrombin receptor antagonist (PAR-1 inhibitor). ***Efficacy:*** In the published PIII TRA 2P-TIMI 50 study 26,449 patients with prior MI, stroke or peripheral artery disease were randomised to standard antiplatelet regimens (aspirin or aspirin plus ADP inhibitor) with either placebo or vorapaxar. The primary outcome was death from cardiovascular causes, MI, or stroke. At 3 years, 9.3% and 10.5% on vorapaxar and placebo, respectively, had a primary event (HR 0.87, p<0.001). ***Safety:*** Moderate/severe bleeding occurred in 4.2% on vorapaxar vs. 2.5% on placebo (p<0.001). In the above study, after 2 years, treatment in those with a history of stroke was discontinued due to risk of intracranial haemorrhage.				

Clevidipine **injection** *Cleviprex* The Medicines Company	***Indication:*** Rapid reduction of blood pressure (BP) in the perioperative setting.	***Current status:*** Approved in UK Nov 2011.	***Predicted UK launch:*** 2012	***National guidance:*** None relevant. ***Reviews:*** No recent reviews.
Target population: Perioperative hypertension may affect 25% of hypertensive patients undergoing surgery. ***Sector:*** Secondary care.		***Implications:*** Clevidipine is the first drug specifically licensed for the management of perioperative hypertension. ***Financial:*** Likely to be more expensive than currently available generic options. ***PbR:*** Likely in tariff.		
Pharmacology: Ultra short-acting dihydropyridine calcium channel antagonist given by i.v. infusion. ***Efficacy:*** Pooled results from PIII studies (ECLIPSE 1, 2 & 3) are published. In 1,964 patients undergoing cardiac surgery, clevidipine was more effective than glyceryl trinitrate (p=0.0006) or sodium nitroprusside (p=0.003) and equivalent to nicardipine in maintaining BP within a pre-specified acceptable range. ***Safety:*** See prescribing data.				
Imatinib **oral** *Ruvise* Novartis	***Indication:*** Pulmonary arterial hypertension (PAH), severe.	***Current status:*** PIII in EU with plans to file in 2012. US filing withdrawn Aug 2012.	***Predicted UK licence extension:*** 2013	***National guidance:*** None relevant. ***Reviews:*** NHSC Sep 2010.
Target population: Incidence of PAH is estimated at 2-8 per million and the prevalence at 15-26 per million. ***Sector:*** Centres that are part of the National Pulmonary Hypertension Service (see 2011 audit report).		***Implications:*** Imatinib is an additional option for patients uncontrolled on standard therapies. It represents a new treatment option. ***Financial:*** As an add-on therapy, at current prices, imatinib 400 mg/day (*Glivec*) costs about £1,700/month. Price for *Ruvise* is currently unclear but could be in line with other treatments for PAH. ***PbR:*** Tariff excluded.		
Pharmacology: Bcr-Abl protein tyrosine kinase inhibitor. ***Efficacy:*** In a published 24-week PII study (n=59), there was no difference between imatinib or placebo (p=0.21) in the primary outcome of change from baseline in the 6-minute-walk distance (6MWD). There were significant changes in the secondary outcome measures of pulmonary vascular resistance (p<0.01) and cardiac output (p=0.02). In a post-hoc subgroup analysis among severely affected patients a significant increase in 6MWD was seen and in an open-label extension study in 16 patients treated for up to 3 years, initial improvement in 6MWD was maintained. Preliminary data from the 24-week PIII IMPRESS study (n=202) are in line with these results. ***Safety:*** See emc.medicines.org.uk.				
Defibrotide **injection** *Defitelio* Gentium	***Indication:*** Hepatic veno-occlusive disease (VOD) - prevention and treatment in haematopoietic stem-cell transplant (HSCT) in adults and children.	***Current status:*** Filed in EU May 2011 with orphan and accelerated assessment status. Available on a named patient basis.	***Predicted UK launch:*** 2012	***National guidance:*** None relevant. ***Reviews:*** NHSC Aug 2011, LNDG due TBC.
Target population: VOD is a leading cause of morbidity and mortality after HSCT. Without treatment over 85% of those with severe VOD die within 100 days of HSCT. ***Sector:*** Secondary or tertiary care		***Implications:*** Supportive care is the current treatment option. Defibrotide will be the first specific therapy for VOD. ***Financial:*** Likely to be expensive. Based on a dose of 25mg/kg/day, current named patient cost is around £1,000/day. ***PbR:*** Transplant services tariff excluded.		
Pharmacology: Cytokine modulator. For prevention of VOD it is given by 2 hour i.v. infusion every 6 hours on the same day as the pre-conditioning transplant regimen and continued until at least day 30 or until discharge (minimum 14 days treatment). For treatment defibrotide is given every 6 hours for at least 14 days. ***Efficacy:*** *Prevention:* In a published PIII study comparing defibrotide prophylaxis with standard of care in 356 paediatric patients the incidence of VOD at 30 days post HSCT was 12% in the defibrotide group vs. 20% in the control group (p<0.05, NNT=13). *Treatment.* In a PIII trial (n=134) in patients with severe VOD and multi-organ failure, 24% in the defibrotide group achieved a complete response at 100 days (primary outcome) vs. 9% in the historical control group (p<0.02, NNT=7). Mortality rate at day 100 (secondary outcome) was not significantly different between groups (62% vs. 75%, respectively, p<0.06). ***Safety:*** No safety concerns have been reported to date, with the frequency of adverse events comparable to control.				

Lomitapide **oral** Aegerion Pharma-ceuticals	***Indication:*** Hypercholesterolaemia, familial homozygous (HoFH).	***Current status:*** Filed in EU Mar 2012 with orphan status.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** Familial hypercholesterolaemia: clinical guideline, quality standard due Aug 2013. ***Reviews:*** No recent reviews.
Target population: HoFh is estimated to affect one in a million people. ***Sector:*** Secondary and primary care.		***Implications:*** Lomitapide may be an option for patients with HoFH with an inadequate response to current therapy. Treatment may reduce the requirement for LDL apheresis in some patients. Oral treatment is an advantage over its competitor mipomersen below. ***Financial:*** Likely to be expensive, but may reduce need for LDL apheresis. Monitoring of liver fat content and liver enzymes will be required. ***PbR:*** Uncertain.		
Pharmacology: Microsomal triglyceride transfer protein inhibitor (first in class) given orally once daily. ***Efficacy:*** 56-week results from a PIII single-arm open-label study in 29 patients with HoFH receiving standard therapy are available. Lomitapide combined with a low-fat diet was added to existing therapy. The mean reduction in LDL cholesterol (LDL-C) from baseline was 40% at 26-weeks and 44% at 56-weeks. Triglyceride levels were reduced by 33% at both time points. Some patients were able to reduce or discontinue LDL apheresis. ***Safety:*** Substantial increases in liver fat content and transient elevations of liver enzymes have been reported. Patients with risk factors for liver toxicity were excluded from the PIII trial. Gastrointestinal adverse effects are common.				
Mipomersen **injection** *Kynamro* Genzyme	***Indication:*** Hypercholesterolaemia (familial), homozygous (HoFH) and severe heterozygous (HeFH) - third- or fourth-line.	***Current status:*** Filed in EU Jul 2011.	***Predicted UK launch:*** 2012	***National guidance:*** As for lomitapide above, Ezetimibe, Mipomersen - suspended due non submission. ***Reviews:*** NHSC Jan 2011, LNDG due TBC.
Target population: Severe HeFH affects around 200 per 100,000 people in the UK. HoFH is estimated to affect one in a million people. ***Sector:*** Secondary care.		***Implications:*** As for lomitapride above. ***Financial:*** Likely to be expensive, but may reduce need for LDL apheresis. ***PbR:*** Uncertain.		
Pharmacology: Apolipoprotein B (apo-B) synthesis inhibitor (first in class) given by weekly s.c. injection. ***Efficacy:*** In a published 26-week PIII study in 51 patients with HoFH, the mean reduction in LDL cholesterol (LDL-C) was 24.7% for mipomersen vs. 3.3% with placebo (p=0.0003). This study also met the secondary outcomes of reduction in apo-B, total cholesterol and non-HDL cholesterol (all p<0.001). In a published PII study in 33 statin-intolerant patients, LDL-C was reduced by 47% after 26 weeks on mipomersen vs. 2.0% on placebo (p=0.001). ***Safety:*** Elevated liver enzymes have been reported, there may be a requirement for frequent liver function testing.				
BNF 3. Respiratory system				
Ivacaftor **oral** *Kalydeco* Vertex	***Indication:*** Cystic fibrosis (CF) - patients ≥ 6 years with a G551D mutation in the CF transmembrane conductance regulator (CFTR) gene.	***Current status:*** Approved in EU Jul 2012 with orphan drug status - see prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** None relevant. ***Reviews:*** NHSC Dec 2010.
Target population: UK incidence of CF is 1 in 2,500 live births and prevalence over 9,300 (15 per 100,000). The G551D-*CFTR* mutation is associated with more severe disease and occurs in 5.7% of patients. ***Sector:*** CF is a specialised service.		***Implications:*** This is the first drug to target the underlying cause of CF, but is only suitable for a small number of patients with a specific gene mutation. ***Financial:*** Funding may be dealt with nationally. US cost is about $294,000/year. ***PbR:*** Likely tariff excluded.		
Pharmacology: Selective potentiator of wild-type, G551D, F508del, and R117H forms of human CFTR. ***Efficacy:*** Patients aged ≥12 years with CF and a G551D-CFTR mutation were randomised to ivacaftor or placebo for 48 weeks in the published VX08-770-102 trial (n=161). The primary outcome of absolute change in predicted FEV_1 at week 24 was 10.4% for ivacaftor vs. -0.2% for placebo (p<0.001). In the secondary outcomes, 67% of patients on ivacaftor were free from pulmonary exacerbation at week 48 vs. 41% on placebo (HR 0.5, p=0.001). Preliminary results from a PIII study in children aged 6-11 years gave similar results. ***Safety:*** Adverse events include headache, upper respiratory tract infection, rash, throat pain and dizziness. Periodic liver function testing is recommended.				

Ataluren **oral** PTC Therapeutics	***Indication:*** Cystic fibrosis (CF) - patients with nonsense mutation (nmCF).	***Current status:*** PIII with orphan status.	***Predicted UK launch:*** Uncertain.	***National guidance:*** None relevant. ***Reviews:*** None.
Target population: UK prevalence of CF is about 15 per 100,000; 10% have the nonsense mutation in the transmembrane conductance regulator (CFTR) gene. ***Sector:*** CF is a specialised service.	***Implications:*** As for ivacaftor. ***Financial:*** Funding is likely to be dealt with nationally. ***PbR:*** Likely tariff excluded.			
Pharmacology: CF transmembrane conductance regulator (CFTR) stimulant. ***Efficacy:*** In a PIII study (n=232) in nmCF patients, there was a 3% difference in the primary outcome of change from baseline in %-predicted FEV1 at 48 weeks (-2.5% change on ataluren vs. -5.5% on placebo, p>0.1). However, in patients not receiving chronic inhaled antibiotics at baseline the 48-week difference was 6.7% (-0.2% vs. -6.9%, respectively, p=0.007, NNT=15), suggesting use of inhaled antibiotics may be confounding results. In a published PII trial (n=30), children with CF and 2 disease-causing CFTR mutations (at least one a nonsense mutation) were given 2 cycles of 14 days treatment with ataluren and 14 days off-treatment. Patients were randomised to one cycle of low dose and one cycle of higher dose treatment. The mean change in CFTR chloride transport across 2 cycles was –4.6 mV (p=0.04) and –3.9 mV (p<0.05) for the 2 groups. ***Safety:*** Adverse events included abdominal pain, rhinitis and CF exacerbation.				
Glyco-pyrronium bromide **inhaler** *Seebri Breezhaler* Novartis	***Indication:*** Chronic obstructive pulmonary disease (COPD).	***Current status:*** Recommended for approval in EU Jun 2012.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** COPD: pathway, quality standard, commissioning guide. ***Reviews:*** None.
Target population: COPD prevalence is estimated at 2-4% but the diagnosed prevalence is about 1.5% (1,500 per 100,000) which increases to 10% in men aged over 75. ***Sector:*** Secondary and primary care.	***Implications:*** NICE guidance describes the place in therapy for long-acting muscarinic antagonists. Glycopyrronium will compete with tiotropium and aclidinium (below). ***Financial:*** Likely to be similar to other long-acting bronchodilators. ***PbR:*** Likely in tariff.			
Pharmacology: A once daily ng acting muscarinic receptor antagonist (LAMA) formulated as a dry powder inhalation. ***Efficacy:*** The published GLOW1 trial (n=822) randomised patients with moderate to severe COPD to 26 weeks of once daily glycopyrrolate or placebo. Trough FEV_1 at week 12 was 1.408 litres with glycopyrrolate vs. 1.301 on placebo (p<0.001). Preliminary data from the 52-week GLOW2 trial (n=1,066) show that glycopyrrolate prolonged the time to first moderate/severe exacerbation (secondary outcome) vs. placebo (HR 0.66, p=0.001), vs. tiotropium (HR 0.61, p=0.001). In GLOW3 (n=108) the primary outcome of endurance time during an ergometry test on day 21 increased by 21% with glycopyrrolate vs. placebo. ***Safety:*** In studies adverse events were similar to placebo.				
Aclidinium **inhaler** *Eklira Genuair* Almirall	***Indication:*** Chronic obstructive pulmonary disease (COPD).	***Current status:*** Approved in EU and US Jul 2012. See US prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** As for glycopyrronium bromide above. **SMC:** Aclidinium due Nov 2012. ***Reviews:*** NPC/UKMi Nov 2011.
Target population: As for glycopyrronium bromide above. ***Sector:*** Secondary and primary care.	***Implications:*** Aclidinium taken twice daily is a competitor to once daily tiotropium but it may have fewer adverse effects. It will also compete with glycopyrronium above. ***Financial:*** Aclidinium will have to be competitively priced with tiotropium. ***PbR:*** Likely in tariff.			
Pharmacology: Selective muscarinic receptor antagonist in a dry-powder inhaler for twice daily administration. ***Efficacy:*** In the published 24-week PIII ATTAIN study (n=828) in moderate to severe COPD the primary outcome was change in trough forced expiratory volume in 1 second (FEV1) at week 24. Aclidinium (200mcg and 400mcg twice daily) increased trough FEV1 vs. placebo (99mL and 128mL, respectively, p<0.0001). In the published ACCORD COPD I study and in the ACCORD COPD II study, mean change from baseline at week 12 in trough FEV_1 for aclidinium 400mcg was 124ml and 72ml, respectively, vs. placebo (p<0.0001 and 0.001, respectively). Data on aclidinium 200mcg once daily has been published. In a published PII study (n=30) aclidinium 400mcg twice daily is compared with tiotropium 18mcg daily and placebo. Mean changes from baseline in FEV1 at day 15 were greater for aclidinium and tiotropium (p<0.001 for both vs. placebo). Long term (52-week) and combination (with formoterol) studies are ongoing. ***Safety:*** The most commonly reported reactions in studies were headache and nasopharyngitis.				

Indacaterol/ glycopyrrolate **inhaler** Novartis	***Indication:*** Chronic obstructive pulmonary disease (COPD).	***Current status:*** PIII.	***Predicted UK launch:*** 2013	***National guidance:*** As for glycopyrronium bromide above. ***Reviews:*** NHSC Aug 2011.
Target population: As for glycopyrronium bromide above. ***Sector:*** Secondary and primary care.		***Implications:*** The first combination inhaler containing a long acting muscarinic antagonist that may be used when maintenance long acting beta agonist is insufficient and an inhaled corticosteroid is not suitable. ***Financial:*** Likely to be similar to other combination products. ***PbR:*** Likely in tariff.		
Pharmacology: Long acting muscarinic receptor antagonist (LAMA) and long acting beta agonist (LABA). ***Efficacy:*** Preliminary PIII data indicate indacaterol/glycopyrrolate is more effective than: salmeterol/fluticasone in terms of FEV_1 in the 26-week ILLUMINATE trial; indacaterol and glycopyrrolate separately in terms of trough FEV_1 in the 26-week SHINE trial; placebo on exercise tolerance in the 3-week BRIGHT trial. ***Safety:*** Safety and tolerability have been assessed in the 52-week ENLIGHTEN trial.				
Pirfenidone **oral** *Esbriet* InterMune	***Indication:*** Idiopathic pulmonary fibrosis (IPF), mild to moderate disease.	***Current status:*** Approved in EU Feb 2011 with orphan status - see prescribing data. UK price negotiations are ongoing.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** Pirfenidone due Apr 2013. ***Reviews:*** LNDG Dec 2011.
Target population: IPF is a group of diseases that cause interstitial lung damage and loss of lung elasticity. The incidence and prevalence is 7-16 and 7-20 per 100,000 people, respectively, and increasing. ***Sector:*** IPF is a specialised service.		***Implications:*** The first treatment specifically licensed for IPF. Current symptomatic treatment includes N-acetyl cysteine and lung transplantation. ***Financial:*** Likely to be significantly more expensive than current unlicensed options but may delay need for transplantation. ***PbR:*** Tariff excluded.		
Pharmacology: Collagen inhibitor. ***Efficacy:*** Two similar trials, CAPACITY 004 and 006, have been published. Both used change in predicted forced vital capacity (FVC) from baseline to week 72 as the primary outcome. In the 004 trial (n=435), FVC change was –8.0% for pirfenidone vs. –12.4% for placebo (p=0.001, NNT=23). In trial 006, there was no significant difference between pirfenidone and placebo groups. ***Safety:*** See prescribing data.				

BNF 4. Central nervous system

Loxapine inhalation *Adasuve* Alexza Pharma-ceuticals	***Indication:*** Acute agitation associated with schizophrenia or bipolar disorder.	***Current status:*** Filed in EU Oct 2011. Manufacturing deficiencies have delayed US approval.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** Clinical guidelines: bipolar disorder, schizophrenia; Commissioning guide (schizophrenia), Loxapine due TBC. **SIGN:** Bipolar disorder. ***Reviews:*** NHSC Aug 2010.
Target population: Patients with schizophrenia or bipolar disorder have an average of 11-12 episodes of acute agitation annually, currently treated with oral (55%) or i.m. (45%) antipsychotics. ***Sector:*** Secondary care.		***Implications:*** Inhaled administration is less invasive than an i.m. injection, so may be preferred. ***Financial:*** Likely to be more expensive than oral antipychotics but similar to newer i.m. injections. ***PbR:*** Likely in tariff.		
Pharmacology: Dopamine D_2 antagonist given by single-dose inhaler. ***Efficacy:*** In the published PIII trial (n=344) agitated in-patients with schizophrenia were treated with up to 3 doses of loxapine 5 or 10mg vs. placebo. Both doses improved changes in Positive and Negative Syndrome Scale–Excited Component (PANSS-EC) score (5mg p<0.0004, 10mg p=0.0001, vs. placebo). A published PIII trial compared loxapine 5mg or 10mg to placebo in in-patients with bipolar I associated agitation (n=314). Change from baseline in PANSS-EC score 2 hours after the first dose was -8.1 for 5mg, -9.0 with 10mg and -4.8 with placebo (both p<0.0001 vs. placebo). ***Safety:*** Common adverse events include dysgeusia and sedation. No patients experienced respiratory symptoms, but patients with significant acute or chronic pulmonary disease were excluded from studies.				

Lisdexamfetamine dimesylate **oral** *Venvanse* Shire	***Indication:*** Attention-deficit hyperactivity disorder (ADHD) in children and adolescents.	***Current status:*** Filed in EU Jan 2012. Launched in US - see prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** ADHD: clinical guideline, commissioning guide. **SIGN:** Attention deficit and hyperkinetic disorders. ***Reviews:*** None.
Target population: ADHD affects around 5 in 100 school-aged children in the UK. ***Sector:*** Secondary care initiated.		***Implications:*** A once-daily option. US data state the capsule contents can be dissolved in water. ***Financial:*** Likely to be similar to other once daily options. ***PbR:*** Likely in tariff.		
Pharmacology: Amphetamine. ***Efficacy:*** In a 7-week PIII study of patients aged 6-17 years (n=336), lisdexamfetamine (LDX) improved the ADHD rating scale (ADHD-RS-IV) vs. placebo (difference -18.6, p<0.001). In a published trial in adolescents (n=314) mean change from baseline to week 4 in ADHD-RS-IV was -18.3 with 30mg daily, -21.1 with 50mg, -20.7 with 70mg and -12.8 with placebo (all doses p≤0.006 vs. placebo). In a long-term PIII study (n=276), children and adolescents were treated with LDX during an open-label period of at least 26 weeks before entering a 6-week double-blind randomised withdrawal period, where subjects received either LDX or placebo. There were fewer treatment failures (13.5%) in the LDX group vs. placebo (65.8%, NNT=2). ***Safety:*** Reported adverse effects have included decreased appetite, headache, dry mouth and insomnia.				
Phentermine/ topiramate **oral** *Qnexa* Vivus	***Indication:*** Obesity.	***Current status:*** Filed in EU Dec 2010. Approved in US - see prescribing data.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** Obesity guidelines, Phentermine/ topiramate - proposed appraisal. **SIGN:** Obesity. ***Reviews:*** NHSC Apr 2011.
Target population: In 2010, 26% of men and women (>16 years) were classed obese (BMI >30kg/m^2); 42% of men and 32% of women were overweight (BMI 25 to <30kg/m^2). ***Sector:*** Primary and secondary care.		***Implications:*** US licence is for adults with a BMI of ≥30 or a BMI of ≥27 and at least one weight-related condition e.g. hypertension, diabetes or dyslipidaemia. If the EU licence is similar *Qnexa* will compete with orlistat which is currently the only prescribable drug for weight loss. ***Financial:*** Likely to be more expensive than orlistat. ***PbR:*** Likely in tariff.		
Pharmacology: Phentermine is an appetite suppressant and topiramate an anticonvulsant with weight loss properties. ***Efficacy:*** In the published CONQUER study (n=2,487), after 56 weeks, patients had a mean change in body weight of -7.8% on *Qnexa* 7.5mg/46mg, -9.8% on *Qnexa* 15mg/92mg vs. -1.2% on placebo (p<0.0001 for both vs. placebo). 62% on *Qnexa* achieved weight loss of ≥5% vs. 21% on placebo (p<0.0001, NNT=2). 676 patients who completed CONQUER entered an extension study (SEQUEL). After a further 52 weeks, mean weight change from baseline was -9.3%, -10.5% and for 7.5mg/46mg, 15mg/92mg vs. -1.8% for placebo (p<0.0001). Data from the 28-week EQUATE trial (n=756) are similar. ***Safety:*** Adverse effects include constipation, paraesthesia and dry mouth. In the US use in patients with recent or unstable heart disease or stroke is not recommended. In addition, due to the risk of birth defects and need for pregnancy prevention, it will only be dispensed through specially certified pharmacies.				
Liraglutide **injection** *Victoza* Novo Nordisk	***Indication:*** Obesity.	***Current status:*** PIII.	***Predicted UK licence extension:*** 2013	***National guidance:*** As for phentermine/ topiramate above. ***Reviews:*** None
Target population: As for phentermine/ topiramate above. ***Sector:*** Initiated in secondary care with continued use in primary care.		***Implications:*** It is likely liraglutide injectable will be preferentially used in overweight patients with diabetes. It will have the advantage over exenatide which, although causes weight loss, is not specifically licensed for obesity. The liraglutide dose for obesity is much higher than for diabetes. ***Financial:*** Based on a 3mg daily dose current cost of liraglutide is about £183/month vs. £32/month for orlistat 120mg 3 times a day. ***PbR:*** In tariff.		
Pharmacology: Glucagon-like peptide analogue given by daily s.c. injection. ***Efficacy:*** A 20-week published PII study (n=564) compared liraglutide 1.2mg, 1.8mg, 2.4mg or 3.0mg with placebo and orlistat 360mg/day. Mean weight loss with liraglutide ranged from 4.8 - 7.2kg vs. 2.8kg with placebo and 4.1kg with orlistat. A >5% weight loss was achieved by more patients treated with liraglutide (52.1-76%) than placebo (30%) or orlistat (44%, all p≤0.002 vs. placebo or orlistat). See NPC rapid review. A PIII study (n=422) compared liraglutide 3mg with placebo over 56 weeks following a 12-week low-calorie dietary run-in. Mean reduction in body weight was -6.11% for liraglutide vs. -0.05% for placebo (p<0.0001). A ≥5% reduction in body weight was achieved by 50.5% vs. 21.9% of patients, respectively. ***Safety:*** Adverse effects include gastrointestinal effects, decreased appetite and hypoglycaemia.				

Lorcaserin **oral** *Lorqess* Arena	***Indication:*** Obesity.	***Current status:*** Filed in EU Mar 2012. Launched in US - see prescribing data.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** As for phentermine/ topiramate above, Lorcaserin due Oct 2013. ***Reviews:*** No recent reviews.
Target population: As for phentermine/ topiramate above. ***Sector:*** Secondary care initially.		***Implications:*** After lifestyle modifications, orlistat is currently the only pharmacological agent available for weight loss. Lorcaserin is one of a number of options soon to be available for the management of obesity. ***Financial:*** Likely to be more expensive than orlistat. ***PbR:*** Likely in tariff.		
Pharmacology: Serotonin $5HT_{2C}$ antagonist, first in class. ***Efficacy:*** In the published PIII BLOOM trial (n=3,182) patients received lorcaserin or placebo for at least 1 year. 47.5% on lorcaserin lost ≥ 5% of body weight vs. 20.3% on placebo (p<0.001, NNT=4). After 2 years, weight loss of ≥ 5% was maintained by 67.9% vs. 50.3%, respectively (p<0.01, NNT=6). The 52-week published PIII BLOSSOM trial randomised 4,008 patients to lorcaserin 20mg/day, 10mg/day or placebo. 47.2%, 40.2% and 25%, respectively had ≥ 5% weight loss; 22.6%, 17.4% and 9.7%, respectively, had ≥ 10% loss. In the published PIII BLOOM-DM trial (n=604) in patients with type 2 diabetes on metformin and/or a sulphonylurea received lorcaserin 20mg/day, 10mg/day or placebo. 37.5%, 44.7% and 16.1%, respectively, had ≥ 5% weight loss; 16.3%, 18.1% and 4.4%, respectively, had ≥ 10% loss. ***Safety:*** Adverse events include headache, upper respiratory tract infection, dizziness, nausea. In trials, lorcaserin did not increase the incidence of cardiac valvulopathy.				
Nalfurafine **injection** *Remitch* Fresenius Medical Care	***Indication:*** Dialysis-related uraemic pruritus.	***Current status:*** PIII with orphan status in the EU.	***Predicted UK launch:*** 2013	***National guidance:*** None relevant. ***Reviews:*** None.
Target population: Data from 2003-2004 indicates 42% of patients on haemodialysis have moderate to extreme pruritus. ***Sector:*** Renal services are a specialised service.		***Implications:*** No other treatments are specifically licensed for uraemic pruritus. Options include gabapentin and UVB phototherapy. ***Financial:*** Likely to be more expensive than off-label use of oral agents. ***PbR:*** Uncertain.		
Pharmacology: Kappa opioid agonist. ***Efficacy:*** A published meta-analysis reviewed data from 144 patients on haemodialysis with severe, uncontrolled pruritus. Patients received nalfurafine or placebo by i.v. infusion 3 times a week after haemodialysis. A 100-mm visual analogue scale was used to measure the "worst itching" during the previous 12 hours. At week 2, a mean difference of 9.53mm was found between nalfurafine and placebo (p<0.03). 36% on nalfurafine achieved ≥50% decrease from baseline in worst itching vs. 14% on placebo (p<0.03). ***Safety:*** The meta-analysis found adverse events to be similar to placebo.				
Nalmefene **oral** *Selincro* Lundbeck	***Indication:*** Alcohol dependence.	***Current status:*** Filed in EU Dec 2011.	***Predicted UK launch:*** 2013	***National guidance:*** **NICE:** Alcohol use: pathway, quality standard, commissioning guide. **SIGN:** Alcohol dependence. ***Reviews:*** None.
Target population: In England, alcohol dependence affects around 4% of people aged 16-65 years. 290 prescription items per 100,000 people were dispensed for alcohol dependency in England in 2010. ***Sector:*** Secondary care initiated.		***Implications:*** Unlike existing therapies, nalmefene is used 'as-needed' and taken on the day of perceived risk of drinking. Complete abstinence is not needed so it will be attractive, especially for 'binge' drinking. ***Financial:*** As a new treatment nalmefene could be expensive. ***PbR:*** Mental health services are being brought into PbR during 2012/13.		
Pharmacology: Opioid receptor antagonist administered on an 'as needed' basis before alcohol consumption. ***Efficacy:*** In PIII studies comparing nalmefene with placebo, about two-thirds of patients had previously not been treated for alcohol dependence and no abstinence treatment goals were imposed. Two trials (ESENSE-1, n=598 and ESENSE-2, n=718), evaluated efficacy of nalmefene over 6 months, and one (SENSE, n=665) trial evaluated safety and tolerability over 12 months. In ESENSE 1 and 2, the primary outcomes were a reduction in the number of heavy drinking days (HDDs) and total alcohol consumption (TAC). In ESENSE 1, at 6 months, mean HDDs reduced by 12 days/month and the mean TAC decreased by 54g/day in the nalmefene group vs. 10 days and 42g/day, respectively, for placebo (p<0.05 for both outcomes). In ESENSE 2, mean HDDs reduced by 13 days/month and TAC reduced by 63g/day vs. 11 days/month and 56g/day for HDDs (p<0.05) and TAC (p=0.05), respectively, for placebo. ***Safety:*** The most common adverse events included dizziness, insomnia, and nausea.				

Tafamidis meglumine **oral** *Vyndaqel* Pfizer	***Indication:*** Familial amyloid poly-neuropathy (FAP).	***Current status:*** Licensed in EU Nov 2011 with orphan status - see prescribing data. Launched in Ireland and Sweden.	***Predicted UK launch:*** 2012	***National guidance:*** None relevant. ***Reviews:*** NHSC Apr 2010.
Target population: Transthyretin (TTR) gene mutations cause abnormal amyloid deposits in nerve tissues. FAP has an EU prevalence of 1 in 100,000 and liver transplantation is currently the only treatment; a normal liver produces a stable TTR protein. ***Sector:*** Amyloidosis is a specialised service. The National amyloidosis centre provides a diagnostic and management advisory service; treatment is delivered locally.		***Implications:*** Tafamidis is the first drug licensed for FAP and is indicated for adults with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. ***Financial:*** Tafamidis will be expensive but may prevent or delay liver transplantation. ***PbR:*** Tariff excluded.		
Pharmacology: Amyloid inhibitor that stabilises TTR amyloid to inhibit formation of abnormal amyloid fibrils. ***Efficacy:*** In an 18-month PII/III trial (n=128), 60% of patients on tafamidis vs. 38% on placebo had no disease progression (p=0.04, NNT=5). Patients from this trial entered an open-label 12-month extension study. Additional long-term, data will be obtained until product launch from a further study involving patients who completed previous trials. ***Safety:*** Adverse effects include diarrhoea, abdominal pain, infections and myalgia. See prescribing data.				

BNF 5. Infections

Ceftaroline injection *Zinforo* AstraZeneca	***Indication:*** Community acquired pneumonia (CAP) and Complicated skin and soft tissue infections (CSSIs).	***Current status:*** Approved in EU Aug 2012. Launched in US - see prescribing data.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** Pneumonia due TBC. **SIGN:** Community management of lower respiratory tract infection (update due Nov 2012). ***Reviews:*** LNDG due Sep 2012.
Target population: The annual incidence of CAP is 5-11 per 1,000 adults and results in about 83,000 hospital admissions annually. It is the fifth leading cause of death in the UK. Skin and soft tissue infections are the second most common infection in hospitals. US data show a 29% increase in hospital admissions with CSSIs between 2000-2004. ***Sector:*** Secondary care.		***Implications:*** Ceftaroline is an additional therapy to treat serious infections, especially those due to methicillin-resistant *Staphylococcus aureus*. ***Financial:*** Ceftaroline will compete with current parenteral antibiotics including generically available products. ***PbR:*** Likely in tariff.		
Pharmacology: Broad spectrum cephalosporin given by i.v. infusion twice daily. ***Efficacy:*** *CAP.* In the published PIII FOCUS I and II trials in 1,228 adults with CAP, ceftaroline was non-inferior to ceftriaxone in the pooled modified intention-to-treat (mITT) population, achieving clinical cure rates of 82.6% vs. 76.6%, respectively. *CSSI.* In the CANVAS I and II trials, involving 1,378 adults with CSSIs, ceftaroline was non-inferior to aztreonam plus vancomycin in achieving clinical cure rates in the pooled mITT population (85.9% vs. 85.5%, respectively) and in patients infected with MRSA (93.4% vs. 94.3%). ***Safety:*** Similar safety profile to ceftriaxone.				

Elvitegravir, cobicistat, emtricitabine, tenofovir **oral** *Quad* Gilead	***Indication:*** HIV Infection.	***Current status:*** Filed in EU Dec 2011.	***Predicted UK launch:*** 2013	***National guidance:*** None relevant. ***Reviews:*** LNDG due TBC.
Target population: An estimated 91,500 people were living with HIV in the UK in 2010; an estimated 22,200 were undiagnosed. The prevalence is 150 per 100,000 people. ***Sector:*** Secondary care.	***Implications:*** *Quad* will be the only once-daily, single-tablet regimen containing an integrase inhibitor. ***Financial:*** *Quad* will have to compete with currently available options. ***PbR:*** Tariff excluded.			
Pharmacology: Elvitegravir is an HIV integrase inhibitor. Cobicistat is a CYP3A inhibitor with no intrinsic anti-retroviral activity and used to boost elvitegravir levels to allow once daily dosing. Emtricitabine and tenofovir are nucleoside reverse transcriptase inhibitors. ***Efficacy:*** In a published PIII 48-week study in 708 treatment-naïve patients non-inferiority was demonstrated with *Quad* vs. atazanavir+ritonavir/emtricitabine/tenofovir. The primary outcome of HIV RNA <50 copies/mL was achieved by 89.5% vs. 86.8% patients, respectively. In another published PIII 48-week study (n=700) non-inferiority was demonstrated when *Quad* was compared with efavirenz/emtricitabine/tenofovir; 87.6% and 84.1%, respectively, achieved HIV RNA <50 copies/mL. ***Safety:*** Fewer patients treated with *Quad* than with the atazanavir regimen had abnormal liver function tests. Dizziness, abnormal dreams, insomnia and rash were less common with *Quad* than with the efavirenz regimen.				
Cobicistat **oral** Gilead	***Indication:*** HIV infection (booster).	***Current status:*** Filed in EU May 2012.	***Predicted UK launch:*** 2013	***National guidance:*** None relevant. ***Reviews:*** No recent reviews.
Target population: As for *Quad* above. ***Sector:*** Secondary care.	***Implications:*** A ritonavir-boosted protease inhibitor is currently used in regimens as the third agent. Lower HIV RNA suppression rates may be seen with cobicistat vs. ritonavir but data are lacking. ***Financial:*** Cobicistat will compete with ritonavir. ***PbR:*** Likely tariff excluded.			
Pharmacology: CYP3A inhibitor (derivative of ritonavir) used to boost elvitegravir levels and extend the half-life. Cobicistat has no anti-retroviral activity, unlike ritonavir. ***Efficacy:*** A PIII trial (study 114, n=692) compared a cobicistat-containing regimen with a ritonavir regimen in treatment-naïve patients. The primary outcome of HIV RNA levels <50 copies/mL at 48 weeks was achieved in 85% of those on cobicistat vs. 87% on ritonavir, demonstrating non-inferiority. Mean CD4 cell count increases were 213 cells/mm^3 and 219 cells/mm^3, respectively (p>0.6). A PII study assessed a cobicistat-boosted atazanavir regimen (n=79) vs. ritonavir-boosted atazanavir. At week 24, 84% in the cobicistat group vs. 86% in the ritonavir group achieved the primary outcome of HIV RNA <50 copies/mL. Viral suppression rates were 91% and 96%, respectively, and median CD4 cell count gains were 230 vs. 206 cells/mm^3, respectively. ***Safety:*** Cobicistat has been reported to inhibit renal tubular secretion of creatinine and affect estimated (but not actual) glomerular filtration rate. It may also affect intracellular concentrations of tenofovir, with effects on the proximal tubules.				

Dapagliflozin **oral** *Forxiga* AstraZeneca	***Indication:*** Type 2 diabetes mellitus.	***Current status:*** Recommended for approval in EU Apr 2012.	***Predicted UK launch:*** 2012	***National guidance:*** **NICE:** Diabetes: pathway, quality standard; Dapagliflozin due Mar 2013. **SIGN:** Diabetes. **SMC:** Dapagliflozin due Oct 2012. ***Reviews:*** LNDG due Sep 2012, NPC/UKMI Mar 2011, NHSC Jan 2010.

Target population: In 2011 the UK prevalence of diabetes was 4.45% (about 2.9 million people). It is thought a further 850,000 are undiagnosed. The prevalence is projected to increase to 5 million people by 2025. About 90% of patients with diabetes have type 2 disease.

Sector: Primary and secondary care.

Implications: Dapagliflozin is another oral option for type 2 diabetes and as first in class it will attract interest. Most studies are of relatively short duration (24 weeks); longer studies will help define its place in therapy.

Financial: Spending on diabetes services in 2010 was at least £3.9 billion (4% of the NHS budget). Spending on diabetes drugs increased from £458.6 million in 2004-05 to £649.2 million in 2009-10, a rise of 42% and in 2009-10 represented 7.7% of the total cost of primary care prescribing. Dapagliflozin is likely to be a more expensive option as first in class.

PbR: Likely in tariff.

Pharmacology: Sodium glucose co-transporter type 2 inhibitor; inhibits renal-glucose reabsorption and preserves beta cell mass. First in a new class of drugs.

Efficacy: All outcomes relate to 24-week data unless specified otherwise. *Monotherapy.* In a PIII study dapagliflozin showed greater HbA1c control than placebo in treatment-naïve patients ($p<0.0005$ for 5mg and 10mg). *Add-on combination therapy.* When added to metformin dapagliflozin reduced HbA1c by -0.67 to -0.84% vs. -0.3% with placebo ($p\leq0.0002$, sustained to week 102). In add-on to metformin studies, dual therapy was more effective than monotherapy, with HbA1c reductions ~2.0% with combination vs. ~1.3% with dapagliflozin and ~1.4% with metformin. When added to sulfonylurea therapy, dapagliflozin reduced HbA1c by -0.58 to -0.82% vs. -0.13% with placebo ($p<0.0001$). In the add-on to glitazone study, mean changes in HbA1c were -0.82 to -0.97% with dapagliflozin vs. -0.42% with placebo ($p\leq0.0007$). In comparison to a sulfonylurea, similar reductions in HbA1c were achieved with dapagliflozin and glipizide (-0.52% with both at week 52). When added to insulin, greater reductions in HbA1c were seen with dapagliflozin vs. placebo (-0.79% to -0.96% vs. -0.39%, respectively, $p<0.001$). In a triple therapy study HbA1c reductions with dapagliflozin were greater than placebo when added to sitagliptin ± metformin (mean difference -0.48%, $p<0.0001$). Greater weight loss was seen with dapagliflozin vs. placebo when added to metformin (difference of 2.08kg, $p<0.0001$).

Safety: Higher rates of genital and urinary tract infections reflect increases in urinary glucose excretion. A higher incidence of breast and bladder cancers has led to the US authorities raising concerns.

Canagliflozin **oral** Janssen-Cilag	***Indication:*** Type 2 diabetes mellitus.	***Current status:*** Filed in EU Jun 2012.	***Predicted UK launch:*** 2013	***National guidance:*** As for dapagliflozin above. ***Reviews:*** NHSC Apr 2011.

Target population: As for dapagliflozin above.

Sector: Primary and secondary care.

Implications: Canagliflozin is second in class and another option for poorly controlled type 2 diabetes.

Financial: As for dapagliflozin above, canagliflozin is likely to be priced competitively to dapagliflozin.

PbR: Likely in tariff.

Pharmacology: Sodium-glucose co-transporter 2 (SGLT2) inhibitor.

Efficacy: In the PIII CANTATA-MSU study canagliflozin demonstrated superiority vs. placebo as part of a triple therapy regimen ($p<0.001$). In the CANTATA-SU study canagliflozin was similar to glimepiride in terms of HbA1c reduction in a dual therapy regimen. In CANTATA-D2 canagliflozin showed a greater reduction in HbA1c at week 52 vs. sitagliptin (-1.03 vs. -0.66%) as part of a triple therapy regimen in patients poorly controlled on metformin and a sulphonylurea. Canagliflozin also showed improvement in glycaemic control, weight reduction and blood pressure vs. sitagliptin ($p<0.001$). In CANVAS the effects of canagliflozin on cardiovascular events are compared with placebo (n=4,386). Mean study duration will be 4 years and is due to complete in 2013. Further data for canagliflozin in mono (CANTATA-M vs. placebo), dual (CANTATA-D vs. placebo or sitagliptin) or triple (CANTATA-MP vs. placebo) therapy regimens are recently available or studies are ongoing.

Safety: Higher rates of genital and urinary tract infections with canagliflozin reflect increases in urinary glucose excretion.