Scottish Medicines Consortium
Providing advice about the status
of all newly licensed medicines
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Scottish Medicines Consortium response to the Public Petitions Committee on PE1398, PE1399 and PE1401

The Public Petitions Committee has asked the Scottish Medicines Consortium

- What are your views on the issues raised in the petitions?

1. About the Scottish Medicines Consortium (SMC)

The Scottish Medicines Consortium (SMC) welcomes the opportunity provided by the Public Petitions Committee to describe its role and functions in the assessment of new medicines. The purpose of SMC is to assess the comparative clinical- and cost-effectiveness of new medicines and accept for use those that clearly represent good value for money to NHS Scotland. SMC has a remit to advise Health Boards across NHS Scotland and their Area Drug and Therapeutics Committees (ADTCs) on all new prescription medicines, including new formulations and new indications of existing medicines. Advice is issued as soon as practical after a new medicine becomes available for use. Senior NHS managers, representatives of the public and the pharmaceutical industry are involved in the process. The Patient and Public Involvement Group (PAPIG) subgroup of SMC is responsible for ensuring that the patient/carer perspective is always taken into consideration by the SMC.

2. Orphan medicines

Orphan drug legislation was introduced in the EU in 2000 in an attempt to improve the availability of medicines for rare diseases, described as „orphan medicines". This created incentives for pharmaceutical companies to develop medicines for rare diseases. The EU criteria for orphan medicines are those defined by the Committee on Orphan Medicinal Products (COMP) and set out on the European Medicines Agency (EMA) website. In terms of the rarity of the disease, in the EU an orphan drug is defined as one for which the frequency of the disease is less than 5 per 10,000 of the EU population. „Ultra orphan" is a term used by NICE but not, as far as we are aware, formally recognised by relevant regulatory agencies. The number of new treatments for rare disorders has increased over the past 10 years. Over 800 medicines in development have been designated as orphans and there are now 74 orphan medicines with a marketing authorisation from the EMA (i.e. licensed for prescribing in the UK). This reflects the success of the Orphan Drugs Regulation in Europe.

3. SMC methodology

When a new medicine is licensed for use the pharmaceutical company is asked to make a submission on the product, including results of clinical trials and cost effectiveness data, to SMC. SMC has a two stage process. Firstly, the New Drugs Committee (NDC) critically evaluates the submission with the support of medical, pharmaceutical, and health economics experts. The NDC then makes a provisional recommendation that is shared with the pharmaceutical company concerned. The advice from NDC, together with feedback from the

company is then considered by the SMC committee. Patient Interest Group (PIG) submissions, focusing on the difficulties the disease presents for patients and the place of the medicine in addressing patient needs, are also an important part of the SMC"s assessment process. They often supply useful additional perspectives on new medicines and they are very helpful in guiding SMC"s conclusions.

4. SMC assessment of orphan medicines

For an orphan medicine the submitting company is required to make the case for clinical and cost-effectiveness in the same way as for all new medicine submissions. In reaching a decision on whether the medicine can be accepted for use in NHS Scotland, SMC recognises that efficacy data are very often limited due to the rarity of the condition and may therefore accept a greater level of uncertainty in the economic case. SMC explicitly state that we will accept greater uncertainty in the health economic case when assessing a medicine with an orphan indication. There are also situations when a higher cost per Quality Adjusted Life Year (QALY) may be acceptable and this is factored into our process. These additional factors, termed „SMC modifiers", such as whether the medicine: treats a life threatening disease; substantially increases life expectancy and/or quality of life; can reverse, rather than stabilise, the condition; bridges a gap to a "definitive" therapy, or provides a licensed alternative to a previously unlicensed medicine will also be considered in assessing both the level of uncertainty and cost per Quality Adjusted Life Year (QALY). These modifiers are always actively considered when reaching a decision on a medicine with orphan status (according to the EMA Committee on Orphan Medicinal Products (COMP)).

These modifiers form part of a global judgement taken by SMC, which is also influenced by input from clinical experts and Patient Interest Groups as well as the clinical and cost-effectiveness data on the new medicine submitted by the manufacturer.

When a modifier, or any other special issue which may have been highlighted by the sponsor company, by clinical experts and/or by Patient Interest Groups, is a factor in SMC acceptance of an orphan medicine this is stated in the health economics section of the SMC detailed advice document.

5. SMC advice to date on orphan medicines

Up to and including October 2011, SMC has assessed 51 full submissions for orphan medicines of which 10 (20%) have been accepted for use and 21 (41%) accepted for restricted use. The remaining 20 (39%) were not recommended. For a further 12 medicines the manufacturer did not make a submission to SMC so these were not recommended. Three orphan medicines have been accepted for use after assessment through the SMC abbreviated submission process. The corresponding figures for medicines without orphan status assessed by SMC are: up to and including October 2011, 422 full submissions have been assessed of which 127 (30%) have been accepted for use, 189 (45%) accepted for restricted use, and 106 (25%) not recommended. These figures illustrate that the acceptance rate for orphan medicines submitted to SMC (61%) is lower than the acceptance rate for medicines without orphan status (75%) but that this difference is justifiable.

Summary details of the advice relating to all orphan medicines is attached for information. Full details are available on the SMC website.

6. Societal considerations of valuing rarity

Societal considerations are important in relation to medicines for rare diseases. Societal attitudes toward cost effectiveness have been explored in a number of reports produced by

NICE's Citizens' Council including one on Ultra-orphan drugs (November 2004). This concluded that the criteria the NHS should take into account when deciding to pay premium prices for ultra orphan drugs are, in descending order of importance:

• The degree of severity of the disease
• If the treatment will provide health gain, rather than just stabilisation of the condition
• If the disease or condition is life-threatening

Key findings were that rarity on its own is an insufficient reason to justify paying a premium for treatment and that the degree of severity and the amount of health gain are the more critical factors. NICE states that: "Decisions about whether to recommend interventions should not be based on evidence of their relative costs and benefits alone. NICE must consider other factors when developing its guidance, including the need to distribute health resources in the fairest way within society as a whole."

More recent data on the views of the general public on this issue are available from outwith the UK. In a survey of the Norwegian general population, people were asked whether society should pay more to treat rare diseases than it does for common diseases. The results showed that although respondents supported equity of access to healthcare for people with rare diseases, they did not support providing care for people with rare diseases when the cost of that care was at the expense of people with common conditions. Two citizen"s juries held in Canada had similar findings; opting for health policy that would ensure that effective interventions are made available to the largest number of patients. A preference for treating small numbers of patients was expressed only if the patients were severely ill and the treatment could produce substantial health gain to all of them, bringing them back to normal functioning.

There may also be an issue in relation to how rarity is defined. Globally there are over 6000 identified rare diseases, so collectively the number of patients affected by rare diseases is considerable. To illustrate this, the Rarer Cancers Forum states that between 30% and 50% of all cancers are classified as rarer and an estimate recently quoted in the Scottish media is that in total more than 350,000 people in Scotland will be affected by a rare disease.

7. SMC views on the issues raised by Petitions PE1398, PE1399, PE1401

SMC fully supports the principle that people with rare conditions should be able to access clinically and cost-effective interventions including medicines through the NHS. We believe that SMC helps to ensure that new medicines with the most significant benefits are available across Scotland and improves consistency in their availability from one NHS Board to another. Difficult decisions have to be made in order to spend available resources wisely and this is increasingly important in the current fiscal climate. If money is spent on medicines that do not offer good value, it means that this money is not available to be spent for other treatments that could provide benefits to patients (termed the „opportunity cost").

Although the SMC acceptance rate for orphan medicines submitted to SMC (61%) is lower than the acceptance rate for medicines without orphan status (75%), SMC believes that these figures are reassuring because *de facto* the evidence base for orphan medicines is often weaker than for other medicines, the SMC modifiers described above do not always apply to the medicine under review and the prices charged for these drugs can make it impossible for them to meet conventional measures of good value.

SMC believes it is important to highlight the extremely high acquisition costs associated with many orphan medicines. This has attracted recent attention in the medical literature, where it is noted that the pharmaceutical industry already receives incentives to develop medicines

for rare diseases, and arguing that an unintended consequence of the orphan drugs legislation may be exploitation of the rules for profit. Within NHS Scotland we have the Patient Access Scheme (PAS) which allows the pharmaceutical industry to reduce the cost of a drug where the drug has been shown not to be cost effective. This was set up in 2009 to try to help enable access and to date overall, 25 medicines with a PAS have been reviewed by SMC with 13 accepted for use or restricted use contingent on the PAS being available in NHS Scotland.

If more value or weight is to be put on the health improvement associated with treatments for rare conditions than for common conditions this raises important equity issues. There is evidence from England and elsewhere that the public"s willingness to pay for medicines that treat rare diseases is not unlimited. The perspective of patients and the general public in Scotland on willingness to pay for these medicines is not known. SMC and its Patient and Public Involvement Group would be supportive of discussions taking place to harness the views of the general public in Scotland on this issue.

SMC considers the clinical and cost-effectiveness of all new prescription medicines, regardless of severity or whether the condition they treat is common or rare. The principle of trying to ensure that NHS resources are used most effectively, having regard to the premise that the NHS has limited resources which can only be spent once, underpins all our assessments. The members of SMC apply the same decision making framework across all medicines. We believe this is a key strength of the SMC process. SMC believes that its current methodology is robust, objective, transparent and fair and is therefore entirely appropriate for the assessment of medicines with orphan status.

Angela Timoney
SMC Chair

7 November 2011

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	Drug Name	SMC No:	Indication	SMC Advice
1.	**imatinib (Glivec)**	(No. 01/02)	Chronic myeloid leukaemia	**RESTRICTED:** Approved for treatment of chronic myeloid leukaemia under the overall supervision of haematologists/oncologists.
2.	**imatinib (Glivec)**	(No. 08/02)	Non-resectable or metatastic gastrointestinal stromal tumours	**RESTRICTED**: Under the supervision of an oncologist for patients with Kit-positive gastrointestinal stromal tumours (GIST).
3.	**bosentan (Tracleer)**	(No. 32/03)	Grade III pulmonary arterial hypertension	**RESTRICTED:** This medicine was approved by EMEA under the accelerated licensing process, thus evidence of its efficacy is limited. Bosentan may be a potentially useful alternative to epoprostenol for patients with Grade III pulmonary arterial hypertension. It offers major advantages over epoprostenol in its ease of administration. However, there are currently scant data on the effectiveness of these products on patient survival. The hepatotoxicity and teratogenicity of Bosentan have led the EMEA to recommend post-marketing surveillance and the company operates this as a controlled release programme. The cost-effectiveness of Bosentan is impossible to estimate at present, and may be low. Bosentan should only be prescribed for patients who are treated in specialist centres run by physicians experienced in the management of these disorders.
4.	**laronidase (Aldurazyme)**	(No. 100/04)	Enzyme replacement therapy in patients with Mucopolysaccharidosis	**NOT RECOMMENDED:** for the treatment of mucopolysaccharidosis I. Laronidase was approved by the EMEA under exceptional circumstances and has been granted orphan drug status. The evidence of its efficacy is therefore limited. No information is presented in the submission to support the therapy being cost effective and therefore the economic case is not demonstrated. **RESUBMISSION** **NOT RECOMMENDED:** for the treatment of mucopolysaccharidosis I. Laronidase was approved by the EMEA under exceptional circumstances and has been granted orphan drug status. No information is presented in the submission to support the therapy being cost effective.

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5.	**miglustat (Zavesca)**	(No. 133/04)	Gaucher Disease	**ACCEPTED:** for the treatment of mild to moderate type 1 Gaucher disease in patients for whom enzyme replacement therapy is unsuitable. Miglustat should only be initiated by physicians experienced in the management of Gaucher's disease.
6.	**pegvisomant (Somavert)**	(No. 158/05)	Acromegaly	**NOT RECOMMENDED:** For the treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalise IGF-1 concentrations or was not tolerated. Pegvisomant reduces IGF-1 levels significantly, as well as improving some of the clinical manifestations of acromegaly. Although it is acknowledged that this is an orphan drug the cost-effectiveness is poor. **RESUBMISSION** **NOT RECOMMENDED:** for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalise insulin-like growth factor 1 (IGF-1) concentrations or was not tolerated. Pegvisomant reduces IGF-1 levels significantly and improves some of the clinical manifestations of acromegaly. It is acknowledged that this is an orphan drug but the economic case has not been demonstrated.

7.	**anagrelide hydrochloride (Xagrid)**	(No. 163/05)	Reduction of elevated platelet counts in at risk thrombocythaemia	**NOT RECOMMENDED:** For the reduction of elevated platelet counts in 'at risk' patients with essential thrombocythaemia who are intolerant of their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy. The cost effectiveness of anagrelide has not been demonstrated. **RESUBMISSION** **ACCEPTED:** for the reduction of elevated platelet counts in at-risk patients with essential thrombocythaemia who are intolerant of their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy. Anagrelide reduces platelet counts in patients with essential thrombocythaemia who were intolerant of another cytoreductive therapy or whose platelet count could not be controlled by it.
8.	**iloprost (Ventavis)**	(No: 219/05)	Pulmonary hypertension	**RESTRICTED:** For the treatment of patients with New York Heart Association Class III primary pulmonary hypertension as a second-line treatment where bosentan is ineffective or is not tolerated. It is an orphan product and efficacy data are very limited. Iloprost should also be restricted to use only as an alternative in patients receiving other forms of prostacyclin treatment. It is not recommended for patients who would not otherwise have received prostacyclin treatment because it is not cost effective in this situation. It is further restricted only to use by Specialists working in the Scottish Pulmonary Vascular Unit.
9.	**Ibuprofen (Pedea)** **Abbreviated**	(No. 233/06)	Patent ductus arteriosus in pre-term newborn infants	**ACCEPTED:** for the treatment of haemodynamically significant patent ductus arteriosus in pre-term newborn infants of less than 34 weeks gestational age. Safety and efficacy compared to existing alternative treatments has not been formally assessed.

10.	**sildenafil (Revatio)**	(No: 235/06)	Treatment of patients with pulmonary arterial hypertension (PAH), classified as WHO functional class III, to improve exercise capacity.	**RESTRICTED:** is accepted for restricted use within NHS Scotland for the treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity. This is an orphan indication for sildenafil with limited clinical evidence from short-term clinical trials. It is restricted to initiation by specialists working in the Scottish Pulmonary Vascular Unit and by physicians experienced in the management of pulmonary vascular disease.
11.	**sunitinib (Sutent)**	(No: 275/06)	GIST	**NOT RECOMMENDED:** For the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance. Sunitinib compared to placebo delayed tumour progression by approximately five months. The economic case has not been demonstrated. **RESUBMISSION Nov 2009** **ACCEPTED:** is accepted for use within NHS Scotland for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesilate treatment due to resistance or intolerance. Sunitinib compared with placebo delayed tumour progression by approximately five months. Treatment with sunitinib should not be continued if there is evidence of unacceptable toxicity or progression of disease.
12.	**carglumic acid (Carbaglu)**	(No 299/06)	hyperammonaemia due to N-acetylglutamate synthase (NAGS) deficiency	**RESTRICTED:** For the treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency. Limited data from retrospective case analysis indicate that carglumic acid generally allowed patients to maintain normal ammonia levels, growth and psychomotor development. Carglumic acid is restricted to use by experts providing the supraregional specialist service for this disease.

13.	**sodium oxybate (Xyrem)**	(No: 246/06)	Cataplexy in adult patients with narcolepsy	**NOT RECOMMENDED**: for the treatment of cataplexy in adult patients with narcolepsy. In two studies the median percent decrease in weekly cataplexy attacks ranged from 49% to 85% for the dose range included in the product licence. However, the economic case for this product was not demonstrated. **RESUBMISSION AUGUST 2007** **NOT RECOMMENDED:** for the treatment of cataplexy in adult patients with narcolepsy. The manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC.
14.	**Tobramycin (Bramitob)** **Abbreviated**	(No. 314/06) Issued Feb 09	Management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged 6 years and older.	**ACCEPTED:** is accepted for use in NHS Scotland for the management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged 6 years and older. Consideration should be given to official guidance on the appropriate use of antibacterial agents. This preparation offers an alternative to an existing nebuliser solution at a lower cost per dose.
15.	**sorafenib (Nexavar)**	(No. 321/06)	Advanced renal cell carcinoma	**NOT RECOMMENDED:** for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alfa or interleukin-2 based therapy or are considered unsuitable for such therapy. Sorafenib has been compared with best supportive care and has been shown to increase progression-free survival, though the impact on overall survival is uncertain. The cost-effectiveness of sorafenib has not been demonstrated.

16.	**mitotane (Lysodren)**	(No. 328/06)	Advanced adrenal cortical carcinoma	**NOT RECOMMENDED:** for the symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma. The effect of mitotane on non-functional adrenal cortical carcinoma is not established. Mitotane relieves the symptoms of advanced adrenal cortical carcinoma, but there is insufficient evidence to support an increase in survival. The economic case has not been demonstrated. Mitotane should be used only within the context of clinical trials.
17.	**clofarabine (Evoltra)**	(No. 327/06)	Acute lymphoblastic leukaemia (ALL) in paediatric patients (≤ 21 years) who have relapsed or are refractory after receiving at least two prior regimens	**RESTRICTED:** for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients (≤ 21 years) who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. It is restricted to patients in whom clofarabine is being used as a treatment to bridge to HSCT and restricted to use by specialists in paediatric haemato-oncology. It is not cost-effective when used for palliation.
18.	**busulfan IV (Busilvex)**	(No. 337/06)	Conditioning treatment prior to hematopoietic progenitor cell transplantation.	**ACCEPTED:** as part of a combination regimen for conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in paediatric and adult patients. The intravenous preparation offers advantages to patients over the oral formulation in terms of convenience of administration and predictability of blood levels. In adults it should be followed by cyclophosphamide (BuCy2) and in children it should be followed by cyclophosphamide (BuCy4) or by melphalan (BuMel).
19.	**sunitinib 50mg capsule (Sutent)**	(No. 343/07)	Advanced and /or metastatic renal cell carcinoma after failure of interferon-alfa or interleukin - 2	**NOT RECOMMENDED:** for the treatment of advanced and/or metastatic renal cell carcinoma after failure of interferon-alfa or interleukin – 2 therapy. In uncontrolled trials, sunitinib has been associated with tumour responses in patients who have metastatic renal cell cancer. However, the economic case has not been demonstrated.

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20.	**deferasirox, 125,250,500mg dispersible tablets (Exjade)**	(No. 347/07)	Treatment of chronic iron overload due to frequent blood transfusions in patients with beta thalassaemia major aged 6 years and older: and treatment of chronic iron overload due to blood transfusions when	**RESTRICTED:** for the treatment of chronic iron overload associated with the treatment of rare acquired or inherited anaemias requiring recurrent blood transfusions. It is not recommended for patients with myelodysplastic syndromes. Patients with myelodysplastic syndromes, the commonest cause of transfusion-dependent anaemia, were poorly represented in the clinical trial population and the economic case was not demonstrated in this group.
21.	**alglucosidase alfa 50mg powder (Myozyme)**	(No. 352/07)	For long term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid ά-glucosidase deficiency). The benefits in patients with late onset disease has not been established.	**NOT RECOMMENDED:** for the treatment of Pompe disease (acid α-glucosidase deficiency). Treatment in patients with the infantile-form of Pompe disease significantly improved survival compared with historical controls. The evidence is less clear for patients who are already receiving ventilatory support or who have the late-onset form of the disease. The economic case has not been demonstrated. The SMC orphan drug policy requires manufacturers to make complete submissions to allow a comprehensive product assessment similar to all other drug submissions. However, in addition to the usual assessment of clinical and cost-effectiveness, SMC may consider additional factors specific to orphan products. Within this context the particular features of the condition and population receiving the technology and whether a drug can reverse (rather than stabilise) the condition or bridge a gap to a definitive therapy may also be considered. SMC considered the submission in the context of its orphan drug policy.

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22.	**sitaxentan 100mg tablets (Thelin)**	(No. 360/07)	Treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension associated with connective tissue disease	**RESTRICTED:** For the treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity**.** Efficacy has been shown in primary pulmonary hypertension and in pulmonary hypertension associated with connective tissue disease. Data suggest that sitaxentan 100mg daily has a benefit/risk ratio comparable to the other licensed endothelin receptor antagonist. Non-inferiority has not been formally demonstrated as sitaxentan is an orphan drug with limited clinical evidence. Where an endothelin receptor antagonist is indicated, sitaxentan provides an alternative. It is restricted to initiation and prescribing by specialists in the Scottish Pulmonary Vascular Unit. **Note:** sitaxentan (Thelin®) has now been withdrawn from market due to liver toxicity http://www.nelm.nhs.uk/en/NeLM-Area/News/2010---December/10/Pfizer-announces-withdrawal-of-sitaxentan-Thelin-from-market-due-to-liver-toxicity/

23.	**dexrazoxane 20mg/ml for infusion (Savene)**	(No. 361/07)	Treatment of anthracycline extravasation	**NOT RECOMMENDED:** For the treatment of anthracycline extravasation**.** There are data indicating that administration of dexrazoxane is associated with a relatively low rate of surgery and adverse sequelae following extravasation of anthracyclines. However these data are from non-comparative, open-label phase II studies, and there are no data comparing dexrazoxane to Scottish Practice. The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC. **RESUBMISSION SEPTEMBER 08** **NOT RECOMMENDED:** for the treatment of anthracycline extravasation. Data from non-comparative, open-label phase II/III studies indicate that administration of dexrazoxane is associated with a relatively low rate of surgery and adverse sequelae following extravasation of anthracyclines. The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC and in addition the justification of the treatment's cost in relation to its health benefits was not sufficient.
24.	**dasatinib (Sprycel)**	(No. 370/07)	Treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance to or intolerance to prior therapy including imatinib mesylate	**RESTRICTED:** for the treatment of adults with chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesylate. It should be restricted to use in patients who are in the chronic phase of the disease. The manufacturer's justification of the treatment's cost in relation to its health benefits for the accelerated or blast phases was not sufficient to gain acceptance by SMC.
25.	**dasatinib (Sprycel)**	(No. 371/07)	Treatment of adults with Philadelphia chromosome positive (PH+) acute lymphoblastic leukaemia with resistance or intolerance to prior therapy	**NOT RECOMMENDED:** for the treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia with resistance or intolerance to prior therapy. It has been associated with haematological and cytogenetic responses in patients resistant or intolerant to existing treatment. However, the economic case was not sufficiently robust and the manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC.

26.	**idursulfase (Elaprase)**	(No. 391/07)	Long term enzyme replacement therapy with mucopolysaccharidois II	**NOT RECOMMENDED:** for the long-term treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). Idursulfase was approved by the EMEA under exceptional circumstances and has been designated an orphan medicinal product. The manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC and, in addition, they did not present a sufficiently robust economic analysis.
27.	**ziconotide (Prialt)**	(No. 405/07)	Intrathecal treatment of severe chronic pain	**NOT RECOMMENDED** for the treatment of severe, chronic pain in patients who require intrathecal analgesia. Ziconotide, compared to placebo, improved pain scores in patients with chronic severe intractable pain despite treatment with systemic and/or intrathecal analgesia. However, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.
28.	**betaine anhydrous (Cystadane)**	(No. 407/07)	Homocystinuria	**NOT RECOMMENDED** as adjunctive treatment of homocystinuria in line with the manufacturer's licence. The manufacturer did not provide sufficient clinical data to demonstrate efficacy. **RESUBMISSION FEB 09** **NOT RECOMMENDED** as adjunctive treatment of homocystinuria involving deficiencies or defects in cystathionine beta-synthase (CBS), 5,10-methylene-tetrahydrofolate reductase (MTHFR) or cobalamin cofactor metabolism (cbl). Clinical efficacy data for betaine anhydrous are limited. The manufacturer did not present a sufficiently robust economic evaluation to gain acceptance by SMC. **2nd RESUBMISSION AUG 10** **RESTRICTED:** adjunctive treatment of homocystinuria involving deficiencies or defects in cystathionine beta-synthase (CBS), 5,10-methylene-tetrahydrofolate reductase (MTHFR) or cobalamin cofactor metabolism (cbl). **SMC restriction:** patients who are not responsive to vitamin B**6** treatment.

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29.	**rufinamide (Inovelon)**	(No. 416/07)	Seizures associated with Lennox–Gastaut syndrome (LGS) as adjunctive therapy in patients four years and older.	**NOT RECOMMENDED** as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients four years and older. The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC. **RESUBMISSION OCTOBER 2008** **RESTRICTED:** as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients four years and older. Adjunctive rufinamide significantly reduced the frequency of total seizures and tonic-atonic seizures and significantly improved seizure severity when compared to placebo in patients with LGS. Rufinamide is restricted to use in patients who have failed treatment with or are intolerant of alternative traditional antiepileptic drugs.
30.	**imatinib (Gilvec)** **NON-SUBMISSION**	(No: 426/07)	Adult patients with relapsed or refractory as Philadeplphia chromosome positive acute lymphoblastic leukaemia as monotherapy	**NOT RECOMMENDED** for use within NHSScotland for the treatment of adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) as monotherapy. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland.
31.	**imatinib (Gilvec)** **NON-SUBMISSION**	(No: 427/07)	Adult patients with newly diagnosed Philadeplphia chromosome positive acute lymphoblastic leukaemia (PH+ ALL) in combination with chemotherapy	**NOT RECOMMENDED** for use within NHSScotland for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (PH + ALL) in combination with chemotherapy. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland.

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32.	**imatinib (Gilvec)** **NON-SUBMISSION**	(No: 428/07)	Adult patients with myelodysplastic/myeloproliferative diseased (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements	**NOT RECOMMENDED** for use within NHSScotland for the treatment of adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet -derived growth factor receptor (PDGFR) gene re-arrangements. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland.
33.	**imatinib (Gilvec)** **NON-SUBMISSION**	(No: 429/07)	Adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRa re-arrangement	**NOT RECOMMENDED** for use within NHSScotland for the treatment of adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFR? rearrangement. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland.
34.	**imatinib (Gilvec)** **NON-SUBMISSION**	(No: 430/07)	Adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are eligible for surgery	**NOT RECOMMENDED** for use within NHSScotland for the treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland.

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35.	**eculizumab (Soliris)**	(No: 436/07)	Paroxysmal nocturnal haemoglobinuria (PNH)	**NON- SUBMISSION** **NOT RECOMMENDED** for use within NHSScotland for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH). The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland. **FULL SUBMISSION** **NOT RECOMMENDED**: for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH). Evidence of clinical benefit of eculizumab in the treatment of patients with PNH is limited to patients with a history of transfusions. In a controlled study in patients with transfusion-dependent PNH, eculizumab reduced the rate of haemolysis and improved anaemia compared to placebo. Uncontrolled data suggest that eculizumab reduces the incidence of thrombosis in patients with PNH. The manufacturer did not supply any health economic analysis and cost-effectiveness was not demonstrated in an independent economic analysis therefore eculizumab cannot be recommended for use within NHS Scotland.

36.	**trabectedin (Yondelis)**	(No. 452/08)	Treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide.	**NON-SUBMISSION** **NOT RECOMMENDED:** for use within NHSScotland for the treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland. **FULL SUBMISSION JULY 2008** **NOT RECOMMENDED:** for the treatment of patients with advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients. In a phase II randomised study in patients with advanced leiomyosarcoma and liposarcoma in which two trabectedin dose schedules were used, the licensed schedule was superior to the alternative one for the primary endpoint, time to progression. The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC. **RESUBMISSION NOVEMBER 2010** **NOT RECOMMENDED:** for use within NHS Scotland. **Indication under review:** the treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients. In a phase II randomised study in patients with advanced leiomyosarcoma and liposarcoma in which two trabectedin dose schedules were used, the licensed 3-weekly schedule was superior to the alternative one for the primary endpoint, time to progression. The manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC and in addition, the manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC.

				2ND RESUBMISSION JULY 2011 **NOT RECOMMENDED:** for use within NHS Scotland. **Indication under review:** the treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients. In a phase II randomised study in patients with advanced leiomyosarcoma and liposarcoma in which two trabectedin dose schedules were used, the licensed 3-weekly schedule was superior to the alternative one for the primary endpoint, time to progression. The manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC and in addition, the manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC
37.	**nilotinib (Tasigna)**	(No. 440/08)	Chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in adult patients resistant to or intolerant of at least one prior therapy including imatinib.	**RESTRICTED:** for treatment of chronic phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in adult patients resistant to or intolerant of at least one prior therapy including imatinib. It should be restricted to use in patients who are in the chronic phase of the disease. The manufacturer has not made a submission for use in the accelerated phase. As a result we cannot recommend its use within NHSScotland.

38.	**lenalidomide (Revlimid)**	(No. 441/08)	Multiple myeloma patients who have received at least one prior therapy	**NOT RECOMMENDED:** in combination with dexamethasone for the treatment of multiple myeloma in patients who have received at least one prior therapy. Lenalidomide plus dexamethasone significantly increased the time to disease progression compared with dexamethasone alone in multiple myeloma patients who had been treated with at least one prior therapy. The manufacturer did not present a sufficiently robust case and in addition the manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC. **RESUBMISSION APRIL 2010** **RESTRICTED:** In combination with dexamethasone, for the treatment of multiple myeloma patients who have received at least one prior therapy. **SMC restriction:** use in patients who have received at least two prior lines of therapy. Lenalidomide plus dexamethasone significantly increased the time to progression compared with dexamethasone alone in multiple myeloma patients who had been treated with at least one prior therapy. The health economic case was demonstrated only for a sub-population of patients within the licensed indication. Taking into account the orphan drug status of lenalidomide and the substantial survival benefit it appears to offer SMC concluded that the economic case was demonstrated.
39.	**nelarabine (Atriance)**	(No. 454/08)	Patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to, or relapsed following treatment with at least two chemotherapy regimens	**RESTRICTED:** for the treatment of patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to, or has relapsed following, treatment with at least two chemotherapy regimens. It is restricted to patients in whom nelarabine is being used as a treatment to bridge to allogeneic stem cell transplant and restricted to use by specialists in haemato-oncology. It is not cost-effective when used for palliation.

40.	**sorafenib (Nexavar)**	(No. 482/08)	Hepatocellular carcinoma	**NOT RECOMMENDED:** for use within NHS Scotland for the treatment of hepatocellular carcinoma. In one trial in patients with advanced hepatocellular carcinoma, sorafenib was superior to placebo in terms of overall survival, but not for the time to symptomatic progression. The manufacturer's justification of the treatment's cost in relation to its benefit was not sufficient to gain acceptance by SMC. **RESUBMISSION DECEMBER 2010** **NOT RECOMMENDED** for use within NHS Scotland. **Indication under review:** the treatment of hepatocellular carcinoma. In one study in patients with advanced hepatocellular carcinoma, sorafenib was superior to placebo in terms of overall survival, but not for the time to symptomatic progression. The manufacturer did not present a sufficiently robust economic analysis and in addition, the manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC.
41.	**icatibant (Firazyr)**	(No. 476/08)	Symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults (with C1-esterase-inhibitor deficiency).for adults aged 18 years and older	**NOT RECOMMENDED**: for the symptomatic treatment of acute attacks of hereditary angioedema in adults (with C1-esterase-inhibitor deficiency). Icatibant treatment resulted in symptom relief in patients suffering acute abdominal, cutaneous and/or laryngeal attacks of hereditary angioedema. However, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

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42.	**ambrisentan (Volibris)**	(No. 511/08)	Treatment of patients with pulmonary arterial hypertension (PAH) classified as World Health Organisation functional class (WHO FC) II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.	**RESTRICTED:** for the treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease. Data suggest that ambrisentan has a benefit/risk ratio comparable to other endothelin receptor antagonists. Non-inferiority has not been formally demonstrated as ambrisentan is an orphan drug with limited clinical evidence. Where an endothelin receptor antagonist is indicated, ambrisentan provides an alternative. It is restricted to initiation and prescribing by specialists in the Scottish Pulmonary Vascular Unit or similar specialists.
43.	**stiripentol (DIACOMIT)**	(No. 524/08)	Severe myoclonic epilepsy in infancy (Dravet's Syndrome)	**NOT RECOMMENDED:** for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalised tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome) whose seizures are not adequately controlled with clobazam and valproate. The number of responders with >50% reduction in the number of clonic (or tonic-clonic) seizures was significantly greater in SMEI patients receiving adjunctive stiripentol than in patients receiving placebo. The product did not gain acceptance by SMC as the manufacturer did not present a formal economic evaluation.
44.	**thalidomide (Thalidomide Pharmion)**	(No. 525/08)	Treatment of patients with untreated multiple myeloma	**ACCEPTED:** in combination with melphalan and prednisone, as first line treatment of patients with untreated multiple myeloma, aged 65 years or over or ineligible for high dose chemotherapy. Thalidomide is prescribed and dispensed according to the Thalidomide Pharmion Pregnancy Prevention Programme. In the pivotal trial in patients aged 65 to 75 years, at 51.5 months median follow-up, the addition of thalidomide to melphalan and prednisone gave an overall survival advantage of 18.4 months.
45.	**cladribine (Litak)** Abbreviated	(No. 537/09)	Hairy cell leukaemia	**ACCEPTED:** for the treatment of hairy cell leukaemia. In patients for whom cladribine is an appropriate agent for this indication, the 2mg/ml solution allows administration by subcutaneous bolus injection over five consecutive days rather than by continuous intravenous infusion of the existing 1mg/ml solution for seven consecutive days. This may confer advantages in terms of convenience to patients and service delivery at a lower cost per course.

46.	**Caffeine citrate**	(No. 550/09)	Treatment of apnoea of prematurity	**RESTRICTED:** is accepted for restricted use within NHS Scotland for the treatment of apnoea of prematurity. Short-term studies have demonstrated the efficacy of caffeine on apnoeic episodes and one longer-term study has shown reduction in disabilities relevant to these infants. It should be restricted to use on the advice of specialists in neonatal paediatrics.
47.	**romiplostim (Nplate)**	(No. 553/09)	Adult chronic immune (idiopathic) thrombocytopenic purpura (ITP)	**RESTRICTED:** for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Romiplostim is also accepted for restricted use as second line treatment for adult non-splenectomised patients where surgery is contra-indicated. Romiplostim is restricted to use in patients with severe symptomatic ITP or patients with a high risk of bleeding. Romiplostim was significantly better than placebo in maintaining platelets at (or above) a minimum target level in previously treated patients with ITP.
48.	**sapropterin (Kuvan)** **NON-SUBMISSION**	(No. 558/09)	Hyperphenylalaninaemia (HPA) in adult and paediatric patients with phenylketonuria (PKU) and for the treatment of hyperphenylalaninaemia (HPA) in adult and paediatric patients with tetrahydrobiopterin (BH4) deficiency.	**NOT RECOMMENDED** for use within NHSScotland for the treatment of hyperphenylalaninaemia (HPA) in adult and paediatric patients with phenylketonuria (PKU) and for the treatment of hyperphenylalaninaemia (HPA) in adult and paediatric patients with tetrahydrobiopterin (BH4) deficiency. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland.
49.	**mecasermin (Increlex) 10mg/ml solution for injection**	(No: 563/09)	Long term treatment of growth failure in children and adolescents	**ACCEPTED:** for the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-1 deficiency (primary IGFD). Mecasermin significantly improved mean height velocity, mean height velocity standard deviation (SD) score and mean cumulative change in height SD score for at least 6 years. Serious adverse effects including hypoglycaemia and tonsillar hypertrophy are common and long-term safety data are lacking.

50.	**hydroxycarbamide (Siklos®)** **NON-SUBMISSION**	(No. 582/09)	Prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in paediatric and adult patients suffering from symptomatic Sickle Cell Syndrome	**NOT RECOMMENDED** for use within NHS Scotland for the prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in paediatric and adult patients suffering from symptomatic Sickle Cell Syndrome. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHS Scotland.
51.	**imatinib (Glivec)**	(No. 584/09)	Adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive gastrointestinal stromal tumours (GIST)	**NOT RECOMMENDED:** for the adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive gastrointestinal stromal tumours (GIST). Imatinib, given for a period of one year, significantly improved the estimated one year recurrence-free survival compared with placebo. This treatment effect began to reduce six months after stopping imatinib. The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC. **RESUBMISSION AUGUST 2010** **RESTRICTED:** for adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive gastrointestinal stromal tumours (GIST). Patients who have a low or very low risk of recurrence should not receive adjuvant treatment. SMC restriction: Imatinib is restricted to use in patients at high risk of recurrence following complete resection (according to the Armed Forces Institute of Pathology (AFIP) risk criteria). Imatinib, given for a period of one year, significantly improved the estimated one year recurrence-free survival compared with placebo and was associated with an increase of 16.4 months in median time to recurrence in patients at high risk of relapse following resection.

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52.	**plerixafor (Mozobil)**	(No. 594/09)	In combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma whose cells mobilise poorly	**ACCEPTED:** in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma whose cells mobilise poorly. Significantly more patients treated with plerixafor than with placebo achieved their target collection of CD 34+ cells required for autologous stem cell transplantation with subsequent sustained engraftment.
53.	**sidenafil (Revatio)**	(No. 596/10)	Treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II, to improve exercise capacity.	**RESTRICTED:** for treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease. It is restricted to initiation by specialists working in the Scottish Pulmonary Vascular Unit or similar specialists. This is an orphan indication for sildenafil with limited clinical evidence from post-hoc analysis of a short-term clinical trial.

54.	**azacitidine 100mg powder for suspension for injection (Vidaza)**	(No. 589/09)	Treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (SCT) with intermediate-2 and high-risk myelodysplastic syndrome (MDS), chronic myelomonocytic leukaemia (CMML) or acute myeloid leukaemia (AML).	**NOT RECOMMENDED:** for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (SCT) with intermediate-2 and high-risk myelodysplastic syndrome (MDS), chronic myelomonocytic leukaemia (CMML) or acute myeloid leukaemia (AML). Azacitidine therapy produced a significant increase in overall survival compared with conventional care regimens in previously untreated higher-risk MDS patients. However, the manufacturer did not present a sufficiently robust economic analysis and their justification for the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC. **RESUBMISSION AUGUST 2011** **ACCEPTED:** is accepted for use within NHS Scotland. **Indication under review:** for treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (SCT) with intermediate-2 and high-risk myelodysplastic syndrome (MDS), chronic myelomonocytic leukaemia (CMML) or acute myeloid leukaemia (AML). Azacitidine therapy produced a significant increase in overall survival compared with conventional care regimens in previously untreated higher-risk MDS patients.
55.	**everolimus 5 and 10 mg tablets (Afinitor)**	(No. 595/10)	Advanced renal cell carcinoma, whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy.	**NOT RECOMMENDED:** for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy. Everolimus, in conjunction with best supportive care (BSC), increased median progression-free survival (PFS) by three months compared with placebo plus BSC in heavily pre-treated patients with metastatic renal cell carcinoma. However, the manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC.

56.	**temsirolimus (Torisel®)** **NON-SUBMISSION**	(No. 617/10)	Treatment of adult patients with relapsed and/or refractory mantle cell lymphoma [MCL].	**NOT RECOMMENDED** for use within NHS Scotland. **Licensed indication under review:** the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma [MCL]. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHS Scotland.
57.	**mifamurtide (Mepact)**	(No. 621/10)	In combination with post-operative multi-agent chemotherapy for the treatment of high grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection, in children, adolescents and young adults.	**NOT RECOMMENDED:** in combination with post-operative multi-agent chemotherapy for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection, in children, adolescents and young adults. Safety and efficacy have been assessed in studies of patients 2 to 30 years of age at initial diagnosis. Mifamurtide has been shown to increase overall survival compared to multi-agent chemotherapy alone in patients under 30 years with newly-diagnosed resectable osteosarcoma. The manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC and in addition the manufacturer did not present a sufficiently robust economic analysis. **RESUBMISSION JULY 2010** **ACCEPTED:** is accepted for use within NHS Scotland. **Indication under review:** in combination with post-operative multi-agent chemotherapy for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection, in children, adolescents and young adults. Safety and efficacy have been assessed in studies of patients 2 to 30 years of age at initial diagnosis. Mifamurtide has been shown to increase overall survival compared to multi-agent chemotherapy alone in patients under 30 years with newly-diagnosed resectable osteosarcoma.

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58.	**eltrombopag (Revolade)**	(No. 625/10)	Adult chronic immune (idiopathic) thrombocytopenic purpura	**RESTRICTED:** for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Eltrombopag may be considered as second-line treatment for adult non-splenectomised patients where surgery is contraindicated. Eltrombopag (Revolade) is restricted for use in both the splenectomised and non-splenectomised patient populations, restricted to use in patients with severe symptomatic ITP or a high risk of bleeding. Eltrombopag has been shown to be significantly more effective than placebo in raising and maintaining platelet counts at (or above) a minimum target level in previously treated patients with ITP.
59.	**ofatumumab (Arzerra)**	(No. 626/10)	Chronic lymphocytic leukaemia (CLL)	**NOT RECOMMENDED:** for the treatment of chronic lymphocytic leukaemia (CLL) in patients who are refractory to fludarabine and alemtuzumab. Interim analysis of a non-randomised, single-arm small study in a subgroup of patients refractory to fludarabine and alemtuzumab found that ofatumumab produced a response rate of 58%. The manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC and in addition the manufacturer did not present a sufficiently robust economic analysis.
60.	**miglustat (Zavesca ®)** **NON-SUBMISSION**	(No. 632/10)	Treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease.	**NOT RECOMMENDED** for use within NHSScotland for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland.

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61.	**trabectedin (Yondelis)**	(No. 634/10)	Relapsed platinum-sensitive ovarian cancer	**NOT RECOMMENDED**: in combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer. In an open-label randomised controlled study trabectedin in combination with PLD was significantly superior to PLD monotherapy in terms of progression free survival. There was a significant difference in an exploratory interim analysis of overall survival in the sub-group of patients with partially platinum-sensitive disease. The manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC and in addition, the manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC.
62.	**canakinumab (Ilaris ®)150 mg/ml, powder for solution for injection** **NON-SUBMISSION**	(No. 658/10)	Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents and children aged 4 years and older with body weight above 15 kg.	**NOT RECOMMENDED** for use within NHSScotland. **Indication under review:** Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents and children aged 4 years and older with body weight above 15 kg. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result SMC cannot recommend its use within NHSScotland.
63.	**amifampridine (Firdapse®)** **NON-SUBMISSION**	(No. 660/10)	For the treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) in adults.	**NOT RECOMMENDED** for use within NHSScotland **Indication under review**: for the treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) in adults. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result SMC cannot recommend its use within NHSScotland.

64.	**histamine dihydrochloride (Ceplene)**	(No. 666/10)	Acute myeloid leukaemia	**NOT RECOMMENDED** for use within NHS Scotland. **Indication under review:** maintenance therapy for adult patients with acute myeloid leukaemia in first remission concomitantly treated with interleukin-2. The efficacy of histamine dihydrochloride has not been fully demonstrated in patients older than age 60 years. In a randomised open-label study, histamine plus interleukin-2 was superior to no treatment for the endpoint of leukaemia free survival (LFS) in a sub-group of patients in first complete remission. In *post hoc* analysis of patients in first complete remission and aged less than 60 years, LFS rates at 36 months were 50% versus 30%. Overall the manufacturer did not present a sufficiently robust clinical or economic case to gain acceptance by SMC.
65.	**velaglucerase (Vpriv®)** **NON-SUBMISSION**	(No. 681/11)	Long-term enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease	**NOT RECOMMENDED** for use within NHS Scotland. **Indication under review:** for long-term enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHSScotland.
66.	**nilotinib (Tasigna)**	(No. 709/11)	Treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia in the chronic phase	**ACCEPTED:** for use within NHS Scotland. **Indication under review:** for the treatment of adult patients with Philadelphia chromosome positive chronic myelogenous leukaemia in the chronic phase. First-line treatment with nilotinib in newly diagnosed patients has resulted in significantly higher molecular and cytogenetic response rates compared to the standard tyrosine kinase inhibitor. Further longer term follow-up data are needed to confirm the duration of this response and assess the impact on disease progression and overall survival.

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Note:

- **Liposomal cytabarine Depocyte (No: 164/05) –** has Orphan status in the United States of America but not in the UK**.**
- **Bexarotene Targretin in cutaneous T-cell lymphoma (No: 14/02) -** has Orphan status in the United States of America but not in the UK**.**

- **OUT OF REMIT: galsulfase** long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis VI (MPS VI).

Summary stats:

	Full submissions	Abbreviated	Non-submissions	All subs
Accepted	**10 (20%)**	**3**	**-**	**13 (20%)**
Restricted	**21 (41%)**	**-**	**-**	**21 (32%)**
Not recommended	**20 (39%)**	**-**	**12**	**32 (48%)**
TOTAL	**51**	**3**	**12**	**66**