Case study 2

Diacomit and severe myoclonic epilepsy in infancy*

Summary

Need

- SMEI affects 0.4 in every 10,000 people. We didn't find an estimate of the number of children with this rare form of epilepsy across the UK, but the estimated patient numbers are: 75 in Scotland, and between 10 and 25 in Wales.
- SMEI causes a number of distressing symptoms in children and increases the chance of mortality.
- Diacomit can help fill a gap for those children whose seizures are not adequately controlled by other treatments and help to reduce the number of seizures.

R&D

- The compound stiripentol (the active ingredient in Diacomit) has been under investigation since the 1970s and first identified by Biocodex in 1978, but it took almost 30 years for approval for a commercial product.
- Despite considerable research, the precise way Diacomit works remains unknown.

Regulatory approval

- Diacomit was approved by the EMA in 2007 based on limited evidence including a trial with 65 patients. Formal safety analysis was not possible. FDA did not grant approval highlighting the scope for different views based on what is likely to be the same or very similar evidence.
- Diacomit was granted conditional approval, with the manufacturer required to conduct further research. This illustrates that there is scope to build up the evidence base, but this will come at a cost and is borne by the manufacturer. It will also take some time with EMA still not lifting the conditional approval in 2012.

Payer approval

- Diacomit costs around £7,600 per patient per year in the UK. We haven't found any estimates of the cost per QALY arising from treatment. Use of Diacomet could offer some savings for the health system, in addition to the benefits for patients and their carers, but this is uncertain.
- Estimates of the budget impact (if Diacomet was recommended for use) is in the order of £52,000 to £130,000 by the fifth year of use in Scotland. We didn't find comparable figures for the rest of the UK.
- There are differences in the speed and approach taken by each country in the UK to appraise the use of Diacomet. SMC and AWMSG produced guidance shortly after approval, within a year. NICE has taken longer, with a clinical guideline in 2012.
- The views of agencies differ: NICE recommends use of stiripentol as a second line option, SMC and AWMSG do not recommend use. However, clinical guidelines differ from technology appraisals, and do not require manufacturer submissions on the economics of their drug. Both SMC and AWMSG didn't recommend its use because of a lack of cost effectiveness evidence.
- AWMSG cites a number of uncertainties including the clinical evidence base, such as the long-effectiveness of treatment. They also note no evidence on the cost effectiveness of Diacomit.

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- In other countries, Diacomet can be funded on a special case basis, for example, via a special access programme in Canada designed for products that are not marketed in Canada and for treatments of diseases that are severe.

Prescription

- Clinicial guidelines from NICE highlight the importance of an expert view in managing SMEI including considering of referral to tertiary care.

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Introduction

Diacomit (stiripentol) marketed by Laboratoires Biocodex, is an anti-epileptic, or anticonvulsant, medicine (EMA, 2012a). It has been shown in clinical trials to be useful as an add-on to clobazam and valproate (and other anti-epileptic medicines) for children with a very rare type of epilepsy called 'severe myoclonic epilepsy in infancy' (SMEI) (EMA, 2012a). SMEI is also known as Dravet's syndrome. Together treatments can help reduce the number of seizures.

Diacomit was awarded orphan drug status for its use in SMEI in 2001, reflecting the small number of patients with SMEI (EMA, 2012a). Marketing approval followed in 2007, with Diacomit being authorised by EMA "for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI or Dravet's syndrome) whose seizures are not adequately controlled with clobazam and valproate" (EMA, 2007a). Diacomet is perceived as fulfilling a treatment gap when previous treatments have been unsuccessful (SMC, 2008e).

Diacomit and severe myoclonic epilepsy in infancy

Need

SMEI is classified as a rare disease with a prevalence rate of 0.4 per 10,000 people (COMP and EMASS, 2011). What this means in practice is that out of 500 children with epilepsy, only one, or at most two, children are likely to have this form of epilepsy (Epilepsy Action, 2012). Based on our searches, we did not find an estimate of the number of children with SMEI across the UK. Within the UK, there are estimated to be around 75 children with SMEI in Wales (AWMSG, 2008c), and between 10 to 25 patients in Scotland (SMC, 2008e). This form of epilepsy is considered very resistant to most forms of currently available treatment (as at 2007) and hence there is an 'urgent unmet clinical need' (Protin, 2007).

SMEI includes a number of symptoms. It can appear during the first year of life with "frequent febrile seizures" – which are fever-related seizures that are rare beyond the age of 5 (National Institute of Neurological Disorders and Stroke, 2011). Early seizures in the first year of life may include clonic, or jerking, movements. After the first year, a range of seizures that can appear include:

- myoclonic jerks, single or multiple muscle jerks, which may involve one part of the body or the whole body;
- atypical absences with brief loss of awareness;
- partial seizures, which may involve loss of awareness;
- non-convulsive status where the child develops a groggy, poorly functional state (Contact a Family, 2012).

From the second year, a developmental slowing or regression occurs, which can be severe. Autism and attention deficit hyperactivity disorder are common at this stage (Contact a Family, 2012). A child's speech and language, in addition to other skills development, may slow right down and seizures may no longer occur when a child has a high temperature but at any time of day and night (Epilepsy Action, 2012).

Throughout childhood, seizures usually continue to be very difficult to control. As it progresses many children become ataxic and unsteady on their own feet. By 12-14 years, seizures tend to become less frequent (Eplilepsy Action, 2012).

The mortality rate for those with SMEI is between 15.9 to 20% by age 20 (ICE Epilepsy Alliance, 2012; Dravetdata.com, 2012).

Epilepsy in children can cause significant worry and concern for their parents (Epilepsy Action, 2011).

Research and development

Diacomit is considered to be one of the most well studied regimens for children with SMEI (ICE Epilepsy Alliance, 2012). The compound stiripentol has been under investigation since the 1970s when it was derived from a series of ethylene alcohols (Trojnar et al, 2005) .

Stiripentol was first identified by Biocodex in 1978 with early clinical development starting in the 1980s. It was used in various clinical trials and in preliminary studies that included all forms of epileptic syndromes – these suggested that stiripentol was best utilised in combination with other anti-epileptic agents (EMA, undated f).

Regulatory approval

The EMA granted Diacomit a conditional marketing authorisation in 2007 (EMA, undated g). The conditional approval included the requirement for the manufacturer to complete a randomised controlled clinical trial with stiripentol as add-on therapy using maximally safe doses of clobazam and valproate by 2009 and a bioavailability study in 24 subjects to determine the relative bioavailability of the stiripentol sachet versus stiripentol capsule by 2007 (AWMSG, 2008a). As of the last update in January 2012, this conditional approval has not been removed (EMA, undated e).

Diacomit and severe myoclonic epilepsy in infancy

The two main trials of Diacomit were used to support marketing approval by EMA and included 65 children between three and 18 years of age. The trials sought to compare the effectiveness of Diacomit (in both capsule or sachet form) with a placebo when added to a child's existing treatment with clobazam and valproate. A patient was classified as a 'responder' (the measure of effectiveness used) if the number of seizures in the second month of treatment was at least 50% lower than the number in the month before treatment was started (EMA, undated f).

In the first trial, 71% of the patients taking Diacomit responded to treatment compared with 5% of the placebo group. Similar results were seen in the second trial. 67% responding to Diacomit and 9% to placebo. However, it is not clear whether this effect is due to Diacomit itself or to increased levels of the other anti-epileptic medicines (EMA, undated f).
It was not possible to perform a formal safety analysis according to demographic factors because of the underlying patient characteristics in trials: children and adolescents of different age groups and different types of epilepsy (Protin, 2007).
Despite previous research the specific way in which stiripentol acts as an anti epileptic medicine has not yet been fully demonstrated (Glenn, 2008).

No dose studies were conducted (Protin, 2007).

Biocodex filed a patent request to the FDA in the US in 2008 but did not get approval (it can be legally prescribed on a 'compassionate-use basis', but it must be imported from a foreign country where it is available for sale) (Miami Children's Brain Institute, 2011). It is also not approved in many jurisdictions (as at 2008) (Glenn, 2008).

Payer approval

The net price for 250 mg of stiripentol capsules, is £248.00. For 500 mg, 60-cap pack it is £493.00. For the powder, stiripentol 250 mg, the net price for a 60-sachet pack is £284.00 and for 500 mg, a 60-sachetpack costs £493.00 (NICE, 2010h). The cost per patient over a year is thought to be in the region of £7,600 (AWMSG, 2008c).

Stiripentol has been subject to consideration by all the three key UK agencies: NICE, SMC and AWMSG. In short the findings are:

- NICE (in a clinical guideline) suggests use of Diacomit as second line option.
- SMC does not recommend Diacomit.
- AWMSG does not recommend Diacomit.

We look at these in more detail below.

NICE

NICE has considered stiripenol in the context of a clinical guideline published in 2012 (CG137). NICE recommends that there is a discussion or referral to a tertiary paediatric epilepsy specialist if Dravet syndrome is suspected. Sodium valproate or topiramate are possible first line treatments, but NICE suggests that clinicians consider clobazam or stiripentol as adjunctive treatment. This places stiripentol as a second line treatment (NICE, 2012e). This is an update on an earlier clinical guideline from 2004 (CG20), which touched on the role of stiripentol in the context of an adjuvant treatment (but this was not a main drug considered in the guideline and was before Diacomet was formally approved) (NICE, 2004b). We did not find a technology appraisal specifically focusing on the use of stiripenol.

SMC

The Scottish Medicines Consortium (SMC) published guidance on Diacomet in 2008 (2008d). This was relatively swift compared to the EMA approval of Diacomet in 2007.

SMC (2008d) do not recommend use of Diacomet. SMC's decision reflected the lack of economic evaluation submission by the manufacturer. This illustrates how important an economic evaluation can be for access, as the absence of such analysis can lead to recommendation

to use it, even with clinical evidence of the benefits of treatment. SMC's guidance (2008d) does recognise the role of Diacomet as a treatment, particularly in light of the view of clinicians that Diacomet meets a need when there are a lack of effective treatments in Dravet syndrome. Their guidance also acknowledges that the manufacturer did provide some relevant economic analysis, but "instead of capturing all relevant costs and outcomes and bringing them together in the form of a ratio (e.g. cost per QALY or cost per seizure free day etc) a cost outcome study [which had been supplied] simply describes the relevant costs and outcomes for the treatment and its comparator" (SMC, 2008d).

The budget impact of Diacomet was estimated at £52,000 for the first year of use, rising to £130,000 by the fifth year of use (SMC, 2008d).

AWMSG

AWMSG (2008c) published their recommendation on Diacomit in 2008. They did not recommend Diacomet, primarily because of a lack of economic evidence submitted by the manufacturer.

Their guidance also highlights a number of uncertainties including (AWMSG, 2008c):

- Limited data in children under 3 and a lack of evidence to support the claim that stiripentol may reduce cognitive and psychomotor impairment experienced by patients with SMEI.
- Trial participants not representing the split between males to females.
- Limited evidence on long-term seizure control for clonic or tonic-clonic seizures. They also noted limited evidence on the control of other types of seizures.
- Uncertainties about whether increasing the existing treatment doses could have brought about the same reduction in seizures seen with the addition of Diacomit.
- No evidence of whether or not stiripentol is cost effective.

AWMSG guidance notes that whilst there was an absence of the cost effectiveness evidence, that a budget impact analysis from the manufacturer suggested that the cost of Diacomit could be more than offset from 2 seizures averted. However, this was uncertain given limited data (e.g. on the number of seizures which result in hospitalisation as not all seizures will result in hospitalisation and hence it is uncertain if the avoided seizures would be cost saving from the NHS perspective). The true budget impact was difficult to predict given uncertainties in the underlying incidence and number of children who could potentially be prescribed Diacomit (as it would be somewhat smaller numbers, between 19 to 38 of the possible 75 children with Dravet syndrome in Wales).

Given the lack of regulatory approval for Diacomit, there are particular challenges in also obtaining funding. A special fund has been set up by the International Dravet Syndrome Epilepsy Action League to help fund Diacomet for those outside of the EU (Glenn, 2008).

In Canada, parents can apply for funding of Diacomit through the Special Access Programme (Dravet.ca, 2012). The Special Access Programme (SAP) provides a route for access. It is designed for non-marketed products, and for treatment of patients who have serious or life-threatening conditions when conventional therapies have failed, are unsuitable, or unavailable. The programme allows a manufacturer to sell a drug that cannot otherwise be sold or distributed in Canada (Health Canada, 2008).

Prescription

Guidance highlights that prescription should be supported by a relevant clinical expert (NICE, 2011a). This highlights the importance of clinical expertise in both the rare disease and how orphan drugs are used in practice.

Clinicians need to carefully consider the prescription of all anti-epileptic drugs. Diacomit is used in

combination, as an add-on to clobazam and valproate and must be recommended only on a patient-by-patient basis. A normal dose is 50 mg per kilogram body weight, divided into two or three doses during the day (EMA, 2012a). The specific prescription and choice of delivery needs to consider diet. Diacomit can be taken in capsule form, which is compatible with a ketogenic diet, or in a powder form, found in a sachet, that is not compatible with a ketogenic diet (Miami Children's Brain Institute, 2011).

Based on our searches, we have not been able to find a breakdown of sales for Diacomit.