ACTELION v ENCYSIVE

Pilot study with Thelin

Actelion Pharmaceuticals UK complained about a pilot clinical and cost effectiveness scheme run by Encysive (UK) whereby patients with pulmonary arterial hypertension (PAH) classified as WHO functional class III, and who were naïve to endothelin receptor antagonist (ETRA) therapy, could be treated with Thelin (sitaxentan).

The scheme was offered for up to 20 patients at each prescribing centre and would run for 6 months from the date of first prescription at that centre. The conditions of the scheme meant that the NHS would pay the treatment cost of only those patients deemed by the treating physician and patient to have responded to Thelin within the stipulated time frame of 24 weeks. If the patient discontinued due to a lack of efficacy or an adverse event, the cost of treatment up to that point would be refunded as a credit note to be used, within 12 months from the date of issue, against further purchases of Thelin.

Actelion alleged that the scheme represented an inducement to prescribe. The company was concerned that the central premise of prescribing, a combined assessment by the clinician based on the features of the patient, his or her needs and the safety and efficacy of the medicine, were undermined by the scheme. The credit note refund against future purchase of Thelin suggested that the only way the NHS could recoup the cost of failed treatment was to prescribe more Thelin; the scheme was thus self-perpetuating. Whilst there was no direct financial inducement for the prescriber, in the current financial climate of the NHS, cost savings were important for all prescribers, and therefore this scheme potentially constituted an indirect inducement to prescribe Thelin. Further, Actelion believed that a prescriber, with a credit note due to expire, would inevitably be pressured to use it and so prescribe Thelin, possibly inappropriately.

Actelion noted that the scheme was only for 20 patients or 6 months at each centre, whichever came first. As this was not a permanent way to guarantee outcomes for the NHS, the scheme could be seen as a way to establish pockets of Thelin patients across the country with limited savings to the NHS or risk to the company. The scheme was presented as a clinical and cost-effectiveness evaluation but there was limited clinical evaluation, which had no recognised standard criteria and was down to individual judgement. Additionally, there was no formal cost-effectiveness evaluation. Actelion alleged that the scheme was misleading in its presentation to potential NHS participants and its content.

Actelion accepted that these types of risk share or outcome guarantee schemes were not necessarily against the Code, each should be judged on its own merits and must demonstrate that there was no inducement to prescribe. Actelion did not suggest that there was any direct financial or other inducement to prescribe to the individual clinician. However, the refund and the length of time it was valid for might lead to an indirect inducement to individual clinicians to prescribe Thelin. The limited nature of this scheme (20 patients or 6 months) and the potentially misleading description further supported the notion that this scheme might be more about gaining prescriptions than saving the NHS money or performing a formal and robust clinical and cost-effectiveness evaluation of sitaxentan.

The detailed submissions from Encysive are given below.

Under the scheme at issue, a centre could initiate Thelin treatment in up to 20 patients (provided they had never previously been treated with either Thelin or Tracleer) over a 6 month period. Once therapy had started then the clinical endpoints (lack of efficacy and/or adverse events) used to determine discontinuation of treatment were entirely up to the discretion of the physician. The physician and patient determined the clinical endpoints. If clinical assessment led to the discontinuation of Thelin at any time within a 24 week evaluation period a credit note, covering the cost of Thelin used to date, would be issued. The credit note was valid for one year and could be used to offset the cost of Thelin for other patients prescribed the medicine.

The Panel considered that, as a matter of principle, it was not necessarily unacceptable to offer some sort of outcomes guarantee with a product; the acceptability of any scheme would depend on the individual arrangements.

The Panel noted that measures or trade practices relating to prices, margins and discounts which were in regular use by a significant proportion of the industry on 1 January 1993 were outside the scope of the Code. The Panel did not accept Encysive's submission that the pilot was exempt from the Code. Outcome guarantee schemes, were not in wide use by the industry on 1 January 1993. Further, the scheme in question related to more than financial arrangements.

The Panel did not agree with Encysive's submission that the pilot was neither conditional upon nor related to any commitment to purchase,

prescribe, administer or recommend any Encysive product. It was not a straightforward refund for failed therapy. The cost of failed therapy could only be recouped if more Thelin was prescribed. The Panel noted the submission that Encysive only provided information about its proposed refund to those at the commissioning level; the company did not tell the prescribers about the rebate. In this regard the Panel queried how the scheme could work given that the prescriber would be responsible for discontinuing therapy and thus starting the process to claim a rebate. Nonetheless, the Panel considered that policy makers, in receipt of credit notes against the future prescription of Thelin, would, at the very least, want to use them and thus recommend more Thelin to be prescribed. In that regard the Panel noted that Clause 18.1 stated that no gift, benefit in kind or pecuniary advantage shall be offered or given, *inter alia*, to administrative staff as an inducement to recommend any medicines, subject to the provisions of Clause 18.2.

The Panel considered that the terms of the pilot scheme were unacceptable. A breach of the Code was ruled which Encysive appealed.

During its consideration of this case the Panel was concerned the scheme was entitled 'A six month pilot clinical and effectiveness evaluation agreement for the treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO function functional class III who are naive to ETRA therapy'. In the Panel's view the scheme did not involve any meaningful clinical or cost effectiveness evaluation of Thelin given that it was clearly stated that the clinical endpoints used to determine success, or otherwise, of therapy were entirely up to the treating physician. It was, in effect, up to each prescriber to make their own mind up as to the clinical value of Thelin.

The Panel considered that the pilot would have the effect of promoting the prescription of Thelin. If treatment failed then the cost of that treatment could be offset only against future prescriptions of Thelin. In the Panel's view the pilot was unacceptable; it was not a *bona fide* evaluation as described and the arrangements were such that administrators would receive financial inducements that would lead them to recommend the further use of Thelin. The Panel decided in this regard to report Encysive to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Panel also required Encysive to suspend the pilot pending the final outcome of the case in accordance with Paragraph 7.1 of the Constitution and Procedure.

Upon appeal by Encysive, the Appeal Board was extremely concerned about the scheme. In particular it considered that the title 'A six month pilot clinical and cost effectiveness evaluation agreement …' suggested a degree of clinical rigour that appeared to be missing. In that regard the Appeal Board noted that there was no protocol, steering group, predetermined clinical endpoints etc associated with the scheme. In the Appeal Board's view the scheme was simply a financial arrangement between Encysive and the treatment centres. The Appeal Board considered that as a risk sharing scheme, the scheme at issue was not a model of good practice.

The Appeal Board noted that the complainant had alleged a breach of the Clause 18.1 of the Code. Clause 18.1 stated 'No gift, benefit in kind or pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine …'. In that regard the Appeal Board noted that a credit note would be issued to cover the cost of the failed Thelin treatment. The credit note was valid for one year and could be used to offset the cost of Thelin treatment either in naïve patients or in those already on therapy. The credit note could be transferred to a centre other than the one to which it was issued. The Appeal Board noted that the credit note was issued to a treatment centre and so in that regard it was not a gift, benefit in kind or pecuniary advantage to any individual. On the narrow grounds of the complaint the Appeal Board ruled no breach of the Code. The appeal was thus successful.

Given the circumstances the Appeal Board decided to take no further action in relation to the Panel's report to it, made in accordance with Paragraph 8.2 of the Constitution and Procedure.

Actelion Pharmaceuticals UK Ltd complained about a pilot clinical and cost effectiveness scheme run by Encysive (UK) Limited for Thelin (sitaxentan). Inter-company dialogue had failed to resolve the matter. Actelion marketed Tracleer (bosentan).

COMPLAINT

Actelion stated that the scheme was reported to be a six-month pilot clinical and cost effectiveness evaluation agreement for the treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class III who were naïve to endothelin receptor antagonist (ETRA) therapy. This pilot scheme was offered for up to 20 patients at each prescribing centre and would run for 6 months from the date of first prescription at that centre. The purpose of the scheme was suggested to be that the NHS would bear the cost of only those patients deemed by the treating physician and patient to have responded to Thelin within the stipulated time frame. If the patient discontinued due to a lack of efficacy or an adverse event, the cost of treatment up to that point would be refunded to the NHS in the form of a credit note to be used against further purchases of Thelin. This credit note would be valid for 12 months from the date of issue.

Actelion alleged that the scheme represented an inducement to prescribe in breach of Clause 18.1 of the Code.

Actelion's concerns were:

- The central premise of prescribing was that of a combined assessment by the clinician based on the features of the patient, his or her needs and the characteristics of the medicine (safety and efficacy date). Actelion considered that this scheme undermined this underlying best practice.
- The refund to the NHS in the form of a credit note against future purchases of Thelin suggested that the only way the NHS could recoup the cost of Thelin treatment failure was to prescribe more Thelin; the scheme was thus self-perpetuating. Whilst Actelion accepted that there was no direct financial inducement for the prescriber, in the current financial climate of the NHS, cost savings were important for all prescribers, and therefore this scheme potentially constituted an indirect inducement to prescribe Thelin.
- The credit note was valid only for 12 months from the date of issue. Should the prescriber not see a suitable patient for a number of months and have a credit note shortly due to expire, Actelion believed that there would inevitably be pressure to use this credit note and so prescribe Thelin. This would not only be an indirect inducement for this prescriber, but might lead to inappropriate prescribing.
- The scheme was only for 20 patients or 6 months at each centre, whichever came first. As this was not a permanent way to guarantee outcomes for the NHS, the scheme could reasonably be interpreted as an opportunity to establish pockets of Thelin patients across the country with limited savings to the NHS or risk to the company.
- The scheme was presented as a clinical and cost-effectiveness evaluation but there was limited clinical evaluation, which had no recognised standard criteria and was down to individual judgement. Additionally, there was no formal cost-effectiveness evaluation. Actelion alleged that the scheme was misleading in its presentation to potential NHS participants and its content.

Actelion accepted that these types of risk share or outcome guarantee schemes were not necessarily against the Code, each should be judged on its own merits and must demonstrate that there was no inducement to prescribe. Actelion did not suggest that there was any direct financial or other inducement to prescribe to the individual clinician. However, the refund and the length of time it was valid for might lead to an indirect inducement to individual clinicians to prescribe Thelin. The limited nature of this scheme (20 patients or 6 months) and the potentially misleading description further supported the notion that this scheme might be more about gaining prescriptions than saving the NHS money or performing a formal and robust clinical and cost-effectiveness evaluation of sitaxentan.

RESPONSE

1 Risk sharing schemes

Encysive submitted that risk sharing and outcome guarantee schemes were recognised by government and industry as a new way of working with the NHS to deliver better health outcomes for patients and improve the uptake of new medicines. They were therefore increasingly common in the UK. Examples were given.

2 Rationale for the pilot

Encysive devised the pilot scheme to comply with the Code and for consistency with both existing cases under the Code and outcome guarantee arrangements and for acceptability to the NHS.

In developing the pilot, the company consulted the national commissioning manager responsible for PAH within the national commissioning group (the national specialised commissioning group), which welcomed the proposals. The company also sought legal advice on the arrangements during their development and got informal advice on the acceptability of the scheme from both the Authority and the Medicines and Healthcare products Regulatory Agency (MHRA). Encysive submitted that the pilot complied fully with all applicable rules and was also acceptable to the NHS, prescribers and, ultimately, of benefit to patients.

Encysive considered that the pilot was purely financial in nature and, therefore, benefited from the trade practice exemption under the Code. Clause 18.1 of the Code excluded from its scope measures or trade practices relating to prices, margins and discounts which were in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993. The Panel had previously considered the acceptability under the Code of a pilot study to assess the feasibility of an outcome guarantee for a statin therapy (Case AUTH/1109/11/00). The Panel noted that similar schemes that reimbursed health authorities might be implemented in the future and considered that, as a matter of principle, it was not necessarily unacceptable to offer some sort of outcome guarantee for a product. The Panel considered Clause 18.1 and determined that the pilot study was not in breach of this clause. It also suggested that the outcome guarantee scheme might benefit from the trade practice exemption and therefore fall outside the scope of the Code and the UK's medicine advertising rules. The scheme was reconsidered in 2006 (Cases AUTH/1807/3/06 and AUTH/1810/3/06) and the Panel accepted that it was not conditional upon or related to any commitment by the PCT to purchase, prescribe, administer or recommend any of the sponsoring company's products. The Panel again ruled no breach of Clause 18.1 of the Code.

On the basis of these decisions and the apparent

lack of challenges to subsequent schemes, Encysive considered that risk sharing or outcome guarantee schemes were similar to a discounting measure and should benefit from the trade practice exemption under the Code. However, the company also recognised that, unlike traditional discounting, risk sharing schemes and other joint working initiatives should be fair, transparent, based on sound and accepted clinical practice, provide additional non-financial benefits for the NHS, and benefit patients. Each of these elements was considered below.

2.1 Fairness

A key element to any outcome guarantee was that it must be meaningful, non-discriminatory and fair.

The pilot was available to all NHS institutions that treated PAH, so it was neither selective nor discriminatory. It was neither conditional upon, nor related to, any commitment to purchase, prescribe, administer or recommend any Encysive product nor was it a reward for past prescribing practices. Liaison between Encysive and payers was at the commissioning, rather than the prescribing level. Encysive's commissioning manager, rather than sales representatives, liaised directly with payers and the company's medical director addressed clinical queries.

Upon entering the pilot, the NHS took on the risk of investing scarce resources in Thelin. By underwriting the cost of failed treatment up to 24 weeks, Encysive helped the NHS apply its resources effectively.

Eligibility was assessed in accordance with Thelin's summary of product characteristics (SPC) and the decision to initiate Thelin treatment rested with the treating physician alone. The NHS bore the cost of only those patients the treating physician deemed to have responded to Thelin within 24 weeks, a period that was consistent with the response period identified in the SPC and that allowed a meaningful assessment of a patient's response.

There was also a fair and meaningful allocation of risk between the parties. The clinical endpoints used in the pilot as a basis for deciding whether to continue or discontinue Thelin were entirely at the discretion of the prescribing physician and the patient, an approach that was entirely appropriate bearing in mind the complexity of PAH and its management. Since the physician alone determined whether the response to Thelin was adequate, Encysive had no involvement in either the enrolment or outcomes decision making process. There could therefore be no argument that the allocation of risk was not meaningful or unfair.

This was a fair arrangement and, in Encysive's view, an example of a successful partnership between the NHS and the pharmaceutical industry.

2.2 Openness and transparency

Patient inclusion criteria and reimbursement under the pilot were transparent, approved by the NHS entities in question and set out in a commercial agreement (copy provided). All parties had a clear understanding of the pilot and its terms.

Encysive fully complied with the Data Protection Act 1998 and at no time before, during or after the pilot did it know or seek information likely to undermine, patient confidentiality.

2.3 Sound and accepted clinical practice

The pilot was based on sound and accepted clinical practice, a fact Encysive confirmed during consultation with key thought leaders for the treatment of PAH in the UK, including leading participants in the development of the Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland.

The recruitment of patients and treatment of PAH under the pilot were consistent with the Thelin SPC. Following inclusion, eligible patients were treated in accordance with existing local, national and international treatment guidelines on PAH and current clinical practice, including the British Cardiac Society guidelines: recommendations on the management of pulmonary hypertension in clinical practice (2001), the European Society of Cardiology guidelines on diagnosis and treatment of pulmonary arterial hypertension (2004) and the National Service Framework for Coronary Heart Disease (NSF for CHD).

Encysive therefore rejected Actelion's allegation that the pilot scheme undermined best practice.

2.4 Additional non-financial benefits

The pilot was intended to help PAH treatment centres comply with DoH guidance on pulmonary hypertension. The NSF for CHD (as amended by the specialised services definition) recommended medical therapy for treating pulmonary hypertension and many PCTs considered the treatment of PAH was an unmet need.

Encysive noted that the National Institute for Health and Clinical Excellence (NICE) was currently producing a multiple technology appraisal on medicines for PAH in adults, including Thelin. This was not expected to be published until April 2008. In the interim, therefore, the pilot would assist the NHS with the equitable distribution of finite funding for patients with PAH within the remit and framework of the NHS specialist commissioning services. The pilot should also improve patient access to medicines for PAH, while in no way being directive about any particular medicine.

2.5 Acceptable from the patient perspective

Patients would be treated according to treatment guidelines agreed with the prescriber. If anything, patients would receive better access to treatment for PAH under the pilot than would otherwise be funded by the NHS.

3 The rebate

Encysive noted that Actelion questioned the acceptability of a credit note as a form of rebate under the pilot. The pilot envisaged that a letter would be sent to the relevant payer if, under the terms of the pilot, the payer wanted to take advantage of the rebate. The letter offered the payer replacement stock within a 12 month period to be used at their discretion. Encysive provided information regarding the availability of the rebate only to the relevant payers; Encysive never communicated with prescribers on rebate issues.

Encysive considered this type of rebate was acceptable under the Code and similar to volume discounts or bonus stock offers, which were common in the industry and fell outside the scope of the Code as measures of trade practices related to prices, margins or discounts in regular use by a significant proportion of the pharmaceutical industry on 1 January 1993. Further, credit notes were generally accepted by the NHS as a method of rebate under risk-share schemes and they should not impose a disproportionate organisational burden on the NHS.

Encysive therefore refuted the suggestion that a credit note valid for 12 months was an inducement to prescribe. The pilot was not conditional upon or related to any commitment by the NHS or individual PAH centres or physicians to purchase, prescribe, administer or recommend any Encysive product nor to gain an interview. Eligibility for the pilot was assessed in accordance with the Thelin SPC. Patients only entered the pilot following the decision to prescribe and no health professional benefited either directly or indirectly under the pilot, so the credit note could not be considered a personal benefit. The credit notes were redeemable by the relevant NHS entity and the pilot was open to all NHS PAH prescribing centres.

The 12 month redemption limit was fair, reasonable and acceptable to the NHS entities that took part in the pilot. First, it was very likely that the payer would be asked to fund the treatment of another patient within a 12 month period. There were currently approximately 1,500 patients on targeted treatment for PAH and the vast majority were on Thelin or Tracleer. Most were treated in one of ten centres.

Encysive noted that when the pilot was conceived there was, and continued to be, a trend towards the centralisation of the commissioning of specialist therapies, further increasing the prospects that prescribing centres would receive a request within the relevant period. With this in mind, the credit note was designed to be transferable from individual PCTs to new [and existing] commissioning bodies.

Finally, as the name suggested, the pilot was a pilot scheme. When designing the scheme the 12 month period was considered to be realistic and appropriate. If, during the pilot, feedback had suggested that a 12 month period was insufficient, this would have been taken into account.

To reiterate, Encysive considered that the use of credit notes as a rebate was acceptable to the industry, the NHS and consistent with the spirit of the Code and previous rulings.

4 Other points raised by Actelion

Encysive noted that Actelion complained that the pilot was not a permanent scheme. This was so but Encysive made clear to the relevant NHS entities from the outset that this programme was a pilot. The industry commonly piloted major initiatives like this before considering a wider roll-out to ensure acceptability with all the relevant parties and to reconcile any problems that might occur during the pilot stage.

Encysive noted that Actelion suggested that the pilot was misleading because it was described as a 'clinical and cost-effectiveness evaluation'. There were obviously elements of independent clinical evaluations by an appropriate expert as defined in the pilot documentation. The appropriateness of a rebate was determined on the basis of that expert's assessment of cost-effectiveness. The pilot was also described as 'A six month pilot scheme for a risk and benefits share agreement for the treatment of patients with Pulmonary Arterial Hypertension (PAH) classified as WHO functional class III who are naïve to ETRA therapy'. As described above, the patient inclusion and exclusion criteria were transparent, based on sound and accepted clinical practice and the ultimate decision on whether or not to prescribe Thelin rested with the physician. Encysive did not consider that the description of the pilot was misleading.

PANEL RULING

The Panel noted that there were currently only two medicines available for the treatment of PAH – Encysive's product Thelin and Actelion's product Tracleer. [This point was corrected by Encysive in its appeal]. A month's treatment with Thelin cost £1,540 and a month's treatment with Tracleer cost £1,541.

Under the conditions of the pilot scheme at issue, a centre treating patients with PAH could initiate Thelin treatment in up to 20 patients over a 6 month period. Such patients had to have never previously been treated with either Thelin or Tracleer. Once therapy had started then the clinical endpoints (lack

of efficacy and/or adverse events) used to determine discontinuation of treatment were entirely up to the discretion of the physician according to the agreement. The slide presentation stated that the physician and patient determined the clinical endpoints. Treatment could be withdrawn any time within a 24 week evaluation period. If clinical assessment led to the discontinuation of Thelin within that time a credit note, covering the cost of Thelin used to date, would be issued. The credit note was valid for one year and could be used to offset the cost of Thelin for other patients prescribed the medicine.

The Panel noted that it had only considered one other similar scheme before (Case AUTH/1109/11/00 and Cases AUTH/1807/3/06 and AUTH/1810/3/06) and so there was very little in the way of precedent to refer to. One of the previous cases had involved a pilot study whereby a statin was guaranteed to achieve certain results in terms of cholesterol lowering in the study population and, failing the achievement of those targets, a financial rebate would be calculated at the end of the study. If the statin performed to target no rebate would be paid. In the pilot study although the rebate would be calculated, no payments would be made. In the other case the Panel had ruled no breach of the Code as the health professionals were not obliged to prescribe the product. The rebate was paid to the PCT for the general purpose of improving primary care services and not conditional upon use of products.

In the previous cases the Panel considered that, as a matter of principle, it was not necessarily unacceptable to offer some sort of outcomes guarantee with a product; the acceptability of any scheme would depend on the individual arrangements.

The Panel noted that measures or trade practices relating to prices, margins and discounts which were in regular use by a significant proportion of the industry on 1 January 1993 were outside the scope of the Code (Clause 1.2 of the Code). The Panel did not accept the submission from Encysive that the pilot was exempt from the Code. Outcome guarantee schemes, were not in wide use by the industry on 1 January 1993. Further, the scheme in question related to more than financial arrangements.

The Panel did not agree with Encysive's submission that the pilot was neither conditional upon nor related to any commitment to purchase, prescribe, administer or recommend any Encysive product. It was not a straightforward refund for failed therapy. The cost of failed therapy could only be recouped if more Thelin was prescribed for use. The Panel noted the submission that Encysive only provided information about its proposed refund to those at the commissioning level; the company did not tell the prescribers about the rebate. In this regard the Panel queried how the scheme could work given that the prescriber would be responsible for discontinuing therapy and thus starting the process to claim a rebate. Nonetheless, the Panel considered that policy makers, in receipt of credit notes against the future prescription of Thelin, would, at the very least, want to use them and thus recommend more Thelin to be prescribed. In that regard the Panel noted that Clause 18.1 stated that no gift, benefit in kind or pecuniary advantage shall be offered or given, *inter alia*, to administrative staff as an inducement to recommend any medicines, subject to the provisions of Clause 18.2.

The Panel considered that the terms of the pilot scheme were unacceptable. A breach of Clause 18.1 was ruled. This was appealed by Encysive.

During its consideration of this case the Panel was concerned the scheme was entitled 'A six month pilot clinical and effectiveness evaluation agreement for the treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO function functional class III who are naive to ETRA therapy'. In the Panel's view the scheme did not involve any meaningful clinical or cost effectiveness evaluation of Thelin given that it was clearly stated that the clinical endpoints used to determine success, or otherwise, of therapy were entirely up to the treating physician. It was, in effect, up to each prescriber to make their own mind up as to the clinical value of Thelin.

The Panel considered that the pilot would have the effect of promoting the prescription of Thelin. If treatment failed then the cost of that treatment could be offset only against future prescriptions of Thelin. In the Panel's view the pilot was unacceptable; it was not a *bona fide* evaluation as described and the arrangements were such that administrators would receive financial inducements that would lead them to recommend the further use of Thelin. The Panel decided in this regard to report Encysive to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Panel also required Encysive to suspend the pilot pending the final outcome of the case in accordance with Paragraph 7.1 of the Constitution and Procedure.

APPEAL BY ENCYSIVE

Encysive submitted that the scheme complied fully with the Code and was consistent with public policy and other risk share schemes approved by the DoH and NICE. Encysive submitted that the Panel's ruling had failed to take account of all the relevant evidence and public policy surrounding the scheme. The Panel appeared not to fully appreciate that the scheme was discussed with key opinion leaders in the management of PAH and negotiated with individual PAH centres at the commissioning level in an open and transparent manner. Any decision to prescribe or discontinue Thelin was entirely at the prescribing physician's discretion, without any

involvement or contact with Encysive. When PAH centres decided to take part in the scheme, communication occurred between hospital pharmacies and Encysive's cold chain distributor and between Encysive and the Specialist Commissioning Groups (SCGs) that commissioned PAH services. Further, the Panel did not fully appreciate the policy and rationale behind joint working arrangements of this type. Credit notes could be applied to patients who were already on Thelin and not just new patients. All of the participating PAH centres had a number of patients who were on Thelin. It would not be necessary, therefore, for physicians to just initiate treatment on new/naïve patients. Moreover, the credit note was transferable between the SCG payers within the NHS.

Encysive submitted that the Panel's ruling was not a consistent interpretation of the Code and case precedents. The underlying principle of the scheme was that Encysive was held accountable for the effectiveness of Thelin and if NHS resource was shown to be wasted then the company provided recompense in the form of a rebate. The rebate was allocated to the NHS as an organisation pursuant to a commercial agreement. No individual benefited financially or otherwise from the scheme. This was a fact that the Panel had previously considered important (Case AUTH/1109/11/00). Credit notes were widely accepted by the authorities as alternatives, and even preferable, to cash rebates. Encysive was dismayed that the Panel suggested that customers could be induced by this form of rebate. The Panel's current determination should require it to investigate and act against the other high profile risk share schemes that use, or offer, credit notes and replacement stock under their guarantees.

Encysive submitted that the Panel failed in its duty to apply the rules of natural justice as its ruling had no evidential basis: in order to demonstrate a breach of Clause 18.1 of the Code, it was necessary to show that a gift or benefit in kind had been offered to individual prescribers or administrative staff. The credit notes were for the benefit of the relevant payer, a key consideration of the Panel in previous cases. The Panel must also show an intention to induce recommendations of its products. The purpose of the scheme was to help alleviate the budgetary constraints under which SCGs typically operated. It was difficult to see how the Panel could sustain its suggestion that Encysive intended to induce recommendations since such interference with the doctor-patient relationship by administrative staff would constitute serious breaches of professional standards and ethical principles by both the administrative staff and prescribers.

Encysive submitted that the Panel's ruling was factually incorrect as it suggested that there were only two treatments for PAH available. This was incorrect. To the extent the Panel relied on this information, the ruling was ill-advised.

Encysive submitted that the Panel's ruling would hinder access to innovative therapies. NHS organisations routinely delayed funding decisions about new medicines until NICE guidance was available. This meant that patients were often denied access to modern medicines for months or years. The Panel's ruling could hinder patient access to innovative medicines. The reason that some medicines were available on the NHS was that a risk share scheme was in place. The Panel's ruling could hinder access to treatments available under risk share schemes. Encysive considered that the Panel's decision would have adverse consequences for current and future joint working initiatives with the NHS, patient access to new medicines and risk sharing schemes in particular.

The following sections contained Encysive's grounds for appeal in more detail.

1 The Panel's ruling failed to take account of all the available evidence and public policy surrounding the scheme

1.1 Summary of the scheme

Encysive noted that the main principles of the scheme were set out in its response. However, the Panel had queried how the scheme actually worked given that the prescriber would be responsible for discontinuing therapy and thus starting the process to claim a rebate. This query suggested that the Panel ruled on the scheme without full knowledge or understanding of how it actually worked. Although Encysive was more than happy to elaborate on points that the Panel did not fully understand, it was not given an opportunity to do so prior to the ruling.

Encysive submitted that the scheme was a joint working agreement between Encysive and the NHS, in particular the SCGs involved in the funding and approval process for patients needing targeted PAH therapy. The National Specialist Commissioning Advisory Group (NSCAG) transferred to the NHS in April 2007 and was now known as the Specialist Commissioning Group. Under the working arrangements, Encysive and the relevant NHS entity agreed to share the risks and benefits associated with the administration of Thelin. These types of joint working arrangements were relatively new and had become known as risk share or outcome guarantee schemes.

Encysive submitted that its scheme involved the company guaranteeing the effectiveness of Thelin over a 24 week treatment period. If this did not occur, Encysive provided the NHS entity participating in the scheme with a credit note. The ultimate decision as to whether or not to prescribe Thelin rested with physicians who were free to prescribe whichever treatment for PAH they wished. The underlying principle was that Encysive was accountable for the effectiveness of Thelin over a 24 week period and, rather than waste the financial resource of the cost of the medicine, Encysive

agreed to recompense the NHS. This ensured that the allocation of this financial outlay was made available for future use. Disseminating new medicines under the terms of such a guarantee provided reassurance to both parties; the company was more likely to get its medicine to those who needed it most, and the NHS had a reassurance of return on investment. The details of the scheme, including the patient inclusion criteria and rebate, were previously provided.

Encysive submitted that to answer the Panel's specific query about the operation of the scheme, it pointed out that the response did not, as the Panel suggested, state that the prescribers would be ignorant of the existence of the scheme and the manner in which it operated. It simply made clear that liaison between the company and payers in respect of the scheme was an on-going process and occurred primarily at the SCG level.

Encysive submitted that it involved key opinion leader prescribers in the PAH field and SCG managers responsible for PAH when developing the scheme. The scheme was offered to all PAH centres and it was for them to decide whether or not to sign up. All participating centres had already included Thelin on their formulary list. If a PAH centre was interested in the scheme, Encysive's commissioning and policy manager, a non-marketing role within the company, talked to the SCGs about the possibility of offering the scheme to that PAH centre and also visited the centre to explain the scheme using the presentation previously provided. The decision whether to prescribe Thelin then rested with the prescriber. The physician or a nurse completed the relevant paperwork which was then faxed to the cold chain distributor.

Encysive submitted that the hospital pharmacist would also be told that a patient had been included in the scheme and would fax the relevant paperwork to Encysive's cold chain distributor which distributed one month's supply of product to the hospital for that patient and the pharmacist must re-order monthly. The hospital/PCT or SCG were invoiced directly.

Encysive submitted that if a physician withdrew a scheme patient from Thelin therapy, the hospital pharmacy informed the cold chain distributor which then informed the company. The company then sent a credit note to the relevant payer. This credit note could be applied against any patient on Thelin therapy, including patients already using the product but who were not in the scheme, and had been designed to accommodate the new NHS pooled budgets that were now emerging for the PAH funding processes and so was transferable between SCGs.

Encysive submitted that the Panel appeared to have misunderstood a number of important features of the scheme:

- The scheme was discussed and agreed at SCG level.
- The SPC for Thelin made it clear that therapy 'should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension'. Treatment was therefore initiated by a very small number of highly specialised physicians at each PAH centre participating in the scheme, who met eligible patients as per their normal practice and decided whether Thelin was an appropriate treatment to prescribe.
- Once the physician had decided to prescribe Thelin under the scheme liaison was between the centre's pharmacy/nurse and Encysive's cold chain distributor.
- When patients were withdrawn, the physician played no role in requesting or receipt of the credit note.

1.2 The title and operation of the scheme

Encysive noted that the Panel queried the appropriateness of the title of the scheme, which in its ruling was incorrect, the correct title was: 'A six month pilot clinical and effectiveness evaluation agreement for the treatment of patients with Pulmonary Arterial Hypertension (PAH) classified as WHO function functional class III who are naïve to ETRA therapy'. The Panel stated the scheme was not a *bone fide* evaluation of Thelin because the clinical end-points were at the discretion of the physician and the patient. Encysive disagreed.

Encysive noted that the title to the scheme was actually decided upon following a consultation with one of the SCG managers prior to rolling out the scheme. The SCG manager said that the term 'risk share' (the original title of the scheme) suggested that the scheme would be an administrative burden. As part of the joint working arrangements, Encysive considered that it was acceptable for the SCGs to have an input into the title of the scheme.

Encysive noted that the Panel's ruling also stated that it was up to each prescriber to make their own mind up about the clinical value of Thelin. The Panel thought that this would provide no meaningful evaluation'. Encysive disagreed, the Panel had placed too much emphasis on the title without first learning the full facts of the scheme. Encysive did not want to impose treatment endpoints for several reasons. PAH was an extremely complex condition that manifested itself in many different ways. The way in which patients responded therefore also differed and was a matter for interpretation by an expert and the patient themselves. Rather than define limited endpoints and response criteria, Encysive considered it appropriate to give physicians the discretion to assess clinical response. In some patients, success might be defined by no further, or a slower rate of, deterioration in their condition. In others, it might be defined as an increased capacity to exercise eg their ability to walk might improve.

Therefore, in Encysive's view, and the view of the SCG managers and key opinion leaders, the title

was neither misleading nor inappropriate. A scheme whereby the value of the product subject to the scheme was determined by prescribers and patients could provide meaningful data. Encysive would, nevertheless, be happy to amend the title of the scheme to, for example, Risk Share or Outcome Guarantee Scheme if that was considered more appropriate.

1.3 Public policy

Encysive submitted that the Panel did not take proper account of the public policy that surrounded joint working initiatives such as this. The NHS was rapidly changing and the DoH encouraged NHS organisations and staff to consider partnership opportunities with the pharmaceutical industry to meet the needs of patients and prescribers in a cost-effective manner. Indeed, the proposals under the draft Code 2008 stated that 'joint working with health authorities and trusts and the like is permitted if carried out in a manner compatible with the Code'.

Joint working was distinctly different from 'sponsorship' whereby pharmaceutical companies simply funded specific events or work programmes. In joint working, goals were agreed jointly by the NHS organisation and company, in the interest of patients, and shared throughout the project. A joint working agreement was drawn up and management arrangements conducted with participation from both parties in an open and transparent manner. For many organisations, this was a new way of working. The DoH's joint working toolkit actually stated that joint working required a different mindset from sponsorship and a collaborative approach. The scheme should be reviewed in this light.

Encysive submitted that the NHS, government and industry had adopted a 'common agenda' to improve patient outcomes through high quality and cost effective treatment and management. The DoH and the ABPI agreed that the common agenda could be achieved through working together to ensure that patients got optimal care, including appropriate use of cost-effective innovative medicines, with support to help them maximise the benefits of treatment.

Encysive noted that the DoH's joint working toolkit stated that this could be achieved through services designed to ensure, amongst others: identification of appropriate patients; optimal numbers of appropriate patients received treatment; appropriate use of innovative medicines that were cost effective for the NHS; measurable improvements in outcomes and a positive patient experience.

Encysive also noted the DoH's Long-Term Leadership Strategy for medicines which stated that NHS payers would increasingly require the demonstration of relative and cost-effectiveness to allow widespread use of new medicines in patients. However, there would be some medicines, like Thelin, and many other orphan medicines, where value could not be demonstrated at launch but for which collection of additional data would provide a good chance of proving value. The strategy acknowledged this and stated that without some give by both industry and government, there was a possibility that these medicines would not be used in the NHS. It specifically referred to the concept of risk sharing at paragraph 6.33:

'A compromise needs to be found that allows a degree of risk-sharing to ensure that the government does not pay for medicines that do not work but that equally, patients get access to medicines that may help them. **These important issues need to be discussed and a solution agreed that meets the needs of payers, patients and industry'** (emphasis added).

Encysive submitted that this position was also made clear in the Office of Fair Trading (OFT) Market Study into the Pharmaceutical Price Regulation Scheme (PPRS), which was issued around the same time as the long-term strategy report. It proposed that manufacturers offer risk sharing agreements where there was a lack of clarity about a value based price at launch and referred to two examples. In particular, it stated: 'we believe that risk sharing is a potentially promising approach for the future for drugs where there is a plausible but unproven value proposition and there are reasonable prospects of data being available in the medium term to make a more thorough determination'. It was clear, therefore, that the NHS was required to identify risk sharing opportunities so that patients did not miss out on effective treatment. The scheme at issue was one such initiative. It was developed based on the underlying public policy considerations above, approved by the NHS entities in question and set out in a commercial agreement. All parties clearly understood the scheme and its terms. The SCG managers consulted about the scheme acknowledged that it assisted their organisations with the equitable distribution of finite funding for PAH patients within the remit and framework of the NHS specialist commissioning services. The scheme should also improve patient access to medicines for PAH, as described above.

2 The Panel's ruling was not a consistent interpretation of the Code and case precedents

Encysive noted that the Panel ruled that the arrangements of the scheme were unacceptable and in breach of Clause 18.1 of the Code. The rationale, the Panel said, was that policy makers, in receipt of credit notes against the future prescription of Thelin, would, at the very least, want to use them and thus recommend more Thelin to be prescribed. The Panel also ruled that outcome guarantee schemes did not benefit from the trade practice exemption under Clause 1.2 of the Code.

Encysive disagreed with this analysis and submitted that it was based on a misinterpretation of the Code and was inconsistent with previous rulings and other high profile risk share schemes.

2.1 Clause 18.1 of the Code

Clause 18.1 of the Code stated 'No gift, benefit in kind or pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine, subject to the provisions of Clause 18.2.' Encysive had not offered any administrative staff a gift, benefit in kind or pecuniary advantage. It had offered the NHS a rebate in the form of a credit note. The rebate did not attach itself to one particular SCG but was transferable between SCGs within the 12 month timeframe. It was not possible to 'induce' an organisation as a whole. In fact, the Oxford English Dictionary defined the verb 'induce' as:

'To lead (**a person**), by persuasion or some influence or motive that acts upon the will, to (into, unto) some action, condition, belief, etc.; to lead on, move, influence, prevail upon (any one) to do something' (emphasis added).

Further, Encysive submitted that a rebate offered to the NHS pursuant to a commercial contract was neither an inducement nor a 'gift, benefit in kind or pecuniary advantage' to a prescriber or administrative staff. It was effectively a cash-equivalent discount allocated to the NHS where the product failed to meet the terms of the company's guarantee. The MHRA Blue Guide recognised 'equivalent business discount schemes' as alternatives to cash rebates. The rebate was not conditional upon the recruitment of new patients as Thelin was already prescribed by each PAH centre that had signed up to the scheme and so existing patients could also benefit. The scheme was conditional in the sense that, where a prescriber chose to prescribe Thelin, the company would guarantee the effectiveness of Thelin pursuant to the terms of the scheme.

Encysive submitted that in addition, there was no voluntary element under terms of the scheme as one would expect when offering or providing a gift. Rather, a credit note supplied under commercial terms such as these was good consideration, as that term was contractually understood, for the NHS agreeing to reimburse Thelin. Consideration was something of value that was necessary for parties to enter into a legally-binding contract. Under the scheme, the NHS was not volunteering to accept the guarantee/rebate (as it would if it were a gift), rather it entered into a legally-binding agreement with Encysive whereby it took on the risk of investing its resources into making Thelin available on the NHS. Such rebates could not, therefore, be considered a gift, benefit in kind or pecuniary advantage. Encysive also referred to the OFT PPRS report, which suggested that risk sharing was merely a mechanism to smooth prices, as opposed to a gift or benefit in kind.

Encysive noted that the supplementary information to Clause 18 followed this reasoning and suggested that a gift, benefit in kind or pecuniary advantage must be a personal benefit. It gave the example of gift vouchers for high street stores.

Encysive noted that when the Panel had previously ruled on the acceptability of a pilot scheme (Case AUTH/1109/11/00), it raised the possibility that the scheme could benefit from the trade practice exemption. In that case, the Panel did not discount the possibility that risk sharing schemes would fall outside the scope of the Code. It was troubling and inconsistent, therefore, for the Panel to rule nearly seven years on that such schemes did not benefit from the trade practice exemption. Encysive further noted that the Panel stated that if any actual rebates had been paid, they would not be considered a gift. This was because the payments would have been payable to a health authority and not to an individual physician. The Panel stated: 'With the pilot study in question, the Panel noted that if payments had been made, they would have been made to the health authority and not to the GPs or the PCG. **No individual health professionals would have benefited either directly or indirectly'** (emphasis added).

Therefore, Encysive submitted that that no gift, benefit in kind or pecuniary advantage (as those terms were discussed above) was offered to any individual health professional or administrative staff to induce a prescription of Thelin. In actual fact, the NHS as a whole received a rebate (as the credit note was transferable) where Thelin did not meet the terms of its guarantee. Any form of rebate (credit notes, replacement stock, cash, future discounting, etc.) supplied under commercial terms such as these was good 'consideration', as that term was contractually understood, for the NHS agreeing to reimburse Thelin. As such, the NHS had not volunteered to accept the rebate but agreed to invest scarce resources by reimbursing the product. Such rebates could not, therefore, be considered a gift, benefit in kind or pecuniary advantage.

2.2 Credit notes as rebates

Encysive disagreed with the Panel's view that the rebate of a credit note against replacement stock of Thelin would at the very least lead to a recommendation that Thelin should be prescribed. Encysive considered that the use of credit notes/replacement stock was acceptable under the Code and similar to bonus stock offers, which were common in the industry and fell outside the scope of the Code as measures or trade practices related to prices, margins or discounts in regular use by a significant proportion of the industry on 1 January 1993. Importantly, credit notes were recognised by the DoH, NICE and the SCGs with whom Encysive entered into joint working arrangements with as acceptable alternatives to cash rebates. In particular,

the use of replacement stock and credit notes in risk share schemes had previously been permitted by the DoH and NICE in another scheme as acceptable to the NHS. During the development of that scheme, the DoH commented on the acceptability of credit notes (with a one month time limit) and replacement stock as a form of rebate under the scheme. It stated: 'We note that [the company's] proposal involves supplying credit notes or replacement stock in the event of patients not responding to [the medicine] because their understanding is that this is easier for provider units to administer. **We are content with this approach** but are equally happy with a cash payment as long as the process remains easy for the NHS to manage locally' (emphasis added).

Encysive submitted that the understanding referred to in this extract was based on a survey carried out by the scheme's sponsor with NHS administrative staff in 10 hospitals as to the acceptability of different forms of rebate. Given the option of a credit note or cash refund, the NHS clearly preferred for credit notes (8/10) as these were easier to track and administrate than cheque refunds. They also helped ensure that the relevant units or functions within the NHS retained their allocated funds, rather than risking their allocation elsewhere within the service. This was particularly important in the specialist commissioning context, where budgets were often hard-fought and tight, and where patients relied on a small number of often costly therapies. Two hospitals preferred replacement stock and none stated a preference for a cash refund. The DoH's letter also confirmed that credit/notes replacement stock benefited the local health economy: 'The company distributes [the medicine] directly to the NHS, so rebates or replacement stock can be given back to the same unit that placed the initial order, **ensuring that the local health economy receives the benefit of the scheme'** (emphasis added).

Encysive submitted that during the development of its scheme, it relied on the above survey and the comments from the DoH as to the acceptability of credit notes for risk share schemes. Encysive also consulted with the SCG Manager responsible for PAH and, as evidenced by the agreement, the credit notes were acceptable. There was little practical difference between the scheme referred to above and the Thelin risk share scheme. In both cases, the terms of the outcome guarantee and the form of the rebate were negotiated at some length and agreed by the DoH.

2.3 Commercial aspects

Encysive submitted that the directors of the company had a statutory duty to exercise reasonable care and skill in running the company. This included monitoring business cash flow and accounts. Cash flow was important to all companies, and particularly smaller ones such as Encysive, because it enabled them to pay their debts as they fell due and so avoid any potential insolvency risk. For this reason, credit notes or replacement stock would usually be the preferred option for a well run company.

Encysive noted the Panel's ruling referred to Cases AUTH/1807/2/06 and AUTH/1810/3/06. In the scheme considered then cash rebates were paid to the PCTs rather than individual GP practices. The rebates were for the general purpose of improving primary care services. The Panel found no breach of the Code. However, that cash rebates of this kind could, in fact, be less attractive to the NHS because such payments could be allocated elsewhere, for example, spent on resurfacing the hospital car park rather than going on patient therapies. This was supported by the statements from the DoH and the survey cited above.

2.4 Pilot scheme

Encysive noted that the scheme was in its pilot stage. It was common in the industry to pilot major initiatives like this before considering a wider roll-out to ensure acceptability with all the relevant parties and to reconcile any problems that might occur during the pilot stage. As with any pilot, if feedback suggested that a cash rebate would be preferred then that was something Encysive would fully consider going forward. However, provided this form of rebate was acceptable to the NHS, which it clearly was, then Encysive submitted that it would be an unreasonable precedent to uphold the Panel's ruling. It would also impose on the PMCPA a positive duty to investigate the other risk share schemes mentioned that used, or offered, credit notes and replacement stock under their guarantees. Such a move would be greeted with dismay by companies complying with the Code, the DoH, NICE, the NHS and many of the patients that benefited from treatment on that basis.

2.5 The conduct of SCG managers, administrative staff and senior physicians

Encysive noted that the Panel had questioned the conduct of the SCG managers, administrative staff in receipt of credit notes for Thelin and, ultimately the senior specialist physicians at the PAH centres involved in the scheme. The Panel's ruling alleged that they would, at the very least, want to use them and thus recommend more Thelin to be prescribed and suggested that credit notes were financial inducements. Encysive was concerned about this allegation and considered the role of the SCG managers as essential in helping patients access some very specialised services. Indeed, the Government's vision for World Class Commissioning, published in December 2007, described the role of commissioners as 'working collaboratively with partners ... to stimulate innovation, efficiency and better service design, increasing the impact of the services they commission to optimise health gains and reductions in health inequalities'. The Panel's ruling suggested that such managers behaved in a corrupt manner by accepting financial inducements. This was in breach of NHS ethical standards that NHS

employees must adhere to when dealing with commercial sponsorship. When entering into joint working arrangements, Encysive trusted that NHS staff and physicians would adhere to NHS ethical guidelines, just as the NHS organisations trusted that the company and its employees would comply with the Code. In particular, the NHS ethical guidance stated that staff working in the NHS were expected, *inter alia*, to: not misuse their official position or information acquired in the course of their official duties, to further their private interests or those of others; ensure professional registration (if applicable) and/or status were not used in the promotion of commercial products or services and to neither agree to practice under any conditions which compromised professional independence or judgement, nor impose such conditions on other professionals. This last point was particularly relevant as it clearly stated that NHS staff must not impose conditions that could compromise professional judgment, ie under a commercial sponsorship arrangement, NHS administrative staff could not recommend to prescribers that they prescribe more Thelin.

Encysive noted that as referred to in the public policy section above, joint working was based on an open and transparent relationship. Mutual trust was recognised by the DoH and the ABPI as fundamental if joint working initiatives were to be successful. Therefore, Encysive trusted that the SCG managers abided by the NHS ethical standards. Similarly, the SCG managers and physicians trusted that Encysive and its employees would abide by the Code and the law. This was evidenced by Encysive's willingness to accept the jurisdiction of the PMCPA following this complaint.

Encysive submitted that the Panel's ruling also suggested that the use of credit notes as a rebate was an indirect inducement to prescribers. Prescribers were typically staff working in the NHS and were subject to the ethical guidelines referred to above. However, physicians were also subject to GMC Good Medical Practice Guidelines 2006, which stated that doctors must act in their patients' best interests when providing treatment. They must not ask for or accept any inducement, gift or hospitality which might affect or be seen to affect their judgment. It added that financial or commercial interests in healthcare, pharmaceutical or other biomedical companies must not affect prescribing or treatment and that these interests must be declared to patients or the healthcare purchaser if there was a possibility that they were relevant. Therefore, it was clear that there were appropriate checks and balances in place to prevent a physician from actually accepting an indirect financial inducement.

The physicians in question were members of a very small number of highly specialist, often eminent, experts in the treatment of PAH. It was difficult to accept that the professional integrity and ethical principles of individuals such as these could be compromised in the manner that the Panel suggested.

Encysive noted that a letter attached from a professor of respiratory medicine stated that he was comfortable with the manner in which the scheme was run. A statement from the Director of the PMCPA, when this GMC guidance was published, suggested that it was up to both parties to maintain ethical integrity. She stated: 'It is essential that doctor's relationships with pharmaceutical companies are professional and transparent at all times. It is up to both parties to ensure that this is so and that the interests of patients are put first.'

Encysive considered that it, the SCG managers, the NHS administrative staff and physicians had maintained the highest ethical standards in running this scheme.

3 The Panel failed in its duty to apply the rules of natural justice as its ruling had no evidential basis

Encysive submitted that the Panel was under a duty to ensure that it applied the rules of natural justice when adjudicating on cases before it. To this end, Encysive considered that the Panel's ruling was procedurally unfair because it completely lacked precedence/evidence. The Panel disagreed with Encysive's submission that the scheme was neither conditional upon nor related to any commitment to purchase, prescribe, administer or recommend any Encysive product based on the fact that the rebate was in the form of a credit note (which had little practical difference to the other scheme discussed above) and allegations it made that policy makers would want to use the credit note as a financial inducement to persuade physicians to prescribe more Thelin. There was no evidence that this was the case. The fact that NHS staff must comply with NHS ethical standards and, in the case of health professionals, GMC or other professional standards, meant that on the balance of probability, NHS staff would not use the credit notes as a financial inducement. When public authorities made a decision or ruling that had no evidential basis, then the decision must be regarded as irrational.

Further, Encysive submitted that the complete lack of evidence went against the well-established principle that persons, including companies, should not be punished in the absence of some conduct or state of affairs that justified liability attaching to a person. This was encapsulated in the general principle that criminal liability required both an unlawful act and an unlawful intention. This maxim was appropriate to apply here as Clause 18.1 of the Code reflected Regulation 21(1) of the Medicines (Advertising) Regulations 1994, as amended. Any person (including a company as a legal person) in breach of Regulation 21(1) was guilty of an offence. In order to prove the offence, it was necessary to prove that a gift or inducement was actually offered or given to a health professional or administrative staff to induce a prescription. The Panel had not evidenced either element.

Encysive did not intend or consider using the scheme to induce prescriptions or recommendations of its products. Encysive hoped that the scheme would simply alleviate some of the NHS's financial or budgetary constraints, thus allowing physicians more freedom to prescribe as they saw fit. Encysive could not have predicted, as the Panel appeared to have done, that these circumstances would at the very least result in behaviour that was unethical and contrary to NHS and GMC rules.

Encysive submitted that the Panel appeared to have a hypothetical and unlikely set of circumstances to find the company in breach. In doing so, it ignored the fact that the scheme involved a commercial relationship between Encysive and the NHS. No inducement was offered to any administrative staff or prescribers, the act required for a breach of Clause 18.1. It also ignored the fact that the rules and ethical principles underpinning the NHS and the practice of medicine precluded the recommendation that the Panel suggested was inevitable. It was therefore difficult to understand how the Panel could have discharged its burden of proving any intention on the part of Encysive.

Encysive submitted that while it was true that the directors of a company owed a duty to its shareholders, both the ABPI and the DoH recognised that companies working in partnership with the NHS gained shareholder value by researching and developing innovative medicines that met clinical need, optimised the use of its medicines in appropriate patients and encouraged more proactive treatment and management of patients. It was important that Encysive developed joint working opportunities to enhance its understanding of the NHS service reconfiguration process and to increase its credibility as a genuine partner in providing care for PAH patients. Encysive submitted that, therefore, that there was no evidence with which to find it in breach of Clause 18.1. As the Panel had observed in the previous cases the scheme did not involve the offer of any inducements to prescribers or administrative staff. Even if this was put aside, the ethical standards expected of NHS staff and GMC-registered physicians provided a robust check against the alleged inappropriate and unethical conduct. The Appeal Board must, therefore, overrule the Panel's decision.

Encysive submitted that it was most concerned about the Panel's ruling in this regard. It suggested many common commercial arrangements between pharmaceutical companies and the NHS were intended at the very least to induce administrative staff to recommend prescription of its products, contrary to Clause 18.1 of the Code. This had cast doubt on the legitimacy of many joint working initiatives and portrayed the industry, the NHS and the medical profession in a poor light

4 The Panel's ruling contained mistakes of fact and therefore the ruling was ill-advised

Encysive submitted that the Panel's ruling stated that there were only two medicines available for the treatment of PAH; Thelin and Actelion's product Tracleer. This was not correct. Treatment options for patients with the disease had evolved to help prolong their survival and improve their quality of life. Conventional treatment for patients with primary and secondary PAH include calcium-channel blockers, anticoagulants, diuretics and oxygen. In addition, oral endothelin-1 receptor antagonists (sitaxentan sodium, bosentan), an intravenous prostacyclin (epoprostenol), an inhaled prostacyclin (iloprost), a subcutaneous prostacyclin (treprostinil) and a phosphodiesterase-5 inhibitor (sildenafil) had also been licensed for the treatment of PAH in various European countries. Of these, Thelin, Tracleer, iloprost (Ventavis) and sildenafil (Revatio) had been authorised through the European centralised procedure. NICE was currently conducting a technology appraisal of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for the treatment of PAH in adults. It was a mistake of fact, therefore, to suggest that there were only two available treatments for PAH. To the extent that the Panel relied on this information in forming its opinion, then the Appeal Board must consider the ruling ill-advised.

5 The Panel's ruling would hinder access to innovative medicines

Encysive submitted that in consultation with the SCGs, it developed the scheme so that appropriate patients could access its treatment in a cost-effective manner. As discussed, the benefit for the SCGs was that the scheme would assist the NHS with the equitable distribution of finite funding for PAH patients. The transferable nature of the credit note meant that the rebate was not restricted to one particular centre but could be used to treat PAH patients in other parts of the country. The scheme therefore helped improve patient access to PAH medicines, while in no way being directive about any particular medicine. Although PAH targeted monotherapy was generally accepted for funding, if the scheme was considered to be in breach of the Code, then there was a risk that patients would find it difficult to access other innovative and costly treatments now and in the future.

6 Summary

Encysive considered that the scheme was a successful example of an open and transparent joint arrangement with the NHS. By entering into a risk sharing arrangement that was acceptable to all the parties involved, Encysive was held accountable for the effectiveness of Thelin. If an NHS resource was shown to be wasted then the company paid the NHS back with a credit note against replacement stock that could be used throughout the country for existing patients taking Thelin. Disseminating new medicines, and in particular medicines with orphan status, under the terms of such a guarantee provided reassurance to both parties; the company was more likely to get its medicine to those who needed it most, and the NHS had a reassurance of return on investment within a 24 week evaluation

period. This was accepted by the SCG managers who agreed to the scheme as a rational and professional way of managing the entry of new, expensive medicines, such as Thelin, into the NHS. The scheme complied with the Code and was consistent with public policy and other risk share schemes approved by the DoH and the NICE.

COMMENTS FROM ACTELION

Actelion noted that Encysive had commented on a number of previous examples of 'risk share' between the pharmaceutical industry and the NHS. Actelion alleged that there were significant differences between the previous cases and the current case, therefore this case should be considered on its individual merits and the reasonable perceptions associated with it.

Actelion alleged that the Encysive scheme still fell within Regulation 21 of the Advertising Regulations, was promotional, and, by incentivising the NHS centre, contravened Clause 18.1 of the Code.

Actelion submitted that a contextual feature of paramount interest was the relative market place of the licensed endothelin receptor antagonists (ERAs); bosentan (Tracleer) and sitaxsentan (Thelin). Tracleer was launched in May 2002, and at the end of 2007 had over 1,000 patients on commercial therapy within the UK/Ireland market. Thelin was authorised by the EMEA in August 2006 and at the end of 2007 (when the scheme in question was being proposed to the specialist centres) Actelion estimated that there were about 40 - 50 patients on commercial supply throughout the same territory. While Encysive could provide more accurate numbers, it was unlikely that any centre involved in the scheme had, in late 2007, even 10 commercially treated patients. This supported Actelion's underlying view that the scheme was designed to accelerate the development of pockets of Thelin prescribing in these centres. Actelion noted Encysive's submission that the credit note could be applied to a patient currently already on Thelin, however the low initial patient numbers at the treating centres would limit the practical application of this option.

Actelion noted that Encysive had suggested that the scheme was developed in consultation with clinical key opinion leaders in PAH and with payers. This did not diminish the company's responsibility for compliance with the Code.

Actelion noted that the professor of respiratory medicine who headed one of the treating centres, had stated that he was completely comfortable with the manner in which the scheme is run. The implication within these various sections was that the clinicians in the PAH centres and the various payers were overall happy with the scheme. Actelion alleged however that Encysive had not fully represented the views of the PAH specialist centres. Actelion had no accurate knowledge regarding which centres the scheme was presented to, the proportion which refused participation and why. At least one of the six adult designated centres did not consider the scheme to be appropriate. Staff at one hospital had told Actelion that they were unhappy with the proposal and did not agree with the principles of the scheme and felt that it put undue pressure on prescribing habits and in order to get a more formal view they discussed the matter with the legal and corporate team within the trust and were advised they should not become involved with it in any way.

Actelion noted that Encysive had made speculative statements regarding the potential negative impact on uptake of innovative treatments, should the Panel's ruling be upheld. Actelion had approached the PMCPA on this specific, *individual* matter, which the PMPCA had reviewed as such. Risk share agreements could be initiated without contravening the Code, therefore there was no justification for Encysive's position.

Actelion alleged that the appeal from Encysive did not alleviate its concerns that this scheme had been misrepresented as a clinical and cost-effectiveness evaluation. There was a lack of common clinical or economic endpoints, and it was clear that individual clinician judgment was all that was needed. It was therefore not possible to make a robust evaluation of clinical or cost-effectiveness. While Encysive stated that the Panel placed too much emphasis on the title, Actelion disagreed, and alleged that the title was a key element in the impression given to customers regarding the scheme. Actelion doubted the extent of material clinical input and endorsement into developing the scheme.

ENCYSIVE'S COMMENTS ON THE REPORT FROM THE PANEL

Encysive acknowledged that it had commented at length as part of the appeal process. It had designed its pilot scheme to comply fully with the Code. In doing so it had taken legal advice and the matter had been discussed with the MHRA and the ABPI.

APPEAL BOARD RULING

The Appeal Board was extremely concerned about the scheme. In particular it considered that the title 'A six month pilot clinical and cost effectiveness evaluation agreement …' suggested a degree of clinical rigour that appeared to be missing. In that regard the Appeal Board noted that there was no protocol, steering group, predetermined clinical endpoints etc associated with the scheme. In the Appeal Board's view the scheme was simply a financial arrangement between Encysive and the treatment centres. The Appeal Board considered that as a risk sharing scheme, the scheme at issue was not a model of good practice. With regard to the other schemes referred to by Encysive the Appeal Board noted that it had not considered any

complaints about these schemes and it appeared that they were different to the Encysive scheme.

The Appeal Board noted that the complainant had alleged a breach of Clause 18.1 of the Code. Clause 18.1 stated 'No gift, benefit in kind or pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine …'. In that regard the Appeal Board noted that a credit note would be issued to cover the cost of the failed Thelin treatment. The credit note was valid for one year and could be used to offset the cost of Thelin treatment either in naïve patients or in those already on therapy. The credit note could be transferred to a centre other than the one to which it was issued. The Appeal Board noted that the credit note was issued to a treatment centre and so in that regard it was not a gift, benefit in kind or pecuniary advantage to any individual. On the narrow grounds of the complaint the Appeal Board ruled no breach of Clause 18.1. The appeal was thus successful.

Given the circumstances the Appeal Board decided to take no further action in relation to the Panel's report to it, made in accordance with Paragraph 8.2 of the Constitution and Procedure.

Complaint received	**5 February 2008**
Case completed	**23 April 2008**