CASE AUTH/2020/7/07 *NO BREACH OF THE CODE*

ANONYMOUS v MERCK SHARP & DOHME

Januvia cost model

A member of a primary care trust (PCT) medicines management team alleged that a computer cost model for Januvia (sitagliptin), which a Merck Sharp & Dohme representative had presented at a PCT meeting, was misleading. The model showed the potential cost impact on a PCT of prescribing Januvia.

The complainant alleged that the model made unsubstantiated claims about hospital costs for heart failure and other hospital costs. Also, the costs of competing medicines did not seem to be right. The average costs of medicines used as an alternative seemed in some cases to be overstated (sulphonylureas) and in others to be understated (glitazones). This seemed to be due to dose errors.

The Panel noted that the Januvia model entitled 'Budgetary impact of Januvia (sitagliptin) for the treatment of type 2 diabetes when patients on diet, exercise plus metformin monotherapy require additional glycaemic control' was described as a one year budget impact model designed to answer the question 'What is the financial impact of using Januvia in my local area?'. The Panel had been provided with printouts of screens of the model. It did not have the model itself.

The Panel was concerned that the first screen and the results summary screen featured the disclaimer 'Whilst MSD has made every effort to ensure that the information in the Januvia Budget Impact Model was correct at the time of its incorporation, MSD takes no responsibility for any omissions, errors or inaccuracies, whether at the time of such incorporation or subsequently. Any individual using the Januvia Budget Impact Model is ultimately responsible for the exercise of his/her own judgement as to its application to any given budget …'. The Panel noted, however, that the Januvia budget impact model was promotional material and as such had to comply with the Code at its time of issue and use. It was thus not acceptable to state that the company was not responsible for errors, omissions or inaccuracies.

The screen describing the purpose of the model referred to the results being estimates. There were three major inputs. The number of patients who might be expected to use Januvia, the daily cost compared to the other oral diabetes medicines and any cost savings from Januvia in relation to a potential reduction in the incidence of adverse events otherwise associated with other diabetes medicines (eg heart failure and hypoglycaemia) or to potential reductions in the need for self-monitoring blood glucose.

The representatives' briefing material stated that the model would answer the question 'What is the financial impact of using Januvia in my local area?' The representatives were then told of the three major inputs into the model and that the user must interpret and apply any results with caution and when discussing the disclaimer to emphasise that the model was to be used as a guide and that all results were simply estimates. The customer must feel comfortable with the accuracy of the calculation if they want to apply them. Representatives were also told that there were 'certain inherent limitations to the results from this particular model, which are attributable to this type of model being speculative in nature'. The representatives were also instructed that the health benefits of using Januvia were not specifically examined except as they impacted on costs eg reduced hypoglycaemia, self-monitoring of blood glucose and incidence of heart failure.

The Panel noted that the complainant was concerned about the costs of heart failure and other hospital costs. The annual incidence rates for heart failure were calculated from the 34.5 month pioglitazone and placebo rates in the PROactive study (Dormandy *et al*). The Panel noted that the study rate for the proportion of pioglitazone patients with at least one heart failure event needing hospital admission 149/2605 (5.72%) was reproduced in Merck Sharp & Dohme's response as the 'non in-patient' rate. It was possible that this error also occurred in the actual model as it was repeated in the cost offsets heart failure screen headed 'probability of heart failure (approximately 3 years)' which stated that 5.72% patients taking glitazones required no hospital admission and 5.07% required hospital admission vs 5.07% and 5.72% respectively in the published paper. It appeared that similar errors were made with the placebo data which was used for the sulphonylurea costs and the Januvia costs. The rates for pioglitazone patients observed by Dormandy *et al* were then applied to rosiglitazone. A footnote (g) to the heart failure section in cost offsets read 'Dormandy et al (2005) recruited high risk patients; that is patients with evidence of macrovascular disease' whereas the published paper stated that eligible study patients had to have evidence of *extensive* macrovascular disease (emphasis added). The study authors noted pioglitazone improved cardiovascular outcome in type 2 diabetics who were at high cardiovascular risk and that their results 'should also be applicable to patients who have not had a macrovascular event …' , nonetheless this was an assumption and had not been proven. Footnote (c) explained that the model assumed that Januvia had the same risk as placebo in Dormandy *et al* and footnote (h) stated 'Note: there is currently no long-term data assessing the risk of heart failure for patients on Januvia'. The assumption that Januvia had the same heart failure risk as placebo had thus been made in the absence of long-term data.

Nonetheless the Panel noted that the Januvia SPC did not refer to any cardiovascular problems associated with therapy. The Panel considered that the footnotes were not adequate warnings about the assumptions made about heart failure incidence rates.

The Panel noted that the costs of heart failure were based on the 1998/9 figures published in UK Prospective Diabetes Study (UKPDS) which estimated the immediate and long-term healthcare costs associated with severe diabetes-related complications. The expected mean hospital in-patient cost of heart failure in 1998/9 was £2,221 and the expected mean annualized non-in-patient cost for macrovascular complications was given as £315. Merck Sharp & Dohme explained that these figures were then inflated to current price levels (£2,971 and £421 respectively). The Panel queried whether it was appropriate to use the expected mean figures, rather than the estimated annual hospital in-patient costs or non-in-patient costs conditional on some costs being incurred. The expected mean reflected the fact that for any complication there was only a probability that the patient would incur a cost.

The Panel noted that the briefing document advised representatives to emphasise that the cost offsets section was optional as it was speculative. Assumptions had to be made because of limited data. Representatives were reminded that the model was based on estimates and not to try to apply precise numbers.

Overall the Panel was concerned about the methodology and assumptions made in the model. The Panel queried whether the model was sufficiently robust given its general comments above. The Panel considered that the heart failure costs were misleading and not capable of substantiation as alleged, breaches of the Code were ruled.

The Panel noted that the cost of competitor products was based on national figures and as such might not reflect local prescribing habits or local costs. The Panel queried whether costs other than those arising from heart failure, hypoglycaemic events and self-monitoring of blood glucose would impact on the cost of Januvia therapy. The Panel did not consider that given the stated purpose of the model (to answer the question 'What is the financial impact of using Januvia in my local area?') that the limitations of the model were sufficiently clear or that the results generated were only estimates. Although local population data could be used, national medicine costs were used. The Panel considered that the model was misleading in this regard and a breach of the Code was ruled.

Upon appeal by Merck Sharp & Dohme the Appeal Board noted the company's submission that only 8.5% of the cost of Januvia could be offset by a potential reduction in the incidence of adverse events associated with other oral treatments for diabetes compared with Januvia (eg heart failure with glitazones and hypoglycaemia with sulphonylureas) or a potential reduction in the need for self-monitoring of blood glucose. It was possible not to include these cost offsets in the estimation. The Appeal Board noted that the model could estimate the cost for a PCT-defined percentage of patients eligible for Januvia or default settings could be used. The Appeal Board considered that by their nature models such as the Januvia budget impact model could only give estimates but that their intended audiences ie appropriate PCT personnel, would understand such constraints.

Although the Appeal Board considered that the transposition of figures for in-patients and non-in-patients from the PROactive study was a most unfortunate error, it noted Merck Sharp & Dohme's submission for the appeal that the error made a difference of less than 0.1% of the calculated cost. In the context of the material in question, the Appeal Board considered that the error had not materially affected the outcome. Although the Appeal Board had concerns about the introductory disclaimer it considered that the limitations of the model were clear and would be understood by the intended audience.

The Appeal Board noted that the complainant was concerned about the costs of heart failure and other hospital costs. The annual incidence rates for heart failure were calculated from the 34.5 month pioglitazone and placebo rates in the PROactive study. The Appeal Board noted that compared with other studies the heart failure rate reported in the PROactive study was a conservative value and as such was not unreasonable. The Appeal Board noted that the heart failure section cited relevant assumptions as did other sections of the cost offsets section.

The Appeal Board did not consider that the heart failure costs were misleading. Within the accepted limits of a health economic model they were capable of substantiation. No breaches of the Code were ruled.

The Appeal Board noted that the calculation of the weighted costs of competitor products was based on national figures and as such might not reflect local prescribing habits. However, the Appeal Board considered that the intended audience would understand such figures and not be misled by them. No breach of the Code was ruled.

An anonymous and non-contactable member of a primary care trust (PCT) medicines management team complained about a computer cost model for Januvia (sitagliptin) produced by Merck Sharp & Dohme.

COMPLAINT

The complainant stated that a representative from Merck Sharp & Dohme had recently visited the PCT to talk about Januvia. As part of the meeting a computer cost model was presented showing the potential cost impact on a PCT.

The complainant alleged that PCTs could be misled by this model for a number of reasons. It made unsubstantiated claims about hospital costs for heart failure and other hospital costs. Also, the costs of competing medicines did not seem to be right. The average costs of medicines used as an alternative

seemed in some cases to be overstated (sulphonylureas) and in others to be understated (glitazones). This seemed to be due to dose errors.

When writing to Merck Sharp & Dohme, the Authority asked it to respond in relation to Clauses 7.2 and 7.4 of the Code

RESPONSE

Merck Sharp & Dohme stated that the Januvia budget model was examined by the Medicines and Healthcare products Regulatory Agency (MHRA) in line with standard pre-vetting procedures, and was approved by it in its current form. Whilst Merck Sharp & Dohme appreciated that approval by the MHRA did not, by itself, indicate Code compliance, it believed that it indicated that the MHRA did not consider the material misleading, as alleged.

The complainant made two primary allegations: that the model made unsubstantiated claims with respect to hospital costs for heart failure; and that the average costs of sulphonylureas and glitazones were incorrectly calculated.

Merck Sharp and Dohme submitted that the purpose of the heart failure section of the budget model was to draw attention to potential cost offsets of Januvia in preference to glitazones, attributable to a higher expected risk of heart failure developing with the latter. Heart failure was a well-recognised adverse event associated with glitazone use.

Far from being 'unsubstantiated', all steps of the heart failure cost offset calculation were illustrated in the model, in the 'Detailed Calculations' section of the 'Cost Offsets' worksheet. The process was summarised as follows.

The cost of heart failure was calculated through the use of three published data sources:

- A publication based on data from the PROactive trial. To date, this was the only published long-term study of cardiovascular outcomes/safety with glitazones. The trial which involved 5,238 type 2 diabetics, sought to estimate the effects of pioglitazone when compared with placebo (in addition to background anti-hyperglycaemic therapy) on macrovascular events, over an average observation time of 34.5 months (Dormandy *et al* 2005).

  This source provided the data on the risk of heart failure for glitazone-managed and non-glitazone-managed patients.

- The United Kingdom Prospective Diabetes Study (UKPDS) group (Clarke *et al* 2003), reported on the development of a model to estimate the immediate and long-term health care costs associated with seven diabetes-related complications in type 2 diabetics. Costs were estimated from data on 5,102 type 2 diabetics included in the UKPDS. Given the increased risks, severity and duration of cardiovascular complications in diabetic patients compared with the non-diabetic population, it was deemed essential to base the model calculations on evidence obtained from diabetic subjects. The UKPDS was widely recognised as the reference study in this area.

  Only immediate costs were incorporated into the Januvia budget impact model, and all costs were in 1998/9 values (see below for how these had been adjusted to current values).

  This source provided the costs associated with heart failure in the UK.

- The annual report, The Unit Costs of Health and Social Care, provided detailed costing information on a variety of medical and social services in the UK. The report also provided data on the annual rate of inflation in the health sector.

  This source was used to inflate the 1998/9 cost-values from Clarke *et al* to 2005/6 levels.

The method of estimating the costs associated with heart failure in the UK could be followed in the 'Detailed Calculations' section of the 'Costs Offsets' worksheet of the model.

1 As shown in the model, the estimation began by using values from table 9 of the PROactive publication. The values provided were separated by treatment group and represented:
- the reported sample sizes (in each arm of the trial);
- the number of patients with heart failure not requiring hospitalisation;
- the number of patients with heart failure requiring hospitalisation.

2 As no single trial provided information on the incidence of heart failure for all therapies considered in this model (metformin, sulphonylureas [SUs], sitagliptin and glitazones), results from the placebo arm of the PROactive trial were assumed to apply to all non-glitazone treatments, inasmuch as heart failure was not a known side-effect of any non-glitazone oral antihyperglycaemic.

   Therefore, by dividing the number of patients with each type of heart failure by the total number in the treatment arm, the 34.5 month incidence of heart failure could be estimated as follows:

	34.5 month incidence of heart failure(%)		
Therapies	**Hospitalisation**	**Non in patient**	**Total**
Glitazone	5.07	5.72	10.79
SU	3.42	4.10	7.52
Metformin+Glitazones (fixed dose combination)	5.07	5.72	10.79
Sitagliptin	3.42	4.10	7.52

3 The third step of the detailed explanation in the model adjusted the 34.5 month incidence rate of heart failure by treatment regimen to an annualised rate.

4 Clarke *et al*, estimated the cost of managing these two forms of heart failure in the UK. Whilst the article was published in 2003, values reported in the publication were in 1998/9 £ sterling.

Although more recent estimates of the costs of heart failure might exist, as the estimate provided by this paper was exclusively in diabetics, it was seen to provide the most appropriate estimate.

Clarke *et al* provided an estimated cost for a 'hospitalised' heart-failure event. Only the costs accruing in the year in which the event occurred were included in the model. The estimated cost for this event was reported as £2,221.

An estimate for the 'non-hospitalised' heart-failure event cost was taken from the paper. It was assumed that the macrovascular event cost reported was representative of the event under analysis, at £315.

As Clarke *et al* estimated cost in 1998/9 values, the costs required inflation to current price levels. This was possible through use of the Hospital and Community Health Services (HCHS) Pay and Prices Index produced by the Personal Social Services Research Unit (PSSRU). This information was presented in the first five columns of the table below. The sixth column represented the cumulative multiplier required to transform 1998/9 values into estimated 2006 values.

Year	Index (1987/8 = 100)	Prices	Pay	Pay & Prices	Cumulative multiplier from 1998/9 prices
1998/9	180.4	2.5	4.9	4.0%	1.00
1999/00	188.6	1.2	6.9	4.5%	1.05
2000/1	196.5	-0.3	7.2	4.2%	1.09
2001/2	206.5	0.1	8.3	5.1%	1.14
2002/3	213.7	1	5	3.5%	1.18
2003/4	224.8	1.5	7.3	5.2%	1.25
2004/5	232	1	4.5	3.2%	1.29
2005/6 (E)	241.3	1.9	5.6	4.0%	1.34

As illustrated in the detailed calculations section of the budget impact model, 1998/9 values must be multiplied by 1.34 (to two decimal places) to obtain estimated 2006 values.

This allowed for the calculation of estimated inflation-adjusted costs of heart failure. These values were £2,971 and £421 for heart failure requiring hospitalisation and not requiring hospitalisation, respectively.

5 By multiplying the annual incidence rates of heart failure for each treatment regimen (step 3 by the costs identified in step 4, the annual average cost of heart failure (per person) could be identified. For a glitazone-based regimen, the total cost associated with heart failure was £60.74, and £41.33 for a non-glitazone based regimen.

6 Annual per patient costs were then multiplied by the number of patients in each treatment arm, as specified in the model. Savings made available through the use of sitagliptin were then presented in the model.

In summary, the projected excess costs associated with heart failure secondary to glitazone use were fully substantiated in the cost model, using the best evidence base available.

Merck Sharp and Dohme stated that the primary alternatives to Januvia in the current UK diabetes market were sulphonylureas and glitazones; there were a number of treatment options available in each class. In addition, each product might have various dosages available and might be recommended with a range of daily dosing levels.

As common sources of cost information such as the Monthly Index of Specialities (MIMS) and the British National Formulary (BNF) only contained details of dose ranges, and the cost per pack/presentation, it was not possible to estimate an accurate 'cost per sulphonylurea treatment day' using these sources.

In order to obtain an accurate estimate, data on average dosing levels and relative sales information for all products (including generics) were incorporated into the model.

Data used in these calculations were captured at the UK level. Therefore, while all costs were representative at the national level, there might be minor discrepancies at the local level, where prescribing rules might exist through local formularies and guidelines. Nevertheless, as noted below, the method by which the national-level figures were calculated was transparent and accessible within the model itself.

The daily treatment costs associated with sulphonylureas, glitazones and fixed-dose combinations of metformin and glitazone were estimated from several sources:

- Pack cost from MIMS, January 2007; and BNF 53 (March 2007).
- IMS Disease Analyser, as interpreted by Merck Sharp & Dohme. This database provided data on the 'average' dose levels of each sulphonylurea, separated by whether it was prescribed generically or by brand. An explanation of the IMS Disease Analyser database was included in the model: 'Note: the IMS Disease Analyser (Mediplus) is a database of anonymous patient records from more than 500 GPs over 10 years. MSD subscribed to the IMS Disease Analyser database and had direct access to the terminal. This analysis was therefore the result of "desk-based research" in house.'
- IMS Dataview 6.0, as interpreted by Merck Sharp & Dohme. This database was used to capture the number of pills of all sulphonylurea and glitazone treatments sold in the entire UK for a 12-month period.

The model contained an explanation of how the daily treatment costs of therapies were estimated, as follows:

'There are multiple brands, pack sizes and prices within each of the classes of oral antidiabetic medication (glitazone, sulphonylurea, metformin). Furthermore, for each product, there is variation in the possible dose strength and number of doses. It was therefore necessary to calculate a weighted cost according to the following steps:

1 The average daily dose of sulphonylurea and metformin from IMS Disease Analyzer. Note: the average dose per day for glitazone was assumed to be one tablet.

2 Applying this average daily dose, the average daily cost per therapy, based on IMS Dataview and MIMS January 2007.

3 Applying this daily therapy cost, the average daily cost per class based on IMS Dataview

A summary example of the weighted calculation for glitazones and glitazone/melformin fixed dose combination can be viewed.'

The full explanation of the method by which the average daily sulphonylurea cost was calculated (data on file, based on IMS Dataview 6.0 and IMS Disease Analyser, as referred to above) was provided.

The reference pack also contained a step-by-step guide on how sulphonylurea costs were estimated. The cost associated with glitazone treatment was a simpler calculation and used an identical methodology. The glitazone calculation was also presented in the budget impact model.

1 The average dose of glitazone was assumed to be one tablet per day, and two tablets per day for fixed dose combinations of metformin and glitazone.

Using the IMS Disease Analyser, the average dose of each sulphonylurea was identified, as presented below:

Molecule	Product	Average daily dose (as identified through IMS Disease Analyser) (mg)
Gliclazide	Generic	150.75
	Diamicron	89.52
Glimepiride	Amaryl	2.92
	Generic	2.82
Glibenclamide	Generic	8.79
	Daonil	8.79
	Euglucon	8.79
Glipizide	Generic	10.01
	Minodiab	10.01
	Glibenese	10.01
Tolbutamide	Generic	1,221,41

Based on the presentations available in the UK, the number of tablets required to meet the daily average dose was calculated. The average cost per tablet was then estimated from each strength of pack. The number of tablets required to meet the average daily dose was then multiplied by the cost per tablet for each pack to estimate the cost per day of sulphonylurea treatment, based on treatment with that particular pack.

2 The estimated proportion of patient days for each treatment (which reflected the relative use of each at a national level) was then multiplied by the average daily cost for each pack to allow an estimate of the average daily cost of SU therapy.

The 'Drug Costs' worksheet of the budget impact model included the option to display an example of a weighted calculation of the daily cost of glitazone and fixed dose combination treatment.

As it was conservatively assumed that the daily glitazone dose was one tablet per day (two tablets per day for fixed dose combination therapy), there was no need to estimate the number of patient days in this calculation. Rather, relative sales through the number of pills sold could be simply calculated.

In conclusion, Merck Sharp & Dohme maintained that the budget impact model for Januvia was transparent, accurate, and reflected to the fullest extent possible the best available evidence base for the costs under consideration. Specifically, the heart failure incidence and costs had been sourced from the most up-to-date and relevant papers available and the costs reflected the cost of medicine actually prescribed.

PANEL RULING

The Panel noted that the Januvia model entitled 'Budgetary impact of Januvia (sitagliptin) for the treatment of type 2 diabetes when patients on diet, exercise plus metformin monotherapy require additional glycaemic control' was described as a one year budget impact model designed to answer the question 'What is the financial impact of using Januvia in my local area?'. The Panel had been provided with printouts of screens of the model. It did not have the model itself.

The Panel was concerned that the first screen featured a disclaimer which stated that 'Whilst MSD has made every effort to ensure that the information in the Januvia Budget Impact Model was correct at the time of its incorporation, MSD takes no responsibility for any omissions, errors or inaccuracies, whether at the time of such incorporation or subsequently. Any individual using the Januvia Budget Impact Model is ultimately responsible for the exercise of his/her own judgement as to its application to any given budget …'. The Panel noted, however, that the Januvia budget impact model was promotional material and as such had to comply with the Code at its time of issue and use. It was thus not acceptable to state that the company was not responsible for errors, omissions or inaccuracies. The disclaimer appeared again on the

results summary screen.

The model featured the following sections: Purpose of the model, Diabetes in the UK, Januvia Population 1 (diabetes), Population II (therapy), Drug costs, Cost offsets and Results summary.

The screen describing the purpose of the model referred halfway down to the results being estimates. There were three major inputs. The number of patients who might be expected to use Januvia, the cost per day compared to the other oral diabetes medication and any cost savings from Januvia in relation to a potential reduction in the incidence of adverse events associated with other diabetes medications compared with Januvia (eg heart failure and hypoglycaemia) or to potential reductions in the need for self-monitoring blood glucose.

The accompanying representatives' briefing material informed representatives that the model was designed to answer the question 'What is the financial impact of using Januvia in my local area?' The representatives were then told of the three major inputs into the model and that the user must interpret and apply any results with caution and when discussing the disclaimer to emphasise that the model was to be used as a guide and that all results were simply estimates. The customer must feel comfortable with the accuracy of the calculation if they want to apply them. The representatives were also told that there were 'certain inherent limitations to the results from this particular model, which are attributable to this type of model being speculative in nature'. The representatives were also instructed that the health benefits of using Januvia were not specifically examined except as they impacted on costs eg reduced hypoglycaemia, self-monitoring of blood glucose and incidence of heart failure.

The Panel noted that the complainant was concerned about the costs of heart failure and other hospital costs. The annual incidence rates for heart failure were calculated from the 34.5 month pioglitazone and placebo rates in the PROactive study (Dormandy *et al*). The Panel noted that the study rate for the proportion of pioglitazone patients with at least one heart failure event needing hospital admission 149/2605 (5.72%) was reproduced in Merck Sharp & Dohme's response as the 'non in-patient' rate. It was possible that this error also occurred in the actual model as it was repeated in the cost offsets heart failure screen headed 'probability of heart failure (approximately 3 years)' which stated that 5.72% patients taking glitazones required no hospital admission and 5.07% required hospital admission. Dormandy *et al* stated that 132/2605 patients did not need hospital admissions (5.07%) and 149/2605 needed hospitalisation (5.72%). It appeared that similar errors were made with the placebo data which was used for the sulphonylurea costs and the Januvia costs. The rates for pioglitazone patients observed by Dormandy *et al* were then applied to rosiglitazone. A footnote (g) to the heart failure section in cost offsets read 'Dormandy *et al* (2005) recruited high risk patients; that is patients with evidence of macrovascular disease'. The Panel noted that according to the published paper eligible study patients had to have evidence of extensive macrovascular disease (emphasis added). The study authors noted pioglitazone improved cardiovascular outcome in type 2 diabetics who were at high cardiovascular risk and that their results 'should also be applicable to patients who have not had a macrovascular event …' , nonetheless this was an assumption and had not been proven. The Panel noted that footnote (c) explained that the model assumed that Januvia had the same risk as placebo in Dormandy *et al* and footnote (h) stated 'Note: there is currently no long-term data assessing the risk of heart failure for patients on Januvia'. The assumption that Januvia had the same heart failure risk as placebo had thus been made in the absence of long-term data. Nonetheless the Panel noted that the Januvia SPC did not refer to any cardiovascular problems associated with therapy.

The supplementary information to Clause 7.2, 'General', stated that 'It should be borne in mind that claims in promotional material must be capable of standing alone as regards accuracy etc.' In general claims should not be qualified by the use of footnotes and the like. The Panel considered that the footnotes were not adequate warnings about the assumptions made about heart failure incidence rates.

The Panel noted that the costs of heart failure were based on the 1998/9 figures published in UKPDS which estimated the immediate and long-term healthcare costs associated with severe diabetes-related complications. The expected mean hospital in-patient cost of heart failure in 1998/9 was £2,221 and the expected mean annualized non-in-patient cost for macrovascular complications was given as £315. Merck Sharp & Dohme explained that these figures were then inflated to current price levels (£2,971 and £421 respectively). The Panel queried whether it was appropriate to use the expected mean figures, rather than the estimated annual hospital in-patient costs or non-in-patient costs conditional on some costs being incurred. The expected mean reflected the fact that for any complication there was only a probability that the patient would incur a cost.

The Panel noted that the representatives' briefing document advised representatives to emphasise that the cost offsets section was optional as it was speculative. Assumptions had to be made because of limited data. Representatives were reminded that the model was based on estimates and not to become distracted by trying to apply precise numbers.

Overall the Panel was concerned about the methodology and assumptions made in the model. The model had to comply with, *inter alia*, Clause 7 of the Code and should not be misleading; all costs should be capable of substantiation. The Panel noted that the cost offsets were described as speculative and thus were not capable of substantiation. The Panel queried whether the model was sufficiently robust given its general comments above. The Panel considered that the heart failure costs were misleading and not capable of substantiation as alleged. A breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted the company's explanation of the calculation of the weighted costs of competitor products. The representatives' briefing material explained that the detail of the calculations for metformin and sulphonylureas were not included as this was more complex and very difficult to summarize. The cost of competitor products was based on national figures and as such might not reflect local prescribing habits. The Panel noted that such costs would not necessarily reflect the actual costs in any locality. The Panel queried whether costs other than those arising from heart failure, hypoglycaemic events and self-monitoring of blood glucose would impact on the cost of Januvia therapy.

The Panel did not consider that given the stated purpose of the model (to answer the question 'What is the financial impact of using Januvia in my local area?') that the limitations of the model were sufficiently clear or that the results generated were only estimates. Although local population data could be used, medicine costs were based on national figures. The Panel considered that the model was misleading in this regard and a breach of Clause 7.2 was ruled.

APPEAL BY MERCK SHARP & DOHME

Merck Sharp & Dohme submitted that the model in question was, for various reasons, withdrawn from use as from 7 December, and would not be recommissioned in its original form. However, the Panel's ruling's in this case contained important and far-reaching implications for the use of any similar cost model by the pharmaceutical industry. As such, Merck Sharp & Dohme thought it appropriate to seek clarification on the conclusions of the Panel at appeal.

Merck Sharp & Dohme stated that the model was submitted to the MHRA as part of the normal vetting procedures for new medicines, and was approved by it. Whilst Merck Sharp & Dohme appreciated that this did not exempt it from its habitual obligations under the Code, the company noted that the MHRA made no amendments to the model as submitted for pre-vetting.

Merck Sharp & Dohme stated that the purpose of the model was simple: to demonstrate, within the accepted levels of tolerance for any health economic assessment, that the use of Januvia, in a reasonable projected proportion of those type 2 diabetics for whom it was indicated, would be expected to have a minimal budgetary impact, when compared with the costs of alternative treatments. The model was used by Merck Sharp & Dohme healthcare managers (not representatives) in their ongoing discussions with appropriate PCT personnel.

Merck Sharp & Dohme submitted that the base case analysis in the model was for a nationally representative population of 100,000 people. For this population, the net cost of Januvia treatment was estimated as, on average, a little under £4,300 per annum – a relatively small and insignificant proportion of overall PCT budgets. By far the greatest contributory factor to this assessment was medicine acquisition costs. A very small contribution (8.5%) was composed of cost offsets resulting from three ancillary benefits of using Januvia: a lower expected incidence of heart failure compared with glitazones; a lower expected incidence of hypoglycaemia compared with sulphonylureas and, as a result of the low risk of hypoglycaemia, a possible reduction in the need for expensive self-monitoring of blood glucose.

Merck Sharp & Dohme noted that the complainant's apparent primary concern about the model, and the great majority of the points considered by the Panel in making its ruling, did not relate to the calculation of medicine acquisition costs per se, but rather the cost offset calculations, especially that concerning the expected rate of heart failure with glitazones. While the latter calculations must, of course, stand on their own merits, Merck Sharp & Dohme noted that, even if all the cost offsets were removed from the calculation (which the model allowed the user to do), the primary conclusion of the model – that Januvia was effectively cost-neutral in terms of PCT budgetary impact – remained unchanged, with an increase in net cost of approximately £399.

Merck Sharp & Dohme submitted that the Panel's ruling of breaches of Clause 7.2 and 7.4 was not made on any single overriding factor, but on a variety of different issues, as addressed below:

Disclaimer statement

Merck Sharp & Dohme noted that the Panel's concern over the wording of this statement. Its original intent was to take account of the difficulties inherent in any health economic analysis with respect to pricing differences or inconsistencies, changing circumstances, assumptions, extrapolations, etc, and to draw the user's attention to the fact that any results or conclusions deriving from the model were, by their nature, estimates, based on the reference data cited in the model. It was certainly not intended to be a carte blanche for the inclusion of inaccurate or misleading statements or data.

For the purposes of clarity, the wording for such disclaimers in future health economic models and documents had been redrafted as follows:

'Merck Sharp & Dohme Limited ("MSD") acknowledges that this [describe in detail] health economic model (the "Model") has been created for the purpose of promoting [add product name].

Whilst the health economic data included in this Model have been checked for accuracy, this Model is intended to be indicative, not predictive, of budget impact. There are certain assumptions, caveats and extrapolations built into the methodology of this Model, some of which are dependent upon input from you (the "User")

The User should note that any results and/or conclusions deriving from this Model are, by their nature, estimates only'.

That said, Merck Sharp & Dohme submitted that, by its very nature, the original disclaimer statement could not represent a breach of the Code, as it did not contain any data or conclusions which, in themselves, could be deemed to be misleading or inaccurate.

'In-patient' versus 'non-in-patient' heart failure incidence

Merck Sharp & Dohme noted that the Panel had correctly identified an inadvertent error in the figures attributed to these two incidence rates, which were accidentally transposed ('in-patient' figures being labelled as 'non-in-patient', and vice versa). Factual errors of this nature were always regrettable, and Merck Sharp & Dohme was grateful to the Panel for noting it. Nevertheless, the error needed to be viewed in the context of the overall effect it had on the conclusions of the model. In fact, it made a difference of approximately £4 out of a total of £4,297 (0.093%). By any standards, unfortunate though the error might have been, it had a negligible impact on the conclusions drawn from the model, and could not reasonably be considered to be misleading in any accepted sense of that term, particularly when viewed in the overall context of a health economic model.

Use of the PROactive study as a benchmark for the assessment of heart failure incidence with glitazone therapy

Merck Sharp & Dohme noted the Panel's apparent concerned that the PROactive study (involving pioglitazone) was not a fair benchmark for the assessment of heart failure rates with glitazone use in the general population.

Merck Sharp & Dohme took advice on the appropriate benchmark trial to use in this assessment. The universal recommendation was that PROactive was the best reference available. This trial was the only long-term glitazone trial focusing specifically on cardiovascular outcomes. Furthermore, the heart failure data arising from it were particularly robust, inasmuch as all cases reported during the trial were subsequently subject to post-hoc independent scrutiny and adjudication by third-party experts.

Merck Sharp & Dohme submitted that it was true that, as a secondary outcome study, PROactive recruited patients with pre-existing macrovascular disease. However, a crucial point was that these pre-existing conditions were ischaemic in nature. The Panel's citation of the study authors' remarks on the effects of pioglitazone on cardiovascular outcome in patients with or without a history of macrovascular events again confused ischaemic events (the events the authors were referring to) and heart failure. Ischaemic heart disease (IHD) and heart failure might, of course, co-exist, but they were quite separate pathological entities. Patients with a history of, or known predisposition to, heart failure would have been excluded from the trial, on account of the well-recognised association between glitazone use and exacerbation or instigation of heart failure, a fact that had been recognized, since launch in the labelling for both pioglitazone and rosiglitazone. In addition, as noted by the Panel, the fact that the PROactive trial included patients with macrovascular disease was noted in the list of assumptions and particular notes appended to the relevant section of the model (see below).

Merck Sharp & Dohme submitted that similar heart failure rates to that observed in PROactive had been seen in other long-term glitazone trials (eg ADOPT, with rosiglitazone) and – with both agents – in a recent meta-analysis (Nesto *et al* 2007). The use of PROactive as the benchmark study was justified and reasonable. The results of PROactive were completely in line with the general body of evidence on this subject and the nature of the study was signalled quite clearly to the user in the appended notes.

Extension of pioglitazone results to rosiglitazone

Merck Sharp & Dohme submitted that the Panel commented in passing that the results from PROactive with pioglitazone had been extended in the model to rosiglitazone as well, implying that this was not a valid extrapolation. On the contrary, as mentioned above, heart failure was a well-recognised side-effect of glitazone use, irrespective of which of the two currently marketed compounds was involved. This was evidenced by the broadly similar heart failure rates between the two agents seen in a recently published meta-analysis examining this issue (Nesto *et al*.). The extension of rates seen with pioglitazone to rosiglitazone use was concordant with available data, and not misleading.

Absence of long-term heart failure data with Januvia

Merck Sharp & Dohme noted that the Panel had noted that the assumption that Januvia would have the same heart failure risk as placebo in the PROactive study had been made in the absence of any long-term data (although, again, it recognised that this fact was stated in the list of assumptions and notes).

While it was true that the maximum trial duration for a published Januvia study was currently 52 weeks, there was a very large difference between the expectation of a heart failure event in glitazone-treated as opposed to Januvia treated patients. The known increased incidence of heart failure with glitazone use was associated with a quite specific and well-recognised pathophysiological precipitating event observed with glitazone agents, namely an increase in fluid volume. As well as leading to peripheral oedema and haemodilution, this increased fluid volume placed an additional load on the myocardium, resulting, in susceptible patients, in an increased risk of developing overt heart failure.

Merck Sharp & Dohme reiterated, as noted by the Panel, the Januvia SPC did not refer to any cardiovascular problems related to therapy. As such, Merck Sharp & Dohme submitted that the assumptions in the model were warranted and not misleading.

The use of 'footnotes'

Merck Sharp & Dohme noted that the Panel had commented on the use of 'footnotes' in the calculation of heart failure incidence rates, citing the supplementary information to Clause 7.2 of the Code. Some of these notes had been referred to above.

Merck Sharp & Dohme queried whether these notes should be considered as footnotes in the generally accepted sense. They were in quite large type, and were not cited at the foot of the page in question, being appended to the cost calculation table to which they referred. As such, Merck Sharp & Dohme submitted that they were addenda and additional information relating to the specific data table, rather than footnotes as such.

Merck Sharp & Dohme submitted that leaving matters of definition aside, the Panel's view raised serious issues concerning the use of any health economic model; and highlighted the very significant differences between such models and the more familiar area of interpreting clinical trials results. In the latter case, the results or findings were usually fairly clear-cut, and Merck Sharp & Dohme fully accepted that inappropriate interpretation or use of such results was not mitigated by the addition of footnotes. Health economics, however, was not an exact science. Any health economic model was built upon a foundation of assumptions and approximations, often more or less speculative in nature. Without such assumptions and approximations, it would be impossible to generate any model whatsoever. Within broad limits, no one set of assumptions was the correct one, although of course some might accord more with common sense and scientific opinion than others. It was thus of crucial importance that the assumptions on which the model was based were completely transparent, so that the user could properly assess the appropriateness of the conclusions to his or her individual circumstances. This was the purpose of the notes appended to the table in question.

Merck Sharp & Dohme noted that the Panel questioned the use of words like 'speculative' to describe the methodology and data used in the model, taking that to mean that the conclusions derived from it were incapable of being robustly substantiated, and thus in breach of the Code. Again, Merck Sharp & Dohme suggested that practically no health economic model was totally substantiable in the strict sense. By necessity, the cost model approach involved ambiguities and uncertainties. The most that could be done was to provide the user with adequate information on which to draw their own judgement as to the relevance of the information provided. The issues around whether the particular assumptions etc in the present model were reasonable ones was addressed elsewhere but Merck Sharp & Dohme submitted that the underlying principle of making these assumptions plain was both sound and necessary.

Heart failure cost calculation

Merck Sharp & Dohme noted that the Panel had queried whether it was appropriate to use the mean expected cost of heart failure (from UKPDS 65), as opposed to the estimated annual cost, conditional on some costs being incurred. Merck Sharp & Dohme submitted that given that PROactive presented the data for in-patient and non-in-patient episodes of heart failure, this might be an understandable viewpoint. However, as the original article was based on a study conducted in the UK, reflecting appropriate treatment and classification patterns, it was decided to base the costs on the final expected (or unconditional) data reported by the authors.

Furthermore, Merck Sharp & Dohme submitted that as the value suggested for in-patient care by the Panel was actually higher than that used in the model, a greater cost offset through the use of Januvia would have been estimated had the Panel's suggestion been implemented; although the cost of non-in-patient care was lower, once values were inflated to current levels using generally accepted criteria (£5,654 and £155, respectively), the total cost offsets increased by around £160. This adjustment represented a change of less than 4% in the overall outcome, and its omission represents a conservative approach to the estimation of cost offsets available through the use of Januvia. Indeed, all assumptions used in the model tended towards the more conservative interpretation of the available data.

Possible hidden costs

Merck Sharp & Dohme noted that the Panel had queried whether costs other than those arising from heart failure, hypoglycaemic events and self-monitoring of blood glucose would impact on the cost of Januvia therapy. Merck Sharp & Dohme took this to mean that the Panel was concerned that there might be other ancillary costs associated with the use of Januvia, and/or other agents assessed, that were not taken account of in the model. Merck Sharp & Dohme submitted that it was not aware of any such additional potential costs. The adverse reactions associated with Januvia use, as detailed in the SPC, were generally non-specific and non-severe, and would not be expected to have any significant impact on the overall cost impact of the product.

Local costs versus national data

Merck Sharp & Dohme noted that the Panel was concerned that, although the stated purpose of the model was to answer the question 'What is the impact of using Januvia in my local area?', the medicine costs involved were based on national figures. The Panel considered this to be so misleading that an additional breach of Clause 7.2 was ruled.

This was a particularly harsh ruling. Self-evidently, members of PCT management teams – at whom this model was directed – would be interested in the impact of Januvia on local budgets, hence the question above. Equally self-evidently, it would be wholly impractical, if not impossible, to produce separate sets of figures for every individual PCT. Nor was it conceivable that acquisition costs within any one PCT

would differ so markedly from average national costs as to render the overall conclusion of the model invalid. It was common practice to estimate the average cost of treatments through the use of data on national prescribing trends, as conducted in this model. A similar methodology was utilised by the Scottish Medicines Consortium.

Merck Sharp & Dohme again emphasised that the purpose of the model was to provide users with a broad assessment of the sort of costs that might be expected to be associated with the use of Januvia in their locality. It was not intended to supply a detailed and accurate local costing correct to the nearest penny; nor would it be expected to do so. In the disclaimer statement, in the briefing document, and at various points within the model itself, it was made quite clear that the costs involved were approximations, and that the data in the model should be interpreted at a local level in accordance with local practice and circumstances. Particular limitations and assumptions inherent in the model were duly noted in addenda to data tables, etc. The fact that the Panel found these statements also to be in breach of the Code evidently raised a significant concern.

Merck Sharp & Dohme submitted that the above dealt with all of the substantive points raised by the Panel in its ruling. To summarise, with the exception of a minor factual error which had a negligible effect on the conclusions drawn from the model, the assumptions and data on which the model was based were reasonable; the limitations and essentially approximate nature of the calculations were clearly signalled at multiple points and overall, the conclusion of the model that use of Januvia in the specified population would not lead to significant increases in local prescribing budgets was fair and warranted.

In all of these respects, Merck Sharp & Dohme maintained its view that the model was not misleading and therefore it appealed the rulings of breaches of Clauses 7.2 and 7.4.

APPEAL BOARD RULING

The Appeal Board noted that the Januvia budget impact model was a one year model designed to answer the question 'What is the financial impact of using Januvia in my local area?' The Appeal Board was provided with printouts of screens of the model. It did not have the model itself.

The Appeal Board noted from Merck Sharp & Dohme's submission that only 8.5% of the cost of Januvia could be offset by a potential reduction in the incidence of adverse events associated with other oral treatments for diabetes compared with Januvia (eg heart failure with glitazones and hypoglycaemia with sulphonylureas) or a potential reduction in the need for self-monitoring of blood glucose. It was possible not to include these cost offsets in the estimation. The Appeal Board noted that the model could estimate the cost for a PCT-defined percentage of patients eligible for Januvia or default settings could be used. The Appeal Board considered that by their nature models such as the Januvia budget impact model could only give estimates but that their intended audiences ie appropriate PCT personnel, would understand such constraints.

The Appeal Board noted that in the model the study rate for heart failure incidence in-patient figures from the PROactive study had been transposed with non-in-patient figures. Although it considered that this was a most unfortunate error, the Appeal Board noted Merck Sharp & Dohme's submission for the appeal that it made a difference of less than 0.1% of the calculated cost. In the context of the material in question, the Appeal Board considered that the error had not materially affected the outcome. Although the Appeal Board had concerns about the introductory disclaimer it considered that the limitations of the model were clear and would be understood by the intended audience.

The Appeal Board noted that the complainant was concerned about the costs of heart failure and other hospital costs. The annual incidence rates for heart failure were calculated from the 34.5 month pioglitazone and placebo rates in the PROactive study. The Appeal Board noted that compared with other studies the heart failure rate reported in the PROactive study was a conservative value and as such was not unreasonable. The Appeal Board noted that the heart failure section cited relevant assumptions as did other sections of the cost offsets section.

The Appeal Board did not consider that the heart failure costs were misleading. Within the accepted limits of a health economic model they were capable of substantiation. No breach of Clauses 7.2 and 7.4 were ruled. The appeal on this point was successful.

The Appeal Board noted that the calculation of the weighted costs of competitor products was based on national figures and as such might not reflect local prescribing habits. However, the Appeal Board considered that the intended audience would understand such figures and not be misled by them. No breach of Clause 7.2 was ruled. The appeal on this point was successful.

Complaint received **16 July 2007**

Case completed **11 January 2008**

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During its consideration of this case, the Panel sought advice from Professor Martin Buxton BA (Soc Sci), Professor of Health Economics and Director of the Health Economics Research Group at Brunel University, and independent health economics consultant, who provided an opinion in a personal capacity.

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