Chapter 6

Claims in advertisements for Angiotensin II Receptor Blockers

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Abstract

Objective

To determine how the pharmaceutical industry deals with evolving clinical evidence in their advertising claims for the different angiotensin II receptor blockers (ARBs) over a 9-year period, and whether a self-regulatory system is effective in ensuring that pharmaceutical promotion is up to standard.

Methods

We examined all advertisements from consecutive issues of the Dutch Journal of Medicine published between 1996-2004. We reviewed the content of advertisements for ARBs and judged whether claims were in agreement with the information available from the approved summary of product characteristics and evidence from cited clinical trials. Subsequently, we reviewed whether the claims had been assessed by the Code of Practice authority.

Results

We identified 28 unique advertisements with in total 290 appearances for seven ARBs. ARBs were the most frequently advertised antihypertensive drug class since 1998. Claims of blood pressure lowering, safety and convenient use were all judged to be sufficiently substantiated. Claims suggesting effects on long-term outcomes started in 1999, and were made in 13 unique advertisements. In 8 cases (56 appearances), claims suggesting protection or risk reduction were not supported by the available information. Some claims seemed to transfer results from a specific patient group to the general population of hypertensive patients. Two cases were reviewed by the Code of Practice authority.

Conclusions

One in every five advertisements for ARBs contained suggestive claims not supported by the information in the summary of product characteristics. The current system of self-regulation cannot ensure that pharmaceutical promotion is always accurate, balanced, and evidence-based.

Introduction

Concerns on the quality of drug advertising exist for many years. Several studies have documented inaccuracies and misleading claims in drug advertisements.[1-7] Individual countries have dealt with this problem in various ways. In Europe, the advertising of medicinal products was harmonised by the Council Directive 1992/28/EEC. In The Netherlands, this Directive was implemented in the form of the Medicinal Products Advertising Decree in 1994. Governments in Europe, Canada and Australia have ceded control of pharmaceutical promotion to Code of Practice authorities. These authorities have developed self-regulatory pharmaceutical advertising codes of conduct to which pharmaceutical companies are expected to adhere. According to these regulations, all claims concerning drugs should be accurate, up-to-date, truthful, correct, verifiable, and may not be misleading.[8;9] Advertising claims must not in any way conflict with the officially approved summary of product characteristics and must encourage rational drug use.[8]

Before a new drug is allowed on the market, it is tested in clinical trials to show its safety and efficacy, at least in terms of intermediate outcomes. This information is included in the summary of product characteristics, and can be used in advertising claims. Once on the market, new information may become available about side effects and long-term outcomes. In addition, new evidence on similar drugs belonging to the same drug class can become available. It is not clear how the pharmaceutical industry deals with this evolving clinical evidence in their advertising claims.

Up to now, studies on pharmaceutical advertising only documented the quality of claims in a particular year, and did not investigate how new research findings were presented in the advertisements over time.[3-7] Better insights in this process can help us identify whether current self-regulatory codes have been effective in ensuring that pharmaceutical promotion is up to standard.

We studied angiotensin II receptor blockers (ARBs) of which the first member was approved and introduced in 1995 and six additional class members became available within the next 8 years in The Netherlands. In 2001, it was shown for two ARBs that they decrease the progression of nephropathy in hypertensive patients with type 2 diabetes.[10-12] One year later, one ARB showed to reduce cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy.[13]

We investigated trends in advertising claims for all ARBs over a 9-year period, determining whether claims were substantiated by scientific evidence in this period.

Methods

Data collection

We reviewed pharmaceutical advertisements appearing between 1 January 1996 and 31 December 2004 in the *Nederlands Tijdschrift voor Geneeskunde* (Dutch Journal of Medicine). This medical journal is published weekly and is among the most widely circulated medical journals in The Netherlands (circulation of 32,000 in 2004). Regarding advertisements for antihypertensive drugs we recorded brand names and therapeutic class (diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors [ACE inhibitors] and ARBs) in the 466 retrieved issues. Advertisements for ARBs which differed in text from other advertisements were defined as unique advertisements.

Advertisement classification

We reviewed the information content of each unique advertisement. We classified each promotional claim as stating or suggesting:

1. effects on intermediate outcomes (e.g. lowering blood pressure)
2. effects on long-term outcomes (e.g. effects beyond intermediate outcomes, including prevention or reduction of cardiovascular and/or renal disease or mortality, by using statements as 'effects on end-organs', 'protection' or 'risk reduction')
3. safety (e.g. excellent tolerability, placebo-like side effect profile)
4. convenience (e.g. low frequency of dosage, no drug interactions)
5. costs (e.g. low price, cost-effective)
6. new formulation
7. other indications than hypertension.

Next, we judged whether the claims were substantiated by cited clinical trials or information in the officially approved summary of product characteristics (**Table 1**). In our assessments, we followed the standpoint of the regulatory agencies, i.e. that positive effects on long-term outcomes can not be derived from proven efficacy on intermediate outcomes. All claims were evaluated independently by three reviewers. Individual classifications were compared, and in case of discrepancy, the advertisement was reviewed again and discussed until a consensus was reached. Claims were categorized as: supported by information in summary of product characteristics (SPC) or a cited clinical trial that was designed to assess this claim and published in a peer-reviewed journal (+); only supported by a cited trial that was either not yet published or not designed to assess this effect for this drug in hypertensive patients (~); or not supported by information in the SPC or a reference to a clinical trial (-). The first category represents claims that are considered sufficiently supported.

Table 1 Clinical trials cited in advertisements of angiotensin II receptor blockers.

Trial	Time	Treatment	Major findings
IDNT [11]	Sept, 2001	ARB vs. placebo CCB vs. placebo ARB vs. CCB	Irbesartan is effective in protecting against the progression of nephropathy due to type 2 diabetes, independent of the achieved reduction in blood pressure.
RENAAL [10]	Sept, 2001	ARB vs. placebo	Losartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy, and it was generally well tolerated.
IRMA-2 [12]	Sept, 2001	ARB vs. placebo	Irbesartan is renoprotective independently of its blood pressure lowering effect in patients with type 2 diabetes and microalbuminuria.
Val-HeFT [21]	Dec, 2001	ARB vs. placebo	Valsartan significantly reduced mortality and morbidity in patients with heart failure not treated with ACE inhibitors.
LIFE [13]	March, 2002	ARB vs. BB	Losartan prevents more cardiovascular morbidity and death than atenolol for similar reduction in blood pressure and is better tolerated.
VALUE [22]	June, 2004	ARB vs. CCB	No difference in morbidity and mortality between valsartan and amlodipine.

ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; BB, beta-blocker.

Subsequently, we examined whether the Code of Practice authority in The Netherlands had reviewed any of the advertising claims during the study period (CGR Foundation).[a]

Analyses

To assess trends, we calculated the proportion of advertisements for each antihypertensive drug class of all advertisements for antihypertensive drugs per year. To show the proportion of specific claims made for ARBs, we calculated the number of appearances of each type of claim divided by the total number of advertisements made for ARBs.

Results

Trends in advertisements

We identified a total of 492 advertisements for antihypertensive drugs during the period 1996-2004 in the Dutch Journal of Medicine. Of these, 290 (59%) were advertisements for ARBs. No advertisements for ARBs were observed in 1996, but ARBs have been the most frequently advertised antihypertensive drug class since 1998 (**Figure 1**).

Overall, 28 unique advertisements appeared for the seven ARBs. The ARBs each showed a different pattern of advertising both in quantity and timing. Some ARBs, e.g. irbesartan, candesartan, and eprosartan, were advertised continuously throughout the study period, whereas others, e.g. losartan, valsartan, and telmisartan, only for limited time periods (**Table 2**).

[a] Available at http://www.cgr.nl.

Table 2 Type of claims in 290 advertisements for seven different angiotensin II receptor blockers.

				Type of claim
Generic name*	Period	No. of ads appearances†	Trade name	Effects on blood pressure
Losartan	1995 – 1996	-	-	-
(March 1995)	1997	10	Hyzaar	
	1998 – 2000	-	-	-
	2001	12	Cozaar	X
	2001 – 2002	13	Cozaar	
	2002	4	Cozaar	
	2003 – 2004	-	-	-
Valsartan	1996 – 2001	-	-	-
(Nov 1996)	2002	2	(Co-)Diovan	X
	2003	-	-	-
	2004	6	(Co-)Diovan	X
	2004	1	(Co-)Diovan	X
	2004	5	Diovan	X
	2004	2	(Co-)Diovan	X
Irbesartan	1997 – 1998	18	Aprovel	X
(Aug 1997)	1998 – 1999	23	Aprovel	X
	1999 – 2000	23	(Co-)Aprovel	X
	2000 – 2001	17	(Co-)Aprovel	X
	2002	3	Aprovel	
	2002 – 2003	8	Aprovel	
	2004	4	(Co-)Aprovel	X
Candesartan	1997	-	-	-
(Oct 1997)	1998	18	Atacand	X
	1998 – 2000	32	Atacand	X
	2000 – 2001	12	Atacand	X
	2000 – 2001	11	Atacand (Plus)	X
	2002 – 2004	-	-	-
Eprosartan	1998 – 1999	-	-	-
(Jan 1998)	2000 – 2002	18	Teveten	
	2002 – 2003	6	Teveten	X
	2004	6	Teveten	X
Telmisartan	1999 – 2000	17	Micardis	X
(Dec 1998)	2001 – 2002	-	-	-
	2003	8	Micardis (Plus)	X
	2004	-	-	-
Olmesartan	2003	-	-	-
(May 2003)	2004	1	Olmetec	
	2004	5	Olmetec	X
	2004	5	Olmetec	X
Total ‡		290		233 (80)

* In brackets is the date of regulatory approval in The Netherlands; † Number of times an advertisement with the same information content for the same trade name appeared;

Table 2 Continued

Type of claim				
Effects on long-term outcomes	Safety	Convenience	Costs	New formulation
-	-	-	-	-
	X			X
-	-	-	-	-
X	X	X		
X				
X	X			X
-	-	-	-	-
-	-	-	-	-
X				
-	-	-	-	-
X		X		
X				
X		X		
X		X		
	X			
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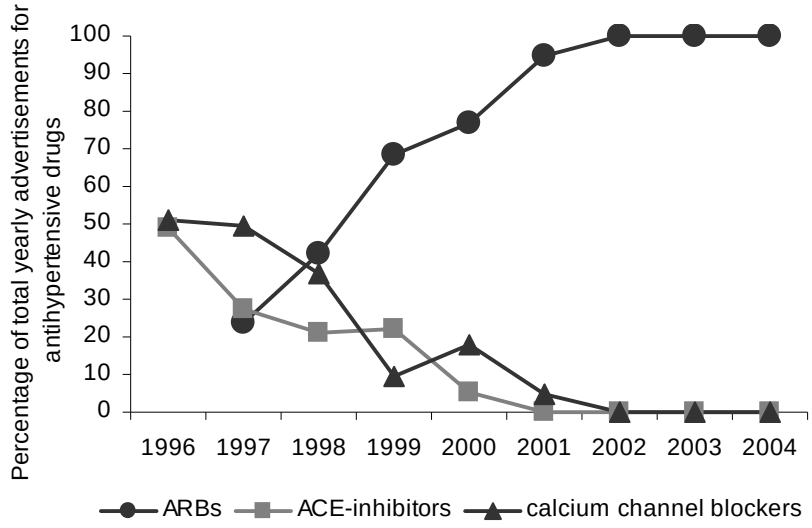
-	-	-	-	-
	X			
	X			
				X
-	-	-	-	-
-	-	-	-	-
		X	X	
X	X	X		
-	-	-	-	-
X		X		
-	-	-	-	-
-	-	-	-	-
				X
				X
				X
85 (29)	157 (54)	56 (19)	6 (2)	36 (12)

‡ Total number of advertisements for angiotensin II receptor blockers (proportion of advertisements with a certain type of claim).

Figure 1 Time trends in the proportion of the total number of advertisements for antihypertensive drugs devoted to different classes of antihypertensive drugs, 1996-2004.



ARB, angiotensin II receptor blocker

Trends in claims

During the whole study period, claims were made regarding efficacy in lowering blood pressure (**Table 2**). In total, 80% (233/290) of the advertisements for ARBs included such a claim. Claims suggesting effects on long-term outcomes started in 1999, and were made in 29% (85/290) of the advertisements. Approximately half (157/290) of the advertisements stated a claim of safety, but their frequency decreased dramatically by 2000. Some advertisements stated that ARBs were convenient in use (19%), mentioned new preparations (12%) or mentioned costs (2%).

Assessment of claims

Most claims were brief and non-specific. Claims regarding efficacy in lowering blood pressure, safety and convenient use were all judged to be sufficiently substantiated by the available information in the summary of product characteristics. Regarding safety, only vague claims were made like 'excellent tolerability' or 'placebo-like side effect profile'. None of the advertisements made specific claims, for instance, referring to the low incidence of side effects such as cough and angioedema or high persistence rates on ARBs.

Table 3 shows the 12 advertising claims made for four ARBs that we classified as stating or suggesting effects on long-term outcomes. These included four unique advertisements (appearing 28 times in total) that were considered to be sufficiently substantiated by the available evidence. For example, '25% more risk reduction for stroke (losartan)', 'renal protection and prevention in hypertensive patients with type 2 diabetes (irbesartan)' were substantiated by the cited trials. The claim '23% reduction of new-onset diabetes (valsartan)'

was supported by the VALUE trial but this was not a primary endpoint of this trial. In eight cases, claims were not substantiated by cited clinical trials or information in the summary of product characteristics. Advertisements with these claims appeared 57 times, which constituted 20% of all advertisements. For losartan, the first of a series of three unique advertisements with claims regarding effects on end-organs was considered premature. At that time, results from clinical trials showing long-term benefits were not yet published and the cited studies only showed effect on intermediate outcomes. In the first advertisement for valsartan, results on hard endpoints in heart failure patients were used in claims for an agent registered only for hypertension. In three subsequent advertisements, the claims 'valsartan protects' and 'a few millimetres reduction in blood pressure decrease gives kilometres cardiovascular protection' were made, again suggesting beneficial effects on morbidity or mortality in hypertensive patients for which there was no evidence provided. For irbesartan, the claim of long-term benefits was expanded to hypertensive patients in general in the last of a series of three unique advertisements. Finally, for telmisartan there were two advertisements appearing during 3 years in which the word 'protection in early morning hours' was used, partly in combination with a remark that this correlates with early morning cardiovascular events.

Complaints about promotional material

During the study period, the Code of Practice authority received complaints regarding two of the claims that we considered as being problematic. One of the complaints focussed on the claim 'significant reduction in mortality and morbidity, as proven in Val-HeFT' and another complaint was made for the claim 'valsartan protects'. The complainant alleged that claims using results from the Val-HeFT trial which consisted of heart failure patients suggested that heart failure was an approved indication for valsartan. The authority, however, did not rule on this complaint. Regarding the claim 'valsartan protects', the authority took the view that this was not in breach of the code since it was generally known that lowering blood pressure reduces the risk of end-organ damage. After this ruling in 2001, the complainant also felt free to make general claims of risk reduction for an ARB without further supporting evidence.

Table 3 Claims for angiotensin II receptor blockers suggesting or stating effects on long-term outcomes.

Product	Claim (literal translation)	Period	No. of ads appearances*	Support for this claim†	
Losartan	'favourable effects on end-organs'	February 2001 to October 2001	12 (1)	~	Cited clinical trials only showed effect on intermediate outcomes.
	'proven renal protection in hypertensive patients with type 2 diabetes and nephropathy'	October 2001 to May 2002	13 (1)	+	Cited RENAAL trial showed renoprotective effect of losartan in hypertensive patients with type 2 diabetes.
	'25% more risk reduction for stroke'	September 2002 to November 2002	4 (1)	+	Cited LIFE trial showed that losartan prevents more morbidity and death than atenolol in hypertensive patients.
Valsartan	'significant reduction in mortality and morbidity, as proven in Val-HeFT'	June 2002	2 (1)	~	Study population of the cited Val-HeFT trial consisted of heart failure patients, while heart failure was not an approved indication for valsartan.
	'valsartan protects'	January 2004 to April 2004	6 (1)	-	No cited trial or information in SPC showing beneficial effects of valsartan on mortality or morbidity in hypertensive patients.
	'23% reduction of new-onset diabetes'	July 2004	1 (1)	~	In the cited VALUE trial new-onset diabetes arose in fewer patients on valsartan than on amlodipine but this was not a primary endpoint of the trial.
	'a few millimetres reduction in blood pressure decrease gives kilometres cardiovascular protection'	July 2004 to October 2004	7 (2)	-	No cited trial or information in SPC showing beneficial effects of valsartan on mortality or morbidity in hypertensive patients.

Table 3 Continued

Product	Claim (literal translation)	Period	No. of ads appearances*	Support for this claim†	
Irbesartan	'renal protection and prevention in hypertensive patients with type 2 diabetes'	March 2002 to June 2002	3 (1)	+	Both the cited IDNT trial and IRMA-2 trial showed renoprotective effect of irbesartan in hypertensive patients with type 2 diabetes.
	'first ARB with an additional indication: treatment of nephropathy in hypertensive patients with type 2 diabetes'	September 2002 to November 2003	8 (1)	+	Based on results of the IDNT trial and IRMA-2 trial, irbesartan received the approval for this additional indication in SPC.
	'powerful authority in risk reduction, power over hypertension'	September 2004 to December 2004	4 (1)	-	No cited trial or information in SPC showing risk reduction of irbesartan in hypertensive patients in general.
Telmisartan	'protection in the early morning hours'	September 1999 to December 2000	17 (1)	~	The cited study assessed the antihypertensive effect and duration of action of telmisartan but not any protective effects. SPC states that beneficial effects of telmisartan on mortality and cardiovascular morbidity are currently unknown.
	'... offers protection against early morning peaks in blood pressure, which fall together with a peak incidence of cardiovascular events'	February 2003 to October 2003	8 (1)	~	The cited studies cited assessed the antihypertensive effect and duration of action of telmisartan, and did not show beneficial effects of telmisartan on cardiovascular events.

SPC, summary of product characteristics. * Number of times this advertisement with this claim appeared; number of unique advertisements in brackets. † Supported by information in SPC or a cited clinical trial that was designed to assess this effect (+), only supported by a cited trial that was either not yet published or not designed to assess this effect for this drug in hypertensive patients (~) or not supported by information in the SPC or a reference to a clinical trial (-).

Discussion

To our knowledge, this is the first study assessing the effects of evolving clinical evidence on pharmaceutical marketing claims in journal advertisements. We found that ARBs have been the most frequently advertised antihypertensive drug class in The Netherlands since 1998. While awaiting the results of large clinical trials, ARBs were mostly promoted using claims of their efficacy in lowering blood pressure and their excellent safety profile. These claims were all substantiated by information available at the time of regulatory approval.

Starting in 1999, claims suggesting efficacy beyond blood pressure lowering were observed, several of which were not supported by clinical trials or information in the summary of product characteristics. New information regarding good tolerability and high persistence rates on ARBs was not prominently used in the advertisements.

It is well-known that the pharmaceutical industry spends large amounts of money on promoting its products. This is particularly the case in a field in which several drugs compete for the same patient population, and pharmaceutical companies need to develop campaigns to distinguish between almost identical products. Under these circumstances, clinical research on long-term outcomes becomes part of a race to obtain results to strengthen the market position of a drug. Also in our study we observed advertisements with imprecise interpretation of scientific evidence. Just before the first results of trials on hard endpoints became available, losartan started to use the claim of beneficial effects on end-organs. Although with hindsight one could argue that this claim was correct, at that time it was not sufficiently substantiated. It has been shown that claims based on the results that have not yet been scrutinized and published in a peer-reviewed journal, can be overly optimistic.[14] Soon after the first trials on hard endpoints in hypertensive patients had been completed for some of the ARBs, advertisements for valsartan started to claim risk reduction using results from a trial evaluating effects in heart failure patients. It is not allowed to promote drugs for non-approved indications, and the advertisements indeed only mentioned the approved indication of hypertension. Advertisements for irbesartan showed that after a period of using claims clearly substantiated by clinical trials, also more general claims are made that are not based on such evidence.

Previous studies showed that the number of references to clinical trials in drug advertisements has increased in recent years, but many claims were still not adequately substantiated by these references.[5-7] These findings are troublesome, since research shows that drug advertising serves as an important source of information for physicians.[15;16] Although many physicians perceive themselves as paying little attention to drug advertisements, advertising has been shown to influence physicians' beliefs about the effectiveness of drugs.[15]

We defined general claims of 'protection' or 'risk reduction' as claims suggesting beneficial effects on long-term outcomes. This position was also taken by the Code of Practice authority

when they reviewed one of these claims but they did not object against using such a claim for a drug that had only proven to lower blood pressure. This differs from the standpoint of the regulatory agencies that we also used in our assessments, i.e. that positive effects on long-term outcomes can not be derived from proven efficacy on intermediate outcomes. After this ruling of the Code of Practice authority, another manufacturer also felt free to make general claims of risk reduction without further supporting evidence.

We assessed claims of 'placebo-like side effect profile' as adequately substantiated when the summary of product characteristics mentioned that the incidence pattern of side effects was comparable to a placebo. In the UK, however, complaints about claims of 'placebo-like tolerability' for both valsartan and irbesartan were reviewed in 2003 and 2004 by the Medicines and Healthcare products Regulatory Agency (MHRA).[b] This governmental agency, which is complimentary to the self-regulation by the pharmaceutical industry, considered this claim to be misleading as it implied that there were no drug associated side effects and suggested that the product was 'safer' than alternative medicines. In this respect the MHRA appears to take a different position than the self-regulatory Prescription Medicines Code of Practice Authority in the UK, which accepted that 'placebo-like tolerability' was a characteristic that could be attributed to various agents in the class of ARBs.[c]

Regulations and self-regulatory systems are probably effective in preventing some drug promotion abuses by providing the opportunity to submit complaints and by ruling against code violations.[6] Clear violations of specific requirements, such as referring to a clinical trial before it is published, were judged as breaching the Code of Practice. Rules on vague or suggestive claims are more difficult to make. Only two of the claims we considered as being problematic were reviewed by the Code of Practice authority. We do not know how many complaints were settled out of court.

These findings show the potential weaknesses of the current system. It has been suggested that there should be an active monitoring system for recognizing violations, independent monitoring committees, and effective sanctions for code violations.[3;7;17;18] The British example clearly shows that a governmental committee may be more critical in judging whether a claim might mislead the prescribers than a self-regulatory authority. Aside from a stricter control of the regulations, it has also been recommended to tighten them up.[19] Some specific requirements could be formulated to counter the observed problems. One could think of rules for mentioning the approved indication as well as the studied patient population on which claims are based clearly in the advertisement itself. Furthermore, a clear warning statement could be required in advertisements for drugs that have not yet proven efficacy on relevant

[b] The cases are in the section advertising complaints published on 2 April 2004 and 5 May 2004, available at http://www.mhra.gov.uk.

[c] The case is in the Code of practice Review, number 30, November 2000, available at http://www.abpi.org.uk/links/assoc/pmcpa.asp.

long-term outcomes. This would be on par with the European Medicines Agency guidelines from 1997 which state that the summary of product characteristics should explicitly mention when beneficial effects on mortality and cardiovascular morbidity are unknown until the results from adequate trials supporting this effect are available.[20] A strength of this study is that we collected data over a long time period enabling to assess the effects of evolving clinical evidence on marketing claims. During the study period, new evidence regarding efficacy and safety became available for the drug class studied.

There are some limitations. First, although we investigated all journal advertisements in the most widely circulated national medical journal, this may not reflect the frequency or types of claims in other medical journals nor in other types of promotion. Second, we assessed the textual content of the advertisements, whereas drugs are promoted through text as well as colourful, attention-grabbing images which can also inform and mislead the reader.[1]

In conclusion, this study showed that twenty percent of all ARB advertisements contained claims suggesting benefits that were not supported by the cited scientific evidence or the summary of product characteristics. Most of these claims were not reviewed by the self-regulatory authority. At this moment, physicians cannot fully rely on the current system of self-regulatory codes for pharmaceutical promotion. Before drawing conclusions from advertising claims, they need to investigate the supporting information themselves. An additional monitoring agency and tightened rules might help to ensure that pharmaceutical promotion is accurate, balanced, and evidence-based.

Acknowledgments

We have send this manuscript to Merck Sharpe & Dohme BV, Sanofi-Aventis BV, Boehringer Ingelheim BV and Novartis Pharma BV to offer them an opportunity to react on our results. They considered the criticised advertising claims to be legally correct according to the current codes and regulations, and felt supported in this by the rulings of the Code of Practice authority. Regarding telmisartan and losartan, our assessment that the claims suggested effects on long-term outcomes were disputed.

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