



## Superior efficacy of new medicines?

Johan C. F. Luijn, Frank W. J. Gribnau, Hubert G. M. Leufkens

### ► To cite this version:

Johan C. F. Luijn, Frank W. J. Gribnau, Hubert G. M. Leufkens. Superior efficacy of new medicines?. European Journal of Clinical Pharmacology, 2010, 66 (5), pp.445-448. 10.1007/s00228-010-0808-3 . hal-00576094

**HAL Id: hal-00576094**

**<https://hal.science/hal-00576094>**

Submitted on 12 Mar 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



### Superior efficacy of new medicines?

Journal:	<i>European Journal of Clinical Pharmacology</i>
Manuscript ID:	EJCP-2009-0399.R1
Type of submission:	Special Article
Date Submitted by the Author:	16-Feb-2010
Complete List of Authors:	van Luijn, Johan; Utrecht Institute for Pharmaceutical Sciences, Pharmacoepidemiology and Pharmacotherapy; Health Care Insurance Board, Research and Development Gribnau, Frank; Radboud University Medical Centre, Pharmacology and Toxicology Leufkens, Hubert; Utrecht Institute fir Pharmaceutical Sciences, Pharmacoepidemiology and Pharmacotherapy

Superior efficacy of new medicines?

Johan C.F. van Luijn<sup>1,2</sup>, Frank W.J. Gribnau<sup>3</sup>, Hubert G.M. Leufkens<sup>1</sup>

<sup>1</sup> Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht, Netherlands.

<sup>2</sup> Health Care Insurance Board, Diemen, Netherlands

<sup>3</sup> Department of Pharmacology and Toxicology, Section Clinical Pharmacology and Toxicology, Radboud University, Medical Centre, Nijmegen, Netherlands

Word count/tables

Words abstract: 149

Deleted: 25

Words article: 1530

Deleted: 410

Table: 1

Figure: 1

Correspondence:

Prof. H.G.M. Leufkens

Division of Pharmacoepidemiology and Pharmacotherapy,  
Utrecht Institute for Pharmaceutical Sciences,  
Faculty of Science, Utrecht University,  
PO Box 80.082, 3508 TB, Utrecht, The Netherlands.

[H.G.M.Leufkens@uu.nl](mailto:H.G.M.Leufkens@uu.nl)

Tel: +31 30 253 7324

Fax: +31 30 253 9166

## Abstract

### *Purpose*

To give an overview of and to discuss new authorized medicines with an improved efficacy.

### *Methods*

[The analysis focused on new medicines with an improved efficacy based on randomised active control trials.](#)

Information on comparative efficacy was obtained from the EMEA European Public Assessment Reports.

Deleted: of new medicines

### *Results*

Between 1999 and 2005 we identified 122 new medicines with a new active substance; for 13 (10%) medicines superiority was demonstrated [in case of a statistically significant difference in primary clinical endpoints](#).

### *Conclusions*

A proven advantage in efficacy at an early stage of drug development is the exception rather than the rule. The absence of evidence for differences between medicines does not mean the absence of differences. Optimal pharmacotherapy would benefit from more comparative research in the development of new medicines. Results of comparative trials need a critical evaluation of their specific value to clinical practice. Prescription data may be helpful.

### **Keywords:**

Randomized active control trials, superiority trials, comparative information, market authorization, added therapeutic value

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Introduction

The goal of developing new medicines should be an improvement in treatment: the new medicine should benefit patients when compared to previously existing options [1-4].

Field Code Changed

This added therapeutic value might lie in different properties such as efficacy, safety, applicability, convenience of administration, etc., the first two of which are considered as the most important: a new, more efficacious and/or safer medicine.

Demonstrating any improvement is not an explicit condition for being granted marketing authorization. Data on quality, efficacy and safety are therefore needed in order to demonstrate a favourable benefit/risk ratio when treating a patient for the claimed therapeutic indication. For that purpose, placebo controlled trials provide robust evidence [5,6]. However, regulatory authorities also want to be sure that, for new medicines for which good alternatives are available, the possibility has been excluded that patients are treated with a product that is less efficacious or less safe [7]. Files submitted to the regulatory authorities can include studies that demonstrate efficacy by confirming the absence of a difference (equivalence trial), or by showing that the new medicine is no worse than an existing medicine (noninferiority trial). Besides this, efficacy can also be demonstrated by showing an improved efficacy compared with a medicine already used in practice for the same claimed therapeutic indication (superiority trial). It goes without saying that the results of these trials are particularly interesting as they inform us how new medicines, accurately estimated for their efficacy, contribute to an improvement in treatment for patients. Statistics on the extent of superior medicines as a result of the marketing authorization process are scarce.

Field Code Changed

Field Code Changed

The aim of this study is to give an overview of and to discuss new authorized medicines with an improved efficacy.

Methods

We did a further analysis of the data from a previous study about the availability of comparative information on new medicines at the moment of European market authorization [8]. We therefore analyzed the European Public Assessment Reports (EPARs) of the European Medicines Agency (EMA) between 1999 and 2005 on new medicines with a new active substance [9]. The analysis focused on new medicines with an improved efficacy based on randomised active control trials (RaCTs). Data about the RaCTs, extracted from the EPARs included therapeutic indication, objective, comparator, design, clinical endpoints, results and the conclusion of the Committee for Medicinal Products for Human Use (CHMP) on comparative efficacy.

Field Code Changed

Field Code Changed

Deleted: trials

Deleted: also

Results

Between 1999 and 2005 we identified 122 new medicines with a new active substance, of which 58 (48%) had been studied in comparison with existing medicines. Of the main/pivotal active control trials (N=153), the objective of 15 (10%) was to show superiority: for 4 trials this objective failed. For bimatoprost, fondaparinux,

peginterferon alfa-2a, peginterferon alfa-2b and tipranavir the objective demonstrating superiority was realized. A difference in efficacy was also demonstrated in 13 trials with the primary objective to show noninferiority or equivalence. The medicines were considered as superior in case of a statistically significant difference in primary clinical endpoints. In total superiority was demonstrated in 24 trials for 13 (10%) new medicines (see table 1).

## Discussion

Ideally, claims regarding an added value of a new medicine should be based on the results of comparative trials [3,10]. In a previous study we found that nearly one out of two new medicines had been studied in a randomized active control trial [8]. Further analysis of the data on comparative efficacy shows that an improvement was demonstrated for only one out of ten new medicines. Despite this small number, the conclusion cannot simply be drawn that the advance in pharmacotherapy is restricted to these new medicines. Nevertheless, this means there is sufficient reason to adopt a critical attitude towards claims of pharmaceutical companies regarding an added value of their new products.

A number of observations can be made regarding this result. Firstly, our analysis excluded new medicines for which no alternative was available and for which, inevitably, a comparative trial was lacking. However, developed as the first medicinal therapy for life-threatening or serious diseases, such medicines – for example, orphan drugs - can rightfully be considered an improvement in the treatment of patients. Secondly, we only focused on differences in efficacy and not on properties such as safety, applicability or convenience of administration. The reason is that main/pivotal trials are used in particular for demonstrating efficacy. Nevertheless, new medicines whose efficacy is equivalent or noninferior may have advantages in safety. For example, tenecteplase used in the treatment of suspected myocardial infarction; based on a study in 17005 patients, although it shows equivalence compared to alteplase, the safety profile seems to be in favour of tenecteplase [11].

Another reason for the small number of innovations is that, for granting market authorization, demonstrating advantages is not an objective in itself. So there is no need or requirement to conduct a trial with such an objective. Moreover, pharmaceutical companies would be taking a substantial risk, as failure to demonstrate superiority over a less expensive existing drug could be a financial disaster. The fact that, on the other hand, a positive result could be expected to lead to substitution of the comparator, appears to carry less weight.

Furthermore, we should comment that whether the 13 medicines in our analysis really are an improvement in therapy depends on a sound review of all relevant properties, the clinical relevance of the differences and the appropriateness of the comparator. It is important always to weigh up the advantages and disadvantages meticulously. This also applies to the medicines in our study, as far as possible with the data in the EPAR. For most studies the EPAR did not provide the basic details of trial design and results in a uniform fashion.

According the EPAR, the efficacy of bimatoprost and travoprost is superior to timolol in the treatment of glaucoma, but their safety profile is inferior due to a higher frequency of ocular side effects. The trial on

Deleted: This was also the case for 13

Deleted: /

Deleted: trials, as the result was a statistically significant difference in efficacy

Deleted: S

Deleted: The medicines were considered as superior in case of a statistically significant difference in primary clinical endpoints.¶

Deleted: Table 1 - New medicines (1999-2005) with an improved efficacy ¶

¶ New medicine ... [1]

Field Code Changed

Field Code Changed

Deleted: .

Deleted:

Field Code Changed

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

tipranavir demonstrates a superior antiviral activity, but also a higher frequency of hepatic events and lipodystrophy. Moreover, comparative efficacy is always linked to a specific comparator, therapeutic indication and type of patients. Emtricitabine was more efficacious compared with stavudine in naive HIV-infected patients. However, its efficacy was inferior in comparison with lamivudine in the same type of patients; its efficacy was similar in a study that compared it with lamivudine in experienced patients.

Regarding the appropriateness of the comparator, we can conclude, referring to a previous study, that the choice of the compator in the trials that demonstrated superiority was in line with recommendations on standard treatment [12].

Another issue in a critical evaluation of demonstrated superiority is the choice of the primary clinical endpoint. A composite endpoint was used for fondaparinux; analysis of all the endpoint events shows that the incidence of symptomatic venous thromboembolic events, including pulmonary embolism, was not significantly different between treatment groups [13,14].

Field Code Changed

Deleted: [12,13]

Deleted: ¶

Furthermore, we have to realise that drawing a conclusion of superiority based on a statistically significant difference says nothing about its practical significance. The absolute differences in change of glycated haemoglobin (HbA1c), demonstrated for insulin aspart and insulin glulisine compared to regular insulin, were, at best, of limited clinical relevance. Moreover, there was no relevant difference regarding the incidence of hypoglycaemic events. In this context it is interesting to follow developments in the prescription of fast-acting insulin in the treatment of diabetes, as the results of clinical studies may not always be reflected in practice

[15,16]. For prescription data, we used the GIP database of the Health Care Insurance Board in the Netherlands.

Field Code Changed

Deleted: [14,15]

This database contains data on the prescription of extramural medicines, obtained from health insurance organisations and based on a sample of more than 12 million people. Graph 1 shows developments in the usage before and after the introduction of insulin aspart. The degree to which insulin aspart is used cannot be completely explained on the results of the premarketing trials. The more rapid onset and shorter duration of action of the insulin analogue is thought to facilitate a more flexible life style in comparison with the use of soluble human insulins [17]. However, this should also apply to insulin lispro, which can be regarded as being comparable to insulin aspart [18].

Field Code Changed

Deleted: [16]

Field Code Changed

Deleted: [17]

Finally, significant advantages as well as disadvantages of new medicines may only become evident during the course of time, on the basis of further study and experience. This means that assessing the added value of a new medicine is not a one-off incident but a continual process, supported by monitoring usage by means of prescription data.

This study shows and discusses how proven superiority, in the sense of well-demonstrated advantages in efficacy at an early stage of drug development, is the exception rather than the rule. The absence of evidence for differences between medicines does not mean the absence of differences. Insight into differences and similarities between medicines, however small they may be, is important in order to make the right choice for the right patient in clinical practice. Therefore, optimal pharmacotherapy would benefit from more comparative research in the development of new medicines. This study also shows that the results of comparative trials need a critical evaluation of their specific value to clinical practice. Prescription data may be helpful.

**Funding:** The authors have no support or funding to report

**Competing interest:** The authors have declared that no competing interests exist

For Peer Review



Reference List

1. Dent TH and Hawke S (1997) Too soon to market. *BMJ* 315:1248-1249

2. Gale EA and Clark A (2000) A drug on the market. *Lancet* 355:61-63

3. Henry D and Hill S (1995) Comparing treatments. *BMJ* 310:1279

4. International Society of Drug Bulletins (2001) ISDB declaration on therapeutic advance in the use of medicines Paris. International Society of Drug Bulletins

5. Lewis JA, Jonsson B, Kreutz G, Sampaio C, van Zwieten-Boot B (2002) Placebo-controlled trials and the Declaration of Helsinki. *Lancet* 359:1337-1340

6. The European Agency for the Evaluation of Medicinal Products (2000) Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96) London, EMEA

7. Koopmans PP, de Graeff PA, Zwieten-Boot BJ, Lekkerkerker JF, Broekmans AW (2000) Clinical evaluation of efficacy and adverse effects in the (European) registration of drugs: what does it mean for the doctor and the patient? (in dutch). *Ned Tijdschr Geneeskd* 144:756-761

8. van Luijn JCF, Gribnau FW, Leufkens HG (2007) Availability of comparative trials for the assessment of new medicines in the European Union at the moment of market authorization. *Br J Clin Pharmacol* 63:159-162

9. The European Agency for the Evaluation of Medicinal Products (2009) European Public Assessment Reports. <http://www.emea.europa.eu/htms/human/epar/eparintro.htm>. Accessed October 2009.

10. Kaplan W (2004) Comparative effectiveness of medicines and use of head-to-head comparative trials In: Kaplan W (2004) Priority medicines for Europe and the world. Den Haag, Ministry of Health, Welfare and Sport

11. Van De Werf F, Adgey J, Ardissino D, et al. (1999) Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 354:716-722

12. van Luijn JCF, van Loenen AC, Gribnau FWJ, Leufkens HGM (2008) Choice of comparator in active control trials of new drugs. *Ann Pharmacother* 42:1605-1612

13. Heit JA (2002) The potential role of fondaparinux as venous thromboembolism prophylaxis after total hip or knee replacement or hip fracture surgery. *Arch Intern Med* 162:1806-1808

14. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR (2002) Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med* 162:1833-1840

15. Heerdink ER, Urquhart J, Leufkens HG (2002) Changes in prescribed drug doses after market introduction. *Pharmacoepidemiol Drug Saf* 11:447-453

16. Wathen B and Dean T (2004) An evaluation of the impact of NICE guidance on GP prescribing. *Br J Gen Pract* 54:103-107

17. Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L (2000) Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care* 23:583-588

18. Plank J, Wutte A, Brunner G, et al. (2002) A direct comparison of insulin aspart and insulin lispro in patients with type 1 diabetes. *Diabetes Care* 25:2053-2057

**Formatted:** Hyperlink, Do not check spelling or grammar

**Formatted:** Indent: Before: 0 pt, Hanging: 27 pt, Tabs: 18 pt, Right + 27 pt, Left

**Deleted:** Reference List¶

1. . Dent TH and Hawke S (1997) Too soon to market. *BMJ* 315:1248-1249¶

2. . Gale EA and Clark A (2000) A drug on the market. *Lancet* 355:61-63¶

3. . Henry D and Hill S (1995) Comparing treatments. *BMJ* 310:1279¶

4. . International Society of Drug Bulletins (2001) ISDB declaration on therapeutic advance in the use of medicines Paris, International Society of Drug Bulletins¶

5. . Lewis JA, Jonsson B, Kreutz G, Sampaio C, van Zwieten-Boot B (2002) Placebo-controlled trials and the Declaration of Helsinki. *Lancet* 359:1337-1340¶

6. . The European Agency for the Evaluation of Medicinal Products (2000) Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96) London, EMEA¶

7. . Koopmans PP, de Graeff PA, Zwieten-Boot BJ, Lekkerkerker JF, Broekmans AW (2000) Clinical evaluation of efficacy and adverse effects in the (European) registration of drugs: what does it mean for the doctor and the patient? (in dutch). *Ned Tijdschr Geneeskd* 144:756-761¶

8. . van Luijn JCF, Gribnau FW, Leufkens HG (2007) Availability of comparative trials for the assessment of new medicines in the European Union at the moment of market authorization. *Br J Clin Pharmacol* 63:159-162¶

9. . The European Agency for the Evaluation of Medicinal Products (2009) European Public Assessment Reports. <http://www.emea.europa.eu/htms/human/epar/eparintro.htm>. Accessed October 2009.¶

10. . Kaplan W (2004) Comparative effectiveness of medicines and use of head-to-head comparative trials In: Kaplan W (2004) Priority medicines for Europe and the world. Den Haag, Ministry of Health, Welfare and Sport¶

11. . Van De Werf F, Adgey J, Ardissino D, et al. (1999) Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 354:716-722¶

12. . Heit JA (2002) The potential role of fondaparinux as venous thromboembolism prophylaxis after total hip or knee replacement or hip fracture surgery. *Arch Intern Med* 162:1806-1808¶

13. . Turpie AGG, Bauer KA, Eriksson BI, Lassen MR (2002) Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med* 162:1833-1840¶

14. . Heerdink ER, Urquhart J, Leufkens HG (2002) Changes in ... [2]

Page 4: [1] Deleted

Luijn, J.C.F. van

2/16/2010 9:10:00 AM

Table 1 - New medicines (1999-2005) with an improved efficacy

New medicine	Indication	Comparator
Bimatoprost	Glaucoma	Timolol
Capecitabine	Colorectal cancer	5-FU/Folonic acid
Emtricitabine	HIV-infections (combination)	Stavudine
Fondaparinux	Prevention of venous thromboembolic events	Enoxaparine
Insulin aspart	Diabetes mellitus type 1	Insulin regular human
Insulin glulisine	Diabetes mellitus type 2	Insulin regular human
Lopinavir	HIV-infections (combination)	Nelfinavir
Peginterferon alfa 2a	Chronic hepatitis C	Interferon alfa 2b
Peginterferon alfa 2b	Chronic hepatitis C	Interferon alfa 2a
Tipranavir	HIV-infections (combination)	Interferon alfa 2b
Travoprost	Glaucoma	Protease inhibitors
Voriconazole	Invasive aspergillosis	Timolol
Zoledronic acid	Hypercalcaemia (tumour-induced)	Amfotericin B (conv)
		Pamidronate

Page 7: [2] Deleted

Luijn, J.C.F. van

2/15/2010 1:28:00 PM

## Reference List

1. Dent TH and Hawke S (1997) Too soon to market. *BMJ* 315:1248-1249
2. Gale EA and Clark A (2000) A drug on the market. *Lancet* 355:61-63
3. Henry D and Hill S (1995) Comparing treatments. *BMJ* 310:1279
4. International Society of Drug Bulletins (2001) ISDB declaration on therapeutic advance in the use of medicines Paris, International Society of Drug Bulletins
5. Lewis JA, Jonsson B, Kreutz G, Sampaio C, van Zwieten-Boot B (2002) Placebo-controlled trials and the Declaration of Helsinki. *Lancet* 359:1337-1340
6. The European Agency for the Evaluation of Medicinal Products (2000) Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96) London, EMEA
7. Koopmans PP, de Graeff PA, Zwieten-Boot BJ, Lekkerkerker JF, Broekmans AW (2000) Clinical evaluation of efficacy and adverse effects in the (European) registration of drugs: what does it mean for the doctor and the patient? (in dutch). *Ned Tijdschr Geneesk* 144:756-761
8. van Luijn JCF, Gribnau FW, Leufkens HG (2007) Availability of comparative trials for the assessment of new medicines in the European Union at the moment of market authorization. *Br J Clin Pharmacol* 63:159-162
9. The European Agency for the Evaluation of Medicinal Products (2009) European Public Assessment Reports. <http://www.emea.europa.eu/htms/human/epar/eparintro.htm>. Accessed October 2009.
10. Kaplan W (2004) Comparative effectiveness of medicines and use of head-to-head comparative trials In: Kaplan W (2004) Priority medicines for Europe and the world. Den Haag, Ministry of Health, Welfare and Sport
11. Van De Werf F, Adgey J, Ardissino D, et al. (1999) Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 354:716-722
12. Heit JA (2002) The potential role of fondaparinux as venous thromboembolism prophylaxis after total hip or knee replacement or hip fracture surgery. *Arch Intern Med* 162:1806-1808
13. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR (2002) Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med* 162:1833-1840

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

14. Heerdink ER, Urquhart J, Leufkens HG (2002) Changes in prescribed drug doses after market introduction. *Pharmacoepidemiol Drug Saf* 11:447-453

15. Wathen B and Dean T (2004) An evaluation of the impact of NICE guidance on GP prescribing. *Br J Gen Pract* 54:103-107

16. Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L (2000) Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care* 23:583-588

17. Plank J, Wutte A, Brunner G, et al. (2002) A direct comparison of insulin aspart and insulin lispro in patients with type 1 diabetes. *Diabetes Care* 25:2053-2057

For Peer Review

## Superior efficacy of new medicines?

Johan C.F. van Luijn<sup>1,2</sup>, Frank W.J. Gribnau<sup>3</sup>, Hubert G.M. Leufkens<sup>1</sup>

<sup>1</sup> Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht, Netherlands.

<sup>2</sup> Health Care Insurance Board, Diemen, Netherlands

<sup>3</sup> Department of Pharmacology and Toxicology, Section Clinical Pharmacology and Toxicology, Radboud University, Medical Centre, Nijmegen, Netherlands

### Word count/tables

Words abstract: 149

Words article: 1530

Table: 1

Figure: 1

### Correspondence:

Prof. H.G.M. Leufkens

Division of Pharmacoepidemiology and Pharmacotherapy,  
Utrecht Institute for Pharmaceutical Sciences,  
Faculty of Science, Utrecht University,  
PO Box 80.082, 3508 TB, Utrecht, The Netherlands.

[H.G.M.Leufkens@uu.nl](mailto:H.G.M.Leufkens@uu.nl)

Tel: +31 30 253 7324

Fax: +31 30 253 9166

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Abstract**

***Purpose***

To give an overview of and to discuss new authorized medicines with an improved efficacy.

***Methods***

The analysis focused on new medicines with an improved efficacy based on randomised active control trials. Information on comparative efficacy was obtained from the EMEA European Public Assessment Reports.

***Results***

Between 1999 and 2005 we identified 122 new medicines with a new active substance; for 13 (10%) medicines superiority was demonstrated in case of a statistically significant difference in primary clinical endpoints.

***Conclusions***

A proven advantage in efficacy at an early stage of drug development is the exception rather than the rule. The absence of evidence for differences between medicines does not mean the absence of differences. Optimal pharmacotherapy would benefit from more comparative research in the development of new medicines. Results of comparative trials need a critical evaluation of their specific value to clinical practice. Prescription data may be helpful.

**Keywords:**

Randomized active control trials, superiority trials, comparative information, market authorization, added therapeutic value

## Introduction

The goal of developing new medicines should be an improvement in treatment: the new medicine should benefit patients when compared to previously existing options [1-4].

This added therapeutic value might lie in different properties such as efficacy, safety, applicability, convenience of administration, etc., the first two of which are considered as the most important: a new, more efficacious and/or safer medicine.

Demonstrating any improvement is not an explicit condition for being granted marketing authorization. Data on quality, efficacy and safety are therefore needed in order to demonstrate a favourable benefit/risk ratio when treating a patient for the claimed therapeutic indication. For that purpose, placebo controlled trials provide robust evidence [5,6]. However, regulatory authorities also want to be sure that, for new medicines for which good alternatives are available, the possibility has been excluded that patients are treated with a product that is less efficacious or less safe [7]. Files submitted to the regulatory authorities can include studies that demonstrate efficacy by confirming the absence of a difference (equivalence trial), or by showing that the new medicine is no worse than an existing medicine (noninferiority trial). Besides this, efficacy can also be demonstrated by showing an improved efficacy compared with a medicine already used in practice for the same claimed therapeutic indication (superiority trial). It goes without saying that the results of these trials are particularly interesting as they inform us how new medicines, accurately estimated for their efficacy, contribute to an improvement in treatment for patients. Statistics on the extent of superior medicines as a result of the marketing authorization process are scarce.

The aim of this study is to give an overview of and to discuss new authorized medicines with an improved efficacy.

## Methods

We did a further analysis of the data from a previous study about the availability of comparative information on new medicines at the moment of European market authorization [8]. We therefore analyzed the European Public Assessment Reports (EPARs) of the European Medicines Agency (EMA) between 1999 and 2005 on new medicines with a new active substance [9]. The analysis focused on new medicines with an improved efficacy based on randomised active control trials (RaCTs). Data about the RaCTs extracted from the EPARs included therapeutic indication, objective, comparator, design, clinical endpoints, results and the conclusion of the Committee for Medicinal Products for Human Use (CHMP) on comparative efficacy.

## Results

Between 1999 and 2005 we identified 122 new medicines with a new active substance, of which 58 (48%) had been studied in comparison with existing medicines. Of the main/pivotal active control trials (N=153), the objective of 15 (10%) was to show superiority: for 4 trials this objective failed. For bimatoprost, fondaparinux,

peginterferon alfa-2a, peginterferon alfa-2b and tipranavir the objective demonstrating superiority was realized. A difference in efficacy was also demonstrated in 13 trials with the primary objective to show noninferiority or equivalence. The medicines were considered as superior in case of a statistically significant difference in primary clinical endpoints. In total superiority was demonstrated in 24 trials for 13 (10%) new medicines (see table 1).

**Discussion**

Ideally, claims regarding an added value of a new medicine should be based on the results of comparative trials [3,10]. In a previous study we found that nearly one out of two new medicines had been studied in a randomized active control trial [8]. Further analysis of the data on comparative efficacy shows that an improvement was demonstrated for only one out of ten new medicines. Despite this small number, the conclusion cannot simply be drawn that the advance in pharmacotherapy is restricted to these new medicines. Nevertheless, this means there is sufficient reason to adopt a critical attitude towards claims of pharmaceutical companies regarding an added value of their new products.

A number of observations can be made regarding this result. Firstly, our analysis excluded new medicines for which no alternative was available and for which, inevitably, a comparative trial was lacking. However, developed as the first medicinal therapy for life-threatening or serious diseases, such medicines – for example, orphan drugs - can rightfully be considered an improvement in the treatment of patients. Secondly, we only focused on differences in efficacy and not on properties such as safety, applicability or convenience of administration. The reason is that main/pivotal trials are used in particular for demonstrating efficacy. Nevertheless, new medicines whose efficacy is equivalent or noninferior may have advantages in safety. For example, tenecteplase used in the treatment of suspected myocardial infarction; based on a study in 17005 patients, although it shows equivalence compared to alteplase, the safety profile seems to be in favour of tenecteplase [11].

Another reason for the small number of innovations is that, for granting market authorization, demonstrating advantages is not an objective in itself. So there is no need or requirement to conduct a trial with such an objective. Moreover, pharmaceutical companies would be taking a substantial risk, as failure to demonstrate superiority over a less expensive existing drug could be a financial disaster. The fact that, on the other hand, a positive result could be expected to lead to substitution of the comparator, appears to carry less weight.

Furthermore, we should comment that whether the 13 medicines in our analysis really are an improvement in therapy depends on a sound review of all relevant properties, the clinical relevance of the differences and the appropriateness of the comparator. It is important always to weigh up the advantages and disadvantages meticulously. This also applies to the medicines in our study, as far as possible with the data in the EPAR. For most studies the EPAR did not provide the basic details of trial design and results in a uniform fashion. According the EPAR, the efficacy of bimatoprost and travoprost is superior to timolol in the treatment of glaucoma, but their safety profile is inferior due to a higher frequency of ocular side effects. The trial on tipranavir demonstrates a superior antiviral activity, but also a higher frequency of hepatic events and



lipodystrophy. Moreover, comparative efficacy is always linked to a specific comparator, therapeutic indication and type of patients. Emtricitabine was more efficacious compared with stavudine in naive HIV-infected patients. However, its efficacy was inferior in comparison with lamivudine in the same type of patients; its efficacy was similar in a study that compared it with lamivudine in experienced patients.

Regarding the appropriateness of the comparator, we can conclude, referring to a previous study, that the choice of the compator in the trials that demonstrated superiority was in line with recommendations on standard treatment [12].

Another issue in a critical evaluation of demonstrated superiority is the choice of the primary clinical endpoint. A composite endpoint was used for fondaparinux; analysis of all the endpoint events shows that the incidence of symptomatic venous thromboembolic events, including pulmonary embolism, was not significantly different between treatment groups [13,14].

Furthermore, we have to realise that drawing a conclusion of superiority based on a statistically significant difference says nothing about its practical significance. The absolute differences in change of glycated haemoglobin (HbA1c), demonstrated for insulin aspart and insulin glulisine compared to regular insulin, were, at best, of limited clinical relevance. Moreover, there was no relevant difference regarding the incidence of hypoglycaemic events. In this context it is interesting to follow developments in the prescription of fast-acting insulin in the treatment of diabetes, as the results of clinical studies may not always be reflected in practice [15,16]. For prescription data, we used the GIP database of the Health Care Insurance Board in the Netherlands. This database contains data on the prescription of extramural medicines, obtained from health insurance organisations and based on a sample of more than 12 million people. Graph 1 shows developments in the usage before and after the introduction of insulin aspart. The degree to which insulin aspart is used cannot be completely explained on the results of the premarketing trials. The more rapid onset and shorter duration of action of the insulin analogue is thought to facilitate a more flexible life style in comparison with the use of soluble human insulins [17]. However, this should also apply to insulin lispro, which can be regarded as being comparable to insulin aspart [18].

Finally, significant advantages as well as disadvantages of new medicines may only become evident during the course of time, on the basis of further study and experience. This means that assessing the added value of a new medicine is not a one-off incident but a continual process, supported by monitoring usage by means of prescription data.

This study shows and discusses how proven superiority, in the sense of well-demonstrated advantages in efficacy at an early stage of drug development, is the exception rather than the rule. The absence of evidence for differences between medicines does not mean the absence of differences. Insight into differences and similarities between medicines, however small they may be, is important in order to make the right choice for the right patient in clinical practice. Therefore, optimal pharmacotherapy would benefit from more comparative research in the development of new medicines. This study also shows that the results of comparative trials need a critical evaluation of their specific value to clinical practice. Prescription data may be helpful.



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

*Funding:* The authors have no support or funding to report

*Competing interest:* The authors have declared that no competing interests exist

For Peer Review

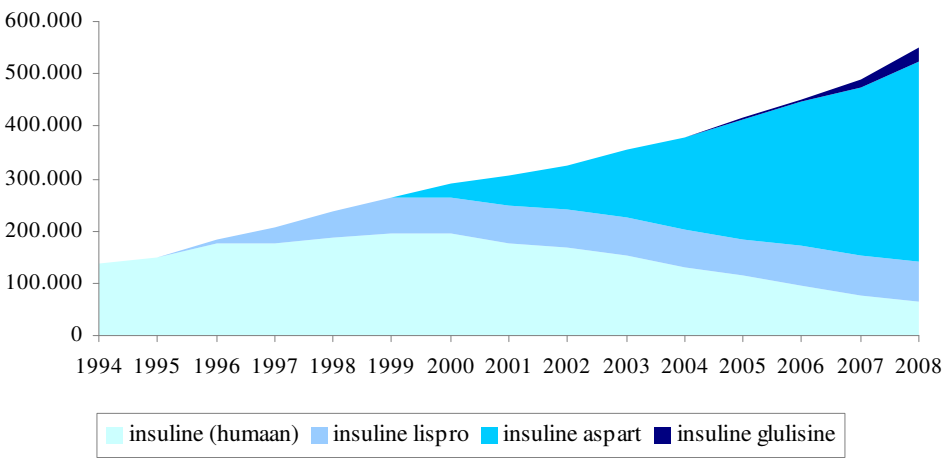
## Reference List

1. Dent TH and Hawke S (1997) Too soon to market. *BMJ* 315:1248-1249
2. Gale EA and Clark A (2000) A drug on the market. *Lancet* 355:61-63
3. Henry D and Hill S (1995) Comparing treatments. *BMJ* 310:1279
4. International Society of Drug Bulletins (2001) ISDB declaration on therapeutic advance in the use of medicines Paris, International Society of Drug Bulletins
5. Lewis JA, Jonsson B, Kreutz G, Sampaio C, van Zwieten-Boot B (2002) Placebo-controlled trials and the Declaration of Helsinki. *Lancet* 359:1337-1340
6. The European Agency for the Evaluation of Medicinal Products (2000) Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96) London, EMEA
7. Koopmans PP, de Graeff PA, Zwieten-Boot BJ, Lekkerkerker JF, Broekmans AW (2000) Clinical evaluation of efficacy and adverse effects in the (European) registration of drugs: what does it mean for the doctor and the patient? (in dutch). *Ned Tijdschr Geneeskd* 144:756-761
8. van Luijn JCF, Gribnau FW, Leufkens HG (2007) Availability of comparative trials for the assessment of new medicines in the European Union at the moment of market authorization. *Br J Clin Pharmacol* 63:159-162
9. The European Agency for the Evaluation of Medicinal Products (2009) European Public Assessment Reports. <http://www.emea.europa.eu/htms/human/epar/eparintro.htm>. Accessed October 2009.
10. Kaplan W (2004) Comparative effectiveness of medicines and use of head-to-head comparative trials In: Kaplan W (2004) Priority medicines for Europe and the world. Den Haag, Ministry of Health, Welfare and Sport
11. Van De Werf F, Adgey J, Ardissino D, et al. (1999) Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 354:716-722
12. van Luijn JCF, van Loenen AC, Gribnau FWJ, Leufkens HGM (2008) Choice of comparator in active control trials of new drugs. *Ann Pharmacother* 42:1605-1612
13. Heit JA (2002) The potential role of fondaparinux as venous thromboembolism prophylaxis after total hip or knee replacement or hip fracture surgery. *Arch Intern Med* 162:1806-1808
14. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR (2002) Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med* 162:1833-1840
15. Heerdink ER, Urquhart J, Leufkens HG (2002) Changes in prescribed drug doses after market introduction. *Pharmacoepidemiol Drug Saf* 11:447-453
16. Wathen B and Dean T (2004) An evaluation of the impact of NICE guidance on GP prescribing. *Br J Gen Pract* 54:103-107
17. Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L (2000) Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care* 23:583-588
18. Plank J, Wutte A, Brunner G, et al. (2002) A direct comparison of insulin aspart and insulin lispro in patients with type 1 diabetes. *Diabetes Care* 25:2053-2057

Table 1 - New medicines (1999-2005) with an improved efficacy

New medicine	Indication	Comparator
Bimatoprost	Glaucoma	Timolol
Capecitabine	Colorectal cancer	5-FU/Folonic acid
Emtricitabine	HIV-infections (combination)	Stavudine
Fondaparinux	Prevention of venous thromboembolic events	Enoxaparine
Insulin aspart	Diabetes mellitus type 1	Insulin regular human
Insulin glulisine	Diabetes mellitus type 2	Insulin regular human
Lopinavir	HIV-infections (combination)	Nelfinavir
Peginterferon alfa 2a	Chronic hepatitis C	Interferon alfa 2b
		Interferon alfa 2a
Peginterferon alfa 2b	Chronic hepatitis C	Interferon alfa 2b
Tipranavir	HIV-infections (combination)	Protease inhibitors
Travoprost	Glaucoma	Timolol
Voriconazole	Invasive aspergillosis	Amfotericin B (conv)
Zoledronic acid	Hypercalcaemia (tumour-induced)	Pamidronate

Graph 1. Development number prescriptions of fast-acting insulins



After the introduction of insulin aspart in 1999 there was a decrease in the number of prescriptions of soluble human insulin, however the use was already decreasing since the introduction of insulin lispro in 1996. Since 2004 insulin aspart is the most prescribed fast-acting insulin. The introduction of insulin glulisine in 2005 had little impact on the number of prescriptions of the other insulins.