Spitzenverband

Draft reflection paper on the wording of therapeutic indication

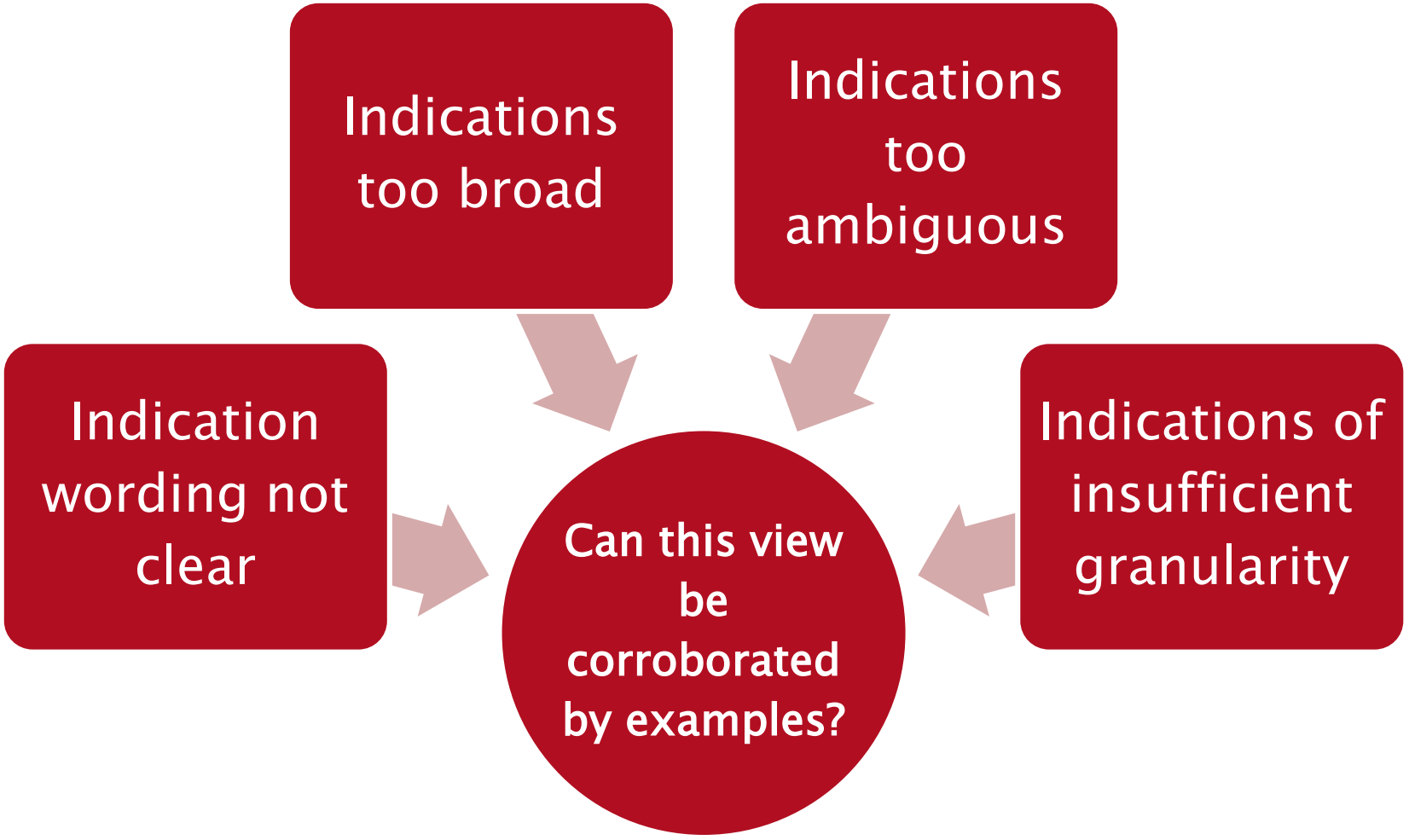
A reflection of payers' concerns regarding SmPC and EPAR

Diemen
June 18th, 2019
Dr Michael Ermisch

Payers' critique on SmPC

Draft for collaborative actions EMA–Payers, MEDEV, June 2017

Spitzenverband



Payers' critique on SmPC

Draft for collaborative actions EMA–Payers, MEDEV, June 2017

Spitzenverband

esip
EUROPEAN SOCIAL INSURANCE PLATFORM

MEDEV
Medicine Evaluation Committee

AIM
Healthcare and social benefits for all

Professor Guido Rasi
Executive Director
European Medicines Agency
30 Churchill Place
Canary Wharf
London E14 5EU

6 August 2018

Payer recommendations on the EPAR and SmPC

Dear Professor Rasi

Why is this important

Spitzenverband

- Marketing authorisation is a legal act – the SmPC is therefore a legal document
- Ambiguities cause legal disputes that may end in court
- The indication delineates on- and off-label use.
  Off-label use may be justified and necessary, but:
  - Doctors and patients need to be aware of off-label uses
  - Off-Label Use limits manufacturers' product liability
  - Different Health systems apply different measures on off label use
- Vagueness is of no worth for doctors and does not increase their freedom of action
- Treatment decisions require the possibility to understand why a drug has been authorised – be it based on data or due to extrapolations. This includes statements on the relevance of endpoints contributing to CHMP decisions.

Clarity on the definition of indication

e.g. Cabozantinib (Cabometyx®) vs Lenvatinib (Lenvima®)

Spitzenverband

Hepatocellular Carcinoma (HCC)

CABOMETYX is indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib.

Hepatocellular carcinoma

Nexavar is indicated for the treatment of hepatocellular carcinoma (see section 5.1).

LENVIMA is indicated as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy (see section 5.1).

Clarity on the definition of indication

e.g. Cabozantinib (Cabometyx®) vs Lenvatinib (Lenvima®)

Spitzenverband

Hepatocellular Carcinoma (HCC)

CABOMETYX is indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib.

Hepatocel

Nexavar is

Clinical data in Hepatocellular Carcinoma 12.11.2018

The safety and efficacy of CABOMETYX were evaluated in a randomized, double-blind, placebo-controlled Phase 3 study (CELESTIAL). Patients (N=707) with HCC not amenable to curative treatment and who had previously received sorafenib for advanced disease were randomized (2:1) to receive CABOMETYX (N=470) or placebo (N=237). Patients could have received one other prior systemic therapy for advanced disease in addition to sorafenib. Randomization was stratified by

Are these indications different regarding disease status?

LENVIMA is indicated as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy (see section 5.1).

Hepatocellular Carcinoma 20.08.2018

The clinical efficacy and safety of lenvatinib have been evaluated in an international, multicenter, open-label, randomised phase 3 study (REFLECT) in patients with unresectable hepatocellular carcinoma (HCC).

Clarity on target populations and subgroups

e.g. Cabozantinib (Cabometyx®)

Spitzenverband

Hepatocellular Carcinoma (HCC)

CABOMETYX is indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib.

Should the indication itself not be limited to certain Child Pugh Scores?

4.2 Posology and method of administration

Patients with hepatic impairment

In patients with mild hepatic impairment no dose adjustment is required. Since only limited data are available for patients with moderate hepatic impairment (Child Pugh B), no dosing recommendation can be provided. Close monitoring of overall safety is recommended in these patients (see sections 4.4 and 5.2).There is no clinical experience in patients with severe hepatic impairment (Child Pugh C), so cabozantinib is not recommended for use in these patients (see section 5.2).

4.3 Contraindications

4.4 Special warnings and precautions for use

Cabozantinib is eliminated mainly via the hepatic route. Closer monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment (see also sections 4.2 and 5.2). A higher relative proportion of patients with moderate hepatic impairment (Child-Pugh B) developed hepatic encephalopathy with cabozantinib treatment. Cabometyx is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) as cabozantinib has not been studied in this population and exposure might be increased in these patients.

Clarity on target populations and subgroups

e.g. Cabozantinib (Cabometyx®)

Spitzenverband

Hepatocellular Carcinoma (HCC)

CABOMETYX is indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib.

Should the indica
not be limited to
Child Pugh Score

5.1 Pharmacodynamic properties

d method of administration

The baseline demographic and disease characteristics were similar between the CABOMETYX and placebo arms and are shown below for all 707 randomised patients:

Male: 82%
Median age: 64 years.
Caucasian: 56%, Asian: 34%
ECOG performance status (PS) 0: 53% or ECOG PS 1: 47%.
Child Pugh A: 99%, Child Pugh B: 1 %

Shouldn't there be a statement on the reasons for extrapolation in the EPAR?

ince only limited data are
o dosing recommendation
se patients (see sections 4.4
airment (Child Pugh C), so

4.4 Special warnings and precaution

Cabozantinib is eliminated mainly via th safety is
recommended in patients with mild or m and 5.2). A
higher relative proportion of patients wit developed
hepatic encephalopathy with cabozantinib treatment. Cabometyx is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) as cabozantinib has not been studied in this population and exposure might be increased in these patients.

Clarity on place in therapy

e.g. Cabozantinib (Cabometyx®)

Hepatocellular Carcinoma (HCC)

CABOMETYX is indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib.

Is it wise to define the place in therapy in dependence of Nexavar?

Sorafenib's place in therapy could change in future… Will Cabozantinib be a valid third or forth line of therapy?

What if other TKI substitute for Sorafenib?

Table 24: Prior Non - radiation Anticancer Therapy for HCC (ITT Population)

Subject Characteristic	Cabozantinib (N = 470)	Placebo (N = 237)
Therapy type for HCC, n (%)[a]		
Systemic therapy	470 (100)	237 (100)
Local liver-directed therapy	209 (44)	113 (48)
Local other locations	2 (0.4)	0
Number of prior systemic anticancer regimens for advanced HCC per subject, n (%)		
0	3 (0.6)[b]	0
1	335 (71)	174 (73)
2	130 (28)	62 (26)
≥3[c]	2 (0.4)	1 (0.4)
Progression on most recent prior systemic agent for HCC, n (%)	459 (98)	231 (97)
Median (range) time from progression on most recent prior systemic agent for HCC to randomization, months	1.61 (0.0, 100.8)	1.68 (0.2, 69.4)
Progression while receiving sorafenib for HCC, n (%)	452 (96)	232 (98)
Progression while receiving sorafenib as most recent prior systemic agent for HCC, n (%)	322 (69)	166 (70)
Sorafenib for HCC at any time, n (%)[a]	470 (100)	237 (100)
Sorafenib for advanced HCC, n (%)	467 (99)	236 (100)
First-line per CRF	454 (97)	228 (96)
Second-line per CRF	25 (5)	18 (8)
Adjuvant sorafenib for HCC	5 (1)	2 (0.8)
Other route of sorafenib administration for HCC	3 (0.6)	1 (0.4)
Median (range) duration of prior sorafenib for HCC, months Total duration of prior sorafenib (months) for HCC, n (%)	5.32 (0.3, 70.0)	4.80 (0.2, 76.8)
< 1 month	11 (2)	8 (3)
≥ 1 to < 3 months	117 (25)	54 (23)
≥ 3 to < 6 months	130 (28)	67 (28)
≥ 6 months	211 (45)	108 (46)
Other prior non-radiation systemic anticancer agents, n (%)[a]		
PD-1/PD-L1 therapies	14 (3.0)	3 (1.3)
Anti-CTLA-4 therapies	3 (0.6)	0
Ramucirumab	8 (1.7)	1 (0.4)
TKI therapies (other than sorafenib)	19 (4.0)	12 (5.1)
Regorafenib	6 (1.3)	2 (0.8)
Axitinib	4 (0.9)	1 (0.4)
Investigational drug	5 (1.1)	3 (1.3)
Lenvatinib	0	1 (0.4)
Cytotoxic chemotherapy[d]	41 (8.7)	30 (13)
Received prior TACE for HCC, n (%)	203 (43)	111 (47)
Median number of prior chemoembolizations per subject [e]	0 (0, 18)	0 (0, 17)
0, n (%)	267 (57)	126 (53)
1, n (%)	70 (15)	32 (14)
2, n (%)	48 (10)	20 (8)
≥ 3, n (%)	85 (18)	59 (25)
Other liver-directed therapy (from surgery CRF), n (%)	54 (11)	30 (13)

[a] Prior systemic agents could be taken together but are summarized separately. Subjects may be counted in more than one category.
[b] Three subjects on the cabozantinib arm received prior systemic anticancer therapy that was administered for adjuvant HCC treatment but not for advanced HCC treatment per the CRFs.
[c] In the cabozantinib arm, Subject 3366-3517 received sorafenib (multiple instances) and doxorubicin, and Subject 9102-3262 received sorafenib and concomitant bevacizumab plus rapamycin (recorded as separate regimens). In the placebo arm, Subject 1513-3278 received sunitinib and multiple instances of sorafenib. These three subjects were not included in the table of eligibility deviations regarding line of therapy.
[d] Specific systemic cytotoxic chemotherapeutic agents received by ≥ 1% of subjects in either arm were: doxorubicin, oxaliplatin, cisplatin, gemcitabine, capecitabine, fluorouracil
[e] Multiple episodes of TACE on the same day were counted as a single administration.
Prior therapies were defined as having a start date prior to first dose of study treatment.

Use in monotherapy or in combination

e.g. Cabozantinib (Cabometyx®) vs Nivolumab (Opdivo®)

Spitzenverband

Renal Cell Carcinoma (RCC)

04.04.2016

OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.

Extension of Indication to add treatment as monotherapy of patients with advanced renal cell carcinoma (RCC) after prior therapy in adults, based on Study CA209025; a phase 3 study of nivolumab vs. everolimus in subjects with advanced or metastatic clear-cell RCC who have received prior anti-angiogenic therapy, and the CA209010 addendum study report; phase 2 dose-ranging study of nivolumab in subjects with progressive advanced/metastatic clear-cell RCC who have received prior anti-angiogenic therapy. As a

Renal Cell Carcinoma (RCC)

CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC):

- in treatment-naïve adults with intermediate or poor risk (see section 5.1)
- in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy

Use in monotherapy or in combination

e.g. Cabozantinib (Cabometyx®) vs Nivolumab (Opdivo®)

Spitzenverband

Renal Cell Carcinoma (RCC)

OPDIVO as monotherapy is indicated for the treatment
therapy in adults.

Extensi
(RCC) a
in subje
the CA
progres

Table 19 – Treatment aspects 21.07.2016 (EMA/664123/2016)

Treatments	Cabozantinib arm: Oral cabozantinib (60 mg) once daily (qd) - yellow film coated tablets	Everolimus arm: Oral everolimus (10 mg) once daily (qd)
Prior therapy/ concomitant therapy	Prior and subsequent cancer and radiation therapies were recorded by study site staff. No concurrent investigational agents were permitted. All medications used by the subject during the period from 28 days before randomization through 30 days after the date of the decision to permanently discontinue study treatment were recorded in the CRFs.	

Renal Cell Carcinoma (RCC)

CABOMETYX is indicated for the treatment of adva
- in treatment-naïve adults with intermediate o
- in adults following prior vascular endothelial

Treatments 22.03.2018 (EMA/235286/2018)

Subjects were treated with one of the following regimens:

- Cabozantinib treatment arm: oral cabozantinib (60 mg) once-daily (qd) (as tablets)
- Sunitinib treatment arm: oral sunitinib (50 mg) qd for 4 weeks (as capsules) followed by a 2-week rest per cycle (approved dosing regimen from the registrational Phase 3 sunitinib study[9]

One cycle was defined as 6 weeks in duration for each treatment arm.

Cross-Referencing

Spitzenverband

- *Where results from subsequent **studies provide further definition or information on an authorised indication**, such information, provided it does not itself constitute a new indication, may be considered for inclusion in section 5.1.*
  (A guideline on summary of product characteristics, September 2009)

- *It is important to note that any supplementary data provided in section 5.1 is to be considered as additional information aiming to provide further details on the scientific basis of the indication, as presented in section 4.1; **it cannot constitute a new indication nor can it be interpreted as a restriction to the indication** (e.g. in terms of population characteristics included in clinical trials or possible use in combination therapy.*
  (Updated reflection paper on the wording of therapeutic indication in the centralised procedure.)

Conceived contradiction: How can further defining a indication not result in an restriction (or widening)?

Section 5.1 is a statutory part of the SmPC (Art. 11, 2001/83/EC), so it's mere existence is not worth mentioning.

Transparency and stringency of decisions

e.g. Fulvestrant (Faslodex®)

Spitzenverband

Fulvestrant is indicated for the treatment of postmenopausal women with estrogen receptor positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-estrogen therapy or disease progression on therapy with an anti-estrogen. The Marketing Authorisation was granted on 10 March 2004.

Transparency and stringency of decisions

e.g. Fulvestrant (Faslodex®)

Spitzenverband

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 October 2010
EMA/CHMP/688361/2010
Human Medicines Development and Evaluation

Assessment Report
For
Faslodex
(fulvestrant)

Procedure No.: EMEA/H/C/000540/II/0018

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

2. Benefit-Risk Balance

The benefit for fulvestrant 500 mg in patients resistant to aromatase inhibitors has not been demonstrated. No statistically significant effect has been observed with fulvestrant 500 mg vs. 250 mg in TTP in the subgroup of subjects who had used an aromatase inhibitor as last endocrine therapy in the pivotal Phase III CONFIRM study (TTP 250 mg 4.1 mo vs. TTP 500 mg 5.4 mo; HR=0.85 (CI 95% 0.67-1.08, p=0.195). In line with the TTP results, there is a trend for a better survival in patients treated with fulvestrant 500 mg compared with the 250 mg group, however it was not statistically significant.

Although secondary endpoints have shown some activity for fulvestrant in terms of overall response rate (ORR) for the 500 mg (7.3%) and the 250 mg (8.3%) doses and clinical benefit (CBR) for the 500 mg (36.2%) and the 250 mg (32.3%) dose, they were not considered firm evidence of a clinically meaningful benefit in the subgroup of subjects who had used an aromatase inhibitor as last endocrine therapy in the CONFIRM study. In addition supportive phase II studies comparing fulvestrant 500 mg vs 250 mg (FINDER1 and FINDER2) have not shown statistically signifficant difference in ORR or CBR between the two treatment arms.

One of the major drawbacks of the pivotal study CONFIRM was the fact that lack of adequate control (placebo) made it difficult to evaluate the efficacy of fulvestrant in subjects with AI as last endocrine therapy. A trend towards higher efficacy for the 500 mg dose was not considered sufficient and there was not enough evidence to justify why fulvestrant at a dose of 250 mg should be regarded as efficacious in patients failing aromatase inhibitor therapy.

Transparency and stringency of decisions

e.g. Fulvestrant (Faslodex®)

Spitzenverband

The Breast 23 (2014) 489–502

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)☆

F. Cardoso [a,*], A. Costa [b,c], L. Norton [d], E. Senkus [e], M. Aapro [f], F. André [g], C.H. Barrios [h], J. Bergh [i], L. Biganzoli [j], K.L. Blackwell [k], M.J. Cardoso [l], T. Cufer [m], N. El Saghir [n], L. Fallowfield [o], D. Fenech [p], P. Francis [q], K. Gelmon [r], S.H. Giordano [s], J. Gligorov [t], A. Goldhirsch [u], N. Harbeck [v], N. Houssami [w], C. Hudis [x], B. Kaufman [y], I. Krop [z], S. Kyriakides [aa], U.N. Lin [z], M. Mayer [ab], S.D. Merjaver [ac], E.B. Nordström [ad], O. Pagani [ae], A. Partridge [af], F. Penault-Llorca [ag], M.J. Piccart [ah], H. Rugo [ai], G. Sledge [aj], C. Thomssen [ak], L. van't Veer [al], D. Vorobiof [am], C. Vrieling [an], N. West [ao], B. Xu [ap], E. Winer [z]

Optimal post-aromatase inhibitor treatment is uncertain. Available options include, but are not limited to, tamoxifen, another aromatase inhibitor (with a different mechanism of action), fulvestrant HD, megestrol acetate and everolimus + aromatase inhibitor.	I A	97% (30) Yes 3% (1) Abstain (31 voters)

Transparency and stringency of decisions

e.g. Fulvestrant (Faslodex®)

Spitzenverband

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 September 2016
EMA/652627/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

IBRANCE

International non-proprietary name: palbociclib

Procedure No. EMEA/H/C/003853/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Study 1023 (PALOMA-3)

Multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial of fulvestrant (Faslodex) with or without PD-0332991 (palbociclib) ± goserelin in women with hormone receptor-positive, HER2-negative metastatic breast cancer whose disease progressed after prior endocrine therapy.

This study was submitted in order to support the indication for palbociclib in combination with fulvestrant.

Previous hormonal regimen for primary diagnosis			
1	133 (38.3)	77 (44.3)	210 (40.3)
>1	214 (61.7)	97 (55.7)	311 (59.7)
Prior tamoxifen [2]	211 (60.8)	104 (59.8)	315 (60.5)
Prior aromatase inhibitors	296 (85.3)	151 (86.8)	447 (85.5)

Transparency and stringency of decisions

e.g. Fulvestrant (Faslodex®)

Spitzenverband

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

29 May 2017
EMA/490887/2017

Assessment report

Invented name: Faslodex

International non-proprietary name: fulvestrant

Procedure No. EMEA/H/C/000540/II/0057

Marketing authorisation holder (MAH): AstraZeneca UK Ltd

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

3.7.3. Additional considerations on the benefit-risk balance

Regarding the extension of the currently approved indication (second line after "anti-oestrogen therapy" to be extended to second line after "endocrine therapy"), the MAH has submitted insufficient evidence to change the conclusions from the previous variation (EMEA/H/C/540/II/0018), and therefore the proposed extension of the already approved indication is not considered sufficiently justified.

Confused? So am I….

Additionally, it would be interesting to know, what data was presented in 2017…

By the way…

…sometimes the complexity of syntax is mind-twisting

- *Verzenios is indicated for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.*

Thanks for your attention – – I look forward to a lively discussion

Dr. Michael Ermisch
Referat Arzneimittel
Abt. Arznei- und Heilmittel

Reinhardtstr. 28
10117 Berlin

arzneimittel@gkv-spitzenverband.de