HTA and Market Access

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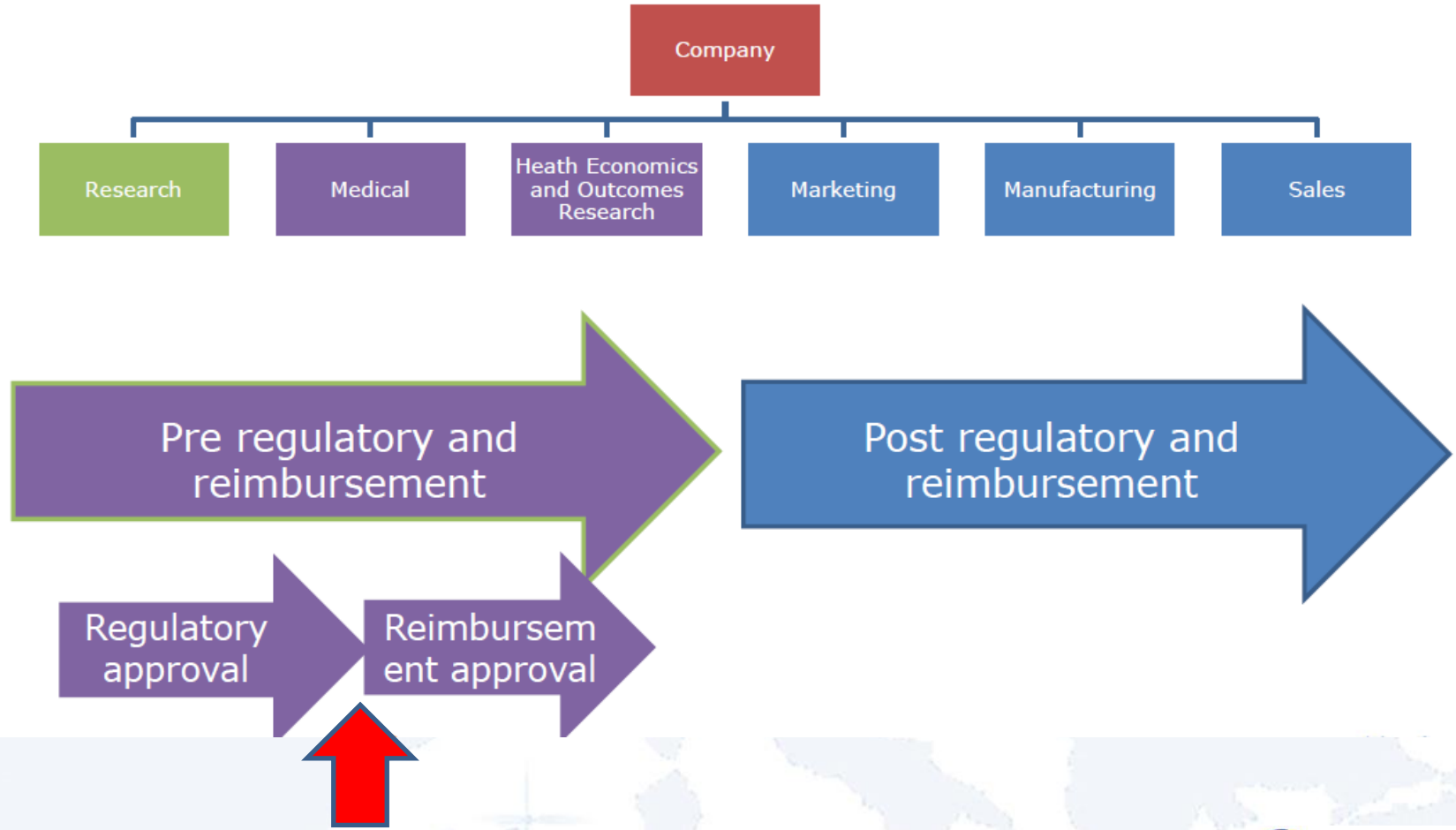
University Hospital of Bordeaux
EURORDIS Summer School
June 2, 2015

Introduction

- All health care systems have three objectives in common:
  - **Quality of care**
  - **Equity**
  - **System sustainability**

Health care resources are limited. Therefore, all health care systems need to make choices regarding services and products that can be covered out of public resources, i.e. they have to set reimbursement priorities, taking all health system objectives into account. Policy measures, such as medicine reimbursement systems, are developed to find a publicly **acceptable balance between these objectives**. (*KCE report 147c 2010 Belgium*)

Medicinal Products



Essential Points

- Paying for medicinal products varies from country to country
- All involve an assessment of SAFETY, EFFICACY and COST EFFECTIVENESS
- Some involve more clinical and consumer input than others
- The agencies bodies competent for the evaluation are part of HTA (health technology assessment)

Some definitions

Efficacy

Extent to which a medicine has the ability to bring about its intended ***effect under ideal circumstances****, such as in a randomised clinical trial*

Q. Can this treatment work ? R. RCT, but limited extrapolability

Effectiveness

Extent to which a medicine achieves its intended ***effect in the usual clinical setting***

Q. Does it work in pratice ? R. CER

Efficiency

Efficiency depends on ***whether a medicine is worth its cost*** *to individuals or society*

Q. Is it worth it? R. HTA (cost-effectiveness studies, budget impact analysis)

Br Med J 1999; 319: 652-3. Aust Prescr 2000; 23: 114–5

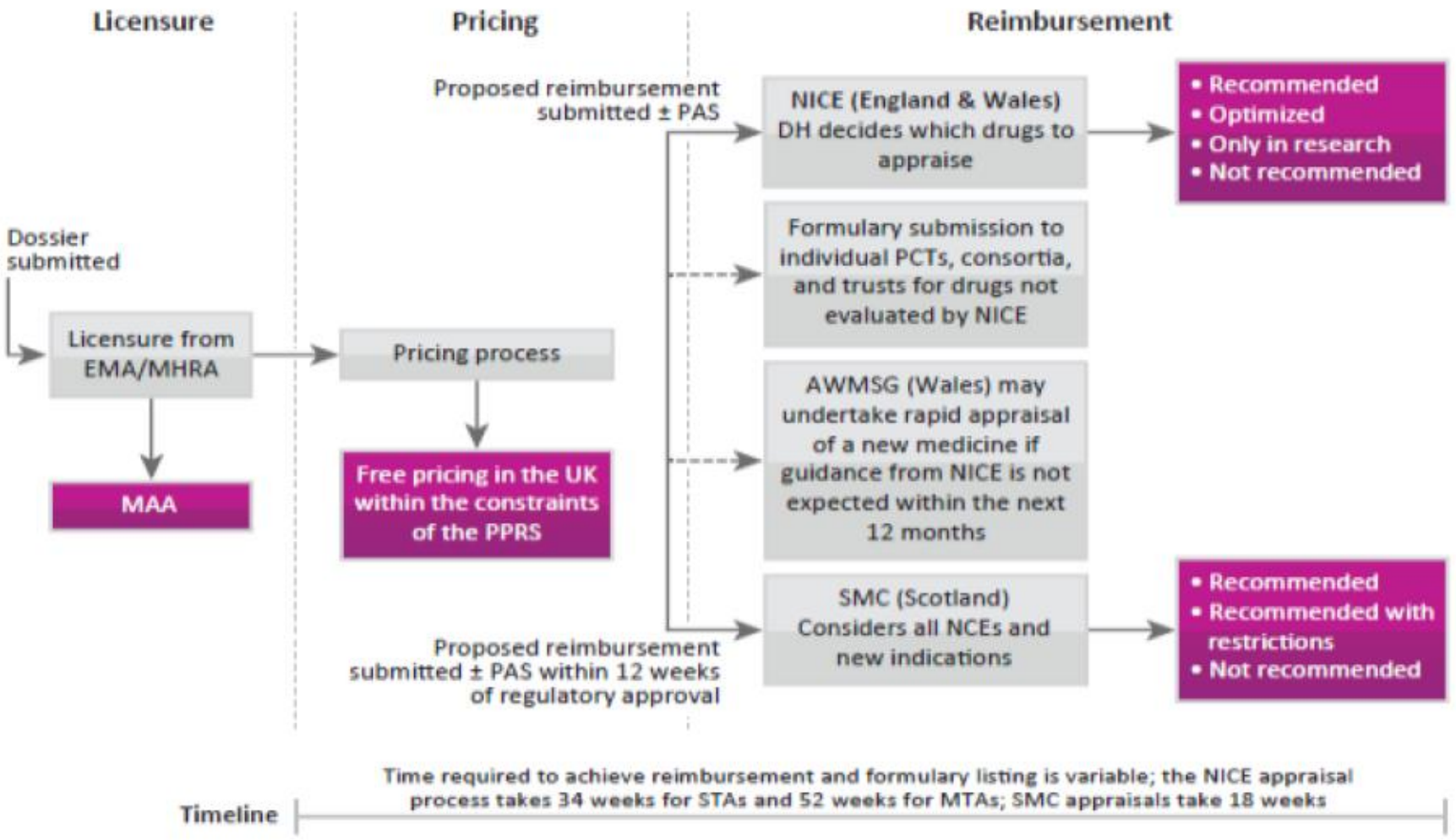
What do HTA agencies require to take a decision on pricing?

- Data on efficacy and safety
  - In general this is determined by the results of clinical trials (Evidence Based Medicine) and assessed during the regulatory approval process. Relative efficacy/safety data are important.
- Assessment of cost efficacy/effectiveness
  - Usually done by comparing new treatment with the current standard of care in large clinical trials (phase III)
    - if this is not an option, other means must be used such as:
      - What clinicians or patients are doing in practice (treatment patterns questionnaires)
      - What patients and consumers would choose (utility studies)

Some examples in Europe

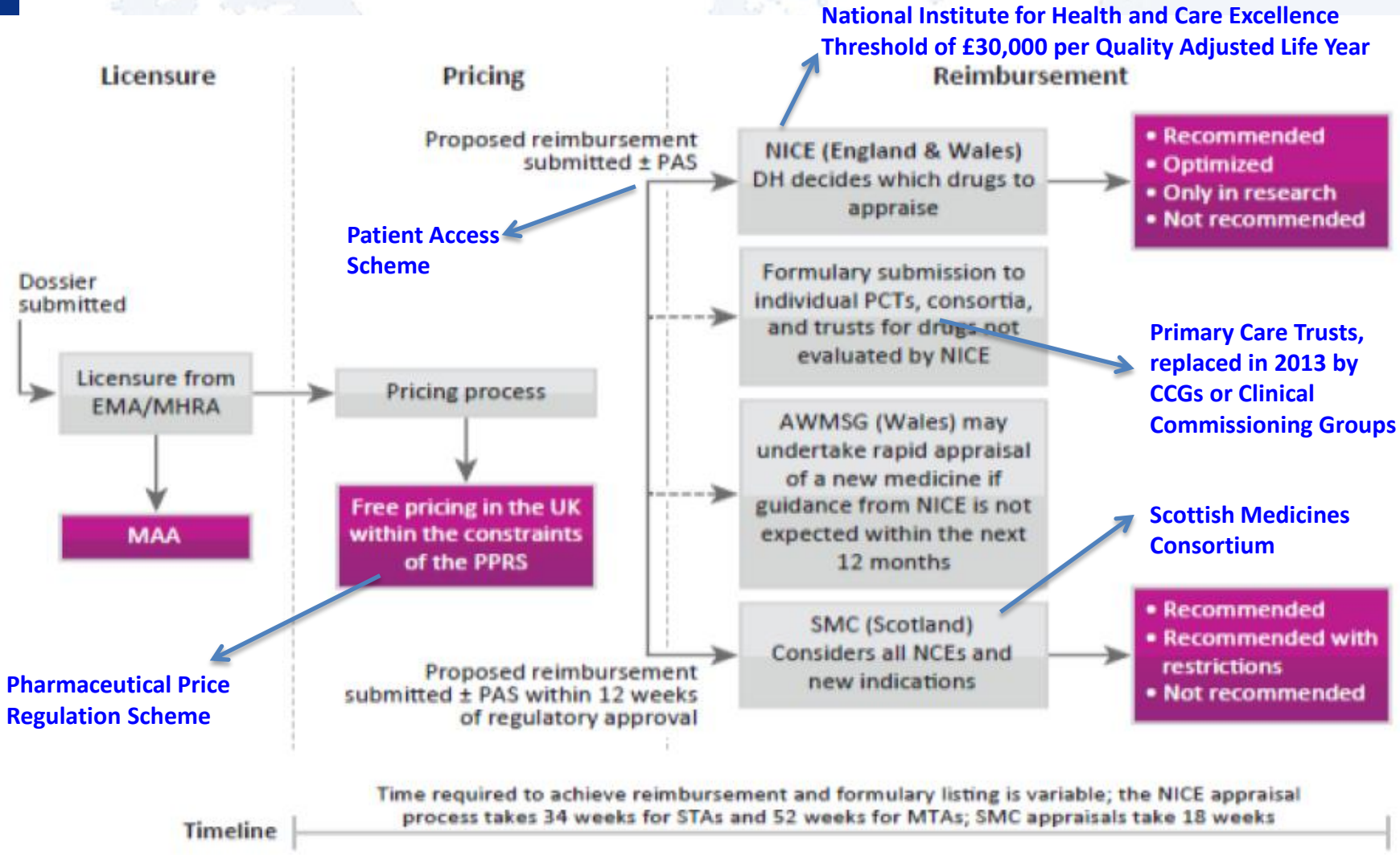
- United Kingdom: NICE
  - the process can be slow and they can recommend against market access even if a product has regulatory approval
- Spain
  - the process is split across national, regional and local levels. At the national level cost effectiveness is a formal requirement; products that are expensive or highly innovative are often assessed regionally
- France: HAS
  - the process is split in clinical and economical parallel evaluation processes. French National Authority for Health (HAS) requires data from active comparator trials.
- Italy
  - HTAs are taking on an increasing role nationally and locally
- Germany
  - the process has become more challenging as fewer companies have emerged with positive results

A closer look at the United Kingdom



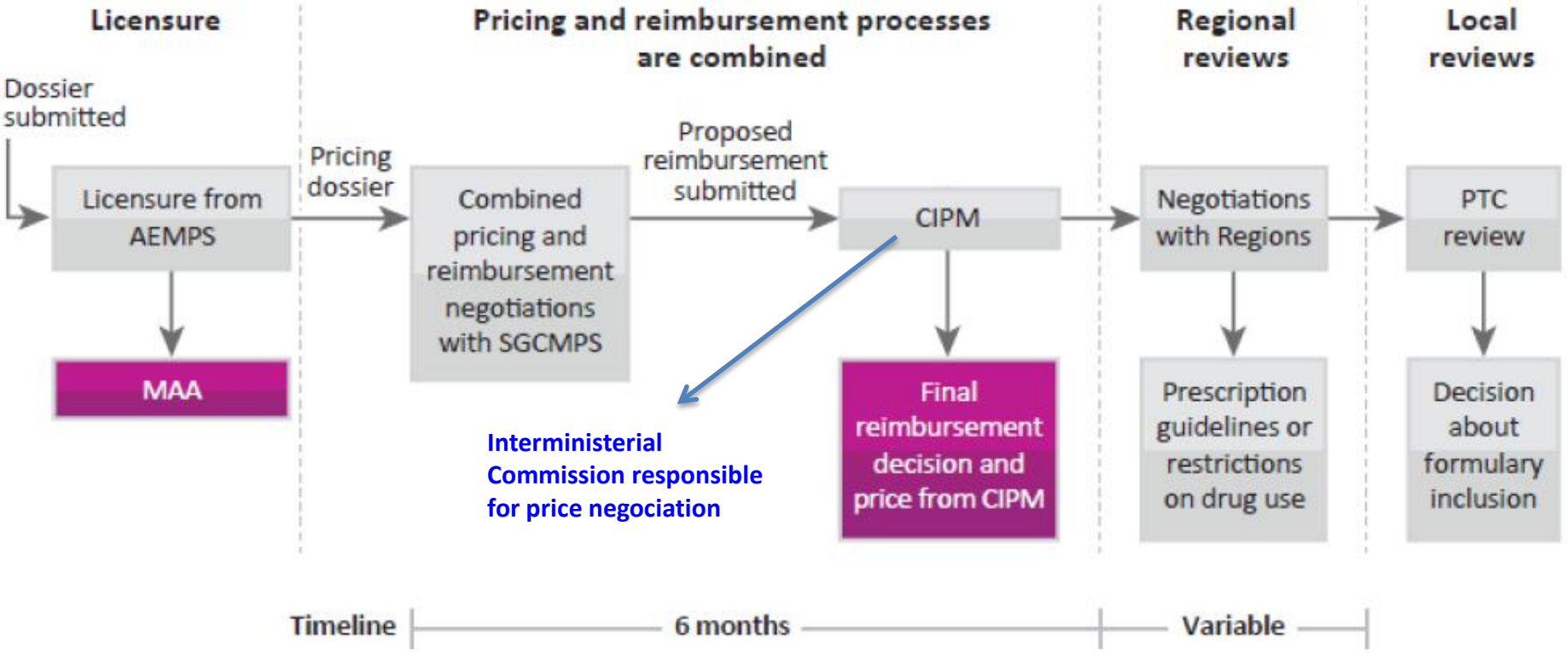
Source: PRMA Insights: Pricing and Reimbursement Success in NSCLC 2nd edition, 2012

A closer look at the United Kingdom



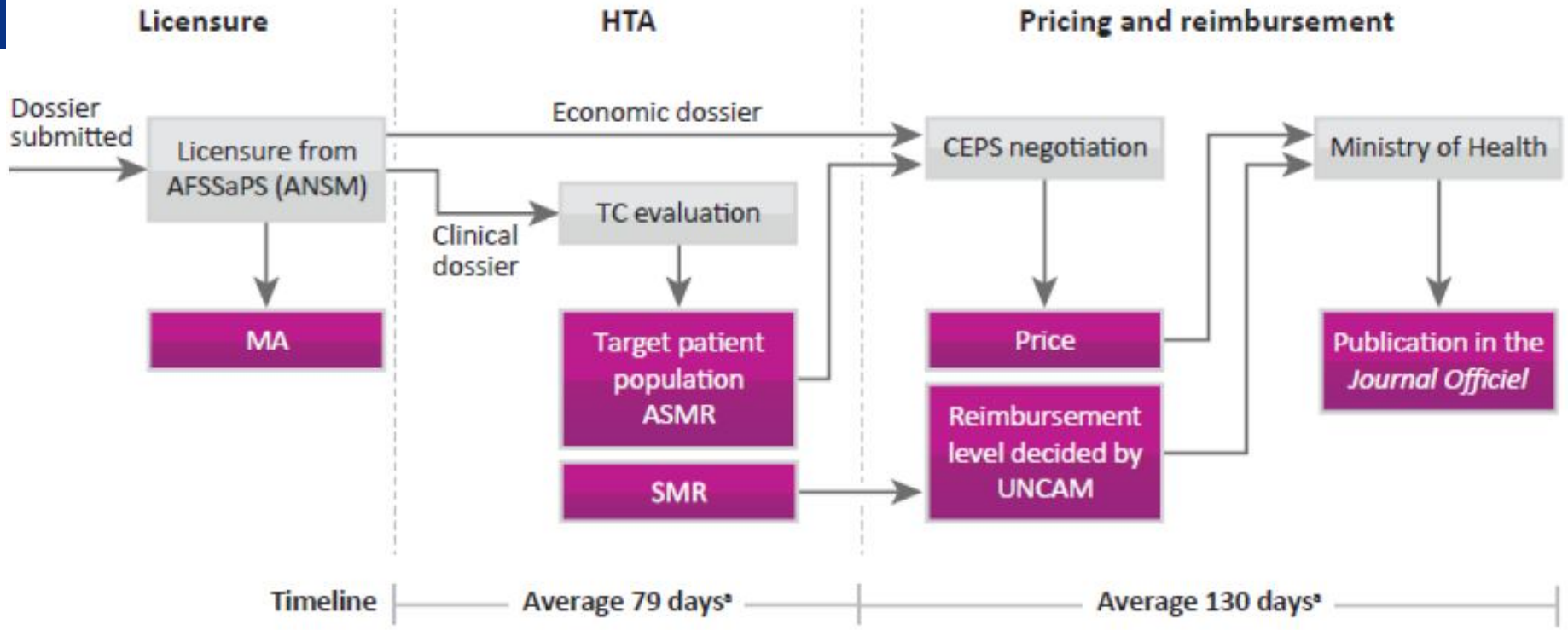
Source: PRMA Insights: Pricing and Reimbursement Success in NSCLC 2nd edition, 2012

Spain



AEMPS – is a public body which belongs to the Ministry of Health. Its mission is to give guarantees to the general public on the quality, safety, efficacy of medicines
SGCMPS- National public health services

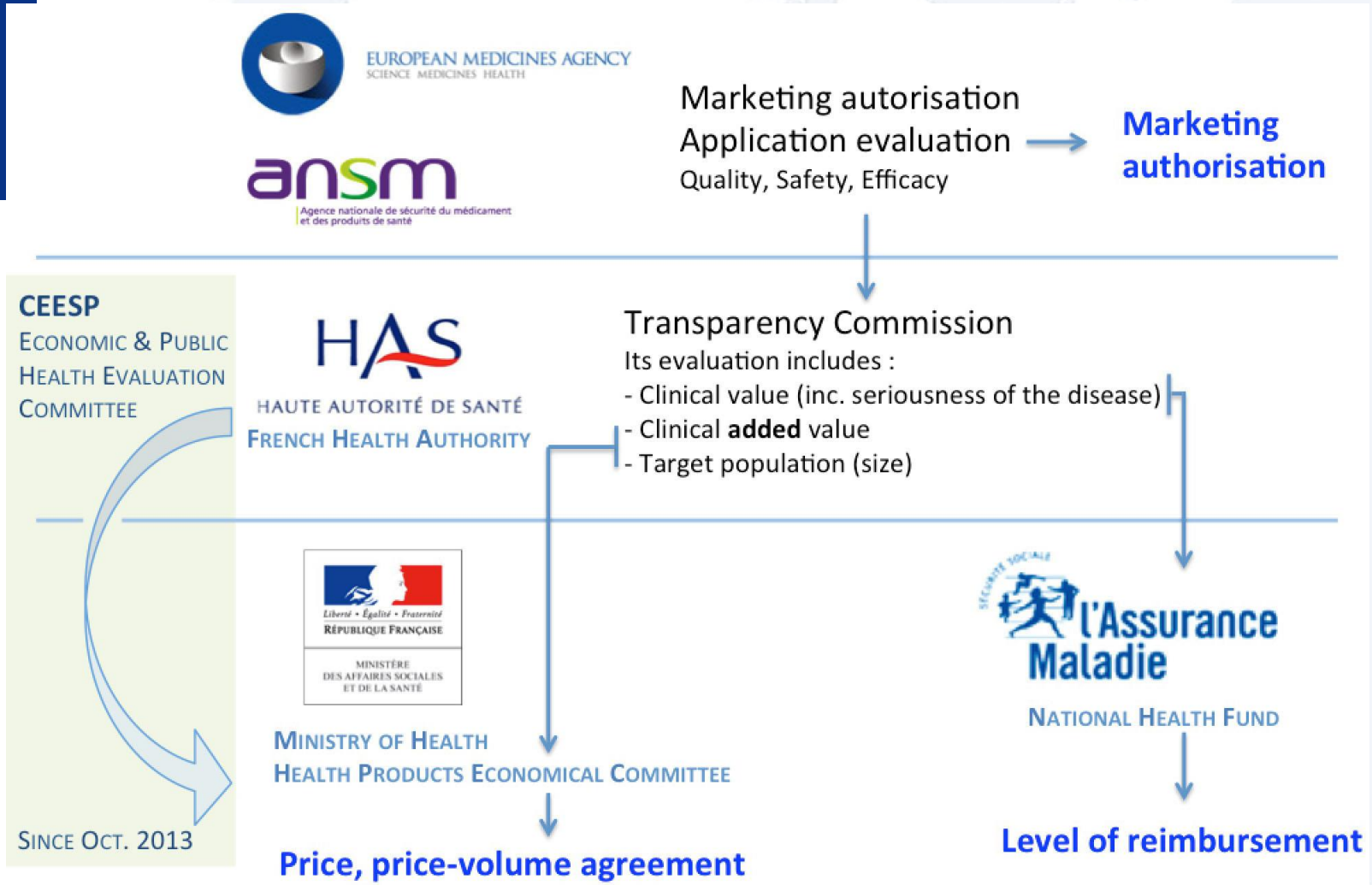
France



Pricing is set after negotiation through HTA

2 sets of rating

Source: PRMA Insights: Pricing and Reimbursement Success in NSCLC 2nd edition, 2012



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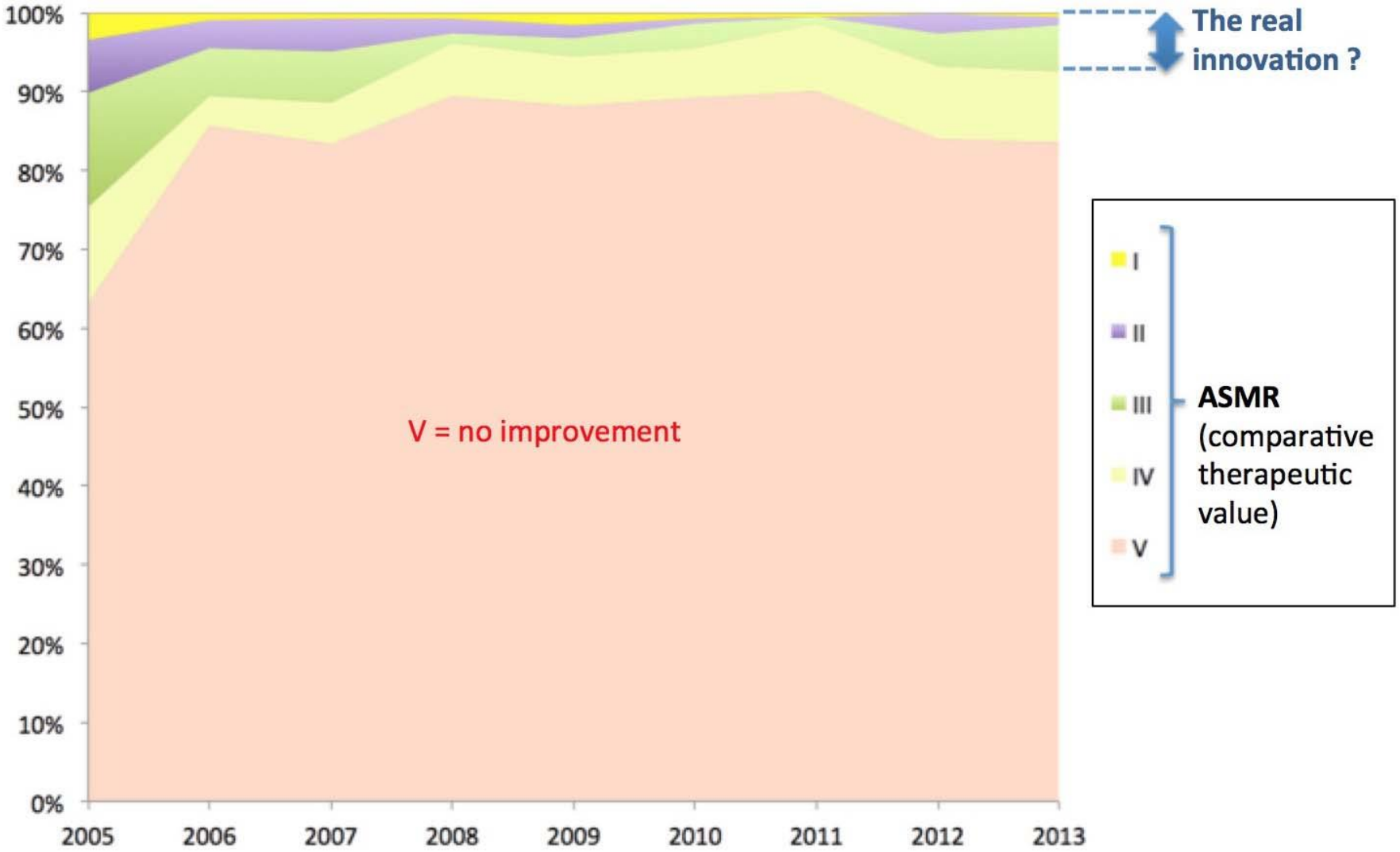
100%
90%
80%
70%
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50%
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2005
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2009
2010
2011
2012
2013
V = no improvement
The real innovation ?
I
II
III
IV
V
ASMR (comparative therapeutic value)

HAS

HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 December 2007

TARCEVA 25 mg, film-coated tablet (369 232-3)
TARCEVA 100 mg, film-coated tablet (369 234-6)
TARCEVA 150 mg, film-coated tablet (369 235-2)
Pack of 30

Applicant: ROCHE

erlotinib

List I
Medicine for hospital prescription only.
To be prescribed only by oncologists or haematologists, or doctors competent in oncology.
Medicinal product requiring specific monitoring during treatment.

*Extension of indication: Treatment of metastatic **pancreatic cancer**, in combination with gemcitabine*

http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-03/tarceva_ct_5077.pdf

EUPATI
European Patients' Academy on Therapeutic Innovation

285 patients received gemcitabine combined with **Tarceva** (261 patients with 100 mg and 24 patients with 150 mg) and 284 patients gemcitabine alone

Table 1 (results for the primary endpoint)

	Tarceva (months)	Placebo (months)	Δ (months)	CI of Δ	HR	CI of HR	p
Overall population							
Median overall survival	6.4	6.0	0.41	-0.54-1.64			
Mean overall survival	8.8	7.6	1.16	-0.05-2.34	0.82	0.69-0.98	0.028
Metastatic population							
Median overall survival	5.9	5.1	0.87	-0.26-1.56			
Mean overall survival	8.1	6.7	1.43	0.17-2.66	0.80	0.66-0.98	0.029
Population with locally advanced disease							
Median overall survival	8.5	8.2	0.36	-2.43-2.96			
Mean overall survival	10.7	10.5	0.19	-2.43-2.69	0.93	0.65-1.35	0.713

The ITT results for the primary endpoint showed a median survival of 6.4 months in the Tarceva-gemcitabine combination group vs 6 months for the gemcitabine monotherapy group showing an absolute **gain of 12 days (p=0.028)**.

An absolute **gain of 26 days (p=0.029)** was observed in favour of the group treated with the combination (5.9 months vs 5.1) in terms of median survival in the metastatic subgroup.

The following **adverse events were more frequent** in patients who received Tarceva: rash (69% vs 30%), diarrhoea (48% vs 36%), weight loss (39% vs 29%) and stomatitis (22% vs 12%).

HAS

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Medicinal product requiring specific monitoring during treatment.

The Transparency Committee **did not recommend inclusion on the list of medicines reimbursed by National Insurance** and on the list of medicines approved for hospital use and various public services in this extension of indication

http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-03/tarceva_ct_5077.pdf

EUPATI
European Patients' Academy on Therapeutic Innovation

Second example in obesity

An example : overweight and obesity

Worldwide obesity has nearly doubled since 1980.

In 2008, more than **1.4 billion adults**, 20 and older, were overweight. Of these over 200 million men and nearly 300 million women were obese.

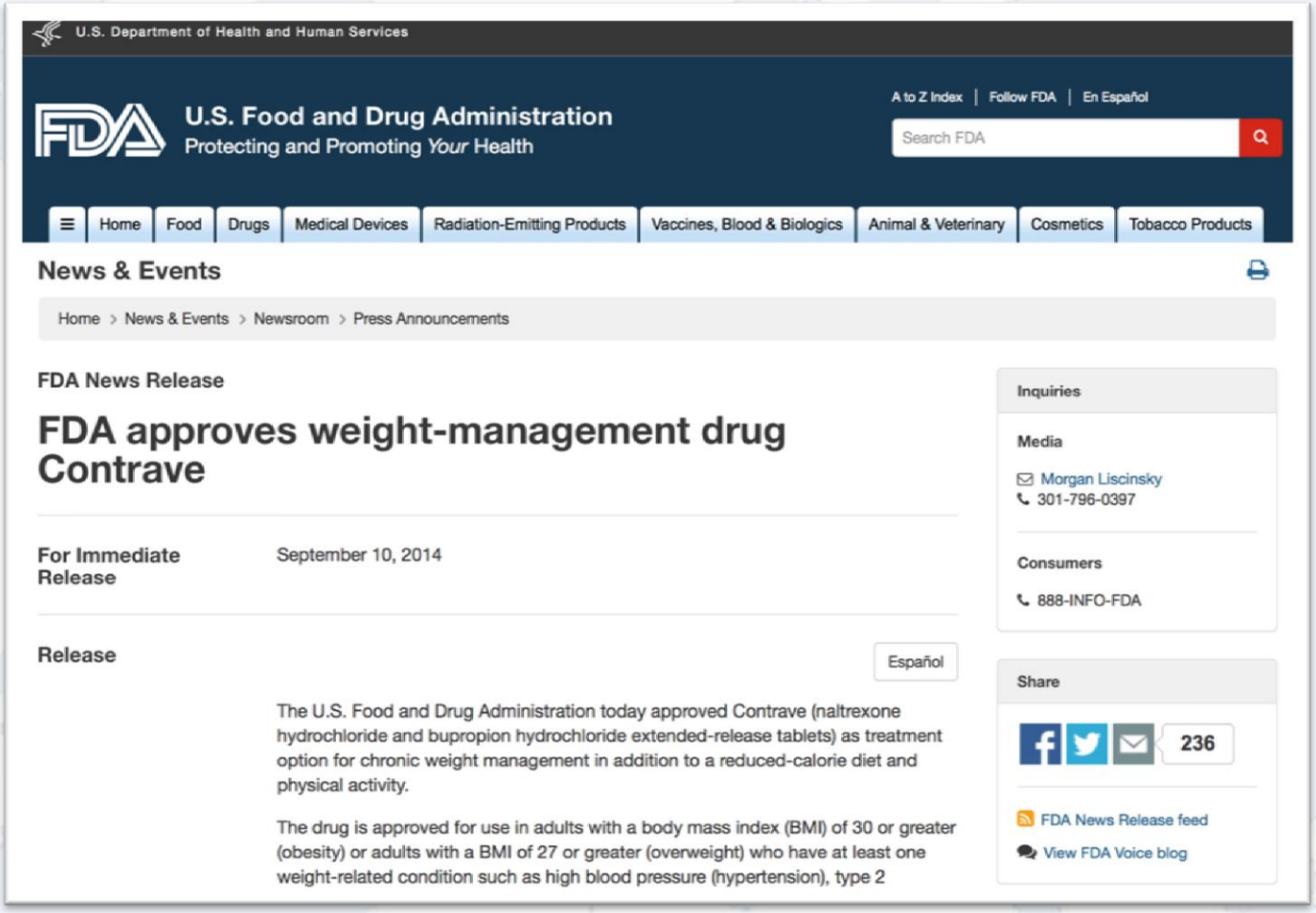
35% of adults aged 20 and over were overweight in 2008, and **11% were obese**.

More than 40 million children under the age of 5 were overweight or obese in 2012.

Huge population (and potential market), in particulier in rich countries : more than a third of the US population is obese, and two-thirds are either obese or overweight

Source : WHO

The most recent medicinal product licensed by the FDA in this indication is Contrave, a fixed combination of naltrexone and bupropion



U.S. Department of Health and Human Services

U.S. Food and Drug Administration
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FDA News Release

FDA approves weight-management drug Contrave

For Immediate Release September 10, 2014

Release

Español

The U.S. Food and Drug Administration today approved Contrave (naltrexone hydrochloride and bupropion hydrochloride extended-release tablets) as treatment option for chronic weight management in addition to a reduced-calorie diet and physical activity.

The drug is approved for use in adults with a body mass index (BMI) of 30 or greater (obesity) or adults with a BMI of 27 or greater (overweight) who have at least one weight-related condition such as high blood pressure (hypertension), type 2

Inquiries

Media

Morgan Liscinsky
301-796-0397

Consumers

888-INFO-FDA

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In the EU, the MAA was submitted to the EMA in 2013, with favourable opinion for MA end of last year

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 December 2014
EMA/787060/2014
Press Office

Press release

Mysimba recommended for approval in weight management in adults

Medicine to be used in addition to reduced-calorie diet and physical activity

The European Medicines Agency (EMA) has recommended granting a marketing authorisation for Mysimba (naltrexone / bupropion) for weight management of overweight or obese adults. The medicine is recommended for use in addition to a reduced-calorie diet and physical activity.

TRUVEN HEALTH ANALYTICS
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BUPROPION
Physical And Pharmaceutical Properties
Proprietary Names
BUPROPION HYDROBROMIDE
Physical And Pharmaceutical Properties
Proprietary Names
BUPROPION HYDROCHLORIDE
Physical And Pharmaceutical Properties
PROPRIETARY NAMES
ADVERSE EFFECTS AND TREATMENT
Incidence of adverse effects.
Effects on the cardiovascular system.
Effects on the cerebrovascular system.
Effects on the pancreas.
Effects on the skin.
Extrapyramidal effects.
Hypersensitivity.
Overdosage.
PRECAUTIONS
Breast feeding.
Children.
Porphyria.
Pregnancy.
INTERACTIONS

Bupropion

MARTINDALE - The Complete Drug Reference | OTHER SOURCES

See also Antidepressants

Bupropion

Physical And Pharmaceutical Properties

- Name Status:BAN, rINN
- Synonyms: Amfebutamone;Bupropión;Bupropione;Bupropionum
- Chemical Name: (±)-2-(tert-Butylamino)-3'-chloropropiophenone
- Molecular Formula: C13H18ClNO
- Molecular Weight:239.7
- CAS Registry: 34911-55-2

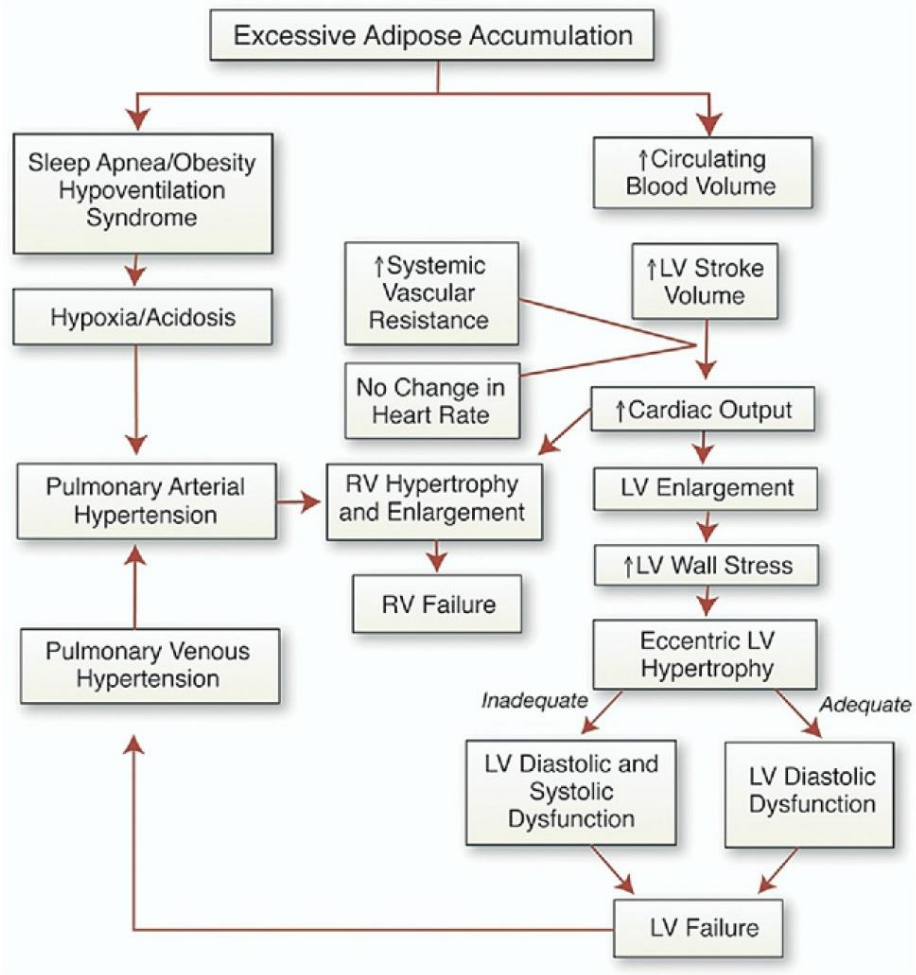

Figure 2 **Pathophysiology of Obesity and Cardiomyopathy**

LV = left ventricular; RV = right ventricular

Obesity or overweight as such does not kill (or exceptionally)

Morbidity and subsequent mortality is driven by **cardiovascular complications**

Am J Med Sci 2001; 321: 225–36
JACC 2009; 53: 1925–32

Treatment rationale

Obesity leads in particular to :

- Dyslipidemia
- Increase in heart rate
- Increase in systolic and diastolic blood pressure, hypertension (6 times more frequent in obese subjects)
- Glucose intolerance and diabetes
- Obstructive sleep apnea

Weight reduction leads to prevention and treatment of cardiovascular diseases with favourable impact on all these conditions

According to Authorities' guidelines, efficacy of these products should be established on the basis of at least a 5% weight reduction

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 26 June 2014
2 EMA/CHMP/311805/2014
3 Committee for Medicinal Products for Human Use (CHMP)

4 Guideline on clinical evaluation of medicinal products used 5 in weight control

6 **Draft**

Draft agreed by Cardiovascular Working Party	26 March 2014
Adopted by CHMP for release for consultation	26 June 2014
Start of public consultation	31 July 2014
End of consultation (deadline for comments)	31 January 2015

7

8 This guideline replaces 'Guideline on clinical evaluation of medicinal products used in weight control'
9 (CPMP/EWP/281/96 Rev.1)

EURORDIS Rare Diseases Europe

4. Efficacy criteria and methods to assess efficacy

4.1. Introduction

Reduction of body weight should be the primary efficacy endpoint in the clinical studies. However, it should preferably be supported by clinically relevant effects on endpoints reflecting the beneficial effect of the documented weight loss.

4.2. Reduction of body weight and related variables

Baseline weight is the subject's weight at randomisation. Weight loss should be documented both as absolute weight loss (kg) and percentage weight loss relative to baseline body weight. Demonstration of a clinically significant degree of weight loss of at least 5- 10% of baseline weight, which is also at least 5% greater than that associated with placebo, is considered to be a valid primary efficacy criterion in clinical trials evaluating new anti-obesity drugs. Proportions of responders in the various treatment arms could be considered as an alternative primary efficacy criterion where response is more than 10% weight loss at the end of a 12-month period.

Proportions of responders with ≥ 5% weight loss should be documented as a secondary endpoint.

Further, the predictive value of weight loss after e.g. 3 months treatment with respect to long term effects should be documented in order to identify a population with expected long term benefit.

Measurements of central adiposity (e.g. waist circumference or waist to hip ratio) should always be documented.

Phase III clinical trials of Contrave

Source : Expert Opin Drug Saf 2014; 13: 831-841

Table 1. Phase III clinical trials for naltrexone SR/bupropion SR.

Trial	Abbreviation	Length of study (weeks)	Number of participants	Objective
Contrave Obese Research I (COR-I)	NB-301	56	1742	Compared safety and efficacy of two doses of naltrexone SR/bupropion SR in overweight and obese patients
Contrave Obese Research-Behavior Modification (COR-BMOD)	NB-302	56	793	Assessed safety and efficacy in overweight and obese patients with controlled hypertension and/or dyslipidemia with or without behavior modification
Contrave Obese Research II (COR-II)	NB-303	56	1496	Tested efficacy in overweight and obese patients with controlled hypertension and/or dyslipidemia with or without diet and exercise
Contrave Obese Research-Diabetes (COR-Diabetes)	NB-304	56	505	Determined safety and efficacy in overweight and obese patients with type 2 diabetes
Cardiovascular Outcomes Study of Contrave in Overweight and Obese Subjects With Cardiovascular Risk Factors	Light Study	Up to 4 years	Approximately 8900	Investigate cardiovascular health outcomes in overweight and obese individuals with cardiovascular risk factors. The study is designed to assess the occurrence of Major Adverse Cardiovascular Events

SR: Sustained-release.

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-4.8%

-4.2%

-5.2%

-3.2%

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-4.2%

-5.2%

-3.2%

Original Article
CLINICAL TRIALS: BEHAVIOR, PHARMACOTHERAPY, DEVICES, SURGERY

Obesity

A Randomized, Phase 3 Trial of Naltrexone SR/Bupropion SR on Weight and Obesity-related Risk Factors (COR-II)

*Caroline M. Apovian[1], Louis Aronne[2], Domenica Rubino[3], Christopher Still[4], Holly Wyatt[5], Colleen Burns[6], Dennis Kim[6], Eduardo Dunayevich[6] for the COR-II Study Group**

Objective: To examine the effects of naltrexone/bupropion (NB) combination therapy on weight and weight-related risk factors in overweight and obese participants.

Design and Methods: CONTRAVE Obesity Research-II (COR-II) was a double-blind, placebo-controlled study of 1,496 obese (BMI 30-45 kg/m^2) or overweight (27-45 kg/m^2 with dyslipidemia and/or hypertension) participants randomized 2:1 to combined naltrexone sustained-release (SR) (32 mg/day) plus bupropion SR (360 mg/day) (NB32) or placebo for up to 56 weeks. The co-primary endpoints were percent weight change and proportion achieving ≥5% weight loss at week 28.

Results: Significantly ($P < 0.001$) greater weight loss was observed with NB32 versus placebo at week 28 (−6.5% vs. −1.9%) and week 56 (−6.4% vs. −1.2%). More NB32-treated participants ($P < 0.001$) experienced ≥5% weight loss versus placebo at week 28 (55.6% vs. 17.5%) and week 56 (50.5% vs. 17.1%). NB32 produced greater improvements in various cardiometabolic risk markers, participant-reported weight-related quality of life, and control of eating. The most common adverse event with NB was nausea, which was generally mild to moderate and transient. NB was not associated with increased events of depression or suicidality versus placebo.

Conclusion: NB represents a novel pharmacological approach to the treatment of obesity, and may become a valuable new therapeutic option.

Obesity (2013) **21**, 935-943. doi:10.1002/oby.20309

TABLE 1 Demographics and baseline characteristics

Demographic/ characteristic[a]	Placebo $N = 495$	NB[b] $N = 1001$
Age, y	44.4 ± 11.4	44.3 ± 11.2
Gender (% female)	84.8	84.6
Race (% White/Black/Other)	84/15/2[c]	83/13/3[c]
Weight, kg	99.2 ± 15.9	100.3 ± 16.6
BMI, kg/m^2	36.1 ± 4.3	36.2 ± 4.5
Hypertension, %[d]	21.4	21.2
Dyslipidemia, %[e]	53.1	55.9

[a]Data are mean ± SD or % of participants for the Randomized population.
[b]NB group includes all participants randomized to NB32 at baseline, regardless of re-rand
[c]Perce
[d]Diagn
tant m
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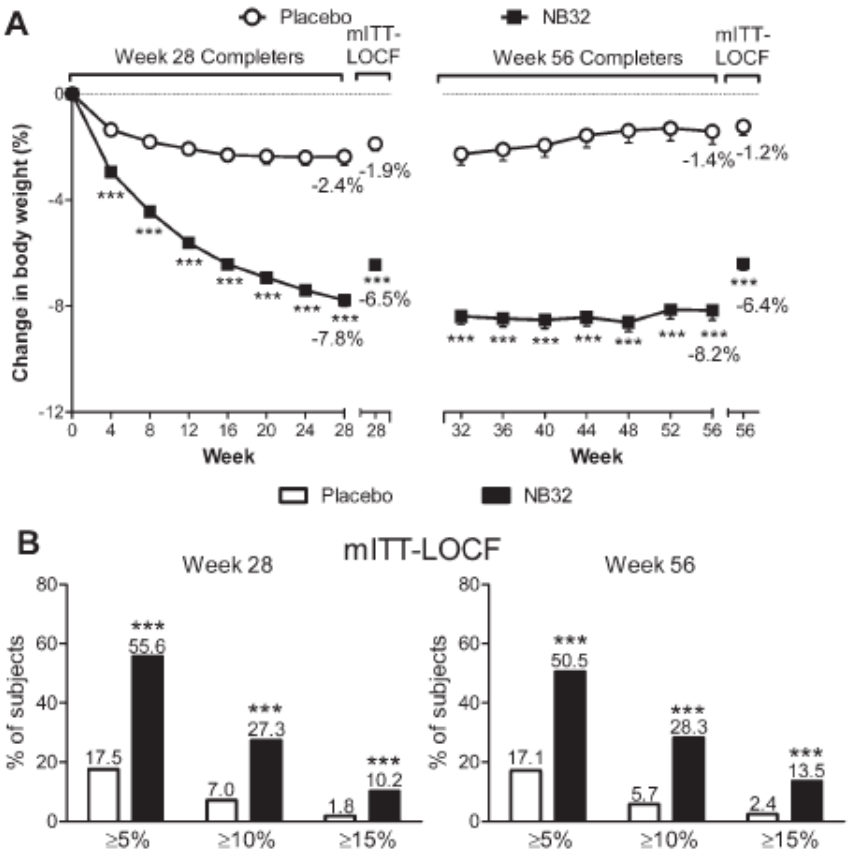
mg/dL

COR II : -5,2% (mITT considering the last weight reported in patients losts during follow-up). Completers at 56 weeks presented -6.8 % but **half** of the patients did not complete the one year treatment (**benefit is based on duration of weight control**). Diabetic patients excluded



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Dyslipidemia, %[e]	53.1	55.9

-1.2% → **98 kg**

-6.4% → **94 kg**

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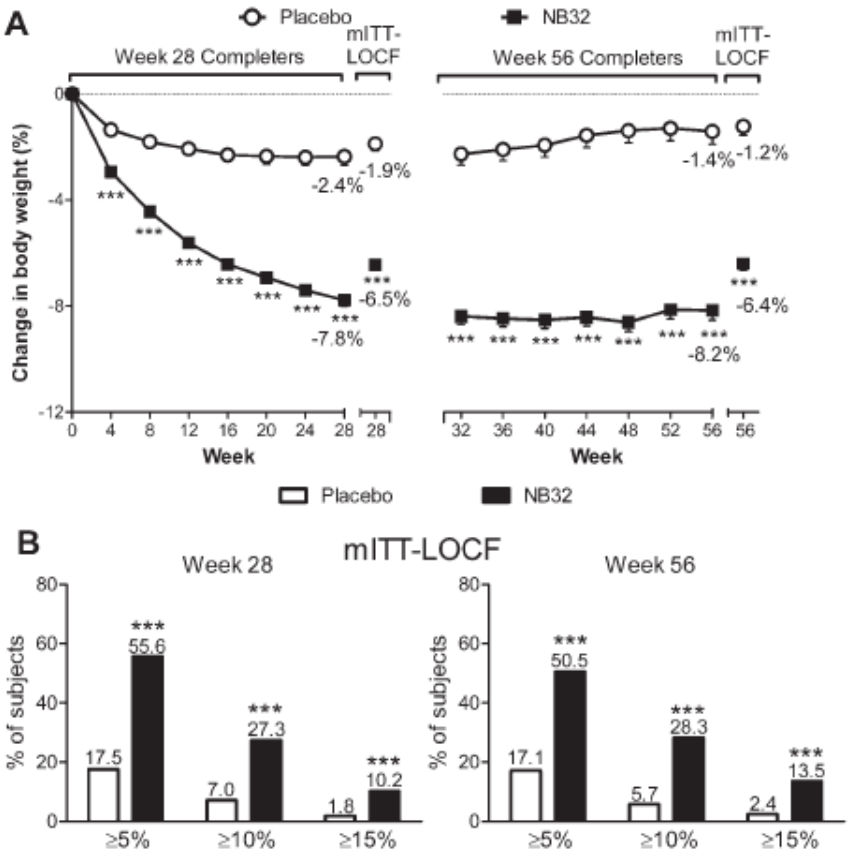

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TABLE 3 Changes in secondary and additional endpoints

Measure[a]	Week 28 Placebo N = 456	Week 28 NB32 N = 825	Week 28 P-value	Week 56 Placebo N = 456	Week 56 NB32[b] N = 702	Week 56 P-value
Waist circumference, cm						
Baseline	108.9 ± 11.7	109.3 ± 11.9		108.6 ± 11.8	109.0 ± 11.8	
Change	−2.7 ± 0.4	−6.2 ± 0.3	<0.001[c]	−2.1 ± 0.5	−6.7 ± 0.3	<0.001
Triglycerides, mg/dL[d]						
Baseline	113.4 ± 1.6	119.0 ± 1.6		112.8 ± 1.6	118.9 ± 1.6	
Percent change (95% CI)	−1.4% (−5.0%, +2.4%)	−7.3% (−9.8%, −4.8%)	0.007[c]	−0.5% (−4.5%, +3.7%)	−9.8% (−12.4%, −7.1%)	<0.001
HDL-cholesterol, mg/dL						
Baseline	51.4 ± 13.1	51.4 ± 13.3		51.6 ± 12.9	51.8 ± 13.6	
Change	−1.4 ± 0.4	+1.2 ± 0.3	<0.001[c]	−0.9 ± 0.5	+3.6 ± 0.4	<0.001
LDL-cholesterol, mg/dL						
Baseline	117.1 ± 32.6	119.8 ± 30.2		116.8 ± 32.9	120.5 ± 30.2	
Change	0.0 ± 1.3	−4.4 ± 0.9	0.004	−2.1 ± 1.3	−6.2 ± 0.9	0.008
hsCRP, mg/L[d]						
Baseline	3.7 ± 2.7	3.9 ± 2.8		3.7 ± 2.8	3.8 ± 2.8	
Percent change (95% CI)	−1.1% (−9.1%, +7.5%)	−9.4% (−14.8%, −3.6%)	0.091	−8.3% (−17.2%, +1.6%)	−28.8% (−33.9%, −23.3%)	<0.001
Fasting blood glucose, mg/dL						
Baseline	94.2 ± 10.4	94.8 ± 11.2		94.2 ± 10.4	95.0 ± 11.3	
Change	−1.7 ± 0.5	−2.1 ± 0.4	0.544	−1.3 ± 0.6	−2.8 ± 0.5	0.051
Systolic blood pressure, mm Hg						
Baseline	118.2 ± 10.5	118.1 ± 10.0		118.2 ± 10.5	117.9 ± 10.0	
Change	−1.2 ± 0.4	−0.9 ± 0.3	0.556	−0.5 ± 0.4	+0.6 ± 0.3	0.039
Diastolic blood pressure, mm Hg						
Baseline	76.8 ± 7.0	76.8 ± 7.0		76.8 ± 7.0	76.7 ± 7.0	
Change	−0.7 ± 0.3	+0.2 ± 0.2	0.017	+0.3 ± 0.3	+0.4 ± 0.2	0.847

Phase III clinical trials of Contrave

Source : Expert Opin Drug Saf 2014; 13: 831-841

Table 1. Phase III clinical trials for naltrexone SR/bupropion SR.

Trial	Abbreviation	Length of study (weeks)	Number of participants	Objective
Contrave Obese Research I (COR-I)	NB-301	56	1742	Compared safety and efficacy of two doses of naltrexone SR/bupropion SR in overweight and obese patients
Contrave Obese Research-Behavior Modification (COR-BMOD)	NB-302	56	793	Assessed safety and efficacy in overweight and obese patients with controlled hypertension and/or dyslipidemia with or without behavior modification
Contrave Obese Research II (COR-II)	NB-303	56	996	Tested efficacy in overweight and obese patients with controlled hypertension and/or dyslipidemia with or without diet and exercise
Contrave Obese Research-Diabetes (COR-Diabetes)	NB-304	56	505	Determined safety and efficacy in overweight and obese patients with type 2 diabetes
Cardiovascular Outcomes Study of Contrave in Overweight and Obese Subjects With Cardiovascular Risk Factors	Light Study	Up to 4 years	Approximately 8900	Investigate cardiovascular health outcomes in overweight and obese individuals with cardiovascular risk factors. The study is designed to assess the occurrence of Major Adverse Cardiovascular Events

SR: Sustained-release.

-4.8%

-4.2%

-5.2%

-3.2%

Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

*Frank L Greenway, Ken Fujioka, Raymond A Plodkowski, Sunder Mudaliar, Maria Guttadauria, Janelle Erickson, Dennis D Kim, Eduardo Dunayevich, for the COR-I Study Group**

Summary

Background Despite increasing public health concerns regarding obesity, few safe and effective drug treatments are available. Combination treatment with sustained-release naltrexone and bupropion was developed to produce complementary actions in CNS pathways regulating bodyweight. The Contrave Obesity Research I (COR-I) study assessed the effect of such treatment on bodyweight in overweight and obese participants.

Methods Men and women aged 18–65 years who had a body-mass index (BMI) of 30–45 kg/m^2 and uncomplicated obesity or BMI 27–45 kg/m^2 with dyslipidaemia or hypertension were eligible for enrolment in this randomised, double-blind, placebo-controlled, phase 3 trial undertaken at 34 sites in the USA. Participants were prescribed mild hypocaloric diet and exercise and were randomly assigned in a 1:1:1 ratio to receive sustained-release naltrexone 32 mg per day plus sustained-release bupropion 360 mg per day combined in fixed-dose tablets (also known as NB32), sustained-release naltrexone 16 mg per day plus sustained-release bupropion 360 mg per day combined in fixed-dose tablets (also known as NB16), or matching placebo twice a day, given orally for 56 weeks. The trial included a 3-week dose escalation. Randomisation was done by use of a centralised, computer-generated, web-based system and was stratified by study centre. Co-primary efficacy endpoints at 56 weeks were percentage change in bodyweight and proportion of participants who achieved a decrease in bodyweight of 5% or more. The primary analysis included all randomised participants with a baseline weight measurement and a post-baseline weight measurement while on study drug (last observation carried forward). This study is registered with ClinicalTrials.gov, number NCT00532779.

Findings 1742 participants were enrolled and randomised to double-blind treatment (naltrexone 32 mg plus bupropion, n=583; naltrexone 16 mg plus bupropion, n=578; placebo, n=581). 870 (50%) participants completed 56 weeks of treatment (n=296; n=284; n=290, respectively) and 1453 (83%) were included in the primary analysis (n=471; n=471; n=511). Mean change in bodyweight was –1·3% (SE 0·3) in the placebo group, –6·1% (0·3) in the naltrexone 32 mg plus bupropion group (p<0·0001 *vs* placebo) and –5·0% (0·3) in the naltrexone 16 mg plus bupropion group (p<0·0001 *vs* placebo). 84 (16%) participants assigned to placebo had a decrease in bodyweight of 5% or more compared with 226 (48%) assigned to naltrexone 32 mg plus bupropion (p<0·0001 *vs* placebo) and 186 (39%) assigned to naltrexone 16 mg plus bupropion (p<0·0001 *vs* placebo). The most frequent adverse event in participants assigned to combination treatment was nausea (naltrexone 32 mg plus bupropion, 171 participants [29·8%]; naltrexone 16 mg plus bupropion, 155 [27·2%]; placebo, 30 [5·3%]). Headache, constipation, dizziness, vomiting, and dry mouth were also more frequent in the naltrexone plus bupropion groups than in the placebo group. A transient increase of around

Lancet 2010; 376: 595–605

This online publication has been corrected.
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See Comment page 567

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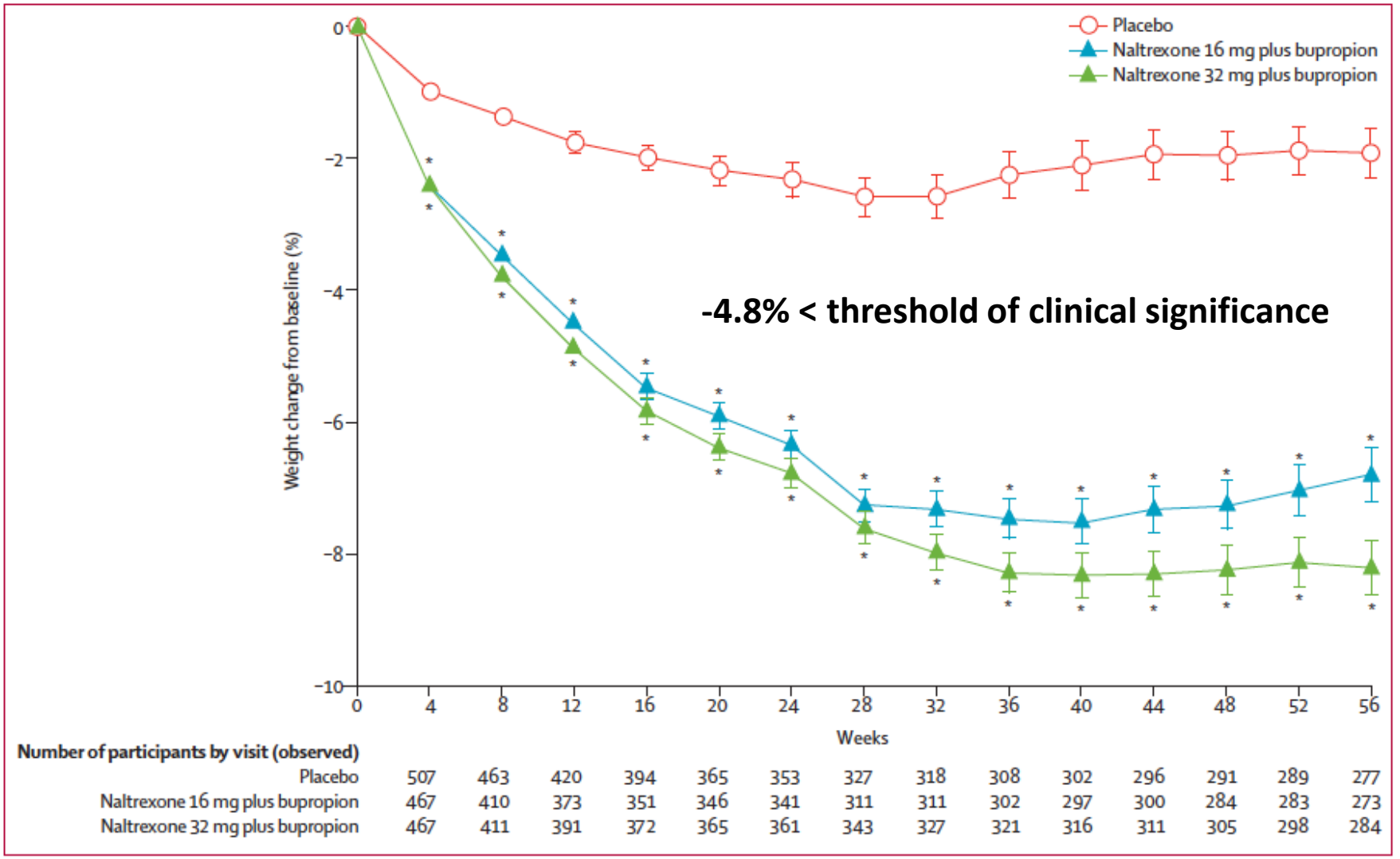


Number of participants by visit (observed)														
Placebo	507	463	420	394	365	353	327	318	308	302	296	291	289	277
Naltrexone 16 mg plus bupropion	467	410	373	351	346	341	311	311	302	297	300	284	283	273
Naltrexone 32 mg plus bupropion	467	411	391	372	365	361	343	327	321	316	311	305	298	284

Figure 2: **Change in bodyweight**

Observed least squares mean (SE) percentage change from baseline in bodyweight and number of participants at each visit during 56 weeks. *p<0·0001 compared with placebo.

	Placebo	Naltrexone 16 mg plus bupropion	Naltrexone 32 mg plus bupropion	p value for comparison with placebo	
				Naltrexone 16 mg plus bupropion	Naltrexone 32 mg plus bupropion
Waist circumference (cm)					
Baseline	110·0 (12·2)	109·8 (11·2)	108·8 (11·3)	..	..
Change	−2·5 (−3·3 to −1·6)	−5·0 (−5·9 to −4·2)	−6·2 (−7·1 to −5·4)	<0·0001*	<0·0001*
Triglycerides (mmol/L)†					
Baseline	1·28 (0·02)	1·23 (0·02)	1·31 (0·02)	..	..
Percentage change	−3·1% (−6·6 to 0·6)	−8·0% (−11·4 to −4·4)	−12·7% (−15·8 to −9·5)	0·0461*	<0·0001*
HDL cholesterol (mmol/L)					
Baseline	1·35 (0·35)	1·35 (0·35)	1·34 (0·35)	..	..
Change	0·00 (−0·02 to 0·02)	0·09 (0·06 to 0·11)	0·09 (0·07 to 0·11)	<0·0001*	<0·0001*
Percentage change	0·8% (−1·0 to 2·5)	7·6% (5·9 to 9·4)	8·0% (6·3 to 9·7)	..	..
LDL cholesterol (mmol/L)					
Baseline	3·10 (0·90)	3·23 (0·84)	3·08 (0·84)	..	..
Change	−0·08 (−0·15 to −0·02)	−0·10 (−0·16 to −0·03)	−0·11 (−0·17 to −0·05)	0·8112	0·4838
Percentage change	−0·5% (−2·6 to 1·6)	−1·5% (−3·6 to 0·6)	−2·0% (−4·0 to 0·1)	..	..
hsCRP (mg/L)†					
Baseline	3·57 (2·81)	3·89 (2·64)	3·83 (2·80)	..	..
Percentage change	−16·7% (−32·7 to 0·0)	−28·0% (−34·1 to −21·4)	−30·0% (−34·8 to −24·7)	0·0150*	0·0076*
Systolic blood pressure (mm Hg)					
Baseline	119·0 (9·8)	119·5 (9·9)	118·9 (9·9)	..	..
Change	−1·9 (−2·7 to −1·2)	0·3 (−0·5 to 1·1)	−0·1 (−0·9 to 0·7)	<0·0001	0·0008
Diastolic blood pressure (mm Hg)					
Baseline	77·3 (6·6)	76·6 (7·2)	77·1 (7·2)	..	..
Change	−0·9 (−1·4 to −0·3)	0·1 (−0·5 to 0·7)	0·0 (−0·5 to 0·6)	0·0150	0·0217
IWQOL-Lite total score‡					
Baseline	71·8 (17·2)	70·7 (17·0)	70·3 (16·5)	..	..
Change	8·6 (−7·5 to 9·6)	11·7 (10·6 to 12·7)	12·7 (11·6 to 13·8)	<0·0001*	<0·0001*
Systolic blood pressure (mm Hg)					
Baseline	119·0 (9·8)	119·5 (9·9)	118·9 (9·9)	..	..
Change	−1·9 (−2·7 to −1·2)	0·3 (−0·5 to 1·1)	−0·1 (−0·9 to 0·7)	<0·0001	0·0008
Diastolic blood pressure (mm Hg)					
Baseline	77·3 (6·6)	76·6 (7·2)	77·1 (7·2)	..	..
Change	−0·9 (−1·4 to −0·3)	0·1 (−0·5 to 0·7)	0·0 (−0·5 to 0·6)	0·0150	0·0217
IDS-SR total score§					
Baseline	6·2 (5·0)	6·5 (5·5)	6·7 (5·5)	..	..
Change	−0·7 (−1·1 to −0·3)	0·0 (−0·4 to 0·4)	−0·3 (−0·7 to 0·1)	0·0080	0·1017

Data are for the primary analysis population. Baseline values are mean (SD); change and percentage change values are least squares mean (95% CI). hsCRP=high-sensitivity C-reactive protein. HOMA-IR=homoeostasis model assessment for insulin resistance. IWQOL-Lite=Impact of Weight on Quality of Life-Lite questionnaire. IDS-SR=Inventory of Depressive Symptomatology Self Report. *Endpoints that were significant according to the prespecified sequential closed testing procedure undertaken to correct for multiple comparisons. †Values that were $\log_{10}$ transformed before statistical analyses (to reduce skewness). Baseline values are geometric mean (SD); percentage change values are least squares geometric mean minus one (95% CI). ‡IWQOL-Lite total score is based on a scale from 0 to 100, where a score of 0–70 indicates severe impairment, 71–79 indicates moderate impairment, 80–87 indicates mild impairment, and 88–100 indicates no impairment. §IDS-SR total score is based on 30 items, where the score can range from 0 to 84; a total score of 13 or lower indicates no depression.

Table 3: Secondary endpoints at 56 weeks

	Placebo	Naltrexone 16 mg plus bupropion	Naltrexone 32 mg plus bupropion	p value for comparison with placebo	
				Naltrexone 16 mg plus bupropion	Naltrexone 32 mg plus bupropion
Waist circumference (cm)					
Baseline	110·0 (12·2)	109·8 (11·2)	108·8 (11·3)	..	..
Change	−2·5 (−3·3 to −1·6)	−5·0 (−5·9 to −4·2)	−6·2 (−7·1 to −5·4)	<0·0001*	<0·0001*
Triglycerides (mmol/L)†					
Baseline	1·28 (0·02)	1·23 (0·02)	1·31 (0·02)	..	..
Percentage change	−3·1% (−6·6 to 0·6)	−8·0% (−11·4 to −4·4)	−12·7% (−15·8 to −9·5)	0·0461*	<0·0001*
HDL cholesterol (mmol/L)					
Baseline	1·35 (0·35)	1·35 (0·35)	1·34 (0·35)	..	..
Change	0·00 (−0·02 to 0·02)	0·09 (0·06 to 0·11)	0·09 (0·07 to 0·11)	<0·0001*	<0·0001*
Percentage change	0·8% (−1·0 to 2·5)	7·6% (5·9 to 9·4)	8·0% (6·3 to 9·7)	..	..
LDL cholesterol (mmol/L)					
Baseline	3·10 (0·90)	3·23 (0·84)	3·08 (0·84)	..	..
Change	−0·08 (−0·15 to −0·02)	−0·10 (−0·16 to −0·03)	−0·11 (−0·17 to −0·05)	0·8112	0·4838
Percentage change	−0·5% (−2·6 to 1·6)	−1·5% (−3·6 to 0·6)	−2·0% (−4·0 to 0·1)	..	..
hsCRP (mg/L)†					
Baseline	3·57 (2·81)	3·89 (2·64)	3·83 (2·80)	..	..
Percentage change	−16·7% (−32·7 to 0·0)	−28·0% (−34·1 to −21·4)	−30·0% (−34·8 to −23·7)	0·0150*	0·0076*
IWQOL-Lite total score‡					
Baseline	71·8 (17·2)	70·7 (17·0)	70·3 (16·5)	..	..
Change	8·6 (−7·5 to 9·6)	11·7 (10·6 to 12·7)	12·7 (11·6 to 13·8)	<0·0001*	<0·0001*
Systolic blood pressure (mm Hg)					
Baseline	119·0 (9·8)	119·5 (9·9)	118·9 (9·9)	..	..
Change	−1·9 (−2·7 to −1·2)	0·3 (−0·5 to 1·1)	−0·1 (−0·9 to 0·7)	<0·0001	0·0008
Diastolic blood pressure (mm Hg)					
Baseline	77·3 (6·6)	76·6 (7·2)	77·1 (7·2)	..	..
Change	−0·9 (−1·4 to −0·3)	0·1 (−0·5 to 0·7)	0·0 (−0·5 to 0·6)	0·0150	0·0217
IDS-SR total score§					
Baseline	6·2 (5·0)	6·5 (5·5)	6·7 (5·5)	..	..
Change	−0·7 (−1·1 to −0·3)	0·0 (−0·4 to 0·4)	−0·3 (−0·7 to 0·1)	0·0080	0·1017

Data are for the primary analysis population. Baseline values are mean (SD); change and percentage change values are least squares mean (95% CI). hsCRP=high-sensitivity C-reactive protein. HOMA-IR=homoeostasis model assessment for insulin resistance. IWQOL-Lite=Impact of Weight on Quality of Life-Lite questionnaire. IDS-SR=Inventory of Depressive Symptomatology Self Report. *Endpoints that were significant according to the prespecified sequential closed testing procedure undertaken to correct for multiple comparisons. †Values that were $\log_{10}$ transformed before statistical analyses (to reduce skewness). Baseline values are geometric mean (SD); percentage change values are least squares geometric mean minus one (95% CI). ‡IWQOL-Lite total score is based on a scale from 0 to 100, where a score of 0–70 indicates severe impairment, 71–79 indicates moderate impairment, 80–87 indicates mild impairment, and 88–100 indicates no impairment. §IDS-SR total score is based on 30 items, where the score can range from 0 to 84; a total score of 13 or lower indicates no depression.

Table 3: Secondary endpoints at 56 weeks

New obesity pill: new hopes, old fears

Corbis

For more on **the US Food And Drug Association** see http://www.fda.gov/

For more on the **Contrave phase-3 trial** see Articles *Lancet* 2010; **376:** 595–605

For more on **obesity statistics** see http://www.cdc.gov/obesity/data/index.html

On Dec 7, 2010, the US Food and Drug Administration (FDA) Endocrinologic and Metabolic Drugs Advisory Committee gave a positive recommendation for the use of Contrave in the treatment of obesity and weight management, signalling a potentially major shift in attitude towards the disorder. Contrave, if finally approved by the FDA on Jan 31, 2011, will be the first new weight-loss drug to be approved for 10 years. The drug is a combination of bupropion, an antidepressant used to help patients to quit smoking, and naltrexone, an opioid antagonist prescribed for alcohol and drug addiction, thought to affect the reward pathway (system in which behaviour is regulated by induction of pleasure).

The use of such a drug to tackle a complex problem like obesity is worrying, especially when the benefits seem modest (a decrease in bodyweight of 5%) compared with the potential risks. Albeit no serious side-effects were recorded in the four phase-3 trials for Contrave (one of which was published in this journal), there are indices of serious risks associated with bupropion, such as suicidal thoughts, seizures, and serious cardiovascular effects. The FDA committee and the drug's manufacturer, Orexigen, agreed that a large trial to assess the risk of major cardiac events associated with Contrave was needed, but that this study could wait until after the approval.

Research into obesity has been fraught with difficulty, with many drugs having been withdrawn from the market in the past for safety reasons. The flexibility shown by the FDA in its ruling on Contrave may be motivated by a desire to encourage pharmaceutical companies to commit more funding into obesity research, as rates of obesity continue to soar. More than a third of the US population is obese, and two-thirds are either obese or overweight. But this drug showed weight loss only when combined with lifestyle modification, and should not be seen as a magic bullet. Governments should address the obesity epidemic through a comprehensive approach, focusing on the underlying causes of obesity, and not promoting medication of a disorder that should be treated with modifications of lifestyle, diet, and exercise. ■ *The Lancet*

Finally :

A very **limited clinical size effect** related to the evaluation criteria for efficacy

A **concern related to the safety profile**, including an effect on blood pressure opposite to the objective of protection against cardiovascular complications

And other issues such as the level of compliance to treatment during clinical trials (usually worse in current care conditions)

Should we consider this example* as a **real, tangible medical progress** according to available data from CTs ? Need for real world/big data to confirm therapeutic benefit ?

* Excerpts of publications and other public data are used in this presentation only for illustrative purpose.

Third example on use of statins

Elders and exposure to statins (French statistics from the National Health Fund, 2012)

22% of 75+ were treated with statins
More than **50%** for primary prevention*

thebmj

BMJ 2014;349:g7820 doi: 10.1136/bmj.g7820 (Published 29 December 2014)

Page 1 of 1

NEWS

Half of over 75s in US are taking cholesterol lowering drugs, report says

Jeanne Lenzer

New York

Nearly half (48%) of all US adults aged 75 or older are taking cholesterol lowering drugs, says a report by the Centers for Disease Control and Prevention's National Center for Health Statistics.[1] However, some professional groups have challenged the report's conclusion that "there is extensive and consistent evidence supporting the use of cholesterol-lowering medication

A professional association that participated in the Choosing Wisely campaign initiated by the American Board of Internal Medicine Foundation has called for doctors to stop routinely prescribing lipid lowering drugs to people over 70. In response to the Choosing Wisely campaign the association, known as AMDA (the Society for Post-Acute and Long-Term Care

* Patients without a previous diagnosis of coronary artery disease, peripheral vascular disease or cerebrovascular disease

Majority of patients included in CTs of statins in primary prevention are <75

An exception :

PROSPER - PROspective Study of Pravastatin in the Elderly at Risk (Lancet 2002; 360: 1623)

Ages between 70 and 82

Inclusion in case of either :

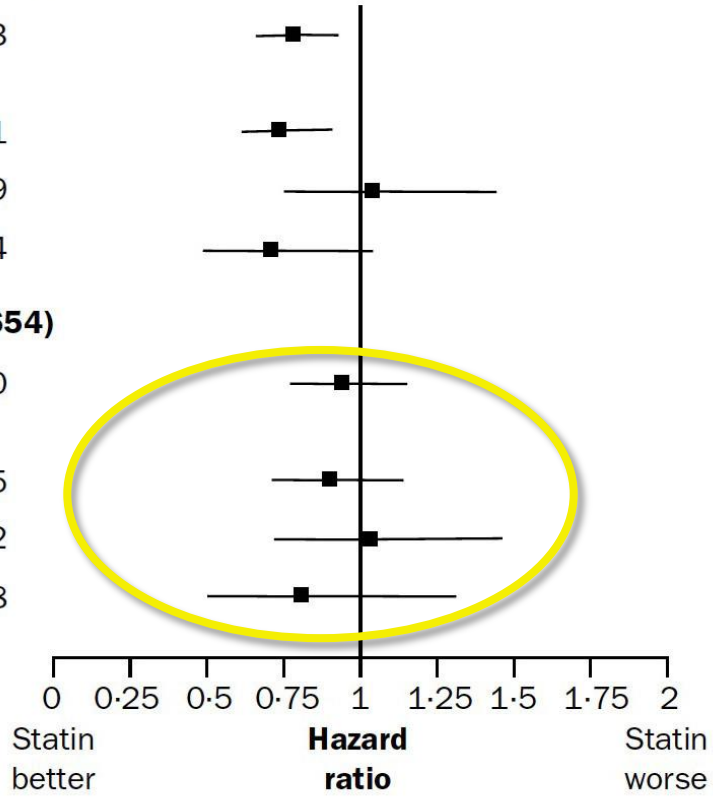
- Pre-existing vascular disease (coronary, cerebral or peripheral)
- Or raised risk of such disease because of smoking, hypertension, or diabetes.

Plasma total cholesterol was required to be 4–9 mmol/L and their triglyceride concentrations less than 6 mmol/L.

Objective : evaluate if treatment with pravastatin reduces the risk of cardiac events, stroke, cognitive decline and disability in those with existing (secondary prevention) and in those at high risk of developing (primary prevention) vascular disease.

No benefit was found in the primary prevention group

	Pravastatin	Placebo
Secondary prevention	**(n=1306)**	**(n=1259)**
CHD death, non-fatal MI, and fatal or non-fatal stroke	227	273
CHD death, non-fatal MI	166	211
Fatal and non-fatal stroke	74	69
TIA	47	64
Primary prevention	**(n=1585)**	**(n=1654)**
CHD death, non-fatal MI, and fatal or non-fatal stroke	181	200
CHD death, non-fatal MI	126	145
Fatal and non-fatal stroke	61	62
TIA	30	38



Major cardiovascular outcomes, according to primary or secondary prevention status of participants

CHD=coronary heart disease. MI=myocardial infarction. TIA=transient ischaemic attack. The primary endpoint of the study is reproduced for comparative purposes.

Meta-analysis aggregating data from 61 prospective studies, total of 900,000 adults, nearly 12 million person years at risk between the ages of 40 and 89 years

Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55 000 vascular deaths

*Prospective Studies Collaboration**

Summary

Background Age, sex, and blood pressure could modify the associations of total cholesterol (and its main two fractions, HDL and LDL cholesterol) with vascular mortality. This meta-analysis combined prospective studies of vascular mortality that recorded both blood pressure and total cholesterol at baseline, to determine the joint relevance of these two risk factors.

Methods Information was obtained from 61 prospective observational studies, mostly in western Europe or North America, consisting of almost 900 000 adults without previous disease and with baseline measurements of total cholesterol and blood pressure. During nearly 12 million person years at risk between the ages of 40 and 89 years, there were more than 55 000 vascular deaths (34 000 ischaemic heart disease [IHD], 12 000 stroke, 10 000 other). Information about HDL cholesterol was available for 150 000 participants, among whom there were 5000 vascular deaths (3000 IHD, 1000 stroke, 1000 other). Reported associations are with usual cholesterol levels (ie, corrected for the regression dilution bias).

Findings 1 mmol/L lower total cholesterol was associated with about a half (hazard ratio 0·44 [95% CI 0·42–0·48]), a third (0·66 [0·65–0·68]), and a sixth (0·83 [0·81–0·85]) lower IHD mortality in both sexes at ages 40–49, 50–69, and 70–89 years, respectively, throughout the main range of cholesterol in most developed countries, with no apparent threshold. The proportional risk reduction decreased with increasing blood pressure, since the absolute effects of cholesterol and blood pressure were approximately additive. Of various simple indices involving HDL cholesterol, the

Lancet 2007; 370: 1829–39

See Comment page 1803

*Collaborators listed in full at end of paper

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EURORDIS Rare Diseases Europe

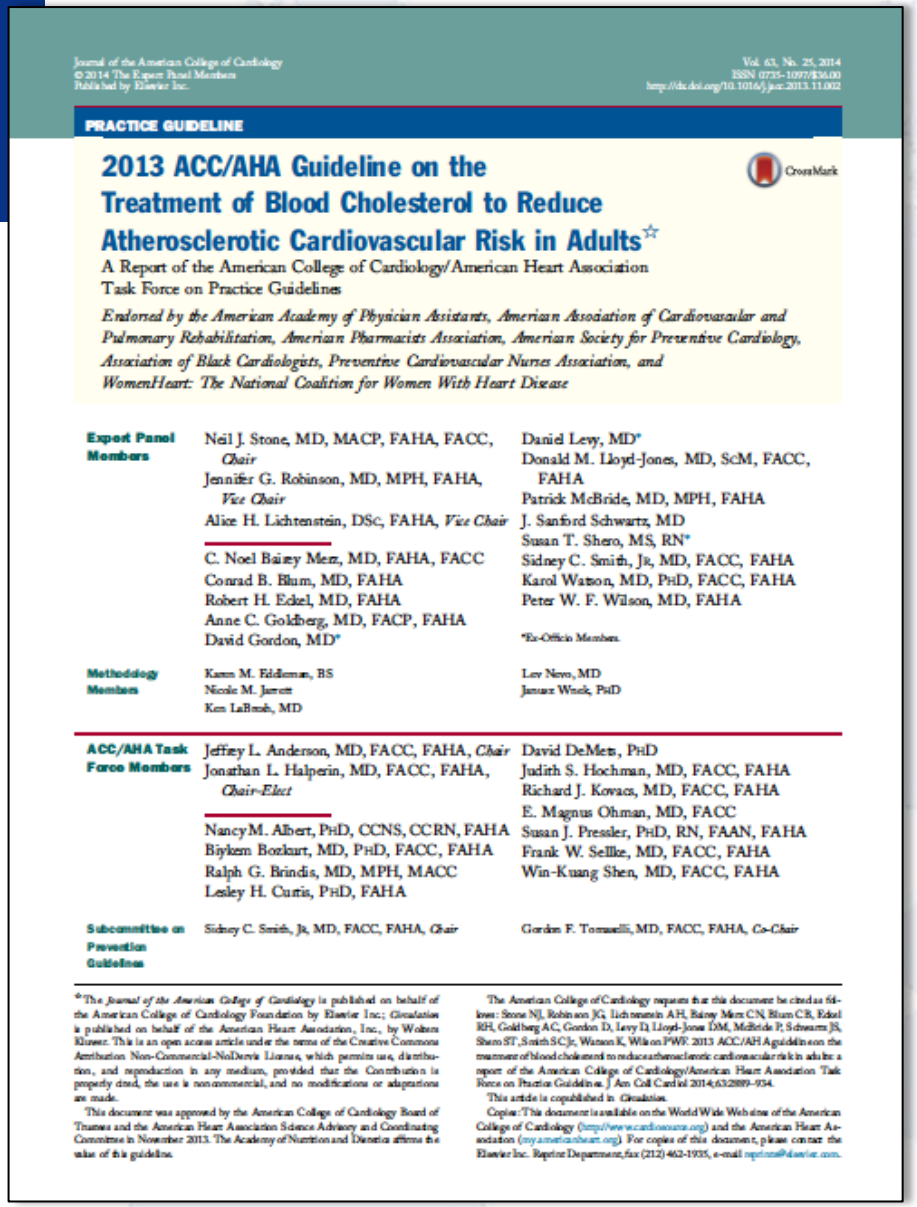
For patients of 70–89 y.o. :

- **No impact of lower cholesterol on mortality**
- Decrease in cardiovascular mortality, lower ischaemic heart disease mortality, increase in other causes of death

	Hazard ratio (95% CI)		
	IHD	Stroke	Other vascular
40–49 years	0·45 (0·42–0·47)	0·87 (0·76–1·00)	0·62 (0·55–0·69)
50–59 years	0·57 (0·55–0·58)	0·91 (0·85–0·97)	0·75 (0·71–0·79)
60–69 years	0·68 (0·66–0·69)	0·93 (0·89–0·97)	0·83 (0·80–0·86)
70–79 years	0·79 (0·78–0·81)	1·02 (0·97–1·06)	0·89 (0·85–0·92)
80–89 years	0·85 (0·82–0·89)	1·05 (0·98–1·11)	1·02 (0·96–1·09)

Hazard ratios for IHD (ischaemic heart disease), stroke and other vascular mortality for 1 mmol/L lower usual total cholesterol

A previous meta-analysis (Ann Epidemiol 2004; 14: 705) reported that total cholesterol showed an inverse relationship with all-cause mortality in elderly over the age of 80



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PRACTICE GUIDELINE

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults☆

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Endorsed by the American Academy of Physician Assistants, American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women With Heart Disease

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Individuals >75 years of age

Few data were available to indicate an ASCVD event reduction benefit in primary prevention among individuals >75 years of age who do not have clinical ASCVD.

Therefore, initiation of statins for primary prevention of ASCVD in individuals >75 years of age requires consideration of additional factors, including increasing comorbidities, safety considerations, and priorities of care.

Large use of statins in elderly, especially for primary prevention of cardiovascular events

Lack of strong evidence on benefit in primary prevention, in particular in a context of relatively limited life expectancy and possible co-morbidities

Increase of mortality with low values of cholesterol

Risk of frequent adverse events (myalgia, athralgia, digestive disorders,…), risk of drug interactions

<u>Consequences</u> at distance of initial market access

Do we need to treat ?
Need for **real life studies** to better assess the use and evaluate impacts on morbidity, QoL and mortality ?
Need for guidelines adapted to these populations to answer precisely to practical situations :
- **Initiation or not** in elderly ? At what age ?
- **When to discontinue a pre-existing statin therapy** ?

2 Qs Is the disease important? Is the medicine important ?

France

Decision-making process

- SMR rating is based on severity of the disease:
  - major
  - important
  - moderate
  - minor
  - insufficient to justify reimbursement
- ASMR (incremental benefit vs SOC) is rated between 1 and 5:
  - major (1)
  - important (2)
  - moderate (3)
  - minor (4)
  - none (5)

ASMR decision criteria

1. Innovative product of significant therapeutic benefit
2. Product of therapeutic benefit in terms of efficacy and/or reduction in side-effect profile
3. Existing product where equivalent pharmaceuticals exist; moderate improvement in terms of efficacy and/or reduction in side-effect profile
4. Minor improvement in terms of efficacy and/or utility
5. No improvement but still granted recommendations to be listed

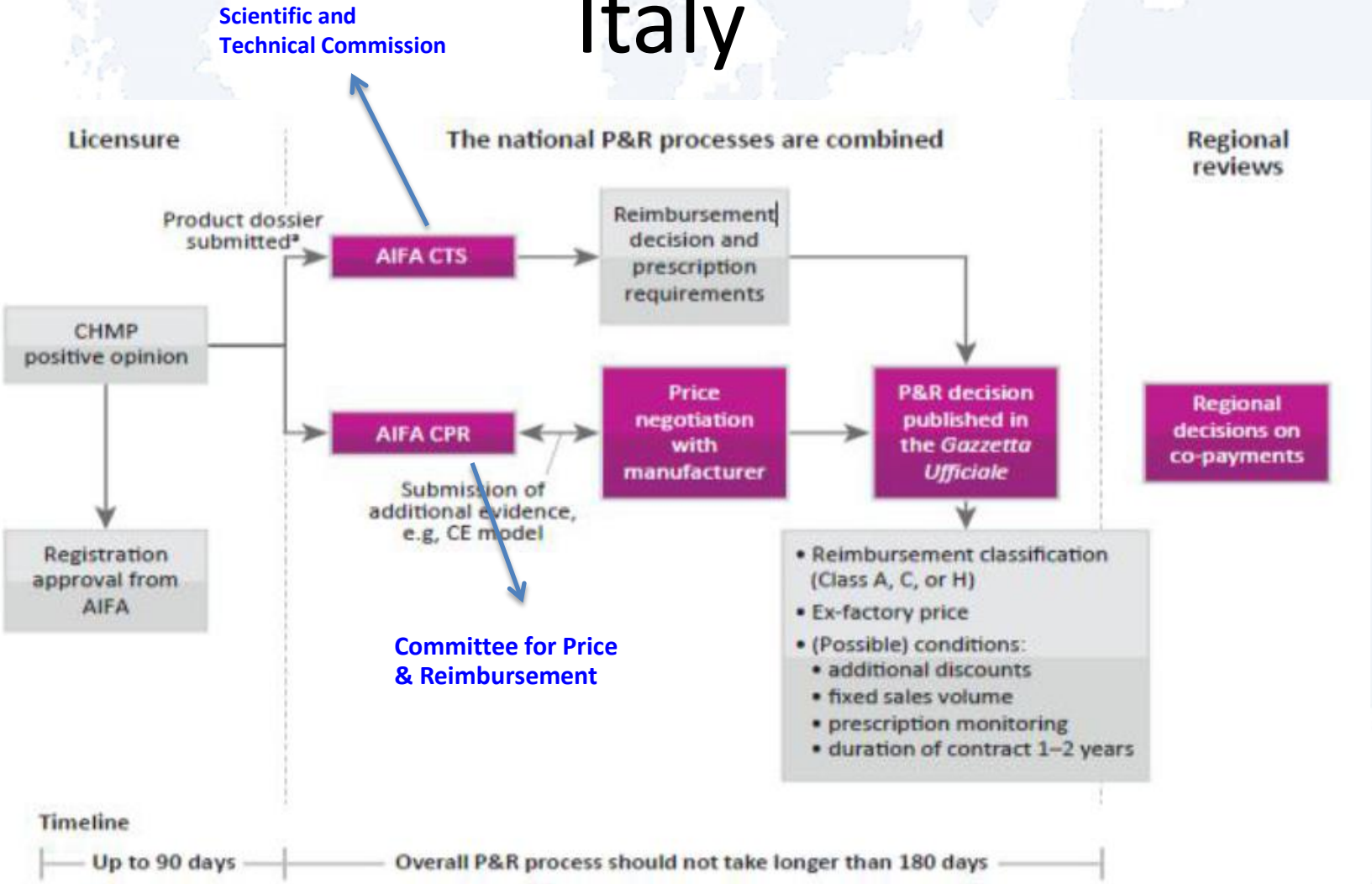
Key trends

- ASMR ratings are getting lower
- SMR ratings are increasingly being used to deny or restrict reimbursement
- Importance of incremental clinical benefit (better efficacy or better safety profile, as evidenced in relevant clinical trials) will increase
- Innovative technologies will require pharmacoeconomic studies showing that they provide cost-savings and improve disease management
- Patient stratification is becoming increasingly important to limit budget impact

France

- The potential for premium pricing has become more challenging in France as the necessary ASMR ratings are being awarded less often
- HAS recently advocated for replacing the SMR and ASMR ratings with a single index (ITR) of comparative "therapeutic benefit"
- Comparative efficacy/effectiveness is increasingly essential to establish value of medicines
- Reimbursement of medicines is more and more targeted to populations in which data from clinical trials is positive
- **Pharmaceutical innovation is not sufficient, proof of significant clinical benefit is necessary**

Italy

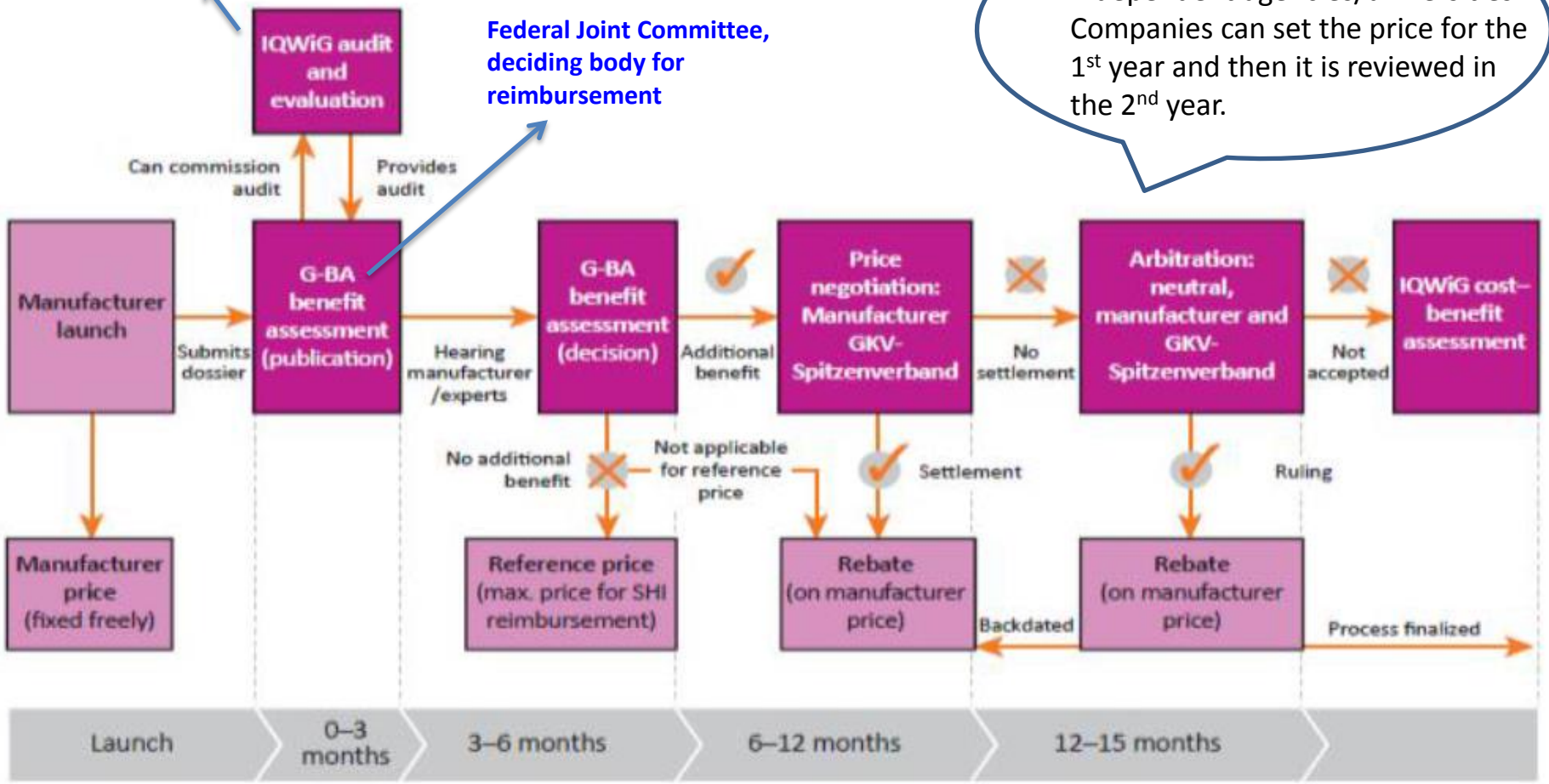

Scientific and Technical Commission
Licensure
The national P&R processes are combined
Regional reviews
Product dossier submitted*
AIFA CTS
Reimbursement decision and prescription requirements
CHMP positive opinion
AIFA CPR
Price negotiation with manufacturer
P&R decision published in the Gazzetta Ufficiale
Regional decisions on co-payments
Submission of additional evidence, e.g. CE model
Registration approval from AIFA
• Reimbursement classification (Class A, C, or H)
• Ex-factory price
• (Possible) conditions:
• additional discounts
• fixed sales volume
• prescription monitoring
• duration of contract 1–2 years
Committee for Price & Reimbursement
Timeline
Up to 90 days
Overall P&R process should not take longer than 180 days

Germany

Independent scientific body, comparative efficacy/safety, health economics

Federal Joint Committee, deciding body for reimbursement

AMNOG sends assessment to independent agencies/universities
Companies can set the price for the 1st year and then it is reviewed in the 2nd year.



SHI : Statutory Health Insurer
GKV : Federal Association of Statutory Health Insurers
AMNOG : Act on the Reform of the Market for Medicinal Products

European payers and HTA authorities

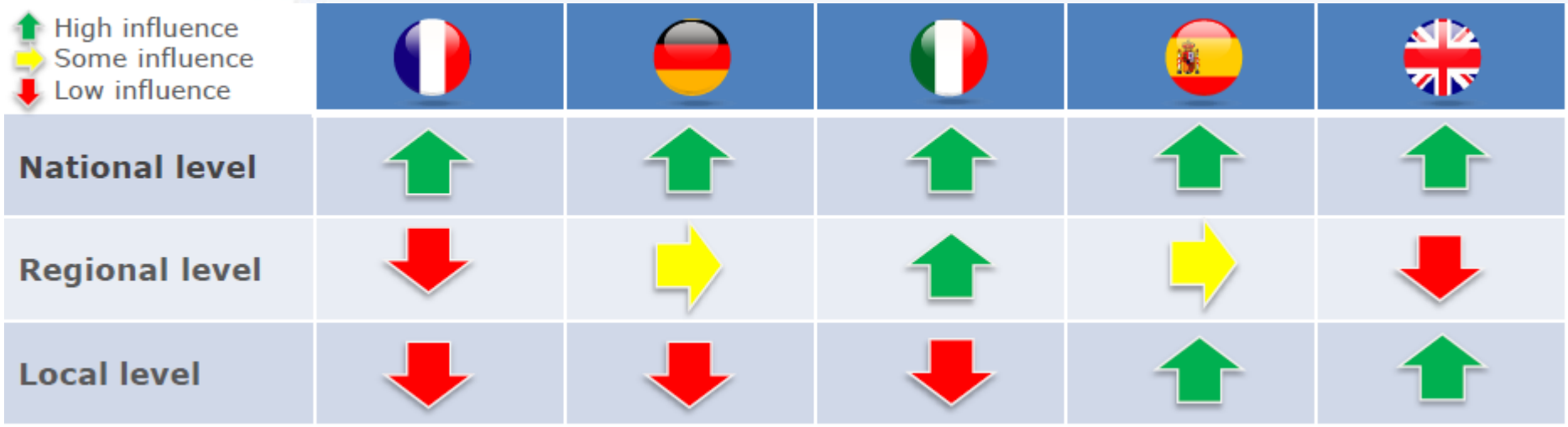
Country	Key agencies	Details
 UK	• NICE • SMC • AWMSG	• Clinical and cost-effectiveness are assessed • Cost-effectiveness is assessed using QALYs; the key threshold is about £30,000 per QALY • The SMC reviews all new products before launch (it is typically the first formal HTA to be completed)
 France	• TC • CEPS • HAS	• A dossier is submitted to the TC after marketing authorization. TC strongly prefers head-to-head data • Incremental therapeutic benefit (ASMR) is assessed and the reimbursed population is identified. • Prices are negotiated with CEPS on the basis of the ASMR and SMR ratings, and may include price–volume agreements with payback clauses • HAS is typically responsible for developing treatment and prescribing guidelines

EU payers and HTA authorities

Country	Key agencies	Details
 Germany	• G-BA • IQWiG	• Free pricing applies for the first 12 months; the price is negotiated after the benefit assessment • The AMNOG legislation introduced in 2011 requires submission of a benefit dossier to the G-BA
 Italy	• AIFA • UVEF	• A file is submitted to AIFA • Products are reimbursed on Class H or A list • Budget impact and head-to-head data are important • Risk-sharing agreements are extensively used, particularly in oncology • Regional autonomy: UVEF is responsible for HTAs in the Veneto region
 Spain	• Ministry of Health • Regional HTA agencies	• Central HTA agency assesses clinical profile and daily cost • HTAs occur mostly at the regional level, with increasing use of cost-effectiveness and coordination at the hospital level • Cost-effectiveness is likely to be required in future

Stakeholder influence/country

- National and regional authorities exert different levels of influence on market access. Addressing only national stakeholder needs may be inadequate in some countries.



Across Europe, market access terms becoming more restrictive

Key market access themes	Comment
• Meaningful clinical differentiation against an active and relevant comparator eg head-to-head	
• Growing importance of subpopulations	• May be significantly smaller than the regulatory population
• Growing importance of cost-effectiveness	• Formal cost-effectiveness requirements at launch 
• Critical importance of HRQoL	• Emergence of more complex composite endpoints 
• Increased use of risk-sharing agreements	
• Regional stakeholders importance	• Make independant decisions 
• Lifecycle market access requirements	• On-going re-assessments 

EURORDIS Rare Diseases Europe

Comparison of submission requirements

Work stream						Comments
Therapeutic benefit						• Prefer hard efficacy endpoints; however, surrogate endpoints if supported by guidelines/KOLs
CE modeling						• Cost per QALY gained is preferred ICER. UK threshold usually £30,000 but rises to £50,000 for EoL treatments
Budget impact modeling						• Price–volume agreements or caps in some countries • Clear ability to define the eligible patient population
HRQoL data						• Utilities are used • HRQoL data may have an impact particularly in chronic diseases and EoL considerations
Head-to-head data vs SOC						• Establishing the SOC or comparator important
Real-world observational data						• Real-world data may help achieve market access
Innovation						• Innovation is a key factor in P&R and can have a significant impact on price

Note: EoL refers to standard of care considerations around the end of life.

Key requirement Nice to have Not required

EURORDIS Rare Diseases Europe

Same data, different access & different reimbursement decisions

Product (indication)	**Clinical data**	**P&R outcomes**
Avastin (mCRC)	Avastin + IFL offers a 4.7 month median improvement in OS vs IFL + placebo (20.3 vs 15.6 months)	✗ Not recommended by NICE or SMC 
		✓ Reimbursed (ASMR 2) 
Nexavar (RCC)	Sorafenib offers a 3 month median improvement in PFS vs placebo (24 vs 12 weeks)	✗ Not recommended by NICE or SMC 
		✓ Reimbursed (ASMR 2) 
		✓ Reimbursed with a mandatory discount (50% for first 2 cycles) 
Nexavar (HCC)	Sorafenib offers a 2.8 month median improvement in OS vs placebo (10.7 vs 7.9 months)	✗ Not recommended by NICE or SMC 
		✓ Reimbursed (ASMR 4) 
		✓ Reimbursed with a mandatory discount (50% for first 2 cycles) 

General trend towards risk-sharing agreements

- Different types of risk-sharing agreement are used:
  - **Risk sharing** (rebate) – reimbursement of drug cost for non-responders
  - **Cost sharing** (discount) – discounted drug price
  - **Payment by results** (rebate) – reimbursement of first cycles for non-responders

- Avastin (in NSCLC, CRC, BC, RCC): 50% reimbursed for the first three cycles; 100% reimbursed for cycles 4–14; cost of subsequent cycles borne by manufacturer
- Sutent (in mRCC): first course of treatment is free
- Torisel (in mRCC): total reimbursement limited to 8 packs (~2 months of therapy); additional cost is paid back by the manufacturer if the patient discontinues treatment during this period

Key areas of HTA critique across countries

	Comparators	Survival data	Eligible population	PRO/Utility data
SMC		✓	✓	✓
NICE	✓	✓		✓
TC	✓	✓		✓
IQWiG			✓	

Across HTAs, the areas of consistent criticism were in the survival data, utility data and choice of comparators.

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